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EDITORIAL

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Sincerely Yours,

Prof. Dr. Alpaslan TANOĞLU
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The relationship between nursing students' mental health literacy levels and holistic nursing competencies

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ABSTRACT

Aims: The study was conducted to examine the relationship between nursing students' mental health literacy levels and holistic nursing competencies.

Methods: This was a descriptive and relational study. The sample of the study consisted of 440 nursing department students at a state university. Data were collected with the Sociodemographic data form, the mental health literacy scale, and the holistic nursing competence scale.

Results: The mean score of the mental health literacy scale total scores of the students was 101.11±8.49, and the mean total score of the holistic nursing competence scale total score was 168.41±40.53. There was a positive relationship between the mental health literacy scale total score and the general ability sub-field (r=0.101) of the holistic nursing competence scale and the professional development sub-field (r=0.095), and this relationship was statistically significant ($p<0.05$).

Conclusion: According to the scale scores, the mental health literacy level of nursing students was low, holistic nursing competencies were at an intermediate level, there was a statistically significant very weak and positive correlation between the MHLS total score and the HNCS general ability (A) sub-field, and the HNCS professional development (B) sub-field. It is recommended that nursing students be given courses on mental health and holistic nursing, and more studies on mental health literacy and holistic nursing and interventional studies that increase students' mental health literacy and holistic nursing competencies.

Keywords: Competency, holistic nursing, literacy, mental health, nursing students

The abstract of the study was presented as an oral presentation at the Muğla Sıtkı Koçman University National Interdisciplinary Student Congress on May 12-14, 2022.

INTRODUCTION

The term mental health literacy was first used by Jorm et al. was defined as "knowledge and beliefs about recognizing, managing, and preventing mental disorders" in 1997.[1-3] Kutcher defined mental health literacy with four components: knowledge of how to achieve and maintain positive mental health; understanding psychiatric disorders and their treatments; reducing stigma related to psychiatric disorders; increasing professional help-seeking behavior and knowing where, when, and how the individual will receive mental health services.[8,10]

A high level of mental health literacy is of great importance in protecting and improving the mental health of individuals. In addition to these initiatives that will positively affect mental health, people's physical and mental health should also be evaluated together.[3-5] To achieve this, it is extremely important to consider individuals physically, socially and spiritually together, in other words, to evaluate them with a holistic approach.[8,10]

The holistic approach is the evaluation of the individual as a whole in a reciprocal relationship with his/her family and environment in terms of physical, mental, emotional, and sociocultural aspects. The suffering individual should be considered not only as a person with the disease, but as a whole in all aspects.[8-10] Holistic nursing care is a special field of nursing practice in which nurses use the nursing knowledge, skills, and theories they have learned to support the care of individuals and the formation of the therapeutic relationship.[11,12] The concept of competence in holistic nursing care is the fulfillment of nurses' personal characteristics, value judgments, attitudes, professional knowledge, competencies, and skills in nursing practices with the awareness of professional obligation. In addition, the continuous and adequate use of the holistic approach, not only in the fields of general health but also in the field of mental health, and determining the holistic competence level of nursing students and working toward achieving such competence will contribute to the development of mental health services.[8,13-14]

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In holistic patient care practices provided by nurses, the bio-psycho-social aspects of individuals are taken into consideration. According to this approach, nurses are responsible for individuals' social, must evaluate their biological, psychological and cultural situations together. In addition, nurses need to offer holistic solutions when planning the health care of individuals.[9] It is of great importance that nurses who care for healthy/sick individuals have good knowledge of mental health as well as physical health, so that they can provide the holistic care that people need.[9-10,12] In order to provide holistic nursing care, especially in nursing education, it is of great importance to evaluate the individual psychologically as well as physically.[9-10,14]

It is predicted that nursing students with high mental health literacy levels and holistic nursing competencies will enable them to evaluate their mental health as a whole as well as the physical health of the people they care for, and thus the nursing care provided will be holistic. The study was conducted to examine the relationship between nursing students' mental health literacy levels and holistic nursing competencies.

METHODS

The study was carried out with the permission of Muğla Sıtkı Koçman University Health Sciences Ethics Committee (Date: 19.04.2021, Decision No: 210028-73). Since the necessity of protecting individual rights was prioritized in the research, the Helsinki Declaration of Human Rights was complied with throughout the study period.

Potential student participants were informed about the research with an informed consent form, and the individuals who agreed to participate were included in the research. It was explained that participation in the research was completely voluntary, that it did not contain any name or sign that would indicate personal information/identity, that they could leave the research whenever they wanted, and that the information obtained would be kept confidential. Each individual participating in the research was treated equally.

This was a descriptive and relational study. The research universe consisted of all students studying in the nursing department of a health sciences faculty of a state university in the spring semester of the 2020-2021 academic year (N=832). According to the sampling determination formula used in cases where the size of the sampling universe is known (5% error and 95% reliability are accepted),[15] it was found that at least 263 participants were needed once the calculation was made, and the students who agreed to participate in the research and filled out the data collection forms formed the sample of the study (n=440).

Data Collection

The data collection process was carried out digitally between 17 June and 30 June 2021 due to the restrictions imposed by the COVID-19 Pandemic. The questionnaires were uploaded to Google Forms[16] by the researcher. The relevant link was sent to the student who is the WhatsApp group leader of each class. The group leader shared the student link in the WhatsApp group and the students filled out the data collection forms by entering the relevant link.

Participants were then asked to complete three different forms. The sociodemographic data form, mental health literacy scale (MHLS) and the holistic nursing competence scale (HNCS). All these scales were in Turkish, and their Turkish translations have all been validated.[11,19]

Sociodemographic Data Form

The Sociodemographic Data Form, prepared by the researcher in line with the literature,[8,13,17,18] consisted of a total of 14 questions about the students' age, gender, high school they graduated from, class, mental health and holistic nursing.

Mental Health Literacy Scale (MHLS)

The scale developed by O'Connor & Casey was adapted into Turkish in 2020 by Tokur Kesgin et al.[19] MHLS is a Likert-type self-assessment tool that is evaluated over a total score of 35 items. The scale has six sub-dimensions: F1, recognizing diseases; F2, information on how to access information; F3, information on risk factors and their causes; F4, information on self-help/treatment interventions; F5, information on accessing professional help; and F6, attitudes that facilitate seeking appropriate help for mental disorders and attitudes toward mental disorders (stigmatization),[19] The Cronbach Alpha coefficient of the scale was 0.89 in the Turkish validity and reliability study[19] and 0.80 in this study. The cut-off score for the Turkish Society on the scale was determined as 109.50 for the Turkish Society, and those who scored above this score were considered to have a high level of mental health literacy.[20] In this study, the MHLS total score and six sub-dimensions were used. The cut-off point of the MHLS was taken as 109.50 according to the mean of the scale total score, and those who scored above this score were considered to have a high level of mental health literacy.

Holistic Nursing Competence Scale (HNCS)

The Scale was developed by Takase & Teraoka and adapted into Turkish in 2019 by Aydın & Hiçdurmaz.[11] It is a 7-point Likert-type scale consisting of 36 items, two parts, and five subfields. The first part (A) contains the general ability subfield, consisting of questions about usual behavior as a person, not as a nurse. The second

part (B) measures competence as a nurse and includes four subfields: Personnel Training and Management, Ethics-Focused Practice, Nursing Care in a Team, and Professional Development. There are no reverse scored items and cut-off points in the scale. An increase in the score obtained from the subscales indicates an increase in holistic nursing proficiency. In the Turkish validity and reliability study of the HNCS, the Cronbach Alpha coefficient was calculated as 0.90.[11] In our study the Cronbach Alpha coefficient was calculated as 0.97.

Statistical Analyses

The IBM SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA) package program was used to evaluate the data. As a result of the statistical analysis, the normality distribution of the data was examined with the Kolmogorov-Smirnov test. It was observed that the data did not demonstrate normal distribution. In addition to descriptive statistical methods (arithmetic mean, standard deviation), comparisons between groups were made with the Kruskal Wallis and Mann Whitney U tests and the Spearman Correlation analysis, and non-parametric Bonferroni analysis was used to determine between which groups there was a significant difference.[21] Therefore, the results were evaluated at the 95% confidence interval and a significance level of $p<0.05$.

RESULTS

According to the results of the research, the mean age of the students participating in the study was 21.06±1.76, 25.9% of them were 21 years old, 68% were female and 26.6% were fourth year students. Of the nursing students, 84.3% stated that there was no individual with a mental illness in their family, 97.7% stated that they thought the holistic approach was important in the nursing profession, and 52% stated that they evaluated their knowledge level about the holistic nursing approach as moderate.

According to the research data, the MHLS total score average of the nursing students was 101.11±8.49, and the mean scores of the MHLS sub-dimensions were as follows: F1, recognizing diseases, 24.14±3.13; F2, information on how to access information, 5.27±1.11; F3, information on risk factors and their causes, 5.55±1.00; F4, information on self-help/treatment interventions, 8.60±1.11; F5, information on accessing professional help, 14.95±2.43; and F6, stigmatization, 43.01±7.15. The mean HNCS total score of the nursing students was 168.41±40.53. The average score of the HNCS sub-fields were as follows: General Ability (A), 34.92±7.01; Personnel Training and Management (B), 38.57±11.03; Ethics-Focused Practice (B), 42.68±12.10; Nursing Care in a Team (B), 33.70±1.81; and Professional Development (B), 18.52±5.69 (**Table 1**).

Table 1. Examination of the distribution of the scores of the mental health literacy scale and holistic nursing competence scale

Scale Score Averages	Min	Max	$\bar{x}$	SD
Mental health literacy scale total score	74	143	101.11	8.49
Mental Health Literacy Scale's Sub-Dimensions				
F1: Recognizing diseases	10	22	24.14	3.13
F2: Information on how to access information	2	8	5.27	1.11
F3: Information on risk factors and their causes	2	8	5.55	1.00
F4: Information on self-help/ treatment interventions	4	12	8.60	1.11
F5: Information on accessing professional help	4	20	14.95	2.43
F6: Stigmatization	2	72	43.01	7.15
Holistic nursing competence scale total score	36	252	168.41	40.53
Holistic Nursing Competence Scale's Sub-Fields				
General ability (A)	7	49	34.92	7.01
Personnel training and management (B)	9	63	38.57	11.03
Ethics-focused practice (B)	9	63	42.68	12.10
Nursing care in a team (B)	7	49	33.70	1.81
Professional development (B)	8	28	18.52	5.69

When the difference between the MHLS and the sub-dimension scores according to the descriptive characteristics of nursing students was examined, the following results emerged. In terms of gender, female students scored higher as follows: F1, recognizing diseases, 3.05±.35; F2, information on how to access information, 1.07±.23; and F3: information on risk factors and their causes, while male students scored higher on the sub-dimension F6, stigmatization, 2.85 ±.48. Fourth-year students' MHLS total score average, 2.96±.21, was found to be higher than that of other groups, as was their score on the following sub-dimensions: F1, recognizing diseases, 3.17±.43; F2, information on how to access information, 1.10±.20; and F5, information on accessing professional help, 5.18 ±.88. The students who responded that they had mental illness in the family scored as follows on F2, information on how to access information, 1.13±.23; and students who responded that they did not have mental illness in the family scored higher on the F6 sub-dimension, stigmatization, 2.70±.45. Students who thought that a holistic approach was important in nursing scored higher on the following sub-dimensions: F1, recognizing diseases, 3.02±.38; F3, information on risk factors and their causes, 2.78±.50; and F5, information on accessing professional help, 5.01±.77. Students who evaluated their knowledge level about the holistic nursing approach as "good" had a higher MHLS total score, 2.99±.37, and a higher mean score on the F5 sub-dimension, information on accessing professional help, 5.17±.82. In addition, these results are statistically significant ($p<0.05$) (**Table 2**).

In our research, the relationship between the MHLS total score, the MHLS' sub-dimensions, the HNCS total score, and the HNCS' sub-fields was examined by correlation analysis. As a result of this analysis, there was a statistically significant very weak and positive correlation between the MHLS total score and the HNCS General Ability (A) sub-field (r=0.101, p=0.033) and the HNCS Professional Development (B) sub-field (r=0.095, p=0.046) (**Table 3**).

Table 2. Investigation of the difference between mental health literacy scale scores according to nursing students' descriptive characteristics

Introductory information	Mental health literacy scale total score $\bar{x}$±SD	Mental health literacy scale sub-dimensions					
		F1[a] $\bar{x}$±SD	F2[b] $\bar{x}$±SD	F3[c] $\bar{x}$ ±SD	F4[d] $\bar{x}$ ±SD	F5[e] $\bar{x}$ ±SD	F6[f] $\bar{x}$ ±SD
Gender							
Female	2.88±.21	3.05±.35	1.07±.23	2.85±.48	4.33±.53	5.04±.73	2.64±.38
Male	2.93±.28	2.93±.45	1.01±.19	2.62±.51	4.23±.59	4.85±.94	2.78±.54
	*U=20641.500	*U=18228.500	*U=18212.500	*U=16329.000	*U=19147.000	*U=18859.000	*U=17972.500
	p=.725	*p=.020	**p=.014	**p=.000	p=.097	p=.070	**p=.012
Year							
1	2.83±.26	2.93±.34	1.01±.22	2.70±.52	4.23±.53	4.80±.84	2.68±.46
2	2.84±.21	2.98±.34	1.02±.23	2.82±.49	4.27±.54	4.91±.78	2.64±.41
3	2.90±.25	2.97±.38	1.06±.20	2.75±.45	4.27±.57	5.03±.63	2.73±.47
4	2.96±.21	3.17±.43	1.10±.20	2.82±.53	4.41±.56	5.18±.88	2.70±.43
	***KW=25.634	***KW=25.244	***KW=14.709	***KW=4.612	***KW=5.999	***KW=12.404	***KW=4.304
	**p=.000	**p=.000	**p=.002	p=.203	p=.112	**p=.006	p=.230
Having a mental illness in the family							
Yes	3.05±.37	1.13±.23	2.86±.48	4.38±.47	5.13±.79	2.57±.38	2.87±.23
No	3.01±.39	1.04±.21	2.76±.50	4.28±.57	4.95±.81	2.70±.45	2.89±.24
	*U=12203.000	*U=10527.500	*U=11480.000	*U=11183.000	*U=10970.500	*U=11131.500	*U=12762.000
	p=.533	**p=.012	p=.151	p=.075	p=.055	**p=.025	p=.969
Is holistic approach important in nursing?							
Yes	2.89±.23	3.02±.38	1.05±.22	2.78±.50	4.31±.55	5.01±.77	2.68±.44
No	2.72±.36	2.66±.52	1.00±.09	2.40±.56	4.00±.52	3.90±1.49	2.76±.61
	*U=1559.500	*U=1229.500	*U=1744.000	*U=1402.000	*U=1615.500	*U=1133.500	*U=1833.500
	p=.137	**p=.019	p=.276	**p=.047	p=.151	**p=.009	p=.425
Evaluation of the levels of holistic nursing approach							
Good	2.99±.37	3.09±.37	1.05±.21	2.75±.48	4.38±.56	5.17±.82	2.68±.41
Middle	2.85±.21	2.98±.31	1.05±.22	2.80±.51	4.24±.49	4.89±.70	2.65±.43
Bad	2.81±.28	2.93±.45	1.04±.22	2.62±.59	4.31±.52	4.36±.1.11	2.67±.50
	***KW=16.955	***KW=7.084	***KW=1.237	***KW=3.790	***KW=6.809	***KW=28.283	***KW=7.668
	**p=.001	p=0.69	p=.744	p=.285	p=.078	p=.000	p=.053

aF1: Recognizing Diseases, bF2: Information on How to Access Information, cF3: Information on Risk Factors and Their Causes, dF4: Information on Self-Help/Treatment Interventions, eF5: Information on Accessing Professional Help, fF6: Stigmatization, *Mann Whitney U Test value=U, **p<0.05, ***Kruskal Wallis Test value=KW

Table 3. Examination of the relationship between nursing students' mental health literacy scale and holistic nursing competence scale scores

Holistic nursing competence scale and sub-fields		Mental health literacy scale and sub-dimensions						
		Mental health literacy scale total score	F1[a]	F2[b]	F3[c]	F4[d]	F5[e]	F6[f]
Holistic nursing competence scale total score*	r	.076	.030	.012	.035	.019	.058	.054
	p	.111	.524	.802	.459	.695	.222	.259
General ability (A)*	r	.101**	.019	-.011	.071	.041	.070	.081
	p	.033	.694	.814	.137	.390	.143	.091
Personnel training and management (B)*	r	.011	-.022	.001	.025	-.024	.028	.022
	p	.823	.651	.985	.595	.615	.561	.649
Ethics-focused practice (B)*	r	.067	.038	-.003	.019	.020	.061	.040
	p	.164	.428	.957	.696	.669	.200	.404
Nursing care in a team (B)*	r	.093	.061	.032	.031	.033	.059	.054
	p	.052	.204	.501	.514	.487	.214	.259
Professional development (B)*	r	.095**	.050	.047	.022	.029	.042	.065
	p	.046	.293	.321	.646	.546	.376	.174

aF1: Recognizing Diseases, bF2: Information on How to Access Information, cF3: Information on Risk Factors and Their Causes, dF4: Information on Self-Help/Treatment Interventions, eF5: Information on Accessing Professional Help, fF6: Stigmatization, *Spearman Correlation Analysis, **p<0.05

DISCUSSION

According to the research data, the MHLS total score average of the nursing students was "101.11±8.49". The cut-off score for the Turkish Society on the scale was determined as "109.50" for the Turkish Society, and those who scored above this score were considered to have a high level of mental health literacy.[20] According to this result, it is thought that the mental health literacy level of nursing students is low. In a study conducted with students studying in health programs[22] and in a study conducted with health professionals,[23] it was determined that the mental health literacy levels of health professionals working outside of mental health units were above moderate but not at the desired level. In a study conducted with nursing students, nearly half of the students stated that their mental health literacy levels were at a low level.[24] In addition, in another study conducted with nursing students, more than half of the students considered themselves inadequate in knowledge, stigmatization, and communication about mental illnesses,[24] in another study,[25] it was found that the mental health literacy levels of the participants who were not interested in mental health issues and who did not have a relative with a mental illness were low. Our research results are similar to the results of these studies. The results reveal the importance of increasing the mental health literacy levels of nursing students.

According to the data of our study, female students' sub-dimensions of recognizing diseases, knowledge of how to access information, knowledge about risk factors and mental health literacy levels were higher than males. In several studies,[5,17,22,25,26] it was found that women's mental health literacy levels were higher than men's, similar to the findings in our study. Another finding related to gender in our study is that men's stigma sub-dimension mean scores were higher than women's. Similar to our study result, a study[5] found that men have higher stigma levels. It is predicted that this result is due to men's lower mental health literacy levels and higher stigma levels.

In this study, it was found that senior students had higher mental health literacy levels and higher sub-dimension mean scores on recognizing diseases, information on how to access information, and information on accessing professional help. These results can be attributed to the fact that the mental health and diseases nursing course is given in the last year in the nursing department curriculum.[27] In a study conducted with nursing students,[24] third year students had higher levels of mental health literacy than first, and second year students. This result is similar to our research results. In line with these results, it was concluded that the mental health and diseases nursing course contributes positively to the level of mental health literacy because it contains detailed information about mental diseases and mental health.

In present study, students who had mental illness in the family had a higher information on how to access information sub-dimension score averages, and those who did not have a family history of mental illness had higher stigmatization sub-dimensions. In a study,[28] students with a relative with mental illness had positive beliefs about mental illnesses, in another study,[25] it was found that the mental health literacy levels of the participants who did not have a relative with a mental illness were low. In line with these results, it is concluded that having a mental illness in the family causes an increase in students' ability to cope with mental illness, an increase in empathy skills, and a decrease in stigmatization.

When the holistic nursing competencies of the students were evaluated, it was determined that they had medium-level holistic nursing competencies. In some studies[8,10,29,30] it was determined that nurses' holistic nursing competencies are high. In our study, the holistic nursing competencies of the students were determined as moderate, and it is thought that the students had awareness about holistic nursing, but this result is not at the desired level. During the data collection phase of the research, the students had been receiving distance education for about a year and a half due to the pandemic. It is thought that this result is related to the students' inability to go to the hospital practice at that time and their inability to evaluate patients one-on-one.

In our research, students who evaluated their knowledge level about the holistic nursing approach as "good" had higher score averages on the sub-dimension, information on accessing professional help. Also, in this study, the relationship between MHLS total score and MHLS' sub-dimensions was examined by correlation analysis. As a result of this analysis, between the MHLS total score and the HNCS General Ability (A) sub-field and between the MHLS total score and the Professional Development (B) sub-field, a statistically very weak and positive correlation was found. This result is attributed to the fact that students were in distance education due to the pandemic, did not have face-to-face hospital practice, and were not able to participate in one-on-one patient care. Although the correlation between scales is weak, there is a positive relationship between the two scales. According to this result, it is thought that increasing the mental health literacy level of students will also increase their proficiency in general skills and professional development sub-domains in holistic nursing competence. The literature was reviewed, but no previous study examining mental health literacy and holistic nursing proficiency could be found. Competence in holistic nursing care is the implementation of nurses' personal characteristics, values, attitudes, knowledge, and skills along with a sense of professional responsibility. Achieving this competence depends on the ethical focus

of nursing practices, continuous education for nurses and nursing students, proper management of the workforce, and professional development.[8,13,14,31] In line with these results, it is considered that nursing students who will enter the nursing profession in the future should have high mental health literacy levels and holistic nursing competencies, be able to evaluate the physical and mental health of the people they care for as a whole, and should be able to contribute greatly to the holistic nursing care provided.

Limitations

This research is limited to the students participating in the research and data collection forms. In addition, due to the COVID-19 Pandemic, another limitation is that the education is distance education and the data collection phase of the research is carried out in a digital environment. Another limitation of the study is that students cannot participate in face-to-face hospital practices and evaluate patients due to distance education due to the COVID-19 Pandemic.

CONCLUSION

According to the results of this research, the following have been determined. The mental health literacy level of nursing students is low, holistic nursing competencies are at an intermediate level, there was a statistically significant very weak and positive correlation between the MHLS total score and the HNCS General Ability (A) sub-field, and the HNCS Professional Development (B) sub-field. Therefore, according to the results of the research, it is recommended that nursing students be given courses on mental health and holistic nursing, and more studies on mental health literacy and holistic nursing and interventional studies that increase students' mental health literacy and holistic nursing competencies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Muğla Sıtkı Koçman University Health Sciences Ethics Committee (Date: 19.04.2021, Decision No: 210028-73).

Informed consent: All students signed free of charge and informed consent form.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

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Outcomes of liver transplantation patients infected with COVID-19: pandemic hospital experience from Turkey

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ABSTRACT

Aims: There are conflicting results for the course of the disease and mortality rates for liver transplantation patients infected with COVID-19. In this study, we aimed to present the outcomes of our liver transplant patients who were hospitalized and followed up in our tertiary hospital, which served as a pandemic hospital for COVID-19.

Methods: Patients hospitalized with the diagnosis of COVID-19 between March 1, 2020 and March 1, 2022 in Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital and Prof. Dr. Feriha Öz Pandemic Hospital were included. In this retrospective observational study, the clinical data of the patients, the need for intensive care hospitalization, and mortality rates were recorded by hospital computer system. The relationships were analyzed with SPSS v20.0.

Results: There were 25996 patients who were hospitalized with the diagnosis of COVID-19 and 28 of them were with the history of liver transplantation. Ages of the liver transplant patients ranged from 18 to 73, with a median age of 52. 82.1% of the patients were male and 17.9% were female. Intensive care unit hospitalization rate was 25% and mortality rate was 14.3%. The relationships according to the age groups revealed that all of the women were under the age of 50 (p=0.008) and the patients who deceased were male patients over the age of 50 (p=0.044).

Conclusion: Mortality rates and intensive care unit requirements of chronically immunosuppressed liver transplant patients with COVID-19 infection were similar with general population. Complete immunosuppression withdrawal should not be urged in this population.

Keywords: COVID-19, infection, liver, mortality, transplantation

INTRODUCTION

Coronaviruses (CoV) are single-stranded, enveloped RNA viruses of Coronaviridae family.[1] The spectrum of diseases caused by CoV in humans ranges from mild infections to severe infections.[2-6] The effect of this virus, which started at the end of 2019 and caused a large number of mortality and morbidity, has decreased with the mutations and developments in the treatment and prevention in the period to date, but it still continues to exist.

Liver transplant patients are a group of patients who are followed and treated cautiously for COVID-19 due to their current conditions and immunosuppressive drugs.[7] The incidence of COVID-19 in liver transplant patients is higher than in the general population.[8] However, there are conflicting results regarding the course of the disease and mortality rates. Liver transplant patients, who were considered a very risky patient group at the beginning of the pandemic, were speculated to have similar risks to other patient groups in the following period.[8] Nevertheless, there is no definitive consensus in this context in the literature, and there is still a need for studies on real-life data and outcomes of liver transplant patients.

In this study, we aimed to present the outcomes of our liver transplant patients for the course of COVID-19 disease and mortality rates who were hospitalized and followed up in our tertiary hospital, which serves as a pandemic hospital for COVID-19.

METHODS

The study was carried out with the permission of University of Health Sciences Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date: 09.03.2022, Decision No: E-46059653-020). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Patients who were hospitalized with the diagnosis of COVID-19 in Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital and Prof. Dr. Feriha Öz Pandemic Hospital between March 1, 2020 and March 1, 2022 were included in the study.

COVID-19 infection has been diagnosed according to the COVID-19 infection guideline recommended by the World Health Organization and published by the "T.C. Ministry of Health General Directorate of Public Health" by the scientific committee. These patients were those with positive real-time fluorescence (RT-PCR) detection of 2019-nCoV nucleic acid, with positive serum 2019-nCoV-specific IgM antibodies, and with thorax CT COVID-19 pneumonia findings. It was not considered COVID-19 if two consecutive tests of 2019-nCoV nucleic acid (sampling time at least 24 hours apart) were negative or if the 2019-nCoV-specific IgM/IgG antibodies were still negative after 7 days. 2019-nCoV nucleic acid detection was tested in nasopharyngeal swabs, sputum, other lower respiratory tract secretions (sputum or airway extracts).

In this retrospective observational study, the clinical and radiological data of the patients, the need for intensive care unit (ICU) hospitalization, and mortality rates recorded in hospital computer systems has been examined.

Statistical Analysis

SPSS Statistics (Version 20.0. Armonk, NY: IBM Corp.) was used for the statistical analysis. A Chi-square test was used to determine the significance of the relationships between categorical variables. A p-value of ≤0.05 was considered statistically significant.

RESULTS

There were 28 patients with the history of liver transplantation among a total of 25996 patients who were hospitalized with the diagnosis of COVID-19 in Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital and Prof. Dr. Feriha Öz Pandemic Hospital between March 1, 2020 and March 1, 2022.

Ages of the study group ranged from 18 to 73, with a median age of 52. 82.1% of the patients were male and 17.9% were female. Demographic characteristics of the liver transplant patient group are presented in Table 1. Seven of the 258 patients were followed up in the intensive care unit, and four of them died.

When the relationships between the age groups of <50 and >50 were evaluated, it was found that all of the women hospitalized and followed up were under the age of 50 (p=0.008) and all of the patients who died were male patients over the age of 50 (p=0.044) (Table 2).

Table 1. Demographic characteristics of the liver transplant patient group

Liver transplant COVID 19 patients	Total (n)	Total %
Gender		
Female	5	17.9
Male	23	82.1
Age		
<50 Years	13	46.4
>50 Years	15	53.6
Year of referral		
2020	15	53.6
2021	9	32.3
2022	4	14.1
Graft dysfunction		
No	28	100
Yes	0	0
Intensive care unit hospitalization		
No	21	75
Yes	7	25
Mortality		
No	24	85.7
Yes	4	14.3

Table 2. Relationships between the liver transplant patient group according to age groups

Liver transplant COVID 19 patients	Age<50 years	Age>50 years	p
Gender			
Female	5	0	0.008*
Male	8	15	
Year of referral			
2020	7	8	0.380
2021	3	6	
2022	3	1	
Smoking			
Missing	6	8	0.569
No	6	5	
Yes	1	2	
Body mass index			
Missing	7	10	0.892
<30 kg/m²	3	3	
>30 kg/m²	3	2	
Immunosuppressive drugs			
Prednisone or prednisolone	4	10	0.067
Tacrolimus	11	13	0.846
Mycophenolate mofetil	7	7	0.925
Time between LT and COVID-19, years			
Median	4	7	0.493
Intensive care unit hospitalization			
No	11	10	0.274
Yes	2	5	
Mortality			
No	13	11	0.044*
Yes	0	4	

*p<0.05 was considered statistically significant.

DISCUSSION

Liver transplant patients need lifelong immunosuppression therapy and are therefore at risk for both community and opportunistic infections throughout their lives.[7] Although COVID-19 is mainly characterized by respiratory symptoms, systemic involvement can also occur. However, there is limited information about the course of COVID-19 disease in liver transplant patients.[9] In our study, we evaluated the patients who needed hospitalization among COVID-19 positive patients with liver transplant who referred to our hospital, which is the reference pandemic hospital of the region and found 14.3% mortality and 25% ICU rates.

In a study conducted in 142 liver transplant patients followed in a transplantation center from Turkey, the authors reported that the incidence of COVID-19 was higher in liver transplant patients than in the general population. However, mortality rates were low. The authors stated that liver transplantation can be continued by following the general precautions during the pandemic period.[8]

In a study of 846 liver transplant patients infected with COVID-19 from Turkey, despite the use of immunosuppressive drugs, the requirement for intensive care and the length of stay in the intensive care unit was found to be low.[10] In the epidemiological study of Canbaz et al.[11] in which all solid organ transplant patients were recruited, the mortality rate in organ transplant patients diagnosed with COVID-19 was found to be 7.38%. In a meta-analysis by Kulkarni et al.[12] involving 18 studies with a total of 1522 COVID-19 infected liver transplant recipients, there was no difference in mortality between liver transplant and non-liver transplant recipients up to 1 year post-transplant period.[12] In the perioperative period, the clinical course was not more severe in those who had COVID-19 in the pre-/post-operative period.[13] Data for morbidity and mortality were also similar in pediatric patients.[14,15]

In the study of another experienced center in Turkey with 250-300 transplants per year, it was shown that COVID-19 vaccination reduced the risk of mortality by 100 fold.[16] In the study of Moon et al.[13] it was shown that vaccinations contributed positively to the course of the disease and reduced the need for intensive care and also reduced mortality. In our study, it is noteworthy that the number of hospitalized patients decreased over the years, although it was not statistically significant. We consider that a possible reason for the higher mortality and morbidity in unvaccinated patients in the early stages of COVID-19 is the lack of vaccination.[16,17] In addition to that, increased experience of healthcare providers about COVID-19, treatment alternatives and different disease courses in mutated variants might also be other reasons. It is also noteworthy that in our study, death times of the deceased patients were in the first year of the pandemic, in 2020. After this first year group of patients who were not vaccinated, in 2021 and 2022, mortality did not occur and also hospital/ICU hospitalizations decreased.

In a prospective cohort study of 111 patients with liver transplant who were hospitalized for COVID-19 in Spain, the mortality rate was found to be 18%, and this rate was lower than the matched general population.[18] Although it was pointed out in this study that the incidence of COVID-19 was higher in liver transplant patients than in the general population, it is not possible to compare this result, because in our study, only COVID-19 positive patients who needed hospitalization were included. Another remarkable result of our study was that all of the patients who died were in the elderly group. This brings to mind the increasing comorbidities with age. In this context, as Bhoori et al.[19] and Webb et al.[20] stated in their studies with liver transplant patients, mortality may increase with the effect of other comorbidities as age progresses. In a study of 16 patients from Turkey, the authors stated that the course of COVID-19 in liver recipients without any underlying disease other than transplantation is similar to that of the healthy population.[21]

Since we did not have detailed information about the comorbidities and drugs used by the patients in our study, it would be inconvenient to make a definite comment on this issue. However, it can be speculated that the fact that only the elderly-not the young-had died in the current study, supports this outcome.

Another important issue in this patient group is the status of immunosuppressive drugs. It is unclear whether immunosuppression is an advantage or a disadvantage in these patients. Some studies offer recommendations for reducing immunosuppression in liver transplant patients.[22] However, the short-term results in patients receiving immunosuppression were the same as in the general population, suggesting that immunosuppression might have a protective effect in these patients.[23] Because of these different views, transplant centers need to monitor their own patients and manage their patients according to these results. In our study, current immunosuppressive treatments were continued in all patients without dose reduction or discontinuation. And mortality rates and ICU requirements were similar with general population.

Our study had some limitations. The main one was the low number of patients. Another limitation was that the comorbidity information that could affect mortality rates could not be obtained due to the retrospective design of the study.

CONCLUSION

Mortality rates and ICU requirements of chronically immunosuppressed liver transplant patients with COVID-19 infection were similar with general population. Complete immunosuppression withdrawal should not be urged in this population.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date: 09.03.2022, Decision No: E-46059653-020).

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

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Distribution of bacteria isolated from urine cultures and resistance pattern of *Escherichia coli* strains in community-acquired urinary tract infections

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ABSTRACT

Aims: Urinary tract infections are one of the most common among community-acquired infections. *Escherichia coli* (*E. coli*) is the most common cause of community-acquired urinary tract infections. In our study, we aimed to determine the correct empirical treatment by determining the resistance profile of *E. coli* strains isolated from urine cultures in our hospital, thus both establishing an effective treatment and preventing the development of resistance.

Methods: Urine cultures of 3145 patients with urinary tract infection symptoms who applied to the infection and clinical microbiology outpatient clinic of our hospital between January 2019 and December 2019 were analyzed retrospectively. Patients with a history of catheter, a history of urinary operations, a history of hospitalization in the last 15 days, contamination in their cultures, and patients under the age of 18 were excluded from the study, and 422 urine cultures with growth were included in the study.

Results: The mean age of the patients included in the study was 49.8±14.7 years, and the gender distribution consisted of 301 females (71.3%) and 121 males (28.7%). *E. coli* was isolated in 313 (77.6%) of these cultures. The antibiotic with the highest resistance rate was trimethoprim-sulfametoxazole (34.8%), while the antibiotics with the lowest resistance rates were fosfomycin and imipenem (0.6%).

Conclusions: Considering that the resistance profiles of microorganisms are different from each other on the basis of country, region, and city, revealing regional resistance patterns can make an important contribution to both establishing effective treatment and preventing the development of antibiotic resistance.

Keywords: Resistance, community acquired, urinary tract infection

INTRODUCTION

Urinary tract infections (UTIs) include infections that target various components of the urinary system, including the urethra, bladder, ureters, and kidneys.[1] Urinary tract infections are one of the most common bacterial infections that can affect individuals of all age groups worldwide and pose a serious burden on both individuals and public health systems.[2,3] While this burden is associated with significant morbidity and mortality for individuals, it is related to health expenditures, loss of productivity, and reduced quality of life in the health system.[4]

"Community-acquired UTIs" (CA-UTIs) is an idiom encountered in daily life, acquired outside of healthcare settings, as well as reflecting the complex relationships between individual behavior, microbial exposure, and local health practices.[2,5] Therefore, the epidemiology of CA-UTIs varies from region to region, depending on sociodemographic factors, health infrastructure, and antibiotic prescribing habits of physicians.[6]

Agents causing CA-UTIs include a spectrum of different bacterial species, particularly *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterococcus faecalis*. Again, the distribution of these bacterial species may differ in different geographic regions, populations, and healthcare settings.[7] Therefore, revealing the common bacterial species that cause CA-UTIs in different geographical areas and determining the resistance profiles of these bacteria have a very important place in establishing the correct antibiotic regimens. This, in turn, is expected to increase the success of treatment while reducing the risk of antibiotic resistance

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development.[8,9] Apart from geographical differences, the existence of different resistance profiles, even in different health institutions, is of great importance in the creation of targeted treatments in the microenvironment and the formation of the right health policies.[10]

In this study, we aimed to reveal the prevalence of CA-UTIs admitted to our hospital, which is a health center that caters to a wide area in the Eastern Anatolia Region of Turkey, and the antimicrobial resistance of the dominant pathogen causing these infections. In this way, with its distribution and resistance profile, it might facilitate the selection of antibiotics that can be preferred primarily in empirical treatment in our province while contributing to the prevention of antimicrobial resistance formation.

METHODS

This study was planned as a retrospective study and carried out with the permission of Van Training and Research Hospital Clinical Researches Ethics Committee (Date:11.03.2021, Decision No: 2021-06). All procedures were carried out in accordance with the ethical rules and principles of the Declaration of Helsinki.

In the study, 3145 urine culture samples taken from patients who applied to the infectious diseases and clinical microbiology outpatient clinics of Van Training and Research Hospital between January 2019 and December 2019 and had urinary tract infection findings were retrospectively analyzed. Samples of patients with a history of catheterization, a history of urological operation, a history of hospitalization in the last 15 days, contamination in their culture, and those under the age of 18 were excluded from the study. Age and gender of the patients, microorganisms isolated from urine cultures, and their resistance profiles were recorded.

Midstream urines of 422 patients included in the study were seeded with sterile loop on 5% sheep blood agar and eosin methylene blue (EMB) agar (bioMerioux, France). It was incubated for 24 hours in a 36°C oven in a 5–10% CO_2 environment. One or two types of growths ≥105 cfu/ml or single type ≥104 cfu/ml were taken into consideration as pure culture. Identification, MIC values determination, and antibiograms were made with BACT / ALERT 3D and PHOENIX 100 device. Antibiotic susceptibility tests were performed on the samples with growth detected by the agar disc diffusion method in accordance with the recommendations of the Clinical Laboratory Standards Institute (CLSI).[11]

RESULTS

The mean age of the patients included in the study was 49.8±14.7 years, and the gender distribution consisted of 301 females (71.3%) and 121 males (28.7%).

In our study, growth was detected in 422 of the 3145 samples. Two microorganisms were isolated in 12 of these samples.

A total of 434 microorganisms were isolated in 422 patients. *E. coli* and *Klebsiella* spp. in five samples, *E. coli* and *Pseudomonas* spp. in two samples, *E. coli* and *Enterococcus* spp. in two samples, *E. coli* and *Streptococcus agalactia* in two samples, and *Enterococcus* spp. and *Staphylococcus* spp. in one sample were isolated together.

The causative agent was determined as *E. coli* in 313 (77.6%) in the microorganism isolated cultures. The distribution of isolated pathogens is given in Table 1.

Table 1. Distribution of microorganisms isolated from urine cultures, n (%)

Uropathogen	n	%
E. coli	313	72.1
Other Gr (-)		
Klebsiella spp.	56	12.9
Pseudomonas spp.	7	1.6
Proteus spp.	5	1.2
Enterobacter cloacae	7	1.6
Staphylococcus spp.	11	2.5
Enterococcus spp.	22	5.1
Streptococcus agalactia	13	3
Total	434	100

E. coli: *Escherichia coli*, Spp: Species pulural

In the evaluation of the *E. coli* resistance profile, the antibiotics to which it was most sensitive were fosfomycin (0.6%) and imipenem (0.6%), while trimethoprim-sulfamethoxazole (TMP-SMX) (34.8%) had the highest resistance rate. The resistance profile of *E. coli* is shown in Table 2.

Table 2. Antibiotic resistance rates of *E. coli* strains isolated from urine cultures, n (%)

Antibiotic Name	Resistance (n)	Resistance (%)
Ampicillin-sulbactam	109	34.8
Ciprofloxacin	97	31
TMP-SMX	113	36.1
Cefuroxime aksetil	69	22
Ceftriaxone	59	18.8
Fosfomycin	2	0.6
Nitrofurantoin	12	3.8
Amikacin	23	7.3
Piperacillin-tazobactam	4	1.3
Imipenem	2	0.6

TMP-SMX: Trimethoprim-sulfamethoxazole

DISCUSSION

Our research assesses the frequency of antibiotic resistance observed in urine cultures caused by *E. coli* isolates within the local population, and it offers

recommendations for outpatient treatment guidance for individuals diagnosed with community-acquired urinary tract infections. Our results indicate that *E. coli* was the predominant strain found in urine samples, comprising 72.1% of all isolates. Similarly, in publications from both our country and abroad, it is observed that the most frequently isolated agent in urine cultures is *E. coli*. Its prevalence varies from region to region, ranging between 54.8% and 81%.[9]

In our study, the majority of cultures were from female participants (71.3%), and published studies have shown that women frequently experience urinary tract infections. This situation is thought to be related to the physiological and anatomical characteristics of women.[12-15]

The antimicrobial susceptibilities of causative pathogens in urinary tract infections can vary based on regions, patients' accompanying diseases and medications, environmental factors, and the inappropriate and widespread use of antibiotics over the years. Therefore, it is necessary to determine region-specific microorganisms and their antimicrobial susceptibilities. Among the tested antibiotics, the highest resistance rates were recorded for TMP-SMX (36.1%), followed by ampicillin-sulbactam (34.8%) and ciprofloxacin (31%).[16]

In the empirical antibiotic treatment of urinary tract infections, quinolones, cephalosporins, fosfomycin, aminoglycosides, and TMP-SMX are generally preferred. In the context of empirical treatment for community-acquired UTIs, the recommended options include nitrofurantoin and fosfomycin, but fluoroquinolones and TMP-SMX are not advised.[17,18]

Quinolones are effective against many uropathogens and are considered among the first-choice drugs for treating urinary tract infections due to their high rates of bacteriological and clinical improvement.[19] Due to the widespread use of quinolones, an increase in quinolone resistance in community-acquired *E. coli* strains has been reported.[20] And in our country, reported quinolone resistance has reached a rate of 40–45%.[21,22] In our study, quinolone resistance was found to be 31%, indicating that it is not suitable for empirical treatment.

Various studies have reported that TMP-SMX resistance in community-acquired *E. coli* strains in our country ranges from 60%.[21,23,24] In our study, TMP-SMX resistance in community-acquired *E. coli* was determined to be 36.1%, which is consistent with the literature. As a result, empirical treatment with TMP-SMX is not recommended for patients under surveillance in our region.

Fosfomycin and nitrofurantoin are the effective antimicrobial agents in vitro against *E. coli*, even in cases of multi-drug resistant (MDR) isolates, among outpatients with community-acquired *E. coli*. The oral single-dose administration of fosfomycin has started to gain significance in the treatment of urinary tract infections caused by *E. coli* due to its ability to reach high concentrations in the urine and low resistance rates.[25] Additionally, studies conducted in our country have reported nitrofurantoin resistance for *E. coli* among outpatient patients to be below 10%.[24,26]

In our study, resistance rates were determined to be 0.6% for fosfomycin and 3.8% for nitrofurantoin, similar to previous studies.[15,21,24] Due to their significant efficacy against *E. coli* and low resistance rates, fosfomycin and nitrofurantoin are recommended as the antibiotic treatments for community-acquired *E. coli* urinary tract infections.

Antibiotic resistance is associated with increased morbidity, mortality, and healthcare expenses. Therefore, understanding local resistance patterns will help prevent inappropriate antibiotic usage and mitigate the risks of antibiotic side effects.

There are certain limitations in our study. The retrospective nature of our data might have led to data loss in determining patient-related risk factors. Conducting our study within a one-year timeframe may have resulted in a lack of assessment regarding resistance trends over the years. In accordance with the literature, patients with a history of urinary surgery and hospitalization in the last 15 days were excluded from the study. However, it may take longer than 15 days for the flora structure of patients with these stories to recover. This may create a bias in evaluating the optimal flora and determining the appropriate antibiotic. The scope of our conclusions is limited because this study was conducted at a single center. With its extensive population size, our study contributes to national data by collecting regional information.

CONCLUSION

Resistance to antibiotics used in the past years in the treatment of CA-UTIs is increasing dramatically. In addition, in CA-UTIs, empirical antibiotic therapy is usually started without waiting for urine culture results. Therefore, knowing the regional resistance pattern is of vital importance for the development of rational drug policies, especially for effective treatment and prevention of resistance development. According to our study, when the antibiotic resistance pattern in our region is evaluated, fosfomycin and nitrofurantoin can be considered at the forefront of empirical treatment among oral treatment options.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Van Training and Research Hospital Clinical Researches Ethics Committee (Date:11.03.2021, Decision No: 2021-06).

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Can high procalcitonin levels be a biomarker for detecting multidrug-resistant Gram-negative bacteremia?

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ABSTRACT

Aims: Clinicians prefer broad-spectrum empirical antibiotic therapy in patients with suspected bloodstream infection (BSI) due to long test turnaround times of conventional methods. We aimed to assess the contribution of procalcitonin (PCT) to the selection of antibiotics to be used in empirical treatment.

Methods: The results of inpatients whose blood cultures and samples for PCT tests had been sent simultaneously between 2018 and 2022 were analyzed retrospectively. Antibiotic susceptibility results of *Enterobacteriaceae*, *Acinetobacter baumannii* complex and *Pseudomonas aeruginosa*, were evaluated for multidrug-resistance (MDR).

Results: Results of 1206 patients who met the inclusion criteria were included in the study. The PCT median value in BSIs caused by the Gram-negative bacteria found to be statistically significantly higher than those caused by the Gram-positive bacteria, fungal and polymicrobial infections ($p<0.05$). The best cutoff value of ROC, with an AUC value of 0.607 (CI: 95%: 0.578-0.635, $p< .0001$), a sensitivity of 72.1%, and a specificity of 55.4%, for distinguishing GN BSIs from other BSIs was determined as 2.5 ng/ml. The PCT median value of MDR pathogens was found to be statistically significantly higher than that of non-MDR pathogens ($p < 0.05$). A ROC analysis was performed, and the AUC distinguishing MDR pathogens from non-MDR was found as 0.633(CI: 95%, 0.586-0.681; $p <0.0001$), with a best PCT cutoff of 11.4 ng/mL, a sensitivity of 54.8%, and a specificity of 66.3%

Conclusion: High levels of PCT can guide empirical antibiotic treatments, with its property to predict GN bacteria and that they might be MDR GN BSIs.

Keywords: Procalcitonin, bloodstream infection, Gram negative bacteriae, multidrug resistance

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INTRODUCTION

Bloodstream infections (BSIs) are one of the most important causes of morbidity and mortality in hospitalized patients.[1] Rapid diagnosis and timely administration of appropriate antibiotics for the causative agent are very critical for increasing patients' survival chances, but rapid identification of pathogens is often delayed due to the current standard microbiological tests. This situation creates problems in daily practice, and antibacterial treatment is often started empirically.[2] On the other hand, fever, which is the main symptom and sign of bacterial infections, can also be seen in many viral infections and non-infectious conditions. Due to the non-specificity of clinical symptoms and the limitations of diagnostic tests, biomarkers are biological molecules that are increasingly popular and used in diagnosis, monitoring of response to treatment, and determination of prognosis.[3-5] There has been an ongoing pursuit of the ideal biomarker in bacteremia/sepsis in the past 30 years. Important data that procalcitonin (PCT) can help the diagnosis and treatment of patients when used alone or in combination with other biomarkers have been obtained.[6]

PCT is a molecule that is encoded by the calcitonin-1 (CALC-1) gene on the first chromosome and is the precursor of calcitonin.[7] It is a precursor acute phase protein that is normally <0.1ng/ml in plasma and has no hormonal effects. The plasma level starts to increase from the fourth hour following acute inflammation.[8] PCT is a preferred biomarker since it has high sensitivity and specificity, has a short half-life (<24 hours), and is easily measurable and inexpensive.[9]

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Although there are many studies on the use of PCT in the diagnosis of bacteremia/sepsis, prediction of the etiologic agent, and early initiation, follow-up, and termination of antibiotic therapy, research into the relationship between PCT and antibiotic resistance is limited. These few studies have been done in specific patient groups, and there have been a lot of recommendations that results need to be tested in more general patient groups and larger populations.[10,11]

In our study, we aimed to contribute to empirical bacteria-targeted antimicrobial therapy by investigating the value of PCT as a biomarker in predicting Gram-negative bacteria and multi-drug resistant Gram-negative (MDRGN) BSIs and using the data we obtained.

METHODS

This retrospective descriptive study was carried out by collecting usage data in compliance with the principles outlined in the Declaration of Helsinki. The study was carried out with the permission of Haydarpaşa Numune Training and Research Hospital Clinical Researches Ethics Committee (Date: 28.08.2023, Decision No: HNEAH-KAEK 2023/160/4257).

Patients and samples: All blood cultures and PCT results sent from inpatients to our laboratory between 2018 and 2022 were retrospectively reviewed on the laboratory information management system

Inclusion Criteria

- Patients 18 years and older,
- Results of patients whose blood cultures and PCT tests were requested simultaneously and whose blood cultures were positive,
- Blood culture and PCT results taken at the time of the first bacteremia attack when the patient had more than one blood culture and PCT result

Exclusion Criteria

- Commonly considered contaminants (except for *Corynebacterium* spp. *C. jeikeium*), *Bacillus* spp. (except for *B. anthracis*), coagulase-negative staphylococci, and other skin flora member microorganisms only if grown in a blood culture set
- Patients with a medical history of immune system disease or a history of malignant tumors (thyroid carcinoma/lung cancer)[12]

Quantitative identification of procalcitonin: Serum PCT level was studied using the VIDAS BRAHMS Procalcitonin kit on the VIDAS 3 (bioMérieux, Marcy l'Etoile, France) instrument operating with the automated Enzyme-linked fluorescent immunoassay (ELFA) method according to the manufacturer's instructions. The lower detection limit of the assay was 0.05 ng/ml and assay sensitivity was 0.09 ng/ml.[12]

Blood culture: Blood samples taken in accordance with the blood culture sampling rules were inoculated into aerobic and anaerobic bottles.[13] Blood culture bottles were incubated in the automated blood culture system (BacT/Alert (bioMérieux, Marcy l'Etoile, France) for 5 days. Vials with a positive signal were Gram-stained and inoculated for subculture on standard solid media. Gram stain results were reported to the clinician as preliminary information.

Identification and detection of multiple drug resistance (MDR): Identification of bacteria was performed on the MALTI-TOF MS system (bioMérieux, Marcy l'Etoile, France), and antibiotic susceptibility tests were performed on the VITEK 2 Compact (bioMérieux, Marcy l'Etoile, France). Antibiotic susceptibility results were evaluated according to EUCAST guidelines.[14]

In the antibiotic susceptibility results, the results of patients with acquired resistance to at least one antibiotic in three or more antimicrobial categories were classified as MDR.[15] The antibiotic susceptibility results of *Enterobacteriaceae*, *Acinetobacter baumannii* complex, and *Pseudomonas aeruginosa* were evaluated in terms of MDR.

Statistical Analysis

All study data were analyzed on the SPSS 26.0 software package (SPSS, Chicago, IL, USA). Values were presented using numbers and percentages. Variables with a normal distribution were presented using mean ± standard deviation values (SD). Variables with a non-normal distribution were represented by medians and interquantile range values (IQR). To analyze each group, the Mann-Whitney U test was applied to two independent samples and the Kruskal Wallis H test to multiple independent samples. Statistical significance was accepted as $p<0.05$. The receiver operating characteristic (ROC) curve analysis was employed to determine cutoff values. The Uden index was used to define the sensitivity and specificity of these cutoff values (Uden index = sensitivity + specificity - 1) and the best cutoff value was determined .

RESULTS

A sample of 1206 patients whose blood culture and PCT tests had been requested simultaneously and who had pathogenic microorganism growth as a result of blood culture were included in the study. While 1,102 patients had been detected to have a single pathogen, polymicrobial pathogens had been detected in 104 patients. Of the patients with a single pathogen, 562 (50.9%) had Gram-negative bacteria, 446 (40.4%) had Gram-positive bacteria, and 94 (8.5%) had fungi.

PCT levels for infections caused by different microbial species: Median PCT levels corresponding to microbial species isolated in six or more patients with monomicrobial bacteremias are shown in Table 1. *Escherichia coli* (n:216, 38.4%) and *Staphylococcus aureus* (n:195, 43.7%) were the most frequently isolated Gram-negative bacteria and Gram-positive bacteria, respectively. *Candida albicans* (n:42, 44.6%) was the fungal species that had been the most commonly detected agent. To assess whether different microbial groups could be distinguished by PCT levels, median values for monomicrobial bloodstream infections caused by different species were compared (Table 1).

Table1. Median PCT levels corresponding to pathogens isolated from six or more BCs with monomicrobial infection

Pathogen	Number of BCs	Median PCT level (IQR) (ng/ml)
GNB*		
Escherichia coli	216	9.59 (2.60-38.30)
Klebsiella pneumoniae	135	9.11 (2.14-30.03)
Acinetobacter baumannii complex	54	10.62 (2.27-55.2)
Pseudomonas aeruginosa	50	5.74 (1.66-33.10)
Enterobacter cloacae	24	5.04 (1.77-30.54)
Serratia marcescens	16	10.67 (1.20-36.40)
Enterobacter aerogenes	12	7.74 (1.28-41.44)
Proteus mirabilis	9	4.65 (1.55-13.95)
Klebsiella oxytoca	6	19.5 (7.41-63.90)
Stenotrophomonas maltophilia	9	8.47 (2.58-69.41)
Ralstonia pickettii	6	0.63 (0.24-12.88)
GPB**		
Staphylococcus aureus	195	2.13 (0.69-8.40)
Enterococcus faecalis	73	1.22 (0.18-4.01)
Enterococcus faecium	45	1.41 (0.51-5.32)
Staphylococcus epidermidis	39	0.70 (0.15-2.47)
Staphylococcus hominis	33	0.49 (0.18-1.76)
Streptococcus mitis/Streptococcus oralis	11	3.08 (0.22-15.9)
Streptococcus pneumoniae	9	7.73 (0.40-22.33)
Staphylococcus haemolyticus	7	0.27 (0.18-30.7)
Streptococcus parasanguinis	6	0.06 (0.44-0.77)
FUNGUS***		
Candida albicans	42	1.63 (0.64-3.87)
Candida parapsilosis	33	1.78 (0.58-7.52)
Candida tropicalis	14	6.5 (036-22.34)

BC, blood culture; GNB, Gram-negative bacteria; GPB, Gram-positive bacteria; IQR, inter quartile range; PCT, procalcitonin
*GNB that were isolated less than six: *Aeromonas salmonicida, Burkholderia cepacia, Citrobacter koseri, Enterobacter hormaechei, Hafnia alvei, Morganella morganii, Providencia stuartii, Pantoea agglomerans, Pseudomonas putida, Salmonella* spp
**GPB that were isolated less than six*: *Enterococcus gallinarum, Enterococcus avium, Enterococcus hirae, Staphylococcus capitis, Staphylococcus cohnii* ssp, *Staphylococcus lugdunensis, Staphylococcus pettenkoferi, Streptococcus dysgalactiae, Streptococcus gordonii, Streptococcus mutans, Streptococcus parasanguinis*
***Fungus that were isolated less than six: *Candida glabrata, Candida kefyr, Candida krusei*

The PCT median caused by *Klebsiella oxytoca*, one of the Gram-negative bacteria, was found at the highest level. This was followed by *Serratia marcescens*, *Acinetobacter baumannii* complex, *Escherichia coli*, and *Klebsiella pneumoniae*. *Streptococcus mitis/Streptococcus oralis*, one of the Gram-positive bacteria, caused the highest PCT median level, and this was followed by *Staphylococcus aureus*. In fungi, the highest PCT median value belonged to *Candida parapsilosis*.

PCT levels in Gram-negative and Gram-positive BSIs: According to analysis results, the PCT median level in BSIs caused by the Gram-negative bacteria (8.45ng/ml; IQR: 2.12-34.35), was found to be statistically significantly higher than the BSIs caused by the Gram-positive bacteria (1.49.ng/ml; IQR: 0.33-6.15), fungal (1.87.ng/ml; IQR: 0.57-7.45), and polymicrobial infections (4.70.ng/ml; IQR: 0.75-18.02) ($p<0.05$). There was no statistically significant difference between the PCT median levels of Gram-positive, fungal, and polymicrobial BSIs ($p>0.05$). The PCT levels in the different groups of microorganisms in the study are shown in Figure 1.

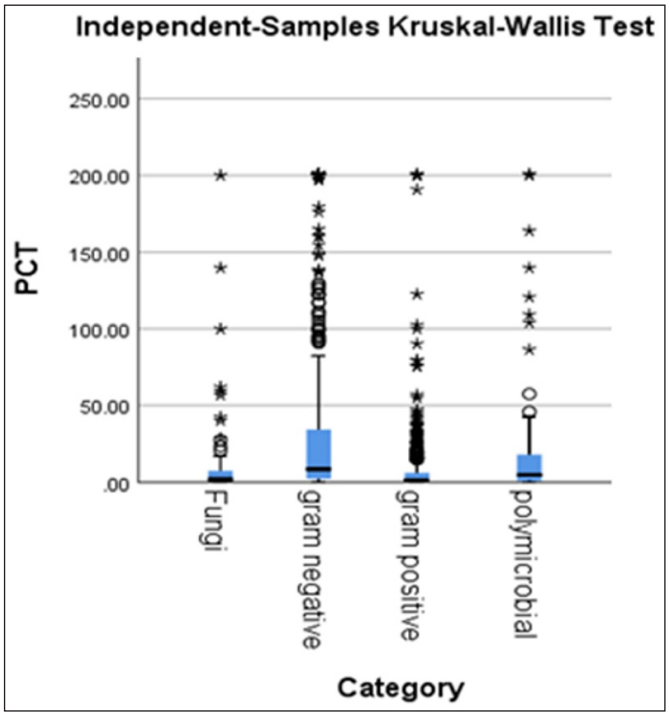

Figure 1. Comparison of PCT levels of microorganisms

A ROC analysis was performed to evaluate the diagnostic accuracy of PCT in predicting Gram-negative BSI. The best cutoff value of ROC, with an AUC value of 0.607 (95% confidence interval: 0.578-0.635, p< 0001), a sensitivity of 72.1%, and a specificity of 55.4%, for distinguishing Gram-negative BSIs from other BSIs was determined as 2.5 ng/ml (Figure 2). Polymicrobial BSIs were not included in the study.

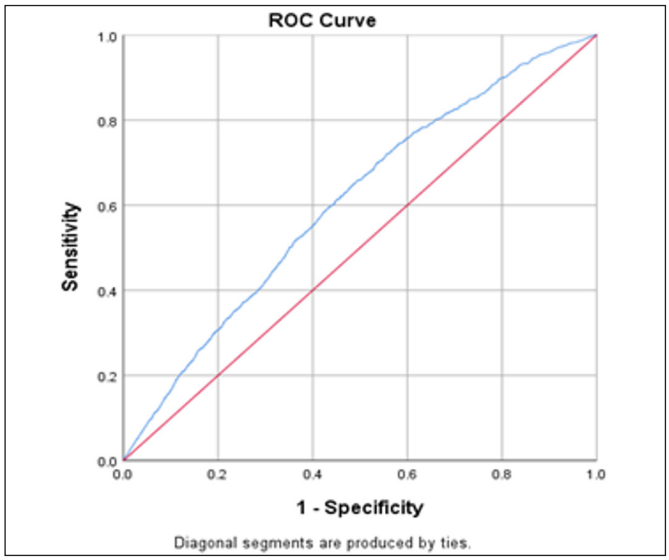

Figure 2. The ROC curve of PCT: Gram-negative bloodstream infections and other blood culture-positive bloodstream infections except for polymicrobial bloodstream

Serum procalcitonin level of multidrug-resistant pathogens and non-multidrug-resistant (nonMDR) pathogens among Gram-negative bloodstream infections: The antibiotic susceptibility results of *Enterobacteriaceae* (n:421), *Acinetobacter baumannii* complex (n:54), and *Pseudomonas aeruginosa* (n:50), which frequently cause Gram-negative BSI, were examined. Of the 277 isolates detected to be MDR, 228 were *Enterobacteriaceae*, 39 were *Acinetobacter baumannii* complex, and 10 were *Pseudomonas aeruginosa*. Polymicrobial BSIs were not included in the study.

In some studies, the PCT median value (12.94 ng/mL; IQR: 3.59-47.08) of MDR pathogens was found to be statistically significantly higher than that of non-MDR pathogens (5.90 ng/mL; IQR: 1.27-18.60) ($p < 0.05$) (Figure 3).

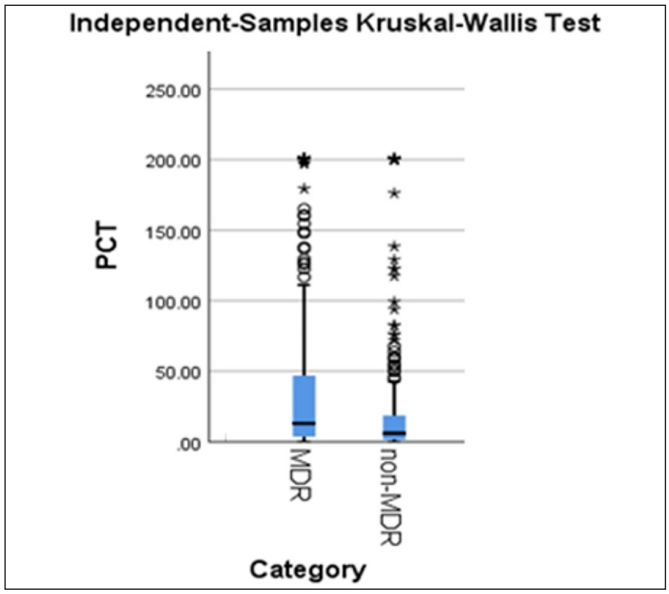

Figure 3. The procalcitonin level of multidrug-resistant Gram negative bacilli (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* complex) was higher than that of non-multidrug-resistant Gram-negative bacilli (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* complex)

A ROC analysis was performed, and the AUC distinguishing MDR pathogens from nonMDR was 0.633 (95% confidence interval, 0.586-0.681; $p < 0.001$), with a best PCT cutoff value of 11.4 ng/mL, a sensitivity of 54.8%, and a specificity of 66.3% (Figure 4).

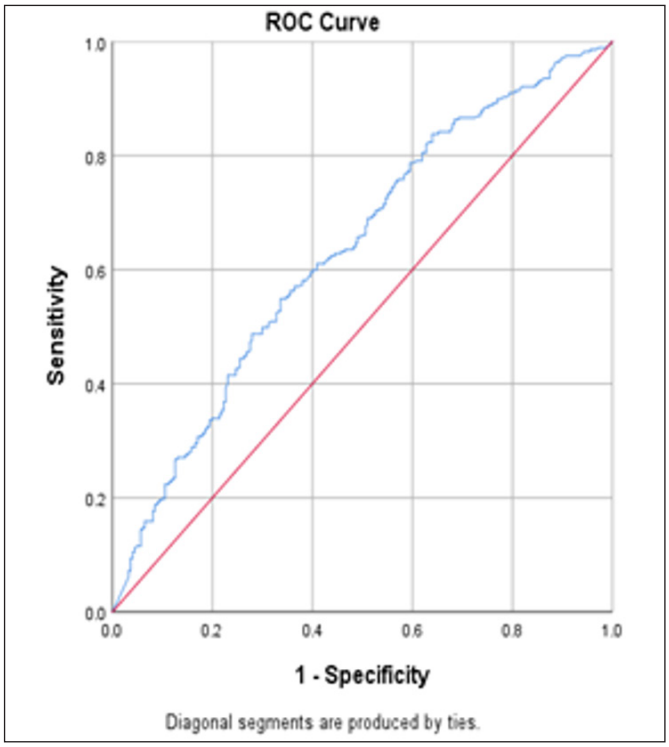

Figure 4. The ROC curve of procalcitonin: procalcitonin ROC curves for multidrug-resistant and non-multidrug-resistant Gram-negative bacilli (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* complex) bloodstream infections

DISCUSSION

In its report published in 2017, the World Health Organization drew attention to Gram-negative MDR and classified *Enterobacteriaceae*, *Acinetobacter baumannii* complex, and *Pseudomonas aeruginosa* as high-priority pathogens requiring urgent development of new antibiotics.[16] They also warned Türkiye in their 2020 report about taking precautions against resistance, especially in Gram-negative bacteria.[17] Although the principles of rational antibiotic use should be followed to avoid the development of resistance, a significant proportion of antibiotics are prescribed empirically, that is, without culture results to guide antibiotic selection, and even before the confirmation of a bacterial infection.[18]

In the recent literature, PCT has been recommended to be used in clinical diagnosis/treatment algorithms as a diagnostic test for early identification of bacterial infections, guide antibiotic selection, and monitor response to treatment.[9,19,20]

It is known to have a good negative prediction for bacterial infections, especially bacteremia, and guide

a more appropriate empirical antibiotic therapy while waiting for definitive microbiological results.[21-24]

Our main findings indicated that the PCT level in Gram-negative BSIs in inpatients was statistically significantly higher than the PCT level in Gram-positive bacteria- and fungi-caused BSIs. We found that a PCT value of ≥2.5 ng/ml could be helpful in predicting patient with a Gram-negative agent-caused BSI, with a sensitivity of 72.1% and a specificity of 55.4%. In addition, PCT levels were found to be statistically significantly higher in MDRGN BSIs (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* complex) than in non-MDR pathogens. ($p<0.05$). We found that a PCT value of ≥11.4 ng/ml could be helpful in predicting patients with a Gram-negative agent-caused BSI, with a sensitivity of 54.8% and a specificity of 66.3% (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* complex). Although the predictive power of PCT on discriminating bacterial infections was not evaluated in our study, many studies indicated that it could help clinicians to decide whether the suspected infection was truly bacterial.[9,25,26] PCT is more specific for bacterial infections since interferon (INF)-g released in response to viral infections inhibits it.[27]

When a patient with suspected infection presents, there are two key questions: Should antibiotics be started? If yes, which ones? The answers to these questions are not simple because a single parameter is not specific or sensitive enough to support the diagnosis.[28]

The review of various studies on the assessment of the diagnostic accuracy of PCT in predicting Gram-negative BSI and a meta-analysis in which 13 studies had been evaluated indicated that there was no single fixed threshold value at which the best performance was achieved and that PCT varied from 1.3 to 16 ng/ml, AUC values from 0.581 to 0.944, sensitivity from 56 to 77%, and specificity from 68 to 87%.[6,12,29-31] We think that differences arise from patients' demographic characteristics, background diseases, comorbidities, the effects of the drugs they use on PCT, criteria for acceptance and rejection of the study, the time when PCT and blood culture have been taken, the difference between the methods/devices used for measurement, cut-off values, and sensitivity and specificity ratios.[6,32]

PCT is not only a better predictor of bacterial infection and sepsis than others but also has some specificity for the type of bacterial infection that causes symptoms. The PCT differences between Gram-negative and Gram-positive bacteria are thought to be due to differences in the cell wall component of bacteria. Lipopolysaccharides found in the cell wall of Gram-negative bacteria are recognized by toll-like receptor 4 (TLR4), while lipoteichoic acid found in the cell wall of Gram-positive bacteria is recognized by toll-like receptor 2 (TLR2). Activation of different receptors causes different gene expression in leukocytes, and as a result, different cytokines are released. In addition, endotoxins released by Gram-negative bacteria are strong inducers of PCT, and higher IL-6 and IL-8 levels in patients infected with Gram-negative bacteria cause these differences in PCT response.[9,33]

Although the guidance of PCT for antibiotic therapy has been evaluated in detail, little is known about whether it can play a role in determining antibiotic susceptibility. Two studies, one conducted on burn patients (*Pseudomonas aeruginosa* and *Acinetobacter baumannii*, *Klebsiella pneumoniae*) and the other on hematology patients with febrile neutropenia (*Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* complex), the PCT values of MDR BSIs were statistically significantly higher than those of non-MDR BSIs in both studies. In the ROC analyses, the best PCT cutoff point was determined as 1.42 ng/mL with 90.9% sensitivity and 88.9% specificity in burn patients and 0.45 ng/mL with 72.6% sensitivity and 51.1% specificity in hematology patients with febrile neutropenia.[10,11]

Watanabe et al.[34] determined that PCT was decisive in GN BSIs and that patients who tested positive for *Escherichia coli* and *Proteus mirabilis*, producing extended-spectrum β-lactamase (ESBL) had statistically significantly higher PCT concentrations than ESBL-negative patients. They stated that distinguishing between ESBL-producing and non-ESBL-producing bacteria according to PCT concentrations could be very helpful in facilitating rapid and appropriate antibiotic therapy, including the use of carbapenems.

In a study on the evaluation of the correlation between MDRGN BSIs (*Acinetobacter baumannii*, *Klebsiella pneumoniae*) developing in COVID-19 patients and inflammatory parameters, the PCT results (0.99; IQR: 0.29-3.83) obtained on the day of hospitalization of patients with MDRGN BSI were significantly higher than the results (0.29; IQR: 0.13-2.59) of control patients with COVID-19 who had not develop bacteremia ($p<0.05$). Except for the PCT value, there was no statistical difference between MDRGN BSI cases and control cases on the day of admission to the COVID-19 ICU in terms of their inflammatory parameters, such as leukocytes, lymphocytes, neutrophils, neutrophil/lymphocyte ratio, platelets, and CRP ($p>0.05$). It was also found that most of the patients admitted to the COVID-19 ICU were prescribed meropenem and piperacillin/tazobactam, most commonly ceftriaxone, and empirical unnecessary antimicrobial therapy was thought to be a risk factor for the development of MDRGN BSIs.[35]

Contrary to all these studies, in a study on the evaluation of hematological and biochemical markers for the early diagnosis of bacteremia caused by *Enterobacteriaceae* bacteria resistant to carbapenems, it was determined that PCT values would not be a predictor of carbapenem resistance.[36]

The examination of approximately 8 million patient data in the USA in 2019 indicated that 37% of inpatients were given empirical antibiotic treatment for Gram-negative bacteria in the first two days of hospitalization and that 22% of all admissions and 61% of presentations receiving empirical treatment for Gram-negative bacteria received broad-spectrum gram-negative antibiotics. In other words, empirical broad-spectrum antibiotic treatment was started for one out of every five hospitalized patients. It was determined that approximately 30% of the patients who received broad-spectrum empirical treatment were not in the intensive care unit, had not undergone surgery, or had not been diagnosed with one of the common infectious syndromes (pneumonia, UTI, sepsis, or bacteremia) described in this study. This group of patients was unnecessarily exposed to broad-spectrum empirical therapy and associated subsequent consequences.[37]

It was shown that recommending antibiotic treatment based on PCT values, developing an institution-specific algorithm considering institutional threshold values, and adding it to antibiotic management algorithms improved antibiotic use.[38]

Considering the results of our study and those of other published studies, the diagnostic algorithm in **Figure 5** was created to distinguish PCT bacterial infections from non-bacterial causes and to identify Gram-negative BSIs and MDRGN BSIs.[39,40]

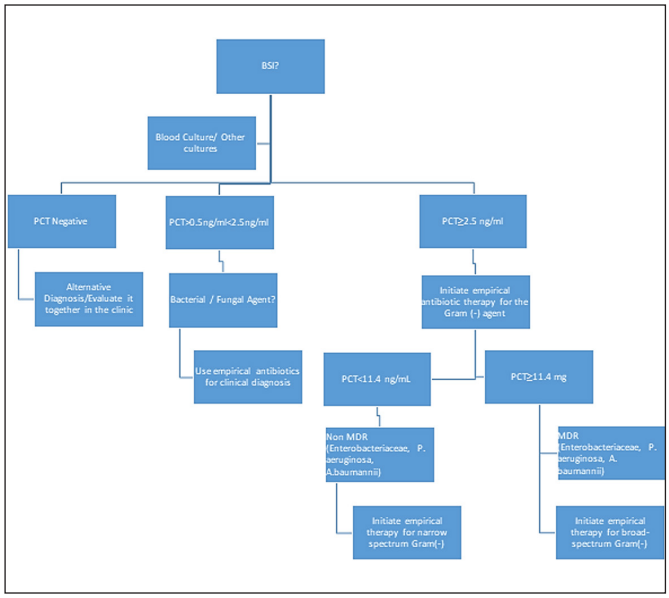

Figure 5. PCT algorithm in suspected bloodstream infection

PCT will help clinicians select the most appropriate empirical therapy in BSIs.[9,20] If the PCT is ≥2.5 ng/ml in cases with suspected infection, it can be assumed that the causative infection agent is Gram-negative bacteria and empirical treatment can be planned accordingly, and unnecessary use of drugs against Gram-positive bacteria and fungi can be avoided. Even if PCT is ≥11.6 ng/ml, MDR Gram-negative bacteria may be the causative agent in patients, and a treatment plan including broad-spectrum antibiotics can be applied. Although broadening the antibiotic spectrum without specific microbial evidence is often criticized for causing antibiotic overuse, considering the high prevalence of MDR in the intensive care unit, PCT-guided broadening of the antibiotic spectrum may be a solution for patients at a high risk of mortality.[41,42]

Although the AUC, sensitivity, and specificity for distinguishing MDRGN BSIs from non-MDR BSIs appear to be relatively poor, it can be tolerated until a definitive diagnosis is made for critically ill patients, as it is preliminary information on how to start antibiotic therapy as soon as possible.[34] In addition, it should not be forgotten that in emergency rooms and ICUs, where rapid decision-making is of critical significance, the time to get the PCT test result is approximately one hour and that it is a test that allows rapid decision-making at the bedside.

In studies in which various algorithms regarding the use of PCT in bacteremia/sepsis are created, the use of different cutoff values and making different recommendations according to the patient population and the clinic where the patient is treated (emergency department, ICU) makes interpretation difficult; however, it is an undeniable fact that PCT guidance also provides benefits such as treatment planning, lower antibiotic exposure, reduced antibiotic-related side effects, reduced risk of antibiotic resistance, shortened hospital stay, and reduced treatment costs.[9,20,28,38,43-45] However, the procalcitonin algorithm is not a stand-alone diagnostic tool, and it is important to use it in conjunction with clinical evaluation. This algorithm provides an additional way for physicians to identify the origin of the infection, but it should be noted that other tests and evaluations are required to make a definitive diagnosis.

To our knowledge, this is the largest study to date on the examination of the clinical utility of PCT for MDR in an unselected patient population with suspected bloodstream infection, but we have several limitations. First, this was a retrospective study and had the inherent limitations of retrospective studies. We did not have detailed information about whether patients had received antibiotic treatment before blood culture sampling, the clinical diagnosis and comorbid conditions of the patients, and whether they had used drugs that may have affected the PCT level.[46]

CONCLUSION

Although PCT threshold values in the management of empirical antibiotic therapy differ in published studies, it is important to adapt and develop an institution-specific algorithm. As with any other antimicrobial management intervention implemented in an institution, the appropriate use of PCT has the potential to improve antibiotic management..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Haydarpaşa Numune Training and Research Hospital Clinical Researches Ethics Committee (Date: 28.08.2023, Decision No: HNEAH-KAEK 2023/160/4257).

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Determination of malnutrition status in hospitalized Turkish Republic citizen and refugee children with different diagnoses

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ABSTRACT

Aims: Malnutrition is defined as changes in the normal body structure due to inadequate nutrition. This study aimed to determine the malnutrition status of Turkish children and refugee children.

Methods: A total of 5528 patients between the ages of 1 month and 18 years who were admitted and followed up in our pediatric health and diseases department between January 2017 and January 2020 were evaluated. The Gomez classification was used to assess malnutrition status. Demographic data, admission diagnoses, and the degree of malnutrition were retrospectively recorded by examining medical records. Both groups were compared in terms of these parameters.

Results: In our study, 5528 patients between the ages between 1 month and 18 years were evaluated. The median age was 4.1 years (min:1 month, max:17 years), with 2274 (41.1%) being female and 3254 (58.9%) being male. Among the cases, 4994 (90.5%) were Turkish, 160 (2.8%) were Afghan, 198 (3.5%) were Iraqi, and 176 (3.2%) were Syrian. According to the Gomez classification, 4379 patients (79.2%) were normal and 1148 patients (20.8%) were malnourished. Among the malnourished patients, 995 (86.7%) were mildly malnourished, 117 (10.2%) were moderately malnourished, and 36 (3.1%) were severely malnourished. 44% (n=16) of severely malnourished patients were under the age of two. The malnutrition rates were 19.7%, 22.5 %, 30.8 %, and 36.4% in Turkish, Afghan, Iraqi, and Syrian patients, respectively. There was a significant difference between Syrian and Turkish patients with mild and moderate malnutrition ($P < 0.05$). A total of 72.3% (n=830) of patients were admitted for reasons related to infections. Malnutrition is more frequently detected in patients with gastrointestinal diseases. None of the patients were admitted solely because of malnutrition.

Conclusion: The rate of malnutrition was significant in both Turkish and refugee children, with higher rates observed among refugee patients admitted to the hospital. Therefore, children admitted to the hospital for any reason should be carefully evaluated for growth and development. Early recognition and appropriate treatment of malnutrition are believed to lead to faster treatment of the underlying diseases causing hospitalization and may help prevent recurrent admissions.

Keywords: Children, Gomez classification, malnutrition, refugee

INTRODUCTION

Malnutrition is a preventable and treatable health problem and is defined as changes in normal body structure due to inadequate nutrition.[1] While malnutrition occurs due to various diseases, trauma or surgical interventions in developed countries,[2,3] the main cause of malnutrition in developing countries is inadequate and irregular nutrition.[4] Malnutrition is a risk factor for sarcopenia, and these two conditions often occur together in children[5] that inadequate protein and energy intake, as well as deficiencies in vitamins and minerals, can contribute to the development and progression of sarcopenia. Moreover, sarcopenia can lead to a decrease in appetite and digestive function, which can further exacerbate malnutrition.

Malnutrition is remarkably high, especially in children aged 0-2, where growth rate is evident.[6-9] Therefore, malnutrition is still an important public health problem for underdeveloped and developing countries. Malnutrition is a condition that occurs when a person's diet does not provide the necessary nutrients for proper growth and development, or when the body is unable to effectively use the nutrients consumed. Anthropometric measures are physical measures of the human body that can be used to assess nutritional status and identify malnutrition.[9-11] Gomez Classification is used in our clinic to determine the malnutrition status in children with protein energy malnutrition. In the classification made by Gomez, malnutrition is according to weight for age; it is classified as light, moderate and severe.

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The significant increase in the risk of death due to infectious diseases in the presence of malnutrition shows how important this problem is for public health. It has been reported that malnutrition are high in hospitalized children. Some studies show that the nutritional status of children worsens between 5% and 27% at discharge.[14] If malnutrition is added to gastroenteritis and respiratory tract infections in children, the risk of death increases approximately twice. It varies according to the total duration and severity of nutritional deficiency, nutritional quality, personal factors such as age, presence of infection. While it is easier to diagnose patients with severe malnutrition, patients with moderate and mild malnutrition can often be overlooked.[15] For this reason, the nutrition of hospitalized children should be questioned in detail, if there is a calorie deficiency, it should be determined, and anthropometric measurements and biochemical parameters should be evaluated.[16] The high number of refugee children living in our country and the fact that these children have to live under poor socioeconomic conditions suggest that they are at greater risk in terms of malnutrition. Although there are not many studies investigating the malnutrition status of hospitalized children, there are limited studies on the malnutrition status of refugee children. The aim of this study is to determine the malnutrition status of Turkish and refugee children hospitalized in the pediatric health and diseases service of a training and research hospital in a city center.

METHODS

The study was carried out with the permission of Kırşehir Ahi Evran University Faculty of Medicine Clinical Researches Ethics Committee (Date: 03.11.2020, Decision No: 2020-16/120). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This is a descriptive study and the population of the study consists of pediatric patients hospitalized in Kırşehir Training and Research Hospital, Pediatric Health and Diseases Service. The sample of the study consists of 5528 pediatric patients aged 1 month to 18 years who were hospitalized and followed up in Kırşehir Training and Research Hospital pediatric health and diseases service between January 2017 and January 2020. Inclusion criteria for the research; hospitalization on the specified dates and exclusion criteria; to have intrauterine growth retardation, to have a history of premature birth, to have a neurometabolic disease, to be syndromic and to have a chronic disease. Patients were divided into groups according to their nationalities and age groups. The age groups were determined as 0-2 years, 3-5 years, 6-12 years and 13-18 years. According to their nationality; They were divided into four groups as Turkish, Afghan, Iraqi, and Syrian. Hospitalization diagnoses, demographic characteristics and malnutrition status of all cases were recorded retrospectively. Sociodemographic characteristics and hospitalization diagnoses of the children included in the study were obtained from the patient file. The anthropometric measurements of the children were measured by the same health personnel at the same time of the day with the same weight and height meter. Weight and height measurements were evaluated using reference values accepted according to the children of our country. 17 Children with protein-energy malnutrition are generally evaluated according to the Gomez and Waterlow classifications. 18 Those whose weight for age is between 90-110% are normal, those between 75-89% are mildly malnourished (Grade 1), those between 60-74% are moderately malnourished (Grade 2), and those below 60% are severe (Grade 3). were accepted as malnourished.[18] SPPS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) statistical package program was used to evaluate the data. Variables mean±standard deviation and Median (Maximum-Minimum) percentage and frequency values were used. Variables were evaluated after controlling for normality and homogeneity of variances (ShapiroWilk and Levene Test). While performing data analysis, one-way analysis of variance was used for comparison of three or more groups and the Tukey HSD test, which is one of the multiple comparison tests, was not provided by the Kruskal Wallis test and the Bonferroni-Dunn test, which is one of the multiple comparison tests, was used. Categorical data were analyzed with Fisher'sExact Test and Chi-Square test. In cases where the expected frequencies are less than 20%, an evaluation was made with the "Monte Carlo Simulation Method" in order to include these frequencies in the analysis. The values of $p<0.05$ and $p<0.01$ were accepted for the significance level of the tests.

RESULTS

In our study, a total of 5528 patients aged 1 month to 18 years were evaluated. The median age was 4.1 years (min: 1 month, max: 17 years), 2274 (41.1%) were girls, 3254 (58.9%) were boys.

The distribution of patients by age and gender is summarized in Table 1.

Table 1. Distribution of cases by age and gender

Gender/age	Female n (%)	Male n (%)
0-2	1094 (41.5)	1542 (58.5)
3-5	538 (41.8)	748 (58.2)
6-12	485 (38.4)	777 (61.6)
13-18	157 (45.6)	187 (54.4)
Total	2274 (41.1)	3254 (58.9)

47.6% (n: 2636) of the patients were 1 month - 2 years old, 23.2% (n: 1286) were 3-5 years old, 22.8% (n: 1262) were 6-12 years old and 6.2% (n : 344) was observed to be between the ages of 13-18. Of the cases 4994 (90.5%) were Turkish, 160 (2.8%) were Afghans, 198 (3.5%) were Iraqi, and 176 (3.2%) were Syrians (Table 2). According to the Gomez classification, 4380 (79.3%) of 5528 patients were normal and 1148 (20.7%) were malnourished. Of the cases, 995 (86.7%) were mildly malnourished, 117 (10.2%) were moderately malnourished and 36 (3.1%) were severely malnourished. The malnutrition degrees of the patients according to age are shown in Table 3. 44% of severely malnourished patients were under 2 years of age (Table 3).

Table 2. Distribution of the cases according to their nationality and gender

Gender / nationality	Female n (%)	Male n (%)
Afganistan C.	72 (45)	88 (55)
Iraqi C.	90 (45.4)	108 (54.6)
Syrian C.	73 (41.4)	103 (58.6)
Turkish C.	2039 (40.8)	2955 (59.2)
Total	2274 (41.1)	3254 (58.9)

C: Citizen

Table 3. Distribution of malnutrition degree of cases according to age and Gomez classification

Malnutrition/age	Slight n (%)	Moderate n (%)	Severe n (%)
0-2	503 (87.4)	56 (9.8)	16 (2.8)
3-5	213 (92.2)	17 (7.3)	1 (0.5)
6-12	226 (67.9)	29 (11)	9 (3.4)
13-18	53 (86.6)	15 (19.3)	10 (12.8)
Total	995 (86.6)	117 (10.2)	36 (3.2)

When the malnutrition status of the patients included in the study was examined according to the nationality and Gomez classification, the malnutrition rate was 19.7% in Turkish children, while this rate was 22.5% in Afghan children, 30.8% in Iraqi children, and 36.4% in Syrian children (Table 4). In addition, 30.1% (n=161) of malnourished children are refugees (Table 5).

Table 4. Distribution of the cases by nationality and malnutrition status

Malnutrition / Nationality	Malnourished n (%)	Normal n (%)
Afganistan C.	36 (22.5)	124 (77.5)
Iraqi C.	61 (30.8)	137 (69.2)
Syrian C.	64 (36.4)	112 (63.6)
Turkish C.	987 (19.7)	4007(80.3)
Total	1148 (20.7)	4380 (79.3)

C: Citizen

Table 5. Malnutrition status in refugee patients

Malnutrition	Malnourished n (%)	Normal n (%)
Refugee	161 (30.1)	373(8.5)
Turkish Citizen	987(69.9)	4007(91.5)
Total	1148 (100)	4380 (100)

The degree of malnutrition depending on the nationality and age of the patients who participated in the study was examined and Table 6 was obtained. Considering the age groups in refugee patients, severely malnourished patients were detected in the 0-2 age group, while severe malnutrition was detected in all age groups in Turkish patients. A significant difference was found in mild and moderate malnutrition between Syrian and Turkish patients ($p<0.05$) (Table 6).

Compared to other refugee patient groups, severe malnutrition has been detected in Syrian patients at advanced ages. This rate was found to be 30.1% for all refugee children (Table 6).

Table 6. Evaluation of malnutrition degrees according to nationalities and age groups

		Nationality				Total	p
		Afgan	Iraqi	Syrian	Turkish		
Age							0.054
0-2 years	n	117	143	116	2365	2741	
	%	4.3%	5.2%	4.2%	86.3%	100.0%	
3-5 years	n	29	41	29	1164	1263	
	%	2.3%	3.2%	2.3%	92.2%	100.0%	
6-12 years	n	26	23	27	1169	1245	
	%	2.1%	1.8%	2.2%	93.9%	100.0%	
13 years and over	n	8	8	6	319	341	
	%	2.3%	2.3%	1.8%	93.5%	100.0%	
Malnutrition Percentage							0.035*
Slight	n	$36^{a,b}$	$58^{a,b}$	47^{b}	857^{a}	998	
	%	3.60%	5.80%	4.70%	85.90%	100.00%	
Moderate	n	$6^{a,b}$	$11^{a,b}$	14^{b}	98^{a}	129	
	%	4.70%	8.50%	10.90%	76.00%	100.00%	
Severe	n	2^{a}	1^{a}	2^{a}	16^{a}	21	
	%	9.50%	4.80%	9.50%	76.20%	100.00%	

p<0,05

Of the malnourished cases included in the study, 72.3% (n=830) were followed up in the ward for infection-related and 27.7% (n=318) for non-infectious reasons. 19.9% (n=228) of all cases had upper respiratory tract infection (URTI), 17.9% (n=206) had lower respiratory tract infection (LRTI), 26.7% (n=306) had gastrointestinal system diseases (GIS), 7.8% (n=90) urinary system infection (UTI), 27.7% (n=318) of the patients followed in the service with other diagnoses (falling down, intoxication, etc.). Among all infection-related cases, malnutrition was found more frequently in hospitalized patients with the diagnosis of gastrointestinal tract infections (Table 7).

Table 7. Distribution of patients with malnutrition according to hospitalization diagnoses

Diagnosis of Hospitalization	n	(%)
Upper Respiratory Tract Infection	228	19.9
Lower Respiratory Tract Infection	206	17.9
Gastrointestinal Tract Infection	306	26.7
Urinary Tract Infection	90	7.8
Other	318	27.7
Total	1148	100

There were no patients hospitalized only for malnutrition.

DISCUSSION

Malnutrition alone is seen as the source of deaths in the world. It is reported that approximately 13 milion children under the age of 5 die every year due to malnutrition. The most severe symptoms of nutritional deficiencies ocur in this age group, where nutritional and energy needs are higher than in other ages. Refugee patients frequently followed up and treated in our hospital. It was concluded that it is necessary to determine the malnutrition status of these patients, especially during the care of patients requiring hospitalization.

Malnutrition has not lost its importance in developing countries. Early diagnosis and treatment are of great importance in order to eliminate its negative effects. The diagonosis of heavy malnutrition patients is much more easier than patients with low or middle malnutrition. However, it is reported that malnutrition rate is high in hospitalized patients. Thats why patients who hospitalize in the European Clinic Nutrition and Metabolism society (ECNM), American Parenteral and Enteral Nutrition society (APEN) and European Pedaitric Gastroenterlogy, Hepatology and Nutrition society (ESPGHAN) are attracting attention. In this way it is stated that both the early treatment of malnutrition related complications and the reduction of hospitalization times can be achieved.

According to our study the prevalance of malnutrition was found to be 20.7% among hospitalized patients over a 3-year period. In a study conducted in Canada with 307 pediatric patients, the rate of malnutrition was found to be 19.5% in children during hospitalization.[19] 1022 Patients who applied to the policlinic of Gül[20] and his collegues was found a malnutrition frequency of 22.3%. In the study conducted by Özer and his collegues the frequency of malnutrition in children aged 1 month to 6 years was found to be 55.1%. In the study conducted by Şahin[21] and his collegeues the frequency of malnutrition was found 44.7%. It is concluded with these studies the rate of malnutrition decreases over the time. However this difference may have arise due to the wider age range of the patients in our study. The fact that almost half of the malnutrate cases are in the first 2 years and 70% are under the age of 5 may support this. In the sutdy conducted by Mevlitoglu[22] and his collegues in which 500 children participated it was seen that similar rates were reported with the increase in age range. Although the malnutrition rate in our country has decreased over time it is noteworthy that the malnutrition rate is much lower (6-10%) in European countries.

We used in our study the Gomez[11] clasification. In our study with 5528 patients we found malnutrition in 20,7% of those hospitalized according to the Gomez classification. Cases with malnutrition 86.7% were mild, 10.2 moderately and 3.1% was severy. In the study by Geylani[15] and his collegues malnutrition was found in 47.3% of 260 children participating in the study and 83 (32%) of them were mildly malnutrate, 24 (9.2%) moderately, 16 (6.1%) severely malnutrate. In a study by JiaCao[23] and his collegues the percentages of children with severe, moderate and mild malnutrition were found to be 9.1% (121), 43.3% (574) and 47.6%(630), respectively. In a study by Pars[24] and his collegues according to the Gomez[11] malnutrition classification system, moderate and severe malnutrition was found in 17.5% (10% moderate malnutrition; 7.5% severe malnutrition) during hospitalization and 25.1% in middle and severy. The reason for this difference may be that the living conditions are better today.[12] In a pilot study conducted in Greece, the prevalence of malnutrition in refugee children was found to be 13%.[13] It has also been reported that malnutrition is common among Palestinian refugee children living in camps in Jordan.[25] In a study conducted in Lebanon, malnutrition was found to be moderate in Syrian refugee children. We evaluated the malnutrition status of refugee child patients who were hospitalized in our hospital due to the high refugee population in our city. The malnutrition rate in refugee patients was found to be higher than in patients who were citizens of the Republic of Turkey. There was no statistically significant difference between malnutrition status and nationality. This may be due to the high number of children who are citizens of the Republic of Turkey. In addition, when the malnutrition degrees of the children included in the study were examined according to age groups, it was determined that malnutrition was more common in the 0-2 age group in all groups. Considering that hospital admissions in this age group are high due to infectious reasons, malnutrition coexistence should be considered, and therefore it can be said that malnutrition should be evaluated at the time of admission to the hospital. Thus, it is thought that serious health problems that may arise from the combination of malnutrition and infection can be prevented. In studies similar to our study, malnutrition was found to be more common in infancy. Considering the living conditions and nutritional status of refugees, refugee children live in more unfavorable conditions than Turks.

CONCLUSION

In the study it was determined that the malnutritrion rate in Turkish children which is higher in hospitalized refugee children should not to be underestimated. It has been determined that malnutrition is more common in Syrian children than in other refugees. It is recommended to carry out studies in which initiatives are planned to evaluate living conditions and nutritional habits in the whole society, especially in vulnerable groups such as refugees. In the sutdy it was determined that children with malnutrition were mostly hospitalized due to gastrointestinal system diseases. Therefore determining the direction of the relationship between infectious diseases and malnutririon; it is recommended to plan studies that reveal whether infection is a cause or a consequence of malnutrition. Since malnutrition is a preventable health problem, it is recommended that children who are hospitalized should be carefully evaluated in terms of growth and development, and early diagnosis and treatment of malnutrition should be provided. Thus, it is thought that with early recognition and appropriate treatment of malnutrition, faster treatment of diseases that cause hospitalization and therefore prevention of recurrent hospitalizations can be achieved.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırşehir Ahi Evran University Faculty of Medicine Clinical Researches Ethics Committee (Date: 03.11.2020, Decision No: 2020-16/120).

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Eating behavior styles and factors associated with disordered eating behaviors in early adolescents: cross-sectional study

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ABSTRACT

Aims: Disordered eating attitudes and behaviors have become a global concern among adolescents. Given that eating behaviors developed during adolescence will determine lifelong adolescent health outcomes, it is important to understand the factors associated with disordered eating behaviors in early adolescents. This study aimed to assess the eating behaviors styles of early adolescents and to determine the relationship between eating behaviors and sociodemographic, lifestyle factors, and dietary patterns.

Methods: This cross-sectional was conducted on 700 middle school students aged 10-14 years old. Sociodemographics, dietary, and lifestyle data were collected using a questionnaire. Anthropometric measurements were performed. The Dutch Eating Behavior Questionnaire Children (DEBQ-C) was used to evaluate adolescents' restrained, emotional, and external eating styles. Mediterranean Diet Quality Index (KIDMED) was used to assess adherence to the Mediterranean diet (AMD).

Results: Girls had higher scores in all three eating styles compared to boys. Students with overweight/obese scored higher in restrained, but lower in external and emotional eating style compared to students with normal weight. Students with excessive energy, carbohydrate, and protein intake had higher external eating but lower restrained eating scores than those with low or normal intake. Being female, higher KIDMED score, less screen time, higher BMI z score, higher waist/hip ratio, and body dissatisfaction were positively associated with restrained eating behavior. Being female (β =0.085, p=0.024), screen time < 2 hours (β =-0.086, p =0.027), and BMI z score (β =-0.211, p =<0.001) were found to be significant predictors of external eating behaviors, while being female and older age were associated with emotional eating behaviors among early adolescents.

Conclusion: There are differences in early adolescents eating behavior styles based on gender, nutritional status, body dissatisfaction, perceived health, screen time, physical activity status, AMD, and dietary intake.

Keywords: Eating behaviors, body image dissatisfaction, dietary intake, lifestyles

INTRODUCTION

Disordered eating behaviors are conditions that involve a range of unhealthy attitudes and behaviors related to eating, body weight and body shape, and involve struggles with self-control. Disordered eating attitudes and behaviors have become a global concern among adolescents.[1] The risk of developing disordered eating behaviors are highest in the middle and late adolescent periods. However, in recent years, it has been reported that the age of onset of eating disorders has shifted to earlier ages.[2] Studies have shown that many factors including genetic factors, gender, lifestyle behaviors, sociodemographic characteristics, environmental factors and psychosocial factors (body dissatisfaction, perceived health) are associated with disordered eating behaviors.[3-5] However, there are limited studies investigating factors associated with disordered eating behaviors among early adolescents.[4]

Emotional eating" refers to eating to cope with negative emotions to relieve stress by ignoring the satiety signal, without internal physiological hunger signals. "External eating" refers to eating in response to stimuli related to food consumption (the sight or smell of food), regardless of hunger and satiety signals. The theory of "restrained eating" reflects the degree to which one consciously restricts food intake (attempts to avoid eating to lose or maintain a certain weight). Previous research has shown that emotional overeating and restrained eating often co-occur with body dissatisfaction and can eventually develop into more extreme diets or inappropriate compensation methods (bulimia nervosa etc.).[6,7]

Given that eating behaviors developed during adolescence will determine lifelong adolescent health outcomes, it is important to understand the factors

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associated with disordered eating behaviors in early adolescents.[7] Furthermore, considering that the presence of disordered eating attitudes and behaviors in early adolescence is an important predictor of eating disorder symptoms in late adolescence and young adulthood, it is essential to determine factors that influence disordered eating attitudes and behaviors during this period. Thus, prevention-focused strategies could be created. When the literature was reviewed, no study was found that examined the eating behaviors of Turkish children in early adolescence and the factors associated with eating behaviors. Therefore, this study aimed to assess the eating behaviors styles of early adolescents and to determine the relationship between eating behaviors and sociodemographic, psychosocial, lifestyle factors, and dietary patterns. This study' findings could provide a framework for an understanding of predictors of eating behaviors among early adolescents and to plan intervention programs.

METHODS

The study was carried out with the permission of İzmir Katip Çelebi University Non-Interventional Clinical Trials Ethics Committee (Date: 27.04.2023, Decision No: 0206), and parental written consent was obtained on behalf of each of the children. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Participants

This cross-sectional study was carried out in early adolescents aged 10-14 years from April to June 2023. The study sample was calculated as 260 by using the sampling formula (N=N-t2-p-q/d2(N-1) þ t2-p-q), which is recommended to be used in cases where the number of individuals in the target group is known, assuming that the standard deviation is 5% and the probability of realisation is 50% since the probability of the phenomenon examined in the light of the literature is not reached. The universe of the study consisted of middle schools in the Karşıyaka district of İzmir province, Turkiye. The sample group of the study consisted of 2 middle schools, which were randomly selected from 19 middle schools affiliated to Karşıyaka District Directorate of National Education. In the selected middle schools, all students were recruited, if they met the inclusion criteria and given consent to participate. The study sample included 700 middle school students of 352 boys and 348 girls. The inclusion criteria were being 10-14 years old, attending grades 5-8 th, and volunteering to participate. Exclusion criteria were: being younger than 10 or older than 14 years old; having a history of chronic disease; the lack of parental approval.

Data collection

Before collecting the data, the schools were visited and the authorized administrator of the school (school principal or deputy school principal) was informed about the study. All 5-6-7-8th grades in the schools were informed about the study, and each volunteer student was asked to deliver an informed consent form to one of their parents and to deliver them to the school administration after they were filled in. The data were collected in the classroom using face-to-face interview techniques by trained research assistants, after informed consent forms were obtained. The researchers explained and clarified the questionnaire to the students before they filled out the questionnaire to avoid mistakes and misconceptions. Afterwards, completed questionnaires were collected from the students.

Questionnaire

The questionnaire consisted of 7 sections. In the first section, socio-demographic characteristics of the students (students age, gender, parents education level, employment status, and the number of siblings) was obtained. In the second section, the eating habits of adolescents were evaluated. In the third section, "Physical activity status was questioned. In the fourth part, anthropometric measurements were taken and recorded. In the fifth section, the Mediterranean Diet Quality Index (KIDMED) questionnaire was applied to evaluate the diet quality of adolescents. In the sixth section, the Dutch Eating Behavior Questionnaire Children (DEBQ-C) scale was applied to evaluate the eating behaviors of adolescents. In the last section, 24-hour food consumption records of adolescents were taken.

Physical Activity Status

The following questions were used to assess students' physical activity status: Do you engage in regular physical activity? (The response possibilities were "Yes" and "No"). Students were asked the following question to determine their average daily screen time: "How many hours do you spend each day watching TV, playing video or computer games, or using a computer for something other than school work?" Screen time was divided into low (≤2 hours/day) and high (> 2 hours/day) categories.[8]

Body Satisfaction and Self-perceived Health

To keep the questionnaire short, body satisfaction was assessed with following question: Are you satisfied with your appearance? (Possible answer 1. yes; 2. no.). Self preceived health was evaluated by asking students the following question: How do you perceive your health in general? (Response options were:1. Bad, 2. Moderate, 3. Good.)

Mediterranean Diet Quality Index (KIDMED)

The KIDMED was used to measure dietary adequacy, and adherence to the Mediterranean diet (AMD). This index consists of 16 statements (12 positive and 4 negative) about the dietary habits of adolescents. "Yes" responses to positive statements about dietary adherence were evaluated as +1 point, "no" responses to statements suggesting less dietary adherence were evaluated as -1 point, and the sums of the scores obtained from the applied index were classified into 3 groups. According to this classification, ≥8 points indicate high AMD (good diet quality), 4-7 points indicate moderate AMD (diet quality should be improved), and ≤3 points indicate low AMD (poor diet quality). It is accepted that the higher the score obtained from the KIDMED questionnaire, the higher the level of AMD.[9] The cronbah's alpha coefficient of the Turkish version of KIDMED was 0.86.[9] In this study, the Cronbach's alpha coefficient was 0.78.

Dutch Eating Behavior Questionnaire Children (DEBQ-C)

In this study, the DEBQ-C, which was adapted for children from the adult version and whose Turkish validity and reliability was performed by Sağlam et al.[10] in 2022, was used to evaluate students' eating behaviors. The test consists of 20 items and has 3 subscales. These subscales are restrictive eating, emotional eating, and external eating. Restrictive eating is obtained by adding the scores of questions 4, 6, 8, 11, 14, 16, and 18; emotional eating score is obtained by adding the scores of questions 2, 3, 9, 12, 12, 15, 17 and 19; and external eating score is obtained by adding the scores of questions 1, 5, 7, 10, 13, and 20. The items in the questionnaire are evaluated with a 5-point Likert scale (1: never, 2: rarely, 3: sometimes, 4: often, 5: very often). The total score of the test is not evaluated, but the 3 subscales are evaluated within themselves. While there is no cut-off point in the scoring of the test, a high total score evaluated within the 3 subscales indicates a negative eating behavior.[10] The Cronbach's alpha reliability coefficient was 0.80, 0.72, and 0.79 for emotional eating, restrained eating, and external eating, respectively.[10] The cronbach's alpha coefficient of the DEBQ was calculated for this study. Accordingly, the cronbach's alpha coefficient was 0.87, 0.75, and 0.74 for emotional eating, restrained eating, and external eating, respectively.

Anthropometric Measurements

The body weight was measured using TANITA BC-532 bioelectrical impedance analyzer. Height was measured with a portable stadiometer in an upright position with the feet side by side, knees straight, heels, hips and shoulder blades in contact with the vertical level and the head in the Frankford plane. Body Mass Index (BMI) was calculated with the formula "BMI=[body weight (kg)/height (m^2)]". Waist, hip, and neck circumferences were measured using a non-flexible tape measure in accordance with the method.[11] BMI and height z scores according to age were determined using the "WHO Antro Plus" program. According to WHO growth curves, adolescents with BMI z scores <-1 SD were considered "underweight", -1 SD ≤-<+1 SD were considered "normal", > +1 SD-< +2 SD were considered overweight, and ≥ +2 SD were considered "obese".[12]

Dietary Intake and Habits

Dietary intake was assessed by 24-h food consumption record. How to fill in the food consumption records was explained in detail to the students trained by the researcher. To verify that students accurately indicated the amount of food they ingested, the "Food and Nutrient Photo Catalogue" was used. The food consumption records were completed by contacting the parents of the students who could not remember or remember incompletely what they ate the previous day. BeBiS (Ebispro for Windows, Germany; Turkish Version/BeBiS 8) was used for analyzing dietary energy and nutrients. The energy and nutrient intakes of the patients were compared according to the dietary reference intake (DRI) and values below 66% were considered as "inadequate intake", 67-133% as "adequate" and above 133% as "excessive intake".[13] Students'main and snack meal consumption status, amount of daily water consumption, and fast food consumption frequencies were questioned to obtain information about the dietary habits.

Statistical Analysis

SPSS 25 software program was used to analyze the data. Descriptive statistics were expressed as mean±standard deviation or median (interquartile range). Categorical variables were presented as frequency and percentage. Kolmogorov-Smirnov test, histogram, and probability graphs were used to evaluate the conformity of the data to normal distribution. In intergroup comparisons, "Independent Samples t test" was used to compare the measurement values of two independent groups with normal distribution, and "one way ANOVA" test was used to compare the measurement values of three or more independent groups. Posthoc tests were carried out when a significant difference was observed between the three groups. Tukey's test was used if variances were homogeneous, and the Tamhane's T2 test was used if variances were not homogeneous. Pearson or Spearman correlation analysis was carried out to evaluate the relationship between the DEBQ subscales and some variables. Linear regression analysis was performed to examine the predictors of restrictive, emotional, and external eating styles. In all analyses, a p- value less than 0.05 was considered statistically significant.

RESULTS

The general characteristics of students are shown in Table 1. Overall, 50.3% were boys and 49.7% were girls, and the mean age was 12.5±1.11 years. While 53.9% of the students had normal body weight, 42.0% were overweight/obese. 31.4% of the students were 8th-grade students. Of the total students, 20.4% had low, 55.1% had moderate, and 24.4% had good AMD.

Table 1. General characteristics of the students

	Boys (n=352)	Girls (n=348)	Total (n=700)
Grade n(%)			
5th	61 (17.3)	79 (22.7)	140 (20.0)
6th	101 (28.7)	88 (25.3)	189 (27.0)
7th	82 (23.3)	69 (19.8)	151 (21.6)
8th	108 (30.7)	112 (32.2)	220 (31.4)
Age ($\bar{x}$±SS)	12.5±1.13	12.5±1.10	12.5±1.11
Height z score ($\bar{x}$±SS)	0.7±1.14	0.5±1.14	0.6±1.15
BMI z score($\bar{x}$±SS)	0.7±1.48	0.5±1.36	0.6±1.43
BMI groups n (%)			
Underweight	13 (3.7)	16 (4.6)	29 (4.1)
Normal	179 (50.9)	198 (56.9)	377 (53.9)
Overweight/Obese	160 (45.5)	134 (38.5)	294 (42.0)
DEBQ-C ($\bar{x}$±SS)			
Restrained Eating	2.6±0.88	2.6±0.88	2.6±0.88
Emotional Eating	1.9±0.93	1.9±0.93	1.9±0.93
External Eating	2.7±0.86	2.7±0.86	2.7±0.86
KIDMED groups n (%)			
Low	65 (18.5)	78 (22.4)	143 (20.4)
Moderate	206 (58.5)	180 (51.7)	386 (55.1)
Good	81 (23.0)	90 (25.9)	171 (24.4)
Dietary Intake median (IQR)			
Energy (kcal)	1581.8 (814.17)	1355.6 (779.5)	1449 (813.20)
Carbohydrate (TE %)	48.0 (14.00)	48.0 (14.00)	48.0 (14.00)
Protein (TE %)	15.0 (5.00)	15.0 (6.00)	15.0 (5.00)
Fat (TE %)	37.0 (12.00)	38.0 (13.00)	37.0 (12.00)

KIDMED: Mediterranean Diet Quality Index; DEBQ-C: Dutch Eating Behavior Questionnaire Children; BMI: body mass index

The eating behaviors of the students according to sociodemographic variables are presented in Table 2. Girls scored higher in all three eating styles compared to boys. Students with overweight/obese scored higher in restrained (p<0.001), but lower in external eating (p<0.001) and emotional eating style (p=0.048) compared to students with normal weight. Students who were dissatisfied with their appearance (body dissatisfaction) scored higher in all three eating styles than those who were satisfied with their appearance. Students who reported engaging in regular physical activity had higher restrained eating scores (p<0.001). Students with > 2 hours of screen time had lower restrained eating scores (p<0.001), and higher external eating scores (p=0.002) than those with ≤2 hours of screen time. The emotional and restrained eating scores of students who perceived their health as "bad" were higher than those who perceived their health as "good" (p=0.015, p=0.034).

The eating behaviors of students according to dietary patterns is presented in Table 3. Restrained eating scores of students with high adherence to the MD were higher than those with moderate and low adherence to the MD (p<0.001). Students who reported skipping main meals had higher restrained eating scores than those who reported not skipping meals (p=0.002). Students who reported eating breakfast regularly had lower emotional (p=0.001) and external eating scores (p=0.006) than those who reported not eating breakfast regularly. Restrained eating scores of students with inadequate energy, carbohydrate, and protein intake were higher than those with excessive energy, carbohydrate, and protein intake. The emotional eating scores of students with excessive energy intake were higher than those with normal and insufficient energy intake (p=0.031). Students with excessive energy, carbohydrate, and protein intake had higher external eating scores than those with low or normal intake (p<0.001). Students who reported consuming fast food 2 times a week or more had higher external (p=0.006) and emotional eating scores (p=0.042) than those who reported not consuming fast food, while students who reported consuming fast food once a week had a higher restrained eating score than those who reported consuming fast food twice or more (p=0.003).

The correlation between students' eating behaviors and some anthropometric and dietary parameters is given in Table 4. Restrained eating score was positively correlated with BMI z score, waist circumference, waist/hip ratio, neck circumference, KIDMED score, protein intake and fat intake, but negatively correlated with age, energy, carbohydrate (TE%) and external eating score. Emotional eating score was inversely correlated with BMI z score, KIDMED score, protein, and fat intake, whereas positively correlated with age, carbohydrate intake and external eating score. There was an inverse relationship between external eating score and BMI z score, waist circumference, neck circumference, waist and neck circumference, and protein (TE%), and a positive relationship between age and energy intake.

According to the results of the regression analysis (enter method), when the significance level corresponding to the F value was taken into account, Model 1, Model 2, and Model 3 established were statistically significant (F=21.915; p<0.001 for Model 1; F=9.116; p<0.001 for Model 2, F = 8.453; p < 0.001) (Table 5). In the first model, age, gender (being female), body dissatisfaction, skipping main meal, KIDMED score, engaging in physical activity, waist/hip ratio, and BMI z score explained 21.2% of the variance in restrained eating behaviours (adjusted R^2=0.212). Except age, all of

these variables significantly predicted restrained eating behavior. Being female, KIDMED score, less than 2 hours of screen time, BMI z score, waist/hip ratio, body dissatisfaction were positively associated with restrained eating behavior. In the second model, age, gender (being female), BMI z score, eating breakfast regularly, KIDMED score, perceived health status (bad) and body dissatisfaction explained 7.5 % of the variance in emotional eating behaviors (adjusted R^2= 0.075). The analysis showed that only age (β=0.076, p=0.044) and being female (β=0.203, p <0.01) significantly predicted emotional eating behavior. In the third model, accounting for age, gender, BMI z score, KIDMED score, body satisfaction, perceived health status (bad), and eating breakfast regularly, the regression model was significant and explained 6.9 % of the variance in external eating scores (adjusted R^2= 0.069). The analysis demonstrated that gender (being female) (β =0.085, p=0.024), screen time < 2 hours (β =-0.086, p=0.027) and BMI (β =-0.211, p <0.001) significantly predicted external eating behavior. There was a significant effect of BMI z score on external eating, indicating that students with higher BMI z score had lower external eating scores. There were no autocorrelation problems in the established models. Durbin Watson's values for each model were between 1.5 and 2.5.

Table 2. DEBQ-C scores of the students according to sociodemographic and lifestyle characteristics

	Restrained Eating	p value	Emotional Eating	p value	External Eating	p value
Gender		<0.001		<0.001		0.003
Boys (n=352)	2.5±0.85		1.7±0.77		2.6±0.82	
Girls (n=348)	2.7±0.89		2.1±1.03		2.8±0.90	
Mother education		0.128		0.856		0.853
Iliterate/Literate (n=52)	2.5±0.79		1.8±0.77		2.6±0.92	
Primary /secondary school (n=225)	2.5±0.92		1.9±0.92		2.7±0.84	
High school (n=281)	2.7±0.86		1.9±0.98		2.7±0.90	
University (n=142)	2.6±0.89		1.9±0.94		2.7±0.81	
Father education		0.187		0.688		0.585
Iliterate/Literate (n=49)	2.4±0.77		2.0±0.94		2.7±0.97	
Primary /secondary school (n=219)	2.5±0.91		1.9±0.91		2.7±0.87	
High school (n=266)	2.6±0.88		1.9±0.96		2.7±0.86	
University (n=166)	2.7±0.89		1.8±0.92		2.6±0.83	
Mother employment status		0.729		0.821		0.747
Unemployed (n=448)	2.6±0.88		1.9±0.93		2.7±0.85	
Employed (n=252)	2.6±0.90		1.9±0.95		2.7±0.88	
BMI groups		<0.001		0.048		<0.001
Underweight/Normal (n=406)	16.9±5.93		14.0±6.88		17.2±5.22	
Overweight/Obese (n=294)	20.4±6.04		13.0±6.08		15.2±4.99	
Body satisfaction		0.001		0.007		0.029
Yes (n=436)	16.6±5.74		13.1±6.13		16.0±4.95	
No (n=264)	18.3±6.29		14.5±7.17		16.9±5.59	
Perceived health		<0.929		0.015		0.034
Bad (n=71)[a]	2.6±0.86		2.2±1.08	a>c~	2.9±0.88	a>c~
Moderate (n=237)[b]	2.6±0.88		1.9±0.93		2.7±0.83	
Good (n=392)[c]	2.6±0.89		1.8±0.90		2.6±0.87	
Screen Time		<0.001		0.066		0.002
≤2 hours (n=310)	2.7±0.88		1.8±0.88		2.6±0.87	
>2 hours (n=390)	2.5±0.87		2.0±0.97		2.8±0.85	
Sleep duration		0.278		0.868		0.603
0-6 hours (n=81)	2.6±0.90		1.9±1.15		2.8±0.92	
6-8 hours (n=376)	2.5±0.89		1.9±0.94		2.6±0.89	
9-12 hours (n=208)	2.7±0.88		1.9±0.86		2.7±0.81	
>12 hours (n=35)	2.5±0.81		2.0±0.83		2.7±0.86	
Engage in physical activity		<0.001		0.131		0.051
Yes (n=488)	2.7±0.89		1.9±0.90		2.6±0.84	
No (n=212)	2.4±0.85		2.0±1.01		2.8±0.92	

DEBQ-C: Dutch Eating Behavior Questionnaire Children; BMI: Body mass index. p values were calculated using one way ANOVA or Independent samples t test. ~Tukey test

Table 3. DEBQ-C scores of students according to dietary patterns

	Restrained eating	p value	Emotional eating	p value	External eating	p value
KIDMED score group						
Low adherence (n=143)[a]	2.3±0.82	<0.001	2.0±0.98	0.109	17.0±5.33	0.268
Moderate adherence (n=386)[b]	2.6±0.89	c>a,c>b,b>a~	1.9±0.91		16.2±5.11	
High adherence (n=171)[c]	2.8±0.86		1.9±0.94		16.2±5.35	
Skipping the main meal						
Yes (n=388)	2.7±0.90	0.002	1.9±0.93	0.885	2.6±0.86	0.191
No (n=312)	2.5±0.85		1.9±0.94		2.7±0.86	
Eating breakfast regularly						
Yes (n=440)	2.6±0.88	0.829	1.8±0.87	0.001	2.6±0.83	0.006
No (n=260)	2.6±0.90		2.1±1.01		2.8±0.92	
Frequency of consumption of fast food						
Never consume (n=88)[a]	2.6±1.00	0.003	1.8±0.98	0.042	2.5±0.86	<0.001
One day a week (n=395)[b]	2.7±0.88	b>c*	1.9±0.93	c>a*	2.6±0.88	c>b,c>a*
Two days or more days a week (n=217)[c]	2.4±0.81		2.0±0.92		2.9±0.81	
Energy intake						
Inadequate (n=362)[a]	2.7±0.90	0.024	1.9±0.91	0.031	2.6±0.83	<0.001
Normal (n=301)[b]	2.5±0.85	a>c~	1.9±0.93	c>a	2.8±0.84	c>a,c>b
Excessive (n=37)[c]	2.4±0.85		2.3±1.07	c>b~	3.1±1.06	b>a~
Carbohydrate intake						
Inadequate (n=87)[a]	2.8±0.94	0.001	1.7±0.77	0.146	2.4±0.74	<0.001
Normal (n=302)[b]	2.7±0.89	a>c~	1.9±0.93		2.6±0.84	c>a,c>b~
Excessive (n=311)[c]	2.4±0.84		1.9±0.97		2.8±0.89	
Protein intake						
Inadequate (n=150)[a]	2.8±0.94	<0.001	1.9±0.99	0.657	2.5±0.86	<0.001
Normal (n=293)[b]	2.7±0.89	a>c,b>c~	1.9±0.90		2.6±0.84	c>a
Excessive (n=257)[c]	2.4±0.84		1.9±0.93		2.8±0.86~	

DEBQ-C: Dutch Eating Behavior Questionnaire Children; KIDMED: Mediterranean Diet Quality Index. p values were calculated using one-way ANOVA or Independent samples t test. Each variable was identified with a different letter (a, b, c) ~Tukey test, *Tamhane's T2 test

Table 4. The correlation between students' DEBQ-C scores and some anthropometric and dietary parameters

	Restrained Eating		Emotional Eating		External Eating	
	r	p	r	p	r	p
Age (years)	-0.111	0.003	0.105	0.005	0.080	0.034
BMI z score	0.331	<0.001	-0.078	0.039	-0.193	<0.001
Waist circumference (cm)	0.261	<0.001	0.005	0.889	-0.124	0.001
Waist/hip ratio	0.244	<0.001	0.008	0.839	-0.050	0.186
Neck circumference (cm)	0.092	0.015	0.049	0.192	-0.092	0.015
KIDMED score	0.153	<0.001	-0.099	0.009	-0.045	0.235
Energy (kcal)	-0.109	0.004	0.038	0.322	0.165	<0.001
Protein (TE %)	0.096	0.011	-0.077	0.044	-0.082	0.031
Carbohydrate (TE %)	-0.109	0.004	0.076	0.047	0.067	0.079
Fat (TE %)	0.076	0.047	-0.050	0.188	-0.035	0.357
Restrained eating score	-	-	-0.040	0.285	-0.134	<0.001
Emotional eating score	-0.040	0.285	-	-	0.507	<0.001
External eating score	-0.134	<0.001	0.507	<0.001	-	-

DEBQ-C: Dutch Eating Behavior Questionnaire Children; KIDMED: Mediterranean Diet Quality Index. p values were calculated using pearson correlation test or spearman correlation test.

Table 5. Multiple Linear Regression Analyses for the Assessment of predictors of DEBQ-C

	Standardized coefficients β	p value	95% Cl	Adjusted R^2	F	Model (p)	Durbin Watson (1.5-2.5)
Restrained Eating				0.212	21.915	<0.001	1.930
Age (years)	-0.014	0.698	-0.068-0.045				
Gender (being female)	0.134	**<0.001**	0.109-0.368				
BMI z score	0.296	**<0.001**	0.137-0.230				
KIDMED score	0.133	**<0.001**	0.015-0.047				
Waist/hip ratio	0.083	**0.035**	0.018-0.514				
Screen time (<2 hours)	0.093	**0.007**	0.045-0.287				
Skipping main meal (Yes)	0.116	**0.001**	0.081-0.333				
Engage in physical activity (Yes)	0.147	**<0.001**	0.152-0.416				
Body dissatisfaction (Yes)	0.090	**0.013**	0.035-0.293				
Emotional Eating				0.075	9.116	<0.001	1.996
Age (years)	0.076	**0.044**	0.002-0.126				
Gender (being female)	0.203	**<0.001**	0.244-0.517				
BMI z score	-0.074	0.055	-0.098-0.001				
KIDMED score	-0.053	0.163	-0.031-0.005				
Body dissatisfaction (Yes)	0.041	0.300	-0.071-0.230				
Eating breakfast regularly (Yes)	-0.066	0.094	-0.279-0.022				
Perceived health (Bad)	0.070	0.067	-0.015-0.451				
External Eating				0.069	8.453	<0.001	2.041
Age (years)	0.006	0.870	-0.054-0.064				
Gender (being female)	0.085	**0.024**	0.019-0.276				
BMI z score	-0.211	**<0.001**	-0.174- -0.082				
Body dissatisfaction (Yes)	0.058	0.149	-0.037- 0.244				
Eating breakfast regularly	-0.073	0.061	-0.269-0.006				
Perceived health (Bad)	0.071	0.063	-0.011-0.423				
Screen Time (<2 hours)	-0.086	**0.027**	-0.285- -0.017				

1)Dummy variables. 0 (ref.): Being male, 1: Being female
2)Dummy variables. 0 (ref.): No skipping main meal, 1: Skipping main meal (yes)
3)Dummy variables. 0 (ref.): No body dissatisfaction, 1: Body dissatisfaction (yes)
4)Dummy variables. 0 (ref.):No engage in physical acticity, 1: Engage in physical activity (yes)
5)Dummy variables. 0 (ref.):Screen time < 2 hours, 1: Engage in physical activity (yes)
6) Dummy variables. 0 (ref.):No eating breakfast regulary, 1: Eating breakfast regularly (yes)

Abbreviations: DEBQ-C: Dutch Eating Behavior Questionnaire Children; KIDMED: Mediterranean Diet Quality Index, BMI: body mass index,

DISCUSSION

This study was conducted to assess the eating behaviors styles of early adolescents and to determine the relationship between eating behaviors and sociodemographic, lifestyle factors, and dietary patterns.

It is well known that sociodemographic variables such as age and gender influence healthy eating behaviors.[14] In a study conducted with 419 Turkish adolescents, it was shown that girls are emotional and external eaters compared to boys.[15] In another study conducted with 346 children aged 10-19 years, the total score and subscale scores of the DEBQ were higher in girls than in boys.[16] Similarly, in this study, girls had significantly higher scores in all three eating styles than boys, and being female was found predictor of three eating styles. These results can be attributed to the fact that cultural pressures that idealize thinness and concerns about body image may influence the development of eating disorders in girls.[3] Consistent with previous studies conducted in adolescents,[5,17] increasing age was found to be a predictor for emotional eating in this study. These results are important for showing that female and older students are in the risk group in terms of eating behaviors and these results can be taken into consideration for health promotion programs.

Body dissatisfaction has been identified as a risk factor for the development of disordered eating behaviors.[18] In studies conducted on Chinese university students,[19] and middle school students,[4] body dissatisfaction was positively associated with the restrained eating style. In line with the literature, this study revealed that body dissatisfaction predicted restrained eating behavior. This result can be explained by the fact that with the onset of physical changes in adolescents, body image gains importance and their desire to be liked and admired increases. In this period, girls try to have thinner or boys try to have more muscular bodies with the desire to have an idealized individual appearance.[20] They constantly compare themselves with idealized bodies. When there is a gap between their real image and ideal image, they

produce negative body images, which can result in restrained eating behaviors.[19] Sze et al.[21] found that emotional eating is associated with lower life satisfaction, poorer mental health, and lower perceived health in Chinese university students. Consistent with Sze et al.[21] study, this study revealed that students who answered the question of how do you find your health as "bad" had high emotional and external eating scores. Taken together, these results suggest that identifying early adolescents with body dissatisfaction or poor health perception is important for the early detection of disordered eating behaviors.

Excessive screen use has been associated with physical activity and disordered eating behaviors.[22] Bawaked et al.[23] found that total screen is negatively correlated with restrained eating and positively correlated with emotional, and external eating behavior in Spanish children. Another study revealed that individuals who engage in physical activity scored higher in terms of restrained behavior than those who did not.[24] Consistent with the literature, less screen and engagement in physical activity were associated with presenting restrained eating behavior in this study. A possible explanation for these findings is that adolescents who engage in physical activity and have less screen time prefer restrictive eating because they pay attention to their nutritional status. Linear regression analysis demonstrated that screen time <2 hours was negatively associated with external eating in this study. This result can be associated with the fact that adolescents who spend a long time in front of the screen may show an external eating tendency as a result of being influenced by food advertisements. It has been reported that screen time may increase eating when satiety is not present due to classical conditioning, diversion from internal hunger and satiety signals, and the prevalence of food-related ads and advertising on TV, and social media platforms.[25]

BMI has been associated with disordered eating behaviors.[5,10] In the present study, adolescents with obesity showed highly restrained and low external and emotional eating styles, and such these findings were also found by Sağlam et al.[10] BMI z score and waist/hip ratio were positively associated with restrained eating behavior in this study. There are different explanations for these results. Van Strien and Oosterveld[26] reported that restrained eaters' lack of self-control causes them to overeat. Some researchers have claimed that the issue of restrained eating would be a behavior exclusive to individuals who are sensitive to weight gain.[27] Since this study is cross-sectional, no conclusions can be drawn about the direction of the relationship. Longitudinal studies are needed to show whether restrained eating is a cause or a reaction to being overweight.

It was shown that as the KIDMED score increased, the restrictive eating behavior increased in university students.[28] Yong et al.[19] showed that university students with high levels of restrained eating tended to consume more fruits and eggs, less sugar-sweetened drinks, and fast food and may thus reduce their energy intake. In parallel with these results, this study found that although restrained eating is positively associated with BMI, a positive relationship is found between high KIDMED score and restrained eating style. Moreover, it was determined that adolescents who skip main meals, consumed fast food less frequently, inadequate energy, carbohydrate, and protein intake had a higher restrictive eating score. Moreover, skipping the main meal was found a predictor of restrained eating in this study. These results suggest that adolescents with restrictive eating tendencies may consume healthy food and skip the main meal to reduce their energy intake. Restrained eating is an attempt at dietary restriction, which means eating less than the desired amount to lose or maintain body weight. In this context, restrained eaters are more concerned with the energy of their diet, which enhances their incentive to suppress their appetite and capacity to minimize unhealthy food intake.

In a study conducted in adults, participants with obesity had higher score on external eating styles than to normal BMI group, in contrast to the results of this study.[29] Similarly, Snoek et al.[17] found that external eating is negatively associated with obesity in adolescents. Marb et al.[30] reported that external eating is associated with a significantly higher energy intake among female adolescents. Consistently, this study showed that students with excessive energy intake and frequent fast food consumption had high emotional and external eating. However, although there was a positive relationship between energy intake and external eating, a negative association was found between external eating and BMI z score. This contradiction can be explained by parental influence. During early adolescence, most food intake is controlled by parents. For example, one study found that parental encouragement was associated with adolescents' consumption of healthy foods.[31] Children and adolescents with higher body weights are subject to more food control and food restrictions.[32] Parents of overweight/obese children are less likely to allow their children to give in to or expose them to unhealthy external cues.[17] This may explain the lower external eating score of early adolescents with overweight and obesity compared to normal-weight adolescents. Another explanation for this conflict that external eating behavior represents a normal tendency in children and tends to decrease with overweight due to modulation of the restrained behavior. In addition, the high restrictive eating score in adolescents with obesity and the positive

relationship between restrained eating and the KIDMED may be associated with parenteral effects. The negative correlation between restrictive eating and external eating is in line with these explanations.

Adolescence is a period of intense emotional changes. During this period, difficulties in emotional regulation can push adolescents to become emotional eaters who tend to consume sweets, salty foods, and other energy-dense foods.[33] Numerous studies conducted on adolescents showed a positive association between emotional eating and consumption of sugary foods, fast foods, high-fat snacks, sweets, and soft drinks.[33,34] Consistently, this study showed that students with excessive energy intake and frequent fast food consumption had high emotional and external eating. These findings suggest that being sensitive to emotional eating and external food cues is associated with unhealthy food consumption. Moreover, in the present study, external eating was positively correlated with emotional eating. This correlation may suggest that emotional eating and external eating both contribute to the facilitation of overeating.[26]

This study has some limitations. First, the causality of the relationship remains unclear, as the study was designed as cross-sectional. Second, data were gathered by self-report, which may result in false reporting and recall bias. However, the present study also has the following strengths: A food consumption record provided more reliable results in calculating dietary intake. To the best of our knowledge, this is the first study to evaluate the associations between eating behaviors and sociodemographic, lifestyle factors, and dietary patterns among early adolescents.

CONCLUSION

The results of study showed that there are differences in early adolescents eating behavior styles based on gender, nutritional status, body dissatisfaction, perceived health, screen time, physical activity status, AMD, and dietary intake. Being sensitive to emotional eating and external food cues is associated with unhealthy food consumption and excessive dietary intake whereas more restrained eating may indicate proneness to healthier food choices and inadequate dietary intake. These issues should be considered when planning healthy nutrition programs for early adolescents. This can make interventions more effective to prevent disordered eating behaviors.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İzmir Katip Çelebi University Non-Interventional Clinical Trials Ethics Committee (Date: 27.04.2023, Decision No: 0206).

Informed consent: Written informed consent was obtained from the parents of children participating in this study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Pathogen distribution and microbial resistance pattern in endotracheal aspirate samples of intensive care unit patients before and after the COVID-19 pandemic

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ABSTRACT

Aims: The aim of this study is to evaluate the distribution of pathogen microorganisms and antimicrobial resistance rates isolated from endotracheal aspirate (ETA) samples of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) polymerase chain reaction (PCR) positive and negative patients followed and treated in the intensive care unit (ICU) of our hospital, and to examine the effect of the COVID-19 (coronavirus disease 2019) pandemic on this.

Methods: In this study, ETA samples sent to the microbiology laboratory from hospitalized patients in Tekirdağ Namık Kemal University Hospital general ICU-1 and general ICU-2 between March 11, 2018 and March 10, 2022 were retrospectively analyzed. During the COVID-19 pandemic, it was used to follow up patients with SARS-CoV-2 PCR positive in ICU-1 and SARS-CoV-2 PCR negative patients in ICU-2. The working period is divided into two parts as pre-pandemic (2018 - 2019) and post-pandemic (2020 - 2021). Bacterial identification and antibiotic susceptibility tests were performed using conventional methods and automated systems. Colistin sensitivity was studied by broth microdilution, and ceftazidime avibactam (CZA) sensitivity was studied by disk diffusion method. Statistical analysis was performed with the chi-square test, $p<0.05$ was considered significant.

Results: A total of 1669 ETA samples from 856 patients were sent to our laboratory over a four-years period, and culture positivity was detected in 63.6% of the samples. With the COVID-19 pandemic, it was found that the culture positivity increased significantly in ETA samples of patients hospitalized in ICU-1, and there were no significant difference in ICU-2. 836 isolates from 1061 specimens were included to the study. The three most commonly isolated pathogens were *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, respectively. While *P. aeruginosa* was the most frequently isolated microorganism in both ICU-1 and ICU-2 in the pre-pandemic period, it was replaced by *A. baumannii* in both clinics with the pandemic, and the increase in the frequency of *A. baumannii* in ICU-1 was statistically significant. Antibiotic resistance rates were generally found to be higher in ICU-1 than in ICU-2, and even in ICU-2, resistance rates to some antimicrobials were found to be decreased. In *A. baumannii*, a statistically significant increase was observed in the resistance rates against all antibiotics, including colistin, in ICU-1, and a significant increase was found in resistance only against amikacin in ICU-2. In *P. aeruginosa*, a significant increase was found in the resistance rates against cephalosporins and carbapenems in ICU-1, ceftazidime, ciprofloxacin and colistin in ICU-2, and a significant decrease in resistance to amikacin in ICU-2. In *K. pneumoniae*, a significant increase was found in the resistance rates against amoxicillin-clavulanate (AMC), ceftriaxone, ertapenem, amikacin and colistin in ICU-1, ertapenem and amikacin in ICU-2, and a significant decrease in resistance to AMC and all cephalosporins in ICU-2. CZA susceptibility in *K. pneumoniae* isolates was examined in 2020 and 2021, and no resistance was found in either clinic.

Conclusion: In our study, it was determined that the culture positivity rate in ETA samples increased, the distribution of pathogen microorganisms and antimicrobial resistance rates changed with the COVID-19 pandemic. For this reason, it is important to follow up possible pathogen microorganisms and antimicrobial resistance rates during similar pandemic periods such as COVID-19.

Keywords: antimicrobial resistance, COVID-19, endotracheal aspirate, pathogen microorganism

This study was previously presented as a poster presentation with the number 'EP-092' at the XL International Turkish Microbiology Congress (16-20 November 2022 Antalya)

INTRODUCTION

COVID-19 (coronavirus disease 2019) infection, a part of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), was first detected in Wuhan, China in December 2019, and then caused a pandemic all over the world. In our country, the first case was reported in March 2020, and many hospitals were determined as pandemic hospitals in order to make treatment of COVID-19 patients.[1,2] COVID-19 may cause many cases such as respiratory tract infection, severe acute respiratory syndrome (SARS), sepsis and multi-organ failure.[3] Bacterial or fungal co-infection is frequently encountered in viral respiratory tract infections. These co-infections negatively affect the state of the existing disease, cause long-term hospitalization, and increase morbidity and mortality. Because of this, rapid diagnosis and initiation of treatment are important for the course of the disease.[4,5]

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Resistance to antimicrobial drugs appears as an increasing public health problem nowadays. Antimicrobial therapy is involved in the treatment of co-infections in COVID-19 patients and is used empirically or for the ruling of nosocomial infection acquired during hospitalization. Though antibacterial agents have no effect on the treatment of the disease, some case series recommend the use of broad-spectrum antibiotics in COVID-19 patients. Unfortunately, the use of broad-spectrum antibiotics brings with the risk of resistance development.[6,7]

The aim of this study; to evaluate the agents isolated from endotracheal aspirate (ETA) samples and antimicrobial resistance rates of patients with positive and negative SARS-CoV-2 polymerase chain reaction (PCR) values that followed and treated in the intensive care unit (ICU) of our hospital, and also to examine the impact of the COVID-19 pandemic on this situation.

METHODS

The study was carried out with the permission of Tekirdağ Namık Kemal University Non-Interventional Clinical Researches Ethics Committee (Date: 28.06.2022, Decision No: 2022.127.06.17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

ETA samples sent to the microbiology laboratory from patients hospitalized in general ICU-1 and general ICU-2 of Tekirdağ Namık Kemal University Hospital (430 bed capacity) between March 11, 2018 and March 10, 2022 were analyzed retrospectively. Our hospital served as a pandemic one during the COVID-19 pandemic. ICU-1 (11 bed capacity) was used for the treatment of intubated patients followed for COVID-19 infection (SARS-CoV-2 PCR positive), ICU-2 (11 bed capacity) was used for the treatment of intubated patients followed for non-COVID-19 reasons (SARS-CoV-2 PCR negative). The time interval included in the study; the date of 11 March 2020, when the first case was detected in our country, was accepted as the starting point, and it was evaluated as two years before the COVID-19 pandemic (11 March 2018 - 10 March 2020) and two years after the COVID-19 pandemic (11 March 2020 - 10 March 2022).

Nosocomial pneumonia, is a lower respiratory infection that was not incubating at the time of hospital admission and that presents clinically two or more days after hospitalization.[8] Because of this ETA samples taken on the possibility of infection 48 hours after the patients were admitted to the intensive care unit were included in the study. Demographic (age, gender) and clinical (inpatient service, clinical sample, pathogen, etc.) data of the patients were taken from the hospital information management system (HIMS).

Microbiological Evaluation

When an intubated patient has a lung infection clinic in our hospital, an ETA sample is requested. According to guidelines,[9] first, stained microscopic examination was performed and it was evaluated whether the sample was a quality sample reflecting the lower respiratory tract. The culture of the ETA sample thought to reflect the lower respiratory tract was examined. Quantitative culture method is done in the microbiology laboratory, and ≥100.000 KOB/ml growth is considered significant. In the case of one or two bacteria grown purely in culture, these microorganisms were considered as pathogens and the antibiogram was studied. ETA samples were incubated in agar with 5% sheep blood agar (Bes-Lab, Turkey), eosin methylene blue (EMB) agar (Bes-Lab, Turkey) and chocolate agar (Bes-Lab, Turkey) for 18-24 hours at 37°C and in 5-10% CO_2 environment. In the case of pure single or double colony growth in culture, isolates were identified by conventional methods (colony morphology, Gram stain, oxidase, catalase and coagulase test) and automated identification system (Vitek2 Compact, Biomerux, France and BD Phoenix System, Beckton Dickinson, USA). Antibiotic susceptibility tests were performed with manual Kirby-Bauer disc diffusion (Bioanalyse, Turkey and Oxoid, UK) and automated antibiogram systems (Vitek2 Compact, Biomerux, France and BD Phoenix System, Beckton Dickinson, USA) in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria(10). Carbapenem resistance in *Klebsiella pneumoniae* isolates was evaluated by the combined disc diffusion method (Bioanalyse, Turkey), ceftazidime avibactam (CZA) resistance has been studied since 2020 and was studied by the disk diffusion method (Bioanalyse, Turkey). Colistin resistance was studied by broth microdilution method (Micronaut-S, Merlin, Germany). Methicillin resistance was determined in staphylococcal isolates by disk diffusion method with cefoxitin disk (Oxoid, UK). Vancomycin and teicoplanin resistance detected in enterococcal isolates was confirmed by gradient test (Bioanalyse, Turkey). In case of detection of yeast in the samples, a factor-colonization distinction was made by interviewing with the relevant clinic. Antifungal susceptibility tests of isolates considered as active agents were determined by microdilution method (Mikronaut-AM, Bruker, Germany) in accordance with EUCAST guidelines. In the repetitive sample of one patient, only the first isolate was included in the study.

The SARS-CoV-2 PCR test was done by using the Bio Speedy SARS-CoV-2 RT-qPCR kit (Bioeksen, Turkey).

Statistical Analysis

The data that was obtained in the study were recorded in the SPSS 22.0 (SPSS Inc, Chicago, IL, USA) program and statistical analyzes were made. Categorical data

were given as percentages. Chi-square test was used to compare independent groups with categorical variables. Cases where the p value was below 0.05 were considered as statistically significant.

RESULTS

1669 ETA samples from 856 patients were sent to our laboratory in four years. Demographic data of patients; 59% male (n=505), 41% female (n=351) (ICU-1 59% male, 41% female; ICU-2 59% male, 41% female), mean age was 66.7±16.2 (17-100) (67.6±16.3 for ICU-1, 65.7±16.1 for ICU-2). There was no difference in age and gender between the patients followed in ICU-1 and ICU-2 (p>0.05).

Significant culture positivity was detected in 63.6% of the samples, no growth was detected in 18%, and oropharyngeal flora elements (OPFE) grew in 18.4% and were considered as contamination. It was found that the frequency of culture positivity in ETA samples that was taken from patients hospitalized in ICU-1 with the COVID-19 pandemic increased statistically significantly (p=0.018). There was no difference in ICU-2 (p=0.596) (Table 1). In our study, the rates of ventilator-associated pneumonia (VAP), a nosocomial pneumonia, were also evaluated for both ICUs before and after COVID-19. VAP rates were detected as 10.6% in ICU-1 and 12.1% in ICU-2 before COVID-19, and increased to 16.7% (23.0% in 2020, 10.3% in 2021) in ICU-1 and decreased to 9.3% (10.9% in 2020, 7.7% in 2021) in ICU-2 after COVID-19. The increase observed in ICU-1 in 2020 was found to be statistically significant (p=0.015), and no significant difference was detected in ICU-2 (p=0.489).

The pathogen microorganism was isolated in 836 of 1061 specimens with culture positivity and were included in this study. Of 836 isolates, 672 (80.4%) were Gram-negative bacteria ((51.1% nonfermenter Gram-negative bacteria (n=427), 26.1% Enterobacterales species (n=218), 3.2% other Gram-negative bacteria (n=27)) , 117 (14.0%) gram-positive bacteria and 47 (5.6%) fungi were identified. Before the pandemic, 80.3% of the isolates in ICU-1 were Gram-negative bacteria, 16.9% were Gram-positive bacteria, and 2.8% were fungi. After the pandemic, 80.3% of Gram-negative bacteria, 11.7% of Gram-positive bacteria, and 8.0% of fungi were determined. In ICU-2, 84.4% Gram negative bacteria, 12.9% Gram positive bacteria, and 2.7% fungi species before the pandemic. After the pandemic, 77.7% of Gram-negative bacteria, 14.4% of Gram-positive bacteria and 7.9% of fungi were determined. In COVID-19 pandemic, it was observed that the frequency of fungal pathogens increased in ETA samples in both clinics, but, this increase was not statistically significant for both clinics (ICU-1 p=0.579, ICU-2 p=0.121) (Table 2).

The four most frequently isolated agents in our study were *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *K. pneumoniae* and *Staphylococcus aureus*, respectively. In pre-COVID-19 pandemic period, ranking of pathogens in ICU-1 *P. aeruginosa* (27.2%), *A. baumannii* (18.3%), *S. aureus* (11.7%), *K. pneumoniae* (8.5%), with the pandemic, this situation changed to *A. baumannii* (31%), *P. aeruginosa* (15.7%), *K. pneumoniae* (14.2%) and *S. aureus* (7.3%). Only the increase in the frequency of *A. baumannii* was statistically significant (p=0.033), no statistically significant difference was found for the other three pathogens (p>0.05). In ICU-2, the pre-pandemic ranking was *P. aeruginosa* (25.9%), *A. baumannii* (20.4%), *K. pneumoniae* (10.9%), *S. aureus* (7.5%). Along with the pandemic, *A. baumannii* (22.8%), *P. aeruginosa* (16.3%), *K. pneumoniae* (15.3%) and *S. aureus* (8.9%) were detected and there was no statistically significant difference in isolation frequency for all four pathogens (p>0.05). While *P. aeruginosa* was the most frequently isolated pathogen in both ICU-1 and ICU-2 before the pandemic, it was replaced by *A. baumannii* in both clinics with the COVID-19 pandemic (Table 2).

Table 1. Distribution of microbiological evaluation of ETA samples by years and clinics (n/%)

Culture result	Before COVID-19				After COVID-19				Total		
	2018		2019		2020		2021				
	ICU 1	ICU 2	ICU 1	ICU 2	ICU 1	ICU 2	ICU 1	ICU 2	ICU 1	ICU 2	Total
Culture positive											
n	124	88	164	82	230	148	128	97	646	415	1061
%	64.6	59.1	66.7	55.8	77.5	63.0	56.6	54.2	67.2	58.6	63.6
Culture negative											
n	26	33	29	23	23	42	66	59	144	157	301
%	13.5	22.1	11.8	15.6	7.7	17.9	29.2	33.0	15.0	22.2	18.0
*Cont											
n	42	28	51	42	44	45	32	23	169	138	307
%	21.9	18.8	21.5	28.6	14.8	19.1	14.2	12.8	17.8	19.2	18.4
Total											
n	192	149	246	147	297	235	226	179	961	708	1669

*Cont: Oropharyngeal Contamination, ETA: Endotracheal aspirate, ICU: Intensive care unit

Table 2. Distribution of pathogens isolated from ETA samples by years and clinics (n/%)

Microorganisms	Before COVID-19								After COVID-19								4 years period					
	2018				2019				2020				2021				Total					
	ICU1		ICU2		ICU1		ICU2		ICU1		ICU2		ICU1		ICU2		ICU1		ICU2		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
***Gram Negative Bac.**																						
*NFGN																						
A. baumannii	21	22.1	17	21.5	18	15.3	13	19.1	53	31.0	26	22.4	32	31.1	20	23.3	124	25.5	76	21.8	200	23.9
P. aeruginosa	23	24.2	21	26.6	35	29.7	17	25.0	33	19.3	22	19.0	10	9.7	11	12.8	101	20.7	71	20.3	172	20.6
S. maltophilia	2	2.1	-	-	15	12.7	2	2.9	8	4.7	2	1.8	8	7.9	5	5.8	33	6.8	9	2.6	42	5.0
Other NFGN	2	2.1	1	1.3	1	0.9	-	-	5	2.9	4	3.4	-	-	-	-	8	1.6	5	1.4	13	1.6
Enterobacterales																						
K. pneumoniae	11	11.6	8	10.1	7	5.9	8	11.8	25	14.6	16	13.8	14	13.6	15	17.4	57	11.7	47	13.5	104	12.4
E. coli	8	8.4	8	10.1	5	4.2	4	5.9	7	4.1	8	6.9	1	0.9	8	9.3	21	4.3	28	8.0	49	5.9
Enterobacter spp.	3	3.3	5	6.4	2	1.7	4	5.9	5	2.9	4	3.4	4	3.9	4	4.7	14	2.9	17	4.9	31	3.7
Others	4	4.2	3	3.8	7	5.9	3	4.4	5	2.9	4	3.4	5	4.9	3	3.5	21	4.3	13	3.7	34	4.1
H. influenzaee	2	2.1	3	3.8	5	4.2	4	5.9	3	1.8	2	1.8	1	0.9	1	1.1	11	2.2	10	2.9	21	2.5
M. catarrhalis	-	-	3	3.8	-	-	-	-	-	-	2	1.8	1	0.9	-	-	1	0.3	5	1.4	6	0.7
***Gram Positive Bac.**																						
S. aureus	13	13.7	4	5.0	12	10.2	7	10.3	8	4.7	9	7.8	12	11.7	9	10.5	45	9.2	29	8.3	74	8.9
S. pneumoniae	4	4.2	1	1.3	4	3.4	4	5.9	5	2.9	4	3.4	1	0.9	3	3.5	14	2.9	12	3.4	26	3.1
*Other GPB	1	1.0	3	3.8	2	1.7	-	-	3	1.8	1	0.8	3	2.9	4	4.7	9	1.8	8	2.3	17	2.0
Fungi																						
Candida spp.	1	1.0	2	2.5	5	4.2	2	2.9	11	6.4	12	10.3	6	5.8	2	2.3	23	4.7	18	5.2	41	4.9
Other Fungi	-	-	-	-	-	-	-	-	-	-	-	-	5	4.9	1	1.1	5	1.1	1	0.3	6	0.7
Total	95	100	79	100	118	100	68	100	171	100	116	100	103	100	86	100	487	100	349	100	836	100

*Gram Negative Bac: Gram Negative Bacteria, NFGN: Non-fermenter Gram Negative Bacteria, Gram Positive Bac: Gram Positive Bacteria, GPB: Gram Positive Bacteria, ETA: Endotracheal aspirate, ICU: Intensive care unit

When the resistance rates of the isolated pathogens were compared before and after the COVID-19 pandemic; In *A. baumannii*, there was a statistically significant increase in the resistance rates against all antibiotics, including colistin in ICU-1, while a statistically significant increase was found in resistance only against amikacin in ICU-2 ($p<0.05$). Significant increase in resistance to cephalosporins and carbapenems in ICU-1 in *P. aeruginosa*, and again significant increase in resistance to ceftazidime, ciprofloxacin and colistin in ICU-2 and finally, a significant decrease in resistance to amikacin was observed in ICU-2 ($p<0.05$). In *K. pneumoniae* significant increase in resistance rates was detected against amoxicillin-clavulanate (AMC), ceftriaxone, ertapenem, amikacin and colistin in ICU-1 and against ertapenem and amikacin in ICU-2, and a significant decrease in resistance to AMC and all cephalosporins in ICU-2 ($p<0.05$). Ceftazidime-avibactam susceptibility was examined in *K. pneumoniae* isolates in 2020 and 2021, and no resistance was found in either clinic. In other Enterobacterales species, a significant increase was observed in resistance rates against ertapenem and amikacin in ICU-1, against cefepime in ICU-2. At the same time a significant decrease was detected in resistance to ceftriaxone, cefepime, meropenem and ciprofloxacin in ICU-1, and to AMC, piperacillin-tazobactam (PRP), imipenem and meropenem in ICU-2 ($p<0.05$) (**Table 3, 4**). While methicillin resistance in isolated *S. aureus* isolates was 24.0% and 27.3% before the pandemic in ICU-1 and ICU-2, respectively, it increased to 35.0% and 33.3% after the pandemic, and there was no statistically significant increase in either clinic (ICU-1 $p=0.088$, ICU-2 $p=0.355$). Before and after the pandemic, no resistance was found to vancomycin, teicoplanin and linezolid in *S. aureus* isolates.

Table 3. Antibiotic resistance rates of A.baumanni and *P. aeruginosa* isolates before and after the pandemic (%)

*Antibiotic	*A. baumannii*				p value		*P. aeruginosa*				p value	
	Before COVID-19 (2018-2019)		After COVID-19 (2020-2021)				Before COVID-19 (2018-2019)		After COVID-19 (2020-2021)			
	ICU1 (n=39)	ICU2 (n=30)	ICU1 (n=85)	ICU2 (n=46)	ICU1	ICU2	ICU1 (n=58)	ICU2 (n=38)	ICU1 (n=43)	ICU2 (n=33)	ICU1	ICU2
PTZ	-	-	-	-	-	-	55.2	44.7	58.1	33.3	0.669	0.102
CAZ	-	-	-	-	-	-	41.4	28.9	72.1	48.5	<0.001	0.004
FEP	-	-	-	-	-	-	37.9	28.9	58.1	33.3	0.005	0.541
IMP	87.2	96.7	98.8	91.3	0.001	0.074	34.5	26.3	51.2	30.3	0.022	0.529
MER	87.2	96.7	97.6	91.3	0.003	0.074	32.8	21.1	48.8	30.3	0.021	0.144
GEN	71.8	80.0	98.8	87.0	<0.001	0.182	-	-	-	-	-	-
AK	69.2	76.7	97.6	93.5	<0.001	0.001	24.1	15.8	23.3	6.1	0.868	0.024
CIP	87.2	96.7	98.8	91.3	0.001	0.074	37.9	15.8	48.8	30.3	0.117	0.019
TMP-SXT	71.8	83.3	91.8	84.8	<0.001	0.700	-	-	-	-	-	-
COL	0.0	13.3	13.0	6.5	0.001	0.106	6.9	0.0	9.3	12.1	0.602	0.002

*TZP: Piperacillin-tazobactam, CAZ: Ceftazidime, FEP: Cefepime, IMP: Imipenem, MER: Meropenem, GEN: Gentamicin, AK: Amikacin, CIP: Ciprofloxacin, TMP-SXT: Trimethoprim-sulphamethoxazole, COL: Colistin, ICU: Intensive care unit

Table 4. Antibiotic resistance rates of *K. pneumoniae* and other Enterobacterales isolates before and after the pandemic (%)

Antibiotic	*K. pneumoniae*				p value		Other Enterobacterales				p value	
	Before COVID-19 (2018-2019)		After COVID-19 (2020-2021)				Before COVID-19 (2018-2019)		After COVID-19 (2020-2021)			
	ICU1 (n=18)	ICU2 (n=16)	ICU1 (n=39)	ICU2 (n=31)	ICU1	ICU2	ICU1 (n=29)	ICU2 (n=27)	ICU1 (n=27)	ICU2 (n=31)	ICU1	ICU2
AMC	66.7	87.5	87.2	54.8	0.001	<0.001	79.3	70.4	81.5	48.4	0.592	0.002
PTZ	66.7	50.0	76.9	45.2	0.115	0.479	34.5	37.0	25.9	22.6	0.167	0.031
CRO	66.7	68.8	79.5	51.6	0.037	0.014	62.1	44.4	40.7	45.2	0.003	0.887
CAZ	66.7	68.8	76.9	48.4	0.115	0.003	55.2	37.0	44.4	45.2	0.120	0.250
FEP	66.7	68.8	74.4	48.4	0.278	0.003	55.2	22.2	37.0	38.7	0.011	0.009
ERT	50.0	25.0	66.7	45.2	0.015	0.003	13.8	11.1	25.9	12.9	0.034	0.663
IMP	50.0	25.0	59.0	29.0	0.201	0.524	10.3	3.7	3.7	0.0	0.096	0.043
MER	44.4	25.0	54.4	29.0	0.157	0.524	10.3	3.7	0.0	0.0	0.001	0.043
GEN	61.1	56.3	69.2	45.2	0.236	0.120	24.1	22.2	14.8	32.3	0.108	0.111
AK	11.1	18.8	61.5	32.3	<0.001	0.035	0.0	3.7	11.1	3.2	0.003	0.700
CIP	72.2	43.8	74.4	45.2	0.750	0.887	34.5	37.0	22.2	35.5	0.042	0.883
TMP-SXT	38.9	50.0	74.4	48.4	<0.001	0.777	34.5	40.7	37.0	35.5	0.883	0.467
COL	5.6	18.8	28.2	19.4	<0.001	1.000	0.0	0.0	0.0	0.0	1.000	1.000

*AMC: Amoxicillin-clavulanate, TZP: Piperacillin-tazobactam, CRO: Ceftriaxone, CAZ: Ceftazidime, FEP: Cefepime, ERT: Ertapenem, IMP: Imipenem, MER: Meropenem, GEN: Gentamicin, AK: Amikacin, CIP:Ciprofloxacin, TMP-SXT: Trimethoprim-sulfamethoxazole, COL: Colistin, ICU: Intensive care unit

DISCUSSION

COVID-19 is considered an pandemic that effects all over the world. Secondary infections added to the existing one effect the patient's prognosis and treatment process, causing patients to stay in the hospital longer than normal and use broad-spectrum antibiotics. In studies evaluating the comorbidity of COVID-19 and infection, it has been reported that the frequency of bacterial and/or fungal co-infection is increased in patients followed in the ICU.[7,11-13] In our study, compared to the pre-pandemic period; In the ETA samples of patients followed up for COVID-19 with the pandemic, culture positivity rates were found to increase statistically significantly. But also it was observed that there was no change in culture positivity rates in the samples of patients followed for reasons other than COVID-19. In addition, with the COVID-19 pandemic, there was a statistically significant increase in VAP rates in ICU-1. This evidence reveals that the frequency of respiratory tract infections increased with COVID-19 in our hospital. In our study, it was also observed that the frequency of fungal isolation in ETA samples increased with the COVID-19 pandemic, although it was not statistically significant. But, this increase is seen not only in ICU-1 where COVID-19 patients are followed, but also in ICU-2 where other patients are followed. We can interpret this result in two different ways. First, COVID-19 may increase the frequency of fungal infections, and second, in the last two years, patients may be receiving less treatments to suppress fungal isolation.

In case of suspicion of infection, it is important to first predict which microorganism is the pathogen and to initiate appropriate empirical treatment. *A. baumannii* and *P. aeruginosa* are reported to be frequently isolated agents in ETA samples found in our country.[14,15] In a study from Iran, *A. baumannii* was isolated most frequently in respiratory samples of patients followed in the ICU due to COVID-19, followed by *S. aureus*.[16] In a study conducted in Colombia, *S. aureus* (34%) and *K. pneumoniae* (26%) were detected.[17] In a study conducted in Siirt, Turkey, ETA samples of COVID-19 positive patients hospitalized in the ICU were compared with the pre-pandemic period and it was determined that the three most commonly isolated pathogens were *A. baumannii*, *K. pneumoniae* and *P. aeruginosa* in both periods, respectively. Again in the same place, while the frequency of *A. baumannii* was 28.5% in the pre-pandemic period, it was found that this rate increased to 54% during the pandemic period, and it was reported that the frequency of *K. pneumoniae* and *P. aeruginosa* decreased.[12] Again, in another study conducted in İzmir, Turkey, it was determined that the isolation frequency of *A. baumannii* in respiratory samples increased statistically significantly during the pandemic period compared to the pre-pandemic period.[18] In our study, the most frequently isolated pathogens were found to be *A. baumannii*, *P. aeruginosa*, *K. pneumoniae* and *S. aureus*, respectively. While *P. aeruginosa* was the most frequently isolated pathogen in both ICU-1 and ICU-2 in the pre-COVID-19 pandemic period, it was observed that *P. aeruginosa* was replaced by *A. baumannii* in both clinics with the COVID-19 pandemic. If we examine the isolation frequency of *A. baumannii* as a percentage, it was seen that it increased from 18.3% to 31% in ICU-1 and from 20.4% to 22.8% in ICU-2. But only the increase in ICU-1 was found to be statistically significant. In addition, with the pandemic, an increase in the frequency of *K. pneumoniae* isolation was detected in both clinics. We can interpret these results in two different ways. First of all, the increase in the frequency of multi-drug resistant (MDR) Gram-negative

bacteria such as *A. baumannii* and *K. pneumoniae* with the pandemic, especially the significant increase in *A. baumannii* in ICU-1, may be because of the increased rates of broad-spectrum antibiotic use with COVID-19. Secondly, we think that the reason for the similar changes in both clinics may be due to the transfer of flora between clinics and/or the new flora being a source of infection in patients after the change of the colonized flora in the ICU. In this respect, it should not be forgotten that good and complete implementation of hospital infection control measures is one of the most important steps in breaking this vicious circle.

While carbapenems are used as the first choice in the treatment of Gram-negative bacterial infections, combined treatment options and colistin are often preferred in the treatment of MDR Gram-negative bacterial infections.[19,20] Cayci et al.[21] found carbapenem resistance at a rate of 35-50% in *K. pneumoniae* isolates, 86.6% in *A. baumannii*, and 11.1% in *P. aeruginosa* in patients diagnosed with COVID-19 in a tertiary hospital in 2020. Rao et al.[22] in which they evaluated samples of COVID-19 patients, found that multidrug resistance rates were high in *K. pneumoniae* and *A. baumannii* isolates, while the rate of susceptible isolates was higher in *P. aeruginosa* isolates. In our study, it was found that carbapenem resistance in *A. baumannii* isolates increased in ICU-1 and decreased in ICU-2. It was determined that in *P. aeruginosa*, it reached the level of 50% by showing a statistically significant increase in ICU-1, but in ICU-2 it increased to 30% and this increase was not significant. Statistical increase in resistance to ertapenem was observed in both clinics in *K. pneumoniae*, and the resistance rates detected against imipenem and meropenem were found to be higher in ICU-1 than in ICU-2. In addition, in our study, it was determined that the resistance rates detected in *A. baumannii* and *K. pneumoniae* isolates, whose frequency increased with the pandemic, were higher than *P. aeruginosa*. Therefore, it should be kept in mind that these two isolates may cause MDR and difficult-to-treat infections in patients hospitalized in the ICUs of our hospital.

In a study conducted in Samsun, Turkey, colistin and tigecycline were found to be the most effective antibiotics in *A. baumannii* isolates isolated from ETA samples of patients hospitalized in the ICU between 2019-2020. In this study, it was reported that the COVID-19 pandemic did not change the resistance rates.[23] In different studies, it has been reported that the rates of colistin resistance are 2.1-42.4% in *A. baumannii*, 2.3-9.0% in *P. aeruginosa*, and 20.6-42.9% in *K. pneumoniae*.[24-27] In the study of Bahçe et al.[12] in which they evaluated the ETA samples of patients hospitalized in the ICU between the years 2019-2021, as before and after the pandemic; They found no resistance to meropenem and colistin in *A. baumannii* isolates in both periods, while resistance to meropenem increased from 65% to 71.4% and colistin resistance from 9.5% to 42.9% in *K. pneumoniae*. In addition, they found that the resistance rates in *P. aeruginosa* isolates increased 31.6-50% to meropenem and 5.3-16.7% to colistin before and after the pandemic, respectively, and, lastly, they reported that resistance rates increased with the pandemic and that it could pose a challenge in treatment. In our study, colistin resistance rates showed a statistically significant increase in *A. baumannii* in ICU-1 and decreased in ICU-2. In *P. aeruginosa*, it was increased in both clinics, but only the increase in ICU-2 was significant. In *K. pneumoniae*, it was observed that while it showed a statistically significant increase in ICU-1, it remained at similar levels in ICU-2. Although the colistin resistance rates we determined for all three isolates are consistent with the literature, it can be thought that the COVID-19 pandemic has affected the colistin resistance rates in our hospital in the form of an increase in resistance, as detected in carbapenems.

Ceftazidime-avibactam (CZA) is a new antibiotic combination with good efficacy against carbapenem-resistant Enterobacterales species and *P. aeruginosa* isolates. Although CZA is a newly used drug, unfortunately, resistance has been reported against this antibiotic.[28,29] In our study, CZA suscebtibility test was evaluated only in *K. pneumoniae* isolates, and between the dates 2020-2021, and no resistance was detected during the pandemic in both clinics.

In summary, antibiotics should be used with caution as they trigger the formation of resistance as well as treat bacterial infections. Some guidelines recommend the use of broad-spectrum antibiotics in patients with COVID-19, and studies have reported that antibiotic use rates increase with the pandemic.[6,30] In our study, it was determined that the resistance rates determined for the three most frequently isolated pathogens in ICU-1 increased in almost all antibiotics with the pandemic compared to the pre-pandemic period. On the other hand, in ICU-2, it was determined that some antibiotics decreased instead of increasing, and the resistance rates in ICU-1 were relatively higher than in ICU-2. Although it is not statistically significant in some antibiotics, we think that the increase in resistance observed in ICU-1 with the pandemic was not detected in ICU-2, which may be due to the intensive antibiotic use policy applied in COVID-19. In addition, the decrease in resistance rates may also have been caused by less use of these antibiotics in practice than before.

In our study, ETA samples were preferred because COVID-19 disease primarily affects the respiratory system and both the change in antibiotic resistance over

the years and the effect of COVID-19 on resistance were evaluated. The number of studies conducted in this way is limited in the literature and there is no study containing data for Region Thrace. For this reason, our study is meaningful because it can be representative for our region. The limitation of our study is that it was designed retrospectively.

COCLUSION

In summary, in our study, it was found that culture positivity rates increased significantly in ETA samples of COVID-19 patients with the pandemic. In addition, it was determined that the distribution of isolated pathogen microorganisms changed, and the antibiotic resistance rates were found to be higher in the ICU-1, where COVID-19 positive patients were followed, compared to the ICU-2, where COVID-19 negative patients were followed. It has even been found that the rates of resistance to some antibiotics show a decrease in the COVID-19 negative patient group. Under all these results, it can be said that the COVID-19 pandemic adversely affected the success of treatment by causing a change in the distribution of pathogen microorganisms isolated in ETA samples in our hospital and an increase in the rates of resistance to some antibiotics. For this reason, it can be said that possible pathogen microorganisms and antimicrobial resistance rates should be followed up during similar epidemic periods such as COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tekirdağ Namık Kemal University Non-Interventional Clinical Researches Ethics Committee (Date: 28.06.2022, Decision No: 2022.127.06.17).

Informed consent: Due to the nature of the study, informed consent is not required.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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The investigation of serum nectin-4 levels in patients with early onset preeclampsia

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ABSTRACT

Aims: We aimed to investigate the level and predictive value of soluble nectin-4 in early onset preeclampsia (EOPE).

Methods: Forty-three patients with EOPE and 41 healthy normotensive pregnant women participated in this prospective case-control study. The groups were matched for gestational age and gravidity. Serum nectin-4 levels were compared between groups. The ROC curve was drawn to show the predictive value of nectin-4 for EOPE. Patients were followed up until the end of labor, and perinatal outcomes were recorded.

Results: The demographic characteristics of the two groups were similar. Serum nectin-4 level was significantly increased in EOPE cases compared to controls (226.46±119.6 ng/ml vs. 156.54±44.8 ng/ml, p=0.001). The ROC showed that at > 160.938, the sensitivity and specificity were 67.44% and 82.93%, respectively [AUC:0.822, (CI:0.724 - 0.897), and (p< 0.001)]. Significant inverse correlations were found between nectin-4 levels and poor obstetric outcomes.

Conclusion: Maternal serum nectin-4 levels were significantly higher in patients with EOPE compared with controls. Increased nectin-4 levels may contribute to the development of EOPE through possible oxidative, immunological, and inflammatory mechanisms adversely affecting trophoblastic cells.

Keywords: Early preeclampsia, nectin-4, preeclampsia, pregnancy

INTRODUCTION

Preeclampsia (PE) is a progressive multisystem disorder of pregnancy associated with new-onset hypertension that typically occurs after the 20th week of pregnancy. It is caused by dysfunction of the placenta and maternal blood vessels and regresses in a variable time interval after labor. PE is classified by time of onset as early-onset PE (EOPE) before 34 weeks and late-onset PE (LOPE) after 34 weeks. Compared with LOPE, EOPE has a higher risk of adverse pregnancy outcomes due to moderately early, very early, and extremely early delivery.[1-3]

Preeclampsia is assumed to be a two-stage disease resulting from defective trophoblast invasion and failure of spiral arterial remodeling as the main step of pathogenesis.[4] The LOPE is more common (90%) and is accepted as a mild maternal reaction to pregnancy.[5] In EOPE (10%), unlike LOPE, due to the improper placental invasion, the diffuse placental ischemia and the resulting oxidative stress begin in early gestation. Therefore, EOPE can lead to severe disease resulting in perinatal and maternal morbidity and mortality.[6]

Numerous inflammatory molecules play a role in the etiopathogenesis of preeclampsia.[7,8] Increased TNFα expression in preeclampsia has been shown to contribute significantly to placental and endothelial damage.[9] The level of disintegrin and metalloprotease 17 (ADAM -17), which is responsible for the formation of soluble TNFα, has been observed to be increased in preeclamptic pregnancies. The ADAM -17 also takes role in the shedding of nectin-4 into systemic circulation. The nectins are calcium-independent immunoglobulin-like cell adhesion molecules and play a central role in cellular junctions, as well as physiological regulations.[10] The placenta expresses for types of nectins; nectin-1, nectin-2, nectin-3 and nectin-4. They are localized at tight junctions and gap junctions of syncitiotrophoblasts.[11] nectin-4 is

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a relatively novel member of the nectin family that has only been detected in placenta and airway epithelium in healthy subjects.[10,12] nectin-4 has been researched since it serves as a viral receptor, is associated with oral and facial malformations, and is currently defined as a marker and potential therapeutic target in several cancers.[13]

Nectin-4 is expressed on the apical cell membranes of syncytiotrophoblasts and, when overexpressed, can induce a cytotoxic effect of NK, similar to EOPE, leading to placental dysfunction. Because nectin-4 is located on the apical cell membranes of syncytiotrophoblasts, it is possible to detect it in the maternal circulation.[10-13] Therefore, we hypothesized that the nectin-4 level might be elevated in EOPE patients, which has not yet been investigated in EOPE.

METHODS

The study was carried out with the permission of University of Health Sciences, İstanbul Kanuni Sultan Süleyman Health Research Center, Clinical Researches Ethics Committee (Date: 13.05.2020, Decision No: KAEK/2020.05.13). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This prospective case-control study was conducted in Istanbul Kanuni Sultan Süleyman Health Center, Department of Perinatology from May to December 2020. The study group composed of 84 patients who referred to perinatology clinics in this process. Informed written consent was obtained from each participant. The data concerning the obstetric and general health of the cases were also recorded (ClinicalTrials.gov Identifier: NCT05098691).

There were 43 patients with EOPE included in the study group, and the 41 normotensive, healthy and gestational age, and gravidity-matched pregnant women, with normal arterial blood pressure, without proteinuria were stated as the control group.

The study group included spontaneous, singleton pregnancies above the 24 weeks of gestations with positive fetal cardiac activity. Exclusion criteria were determined as multiple gestations, eclampsia, HELLP syndrome, chronic hypertension, hypothyroidism, known malignancy, diabetes mellitus, presence of fetal or maternal infection, clinical signs of chorioamnionitis (maternal fever, vaginal discharge, fetal tachycardia), hepatic or renal failure, collagen vascular disease, Placenta previa or pregnancies accompanied congenital fetal abnormalities or aneuploidies. We also excluded patients with systemic diseases, history of preeclampsia, and patients who became pregnant by in vitro fertilization, which could alter the level of nectin-4 in the maternal circulation. In addition, women who were treated with magnesium sulfate, corticosteroids/non-steroidal anti-inflammatory, and illegal drug users were also excluded from the study.

Preeclampsia definition was performed according to the ACOG guidelines(1). After the 20th gestational week,the pregnant women with the systolic blood pressure (BP) ≥ 140/90 mmHg or the diastolic BP ≥ 90 mmHg in least two measurements taken four hours apart with the previous history of normal BP and the presence of proteinuria (≥300 mg/24 h urine collection, or protein/creatinine ratio of ≥0.3 mg/dl, or a dipstick reading of 2+ protein) were diagnosed as preeclampsia.

We were taken blood samples of the cases, during the preeclampsia diagnosis for the study group and during routine antenatal follow up before labor for the control group. The two groups were matched in terms of gestational ages at the time of the maternal blood sample collection. Maternal age, body mass index (BMI), smoking status, gravidity, gestational week, amount of proteinuria, systolic and diastolic BP levels, and serum nectin-4 concentrations were recorded. A calibrated sphygmomanometer was used for the measurement of BP.

Venous blood sampling was performed after one night of fasting for all participants at the time of initial diagnosis. The blood samples were centrifuged at 4000 rpm for 10 minutes at room temperature. The obtained serum samples were frozen immediately and stored at -80°C up to the time of serum analysis. Nectin-4/human poliovirus receptor related protein (PVRL4) levels in the samples were measured using a double-antibody sandwich ELISA (Wuhan USCN Business Co., Ltd). The microtiter plate provided in this kit has been pre-coated with an antibody specific to Poliovirus Receptor Related Protein 4 (PVRL4). Standards or samples are then added to the appropriate microtiter plate wells with a biotin conjugated antibody specific to Poliovirus Receptor Related Protein 4 (PVRL4). Next, Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. After TMB substrate solution is added, only those wells that contain Poliovirus Receptor Related Protein 4 (PVRL4), biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in color. The enzyme-substrate reaction is terminated by the addition of sulphuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450nm±10nm. The concentration of Poliovirus Receptor Related Protein 4 (PVRL4) in the samples is then determined by comparing the O.D. of the samples to the standard curve. All laboratory measurements were performed simultaneously in the same laboratory by the same technician.

Statistical Analysis

All statistical analyses were performed using the RStudio integrated development environment for statistical computing (Affero General Public License v3; published 2011. RStudio for Linux, version v2021.09. 4+403.pro3 Ghost Orchid; September 19, 2022; developed by Posit, PBC.) to analyze the data. Variables were examined using visual (histogram, probability plots) and analytic methods (Kolmogrov-Simirnov/Shapiro-Wilk's test) to determine if they were normally distributed. Levene's test was used to assess the homogeneity of variance. For the non-parametric values, descriptive analyses were presented using medians and quartiles. Mann-Whitney U tests were performed to compare the nonnormally distributed numerical data between groups. For the categorical variables, descriptive analyses were presented using frequency and percentage. Relationships between categorical variables were analyzed using the chi-square test or Fisher's exact test (when the assumptions of the chi-square test assumptions do not apply because of low expected cell counts). The predictive capacity of nectin-4 levels for EOPE was analyzed using ROC (Receiver Operating Characteristics) curve analysis, and the sensitivity, specificity, AUC (Area Under Curve) value, positive likelihood ratio, and negative likelihood ratio were presented. When examining the relationships between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. An overall 5% type- I error level was used to infer statistical significance. A p-value of less than 0.05 was considered a statistically significant result.

Power analysis was performed using G-power software (G-power v3.1.9.2, Kiel College, Kiel, Germany). The difference between two independent means showed that the study reached a power of 0.94.

RESULTS

A total of 84 patients were included in the study. Forty-three of them were diagnosed with EOPE, and 41 were control subjects. There were no statistically significant differences between groups in demographic characteristics such as maternal age, gravidity, body mass index (BMI), and smoking status ($p > 0.05$). The gestational weeks of the groups at maternal serum collection were similar ($p=0.37$). Systolic and diastolic blood pressure were higher in the EOPE group at gestational week at blood sampling ($p< 0.001$). Compared to the control group, serum levels of nectin-4 were significantly higher in the EO preeclampsia group (156.54±44.8 vs. 226.46±119.6, $p=0.001$) (Table 1).

Table 1. The demographic characteristics, amount of proteinuria and serum nectin-4 levels of the cases

	Early-onset preeclampsia group (n=43)	Control group (n=41)	p
Age (years)	26 (21-32)	27 (21-34)	0.110
Gravidity	2 (1-2)	2 (1-3)	0.260
BMI (kg/m²)	28 (25-32)	27 (24-31)	0.370
Gestational age at serum sampling (week)	31 (28-32)	31(29-32)	0.370
Smoking status +/-n (%)	9/34 (29.9%-79.1%)	7/34 (17.1%-82.9%)	0.863
Systolic blood Pressure (mm/Hg)	153 (145-176)	121 (110-128)	<0.001
Diastolic blood pressure (mm/Hg)	97 (88-126)	72 (62-81)	<0.001
Proteinuria (mg/24 hours)	3782 (1161-5247)	N/A	N/A
Nectin-4 levels (ng/ml)	190.173 (141.728-244)	124.79 (100.58-153.247)	0.001

BMI, body mass index; kg/m², milligrams per square meter; mmHg, millimeter of mercur; mg, milligram; ng/ml,nanogram per milliliter.Data are expressed as median (Q1-Q3), or frequency (percentage) where appropriate. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

Compared with the control group, gestational age at delivery was lower in the EOPE group, resulting in lower birth weight and a higher rate of adverse fetal outcomes, including low APGAR scores at the first and fifth minutes and a higher rate of admissions and longer duration of treatment in the neonatal intensive care unit ($p<0.05$) (Table 2).

Table 2. Peripartum outcomes of the groups

	Early-onset preeclampsia group (n=43)	Control group(n=41)	p
Birth weight (gr)	1681 (1156-1865)	3212 (2818-3513)	<0.001
Birth length (cm)	41 (35-44)	46 (44-49)	<0.001
APGAR 1st min.	5 (3-8)	7 (6-9)	<0.001
APGAR 1st min <7	23/20 (53.5%/46.5%)	6/35 (14.6%/85.4%)	<0.001
APGAR 5th min.	7 (5-9)	9 (8-9)	<0.001
APGAR 5th min<7	12/31 (27.9%/72.1%)	1/40 (2.4%/97.6%)	0.003
Gestational age at delivery (weeks)	31 (28-33)	37 (35-39)	<0.001
Gender of babies (male/female)	25/18 (58.1%-41.9%)	21/20 (51.2%-48.8%)	0.676
Mode of delivery (vaginal/ceserean)	5/38(11.6%/88.4%)	25/16(61%/39%)	<0.001
Fetal distress emergency ceserean	10 (23.2%)	2(4.8%)	0.036
NICU admission	23/20(53.5%/46.5%)	10/31(24.4%/75.6%)	0.012
NICU duration(day)	17 (10-32)	0 (0-5)	<0.001

gr, gram; cm, centimetre; min, minute; NICU, neonatal intensive care unit. Data are expressed as median (Q1-Q3), or frequency (percentage) where appropriate. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

The diagnostic value of nectin-4 was tested by ROC analysis. The ROC analysis showed that at > 160.938, the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were 67.44%, 82.93%, 3.95, and 0.39 respectively [AUC:0.822, (CI:0.724 - 0.897), and (p< 0.001)] (Figure 1).

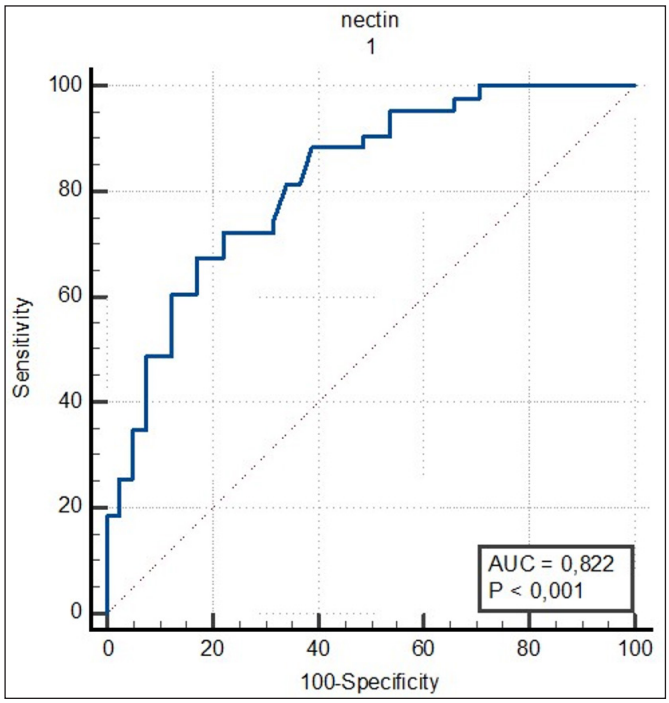

Figure 1. Diagnostic value of nectin-4

Significant inverse correlations were found between nectin-4 levels and poor obstetric outcomes. Also, there was a positive correlation between serum nectin-4 levels and the amount of proteinuria (r=0.58, p<0.001)(Table 3).

Table 3. The correlations between serum nectin-4 levels and intrapartum outcomes

Variable	Nectin-4 levels n	r	p-value
Birthweight	84	-0.27	0.010
Gestational week at birth	84	-0.30	0.005
1st min APGAR score	84	-0.42	<0.001
5th min APGAR score	84	-0.32	0.003
Fetal distress	84	0.58	<0.001
Diyastolic blood pressure	84	0.25	0.020
Proteinuria	43	0.58	<0.001

min, minute.

DISCUSSION

Preeclampsia is a multisystem disorder and one of the most important causes of perinatal morbidity and mortality, especially while the condition is of early onset. Despite the accumulating evidence indicating the underlying cause as the placenta, the etiology of the disease is still elusive. The abnormally shallow trophoblast invasion indicates the possibility of altered expression of adhesion molecules in preeclampsia.[14] Nectins are adhesion molecules which were also shown to be expressed on cellular membranes of trophoblast.[8] In this study, nectin-4 was found to be significantly increased in EOPE compared to gestational week matched healthypregnant women.

Early and late preeclampsia have been assumed as the diseases with distinct characteristics. EOPE is commonly associated with placental dysfunction, low placental volume, abnormal Doppler findings, fetal growth restriction, multiorgan dysfunction, and adverse maternal and neonatal outcomes, whereas late-onset preeclampsia appears rather as a maternal disorder.[4-6] The factors responsible from the pathogenesis of preeclampsia includes abnormal placentation, immunological mechanisms as a key point, and oxidative distress. Abnormal placentation was indicated as the start point of EOPE with a genetic tendency leading to high recurrence risk and running across the generations within same families.[5,15] The level of immunological factors were also reported as more altered in EOPE compared to LOPE.[16] Since the nectin-4 was reported to present on trophoblastic cells, we investigated whether nectin-4 level is related with EOPE or not.

In normal placentation, extravillous trophoblasts are responsible for the deep infiltration of uterine wall and invading the muscular walls of the uterine arteries and endovascular trophoblasts replaces the endothelial cells. This process increases the blood flow to the intervillous space by altering the vascular conductance. In EOPE, impaired growth of the villi has been attributed to the inadequate formation of the cytotrophoblastic shell early in pregnancy. Reduced capacity of trophoblasts to invade the myometrial part of spiral arteries lead to restricted blood supply through the uteroplacental circulation and following hypoxia.[6] The maternal adaptation to fetal antigens includes the maternal tolerization to paternal antigens in seminal plasma at the preconceptual phase is crucial for normal placentation. After conception, recognition of fetal MHC class 1 molecules on trophoblasts as self by regulatory T cells and NK cells allows placentation.[17] The villoustrophoblasts exposed to maternal blood are lack of MHC class I.However, the extravillous trophoblasts which invade the uterus was shown to have a nonclassical MHC class I repertoire (HLA-E and HLA-G in addition to HLA-C) which interact with NK cells and T cell receptors for immune tolerance. Complete failure in immune tolerance results in miscarriage, whereas the partial failure may result in preeclampsia. Besides the invasion process, the systemic immune response was also shown to be responsible for the pathogenesis of preeclampsia.[18] The shedding of the soluble and bound HLA-G isoforms into systemic circulation was

shown to trigger immunomodulatory activities of NK cells and T lymphocytes in pregnancy. The soluble isoforms of HLA-G were reported in decreased levels in preeclampsia, even in the first trimester before the onset of the disease, indicating the disturbed immune modulation.[19-21] Both the impaired trophoblast invasion and systemic inflammatory response provide the basis for hypoxic environment.6

Nectins are adhesion molecules belonging to immunoglobulin superfamily and exhibit structurally related three immunoglobulin-like (V, C, C) domains in their extracellular side. Unlike the other nectins, nectin-4 is mainly expressed during embryogenesis and is only detected in trophoblasts and slightly in trachea in healthy human.[10,12] Ito et al.[8] examined the placental tissues of pre-eclamptic pregnant women (n=20) and uncomplicated pregnancies (n=20) and reported elevated nectin-4 expression in preeclampsia. They reported that trophoblastic cell migration was not impaired by the overexpression of nectin-4. However, the trophoblasts overexpressing nectin-4 were more vulnerable to the NK cell cytotoxicity and the cytotoxic attack by natural killer cells was significantly increased against nectin-4 overexpressing cells.[8] The mean gestational age was similar between the preeclamptic and normal group, on the other hand, the preeclampsia cases were not defined as early- or late-onset and only the severe preeclamptic patients were included. To the best of our knowledge, the current study is the first one to evaluate the maternal serum level of nectin-4 in EOPE.

The previous studies conducted on nectin-4 were generally concentrated on its significance in tumoral activity and poor prognosis in mainly bladder, lung, pancreas, and breast cancers. It was denoted that nectin-4 binds only the inhibitory receptor TIGIT (T-cell immunoreceptor with Ig and ITIM domains). By this way, theincreasing nectin-4 expression was reported to inhibit the NK cell activity more profoundly and decrease the NK response to cancer cells. The studies were also targeted nectin-4 and TIGIT in cancer immunotherapy.[22,23] TIGIT was also shown as a target to be promoted to achieve immune tolerance in repeating miscarriages in the study conducted by Fu et al.[24] The studies on immunomodulatory mechanisms of pregnancy revealed that decidual immune cells of maternal-fetal interface expressing TIGIT, which is a co-inhibitory receptor, triggers immunological tolerance. TIGIT was reported to inhibit NK cells' effector function and suppress their dendritic cell costimulatory ability. The expression of TIGIT in decidual CD4+ T cells and NK cells at the transcriptional level was also shown to be upregulated by progesterone.[24,25] Even though NK cell activity was not evaluated in our study, the literature supports the evidence on increased NK cell activity EOPE. The conflicting data reported by Ito et al.[8] on increased NK cell activity despite the increased nectin-4 expression of trophoblastic cells, however, TIGIT receptivity was not studied. On the other hand, in a recent study, Meggyes et al.[18] investigated the immune checkpoint receptors in EOPE, and they revealed that a subgroup of cytotoxic T lymphocytes had significantly lower levels ofTIGIT in EOPE compared to healthy controls.[19] In this regard, there may bemore complicated mechanisms in the etiology of preeclampsia which may lead to improper functioning of NK cells, TIGIT receptors and in which nectin-4 may be involved.

The inflammatory process and decreased uteroplacental perfusion in EOPE result with hypoxia and oxidative distress. The key inflammatory mediator released from NK and T cells is TNFα.[6,26] TNFα was found to be increased in preeclampsia, even in the early pregnancy, before the onset of the preeclampsia and emphasized as a candidate for predicting preeclampsia.[27] TNFα is released into systemic circulation in the soluble form by shedding via TNFα-converting enzyme, which is identical with ADAM17 (a disintegrin and metalloprotease 17). The expression of protease and sheddase ADAM17 was shown to be induced under hypoxic conditions.[26] ADAM10 and ADAM17 was shown to be increased in preeclamptic pregnancies and ADAM17 was also shown to be responsible from the increase in TNFα in preeclampsia.[28] The soluble nectin-4 is the extracellular domain of nectin-4 that is also released through the shedding into maternal circulation by the proteolytic activity of proteases ADAM-10 and 17.[12,27,29] Through the insight of the literature, the higher soluble nectin-4 levels detected in this study may be a consequence of the hypoxic environment and appears to be consistent with the mechanisms reported in the previous studies carried out on preeclampsia.

The role of angiogenesis for the normal placentation process was thought to support the idea that the disturbances in angiogenesis take role in etiopathogenesis of EOPE.[6] nectin-4 was reported to promote angiogenesis pathways in breast cancer in a recent study conducted by Siddhart et al.[30] They reported that upregulated ADAM-17 leading to shedding of the soluble nectin-4 ecto-domain which subsequently interacts with integrin-β4, the endothelial receptor for laminin taking role in cell adhesion, and promoting angiogenesis via Src, PI3K, AKT and iNOS. Our current study demonstrated increased levels of soluble nectin-4 in preeclampsia, even though, the literature denotes increased antiangiogenic factors and decreased angiogenetic factors as responsible forpreeclampsia

pathogenesis.[30,31] VEGF (vascular endothelial growth factor) is important in the stabilization of endothelial cells in in blood vessels. VEGF and placental growth factor (P1GF)-a member of VEGF family- also contribute to normal proliferation and implantation of trophoblastic cells. In previous studies, VEGF and P1Gf was shown to be decreased in preeclampsia as the main angiogenetic molecules, whereas the antiangiogenic soluble Fms-like tyrosine kinase-1 (sflt1) and soluble endoglin (sEng) increase.[31,32] On the other hand, thedecrease inthe VEGF level in preeclampsia was shown to be the result of increased expression of soluble Fms-like tyrosine kinase-1 (sFlt1) which bind and antagonize the VEGF. Sflt1 and soluble endoglin (sEng) which have been shown to be released by proteolytic activity of ADAM10 and ADAM17, respectively, were reported to increase in preeclampsia.[33,34] As we mentioned before, ADAM 10 and ADAM17 increases in hypoxia, resulting in an increase in soluble nectin-4 levels. In this regard, the aforementioned mechanisms appear to be consistent to support our findingsasincreasedsoluble nectin-4 levelsin EOPE.

It has not been determined at which gestational week the nectin-4 level has the highest diagnostic value for early preeclampsia. However, the studies that examined nectin-4 levels in preeclampsia cases after 24 weeks' gestation found statistically significantly higher nectin-4 levels in preeclampsia cases than in controls, which is consistent with the current study.[35]

Consequently, nectin-4 is a potential novel diagnostic biomarker for EOPE. It could be a valuable biomarker in complicated cases where differential diagnosis is required, such as chronic hypertension and proteinuria, SLE, etc.

Study Limitations

First, the serum samples for nectin-4 were taken after EOPE had developed. It would have been more informative if the serum samples had been taken before EOPE developed, which might indicate whether nectin-4 plays a role in the pathophysiology of EOPE and could be used in predicting EOPE.

CONCLUSION

Our results show that maternal serum nectin-4 level was significantly higher in EOPE than in controls and has diagnostic value for EOPE. A significant inverse association was found between nectin 4 levels and poor obstetric outcomes. It is possible that elevated serum nectin-4 levels contribute to the development of EOPE through oxidative, immunologic, and inflammatory mechanisms acting on trophoblast cells via receptive processes at the molecular level.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, İstanbul Kanuni Sultan Süleyman Health Research Center, Clinical Researches Ethics Committee (Date: 13.05.2020, Decision No: KAEK/2020.05.13).

Informed consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Evaluation of monocyte to high-density lipoprotein cholesterol ratio and other inflammatory markers in hidradenitis suppurativa: a case-control study

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ABSTRACT

Aims: Hidradenitis suppurativa (HS) is an inflammatory disease whose pathophysiology is not yet clearly known, but inflammatory parameters have been used for many years in the diagnosis and follow-up. The aim of this study is to evaluate NLR, PLR, MHR, and hemogram parameters in patients diagnosed with HS without comorbidities and compare them with healthy controls.

Methods: This study include 105 HS patients and 100 healthy volunteers. The medical records and laboratory findings of the participants were reviewed retrospectively. Patients and control group neutrophils, lymphocytes, monocytes, platelets, mean platelet volume (MPV), platelet distribution width (PDW), red cell distribution width coefficient of variation (RDW-CV), high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), Neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), and MHR were compared.

Results: A total of 105 patients [43 (41%) women and 62 (59%) men] and one hundred healthy volunteers [52 (52%) women and 48 (48%) men] participated in the study. The mean of neutrophil count (patient group=5.84±2.27, control group=4.29±1.81, p=0.001), lymphocyte count (patient group=2.78±0.90, control group=2.31±0.63, p=0.001), monocyte count (patient group=0.74±0.39, control group=0.55±0.16, p=0.001), platelet count (patient group=295.63±65.84, control group=274.45±59.06, p=0.007), CRP (patient group=12.71±24.38, control group=2.61±2.21, p=0.039), and MHR (patient group=0.0203±0.0135, control group=0.0114±0.0056, p=0.001) were higher in the patient whereas the mean of HDL-C (patient group=39.02±11.06, control group=52.85±16.46, p=0.001) and PLR (patient group=118.82±60.82, control group=126.07±39.13, p=0.028) were significantly higher in control individuals. The adjusted effect of MHR, NLR, and PLR was re-examined to eliminate the effect that may arise from the difference in age between patients and controls. It was observed that when MHR increased by 0.01 unit, the risk of disease increased significantly by 4.07 times. When NLR increases by 1 unit, the disease increased. significantly by 1.37 times. Both adjusted and unadjusted effects of MHR were significant. When the sensitivity and specificity of MHR, and NLR in differentiating patients were examined, the sensitivity of MHR was found to be 67.4% and its specificity was 72.5% (p=0.001), while the sensitivity of NLR was found to be 61.5% and its specificity was 74.0% (p=0.038).

Conclusions: Our study showed that MHR was more effective in distinguishing HS patients than other inflammatory markers. MHR can be used as a new marker to investigate the inflammatory effect of HS.

Keywords: Hidradenitis suppurativa, hematologic tests, monocytes, cholesterol HDL

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, inflammatory disease that progresses with abscesses, fistulas, and scar formation.[1] Although etiopathogenesis is not clearly known, the principal pathophysiological mechanism of HS is folliculosebaceous units' occlusion and rupturation and excessive immune reaction.[2] HS can occur with many important comorbidities, including metabolic, cardiovascular, endocrine, gastrointestinal, rheumatological, and psychiatric disorders.[3]

Diagnosis is made based on the clinical morphology of the lesions (nodules, abscesses, tunnels and scars), location (axilla, inframammary folds, groin, perigenital or perineal) and progression of the lesion (2 recurrences within 6 months or chronic or permanent lesions lasting ≥3 months).[4]

Counts of leukocytes, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are well-known markers of inflammation and have been used in the diagnosis and follow-up of HS for years.[5]

Recent studies suggested that neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet volume (MPV), and plateletcrit (PCT) are used as indicators of inflammation and severity of inflammatory diseases such as HS, psoriasis, psoriatic

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arthritis.[6,7] Monocytes are sources of oxidative stress and proinflammatory cytokines. High-density lipoprotein cholesterol (HDL-C) has protective activities against inflammation and oxidation by preventing low-density lipoprotein cholesterol's (LDL-C) oxidation and endothelium damage. Many studies have reported that the monocyte/HDL-C ratio (MHR) may be an effective biomarker of systemic inflammation and oxidative stress. Therefore, monocyte-lymphocyte ratio (MLR) has been found to be an indicator of inflammation and prognosis in autoimmune diseases. These markers are used as an inflammatory and prognostic marker in many autoimmunity, metabolic syndrome, cardiovascular diseases, and cancer.[8,9] There are only a few studies investigating the relationship between MHR and HS.[10]

In this research, we aimed to investigate the interrelation of HS with CBC parameters and inflammatory indicator parameters NLR, PLR, and MHR.

METHODS

The study was carried out with the permission of Erzurum Regional Training and Research Hospital Clinical Researches Ethics Committee (Date: 06.06.2022, Decision No: 2022/07-88). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients with HS who were consulted at Erzurum Regional Training and Research Hospital Dermatology outpatient clinic between January 2019 and January 2021 were included in our retrospective study. All patients who presented to our clinic were diagnosed with HS and were retrospectively reviewed. In total, 105 patients satisfying the following inclusion criteria were included: diagnosed with HS by a dermatologist, had complete blood count analysis results during follow-up, did not have any systemic and/or chronic inflammatory diseases (e.g., cardiac diseases, diabetes mellitus, hypertension, hyperlipidemia, and rheumatoid arthritis). The control group consisted of 100 completely healthy volunteers (without known systemic and/or inflammatory disease, non-smoker, acne vulgaris or chronic dermatological disease, and not using regular medication). The participant's hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width coefficient of variation (RDW-CV), white blood cells (WBCs), neutrophils, lymphocytes, monocyte, platelet distribution width (PDW), platelets, MPV, HDL-C, and CRP were recorded. NLR, PLR, MLR, and MHR were determined. In addition, the comparison results of the two groups in terms of hemogram measurements and measurements calculated with formulas are given, and unadjusted effects are without adjusting for the age difference of the groups.

Statistical Analysis

Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA, v21.0) software was used in all procedures. Normality distribution of scale variables was calculated using Kolmogorov-Smirnov test and continuous parameters were compared with Kruskal-Wallis H and/or Mann-Whitney U tests. Independent categorical variables were compared with Pearson chi-square or Fisher tests. If significant results were found in more than two comparisons, Bonferroni correction was applied post-hoc. The success of measurements that showed significant differences between the two groups in separating the groups was examined with the ROC (Receiver Operating Characteristic) curve and a cutoff for these measurements was determined. $P < 0.05$ was considered significant.

RESULTS

One hundred five patients [43 (41%) women and 62 (59%) men] and one hundred healthy volunteers [52 (52%) women and 48 (48%) men] participated in this study. The gender distribution of healthy participants was similar to the patients (p=0.113). The mean age of the patients was 33.25±11.84, and the mean age of the control group was 26.53±5.81. The mean age of the patient group was significantly higher (p=0.001).

As shown in Table 1, the mean of neutrophil count (patient group=5.84±2.27, control group=4.29±1.81, p=0.001), lymphocyte count (patient group=2.78±0.90, control group=2.31±0.63, p=0.001), monocyte count (patient group=0.74±0.39, control group=0.55±0.16, p=0.001), platelet count (patient group=295.63±65.84, control group=274.45±59.06, p=0.007), CRP (patient group=12.71±24.38, control group=2.61±2.21, p=0.039), and MHR (patient group=0.0203±0.0135, control group=0.0114±0.0056, p=0.001) were higher in the patient whereas the mean of HDL-C (patient group=39.02±11.06, control group=52.85±16.46, p=0.001) and PLR (patient group=118.82±60.82, control group=126.07±39.13, p=0.028) were significantly higher in control individuals.

According to Table 1, when the success of MHR, and PLR, which had a significant adjusted effect, in separating patients, was examined; the appropriate cutoff value for MHR was found to be 0.0139, and when those greater than this value were classified as patients, the sensitivity was 71.0% and the specificity was 74%. The ROC curve of MHR is observed in Figure 1.

The appropriate cutoff value for PLR was found to be 112.5, and when those greater than this value were classified as control, the sensitivity was 57% and the specificity was 63%. The ROC curve of the PLR is observed in Figure 2.

Table 1: Comparison of laboratory parameters HS patients separately with the healthy control group

	Grup	N	Mean	SD	Percentiles			P*
					25	Median	75	
Hb (g/dl)	Control Patients	100 104	14.74 15.05	1.42 1.65	13.70 14.00	14.70 15.00	15.90 16.00	0.112
MPV (fl)	Control Patients	99 103	10.15 10.12	1.14 0.83	9.40 9.60	10.20 10.00	10.90 10.80	0.568
Neutrophil (10^9/l)	Control Patients	100 104	4.29 5.84	1.81 2.27	3.31 3.97	3.90 5.55	4.86 6.69	0.001
Lymphocyte (10^9/l)	Control Patients	100 104	2.31 2.78	0.63 0.90	1.88 2.10	2.19 2.70	2.70 3.37	0.001
Monocytes (10^9/l)	Control Patients	100 104	0.55 0.74	0.16 0.39	0.43 0.53	0.54 0.70	0.63 0.89	0.001
Platelet (10^9/l)	Control Patients	100 104	274.45 295.63	59.06 65.84	231.00 252.75	265.50 292.50	314.75 338.75	0.007
CRP (mg/l)	Control Patients	42 55	2.61 12.71	2.21 24.38	0.50 1.20	3.00 3.00	3.16 8.00	0.039
HDL (mg/dl)	Control Patients	46 62	52.85 39.02	16.46 11.06	39.25 30.75	50.50 36..0	62.25 46.00	0.001
MHR	Control Patients	46 62	0.0114 0.0203	0.0056 0.0135	0.0071 0.0130	0.0103 0.0172	0.0152 0.0248	0.001
NLR	Control Patients	100 104	1.94 2.42	0.81 2.03	1.39 1.43	1.75 1.95	2.31 2.62	0.082
PLR	Control Patients	100 104	126.07 118.82	39.13 60.82	93.80 85.48	124.52 107.63	147.78 138.39	0.028

*: Mann-Whitney U test was used. Significant values were shown in bold. MPV: Mean platelet volume; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; CRP: C-reactive protein; MHR:monocyte-high-density lipoprotein ratio

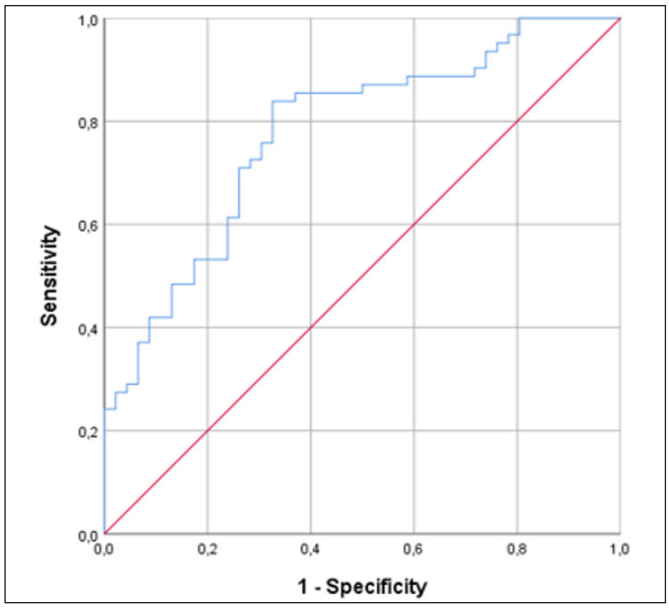

Figure 1. The ROC curve of MHR

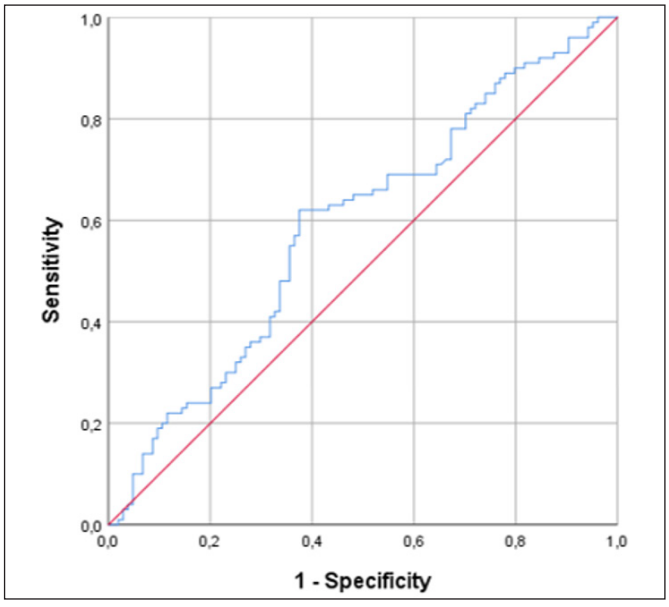

Figure 2. The ROC curve of PLR

Table 2 examined; when MHR increase by 0.01 units, it is seen that the risk of disease rise significantly by 4.07 times. (p=0.001) When NLR increase by 1 unit, the risk of rises increase significantly by 1.37 times. (p=0.038)

On the other hand, the unadjusted effect of the PLR given in Table 1 was significant, but it was not significant when the effect of age difference was eliminated (p=0.784).

While the adjusted effect of NLR was not significant (Table 1), it was significant when the effect of the age difference was removed. Both adjusted and unadjusted effects of MHR were significant. The success of the variables in Table 2 in separating patient and control individuals are given as sensitivity and specificity.

Table 2. Adjusted effects

	OR	95% C.I.for OR		P*	Sensitivite (%)	Spesifite (%)
		Lower	Upper			
MHR	4.070	1.887	8.777	0.001	67.4	72.5
NLR	1.370	1.017	1.845	0.038	61.5	74.0
PLR	0.999	0.993	1.005	0.784	---	---

*: Binary logistic regression model was used. MHR: monocyte-high-density lipoprotein ratio ; NLR: Neutrophil / lymphocyte ratio; PLR: Platelet/lymphocyte ratio

DISCUSSION

In recent years, it has been shown in many studies that biomarkers such as MPV, NLR, and PLR, derived from the complete blood cell count (CBC), can be prognostic indicators in evaluating various inflammatory diseases' activity and in the survival of malignancies.[6,11,12]

There are conflicting data regarding NLR and PLR.[10,13] Although It has been reported in some researches that NLR are higher in patients with HS.[13,14] Çetinarslan et al.[10] showed no significant differences in terms of NLR and PLR between HS patient group and control group. Gambichler et al.[7] suggested that PLR is lower in HS patients. They reported that PLR may not be an appropriate biomarker for disease activity or severity. In our study, while neutrophil, lymphocyte, monocyte, and platelet counts were higher in HS patients than in control group. When the effect of age difference is ignored, the the elevation of NLR was not statistically significant (p=0.082), but when the adjusted impact of of NLR was examined, it was found to be statistically significant higher compared to the control group (p=0.038). Results in the literature and our results indicate that NLR and PLR do not appear to be suitable biomarkers for HS disease.

The main role of platelets is maintaining homeostasis, however, they also play crucial roles in acute and chronic inflammatory reactions. They release large amounts of inflammatory cytokines and help recruit other inflammatory cells to the inflammation site. MPV and PDW are known as platelet activation biomarkers and represent platelet production rate and stimulation.[15-17] It has been shown in previous studies that MPV is a marker of increased platelets' activation and aggregation in inflammatory diseases such as psoriasis, recurrent aphthous stomatitis, and Behçet's disease.[11,18] However, MPV was not found to be related to disease and/or disease activity in some of the inflammatory diseases.[19,20] In the present study, platelet counts were higher in patients, however, MPV values were similar in patients and controls. We think that the fact that our patients consisted of HS patients without comorbidities led to these results. Literature data and our findings suggest that MPV may be more effective in detecting the risk of thrombosis rather than detecting inflammation.

Monocytes and macrophages are the main factors in inflammation development, which leads the development and progression of atherosclerosis. Monocytes that migrate from the circulation to the subendothelial space of the arterial wall are called macrophages and form foam cells by internalizing low density lipoprotein (LDL), very low density lipoprotein (VLDL), and oxidized lipoproteins. Foam cells cause the activation of T lymphocytes, platelets, and other monocytes by synthesizing pro-inflammatory cytokines.[21,22] Moreover, HDL-C inhibits the proinflammatory and pro-oxidant effects of macrophages and the migration of monocytes in addition to eliminating cholesterol from these cells, which exhibits antiatherosclerotic effects. Therefore, the ratio of these two parameters MHR may be a better inflammation marker. Recent studies showed that increased MHR levels may be a predictor biomarker of cardiovascular disease.[17,21,23] In the literature, it has been shown in many previous studies that the frequency of subclinical atherosclerosis and cardiovascular events is increased in patients with HS.[24-26] MHR has been found to be an effective biomarker in diseases in which chronic inflammation plays a role in etiopathogenesis, such as diabetes mellitus and metabolic syndrome.[6,27]

This study revealed that only MHR, an inflammation biomarker, was significantly increased in patients with HS without comorbidities. We found that MHR was a measure to discriminate activation patterns of patients from controls the MHR distinguished HS patients from controls with 71.0% sensitivity and 74% specificity. As shown in **Table 2**, after adjusting age we found that the risk of disease increased by 4.07 times when MHR increased by 0.01 units. Our results suggest that MHR may be an appropriate inflammatory biomarker in HS patients.

The fact that our patient group was selected from HS patients who did not have a chronic disease and did not use systemic medications eliminated additional factors that could affect MHR and other inflammatory markers. This is a factor that adds value to our research.

The fact that our study was retrospective and ESR values could not be evaluated is one of the most important limitations. In addition, since HS could not be staged, its relationship with the stage of the disease could not be determined with biomarkers.

CONCLUSION

As a result, this study makes remarkable contributions to the comprehension of the relationship between MHR and HS disease, which is limited in the literature. Excluding HS patients with comorbidities in our study eliminated additional factors that would affect MHR and other inflammatory markers (NLR, MPV, PLR) revealed that MHR discriminates inflammation in HS more effectively than other markers. MHR should be considered a promising value in distinguishing HS, a chronic inflammatory disease. However, there is a need for prospective studies, with a greater number of patients, to determine whether MHR can be used as an inflammatory or a prognostic marker in patients with HS.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erzurum Regional Training and Research Hospital Clinical Researches Ethics Committee (Date: 06.06.2022, Decision No: 2022/07-88).

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Predictive importance of systemic inflammation response index in de novo brain metastatic small cell lung cancer patients

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ABSTRACT

Aims: The subtype of lung cancer, known as small cell lung cancer (SCLC), tends to have a highly fatal course, especially in advanced stages. In particular, the overall survival durations further decrease in cases of brain metastases in SCLC. There is increasing evidence for the role of systemic inflammation parameters in predicting cancer prognosis, and they appear likely to become potential target markers for clinical treatments in the future. We aimed to evaluate the systemic inflammation response index (SIRI), a novel inflammatory laboratory marker that could predict long-term survival and serve as a potential target marker for clinical treatment, in patients with de novo brain metastatic small cell lung carcinoma (DNBM SCLC)."

Methods: Clinicopathological features of adult patients diagnosed with DNBM SCLC were recorded from the patient registry of the hospital. Patients without medical records were not included in the study. Investigations were carried out to assess the prognostic effect of the SIRI parameter in predicting the 12-month overall survival (OS12) in DNBM SCLC patients, by determining a cut-off value and conducting appropriate statistical analyses, considering p-values (<0.05) as statistically significant.

Results: In this study 256 SCLC patients screened from the hospital database and detected 42 patients with de novo brain metastases (DNBM) were included in the study.The median age of patients was 61; 85.7% of the sample was male while 14.3% was female. When the SIRI marker was 1.79 or below, OS12 in patients was statistically significantly better predicted than in those with values above 1.79 (Cut off ≤ 1.79 AUC: 0.751, sensitivity: 66.7%, specificity: 66.7%; p=0.022). Also, SIRI ≤ 1.79 was found to be an independent variable predicting OS12 in DNBM SCLC patients.

Conclusion: Our study is important in terms of the short overall survival durations observed in DNBM SCLC patients and the identification of conventional laboratory parameters that can be used to predict longer survival durations in these patients.

Keywords: Small cell lung cancer, systemic inflammation, 12-month overall survival, brain metastasis

INTRODUCTION

Lung cancer is one of the most commonly diagnosed cancer types worldwide, with approximately 2 million new cases and 1.79 million deaths annually, making it the leading cause of cancer-related mortality.[1] Furthermore, lung cancer (LC) is a highly heterogeneous group of diseases, classified into two categories: small cell and non-small cell. Small cell lung cancer (SCLC) constitutes approximately 15% of all lung cancers, and it is highly associated with cigarette smoking. Also SCLC is observed at a higher rate in men compared to women and associated with rapid growth, a high tendency for metastasis, and poor survival.[2-3] Timely diagnosis of early-stage cancers is a key factor in improving the prognosis of cancer patients. In this regard, low-dose computer tomography scans can screen for early-stage NSCLC but do not assist in the early diagnosis of SCLC due to its aggressive nature.[4] Therefore, patients with SCLC are generally diagnosed when advanced stage metastatic symptoms occur. Among the common metastatic sites of SCLC are the brain, bones, adrenal glands, liver, colorectum, and lymph nodes. Due to the presence of neuroendocrine cells, SCLC has a higher tendency to metastasize to the liver and brain compared to NSCLC.[5] Brain metastases (BM) are among the common metastatic sites in LC patients, being present in approximately 10% of patients at the time of diagnosis and observed in over 80% of patients during autopsy.[6] Median OS in advanced stage SCLC patients is approximately 12 months, while in those with BM, median OS is around 5 months and the 2-year survival rate in patients with BM is only below 2%.[7,8] Local and systemic inflammation can influence tumor progression and response to treatment. BM consist of various cellular structures, including LC cells, tumor-associated

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fibroblasts, brain parenchymal cells, circulating blood dendritic cells, macrophages, and immune system cells such as B and T lymphocytes.[9] In BM, reactive astrocytes in the tumor microenvironment, along with cells of the innate and adaptive immune systems, play a significant role in inducing tumor proliferation.[10] Furthermore, circulating inflammatory cells (macrophage subtypes, mast cells, neutrophils, T and B lymphocyte subsets) secrete various signaling molecules that facilitate tumor angiogenesis, proliferation, and metastasis.[11,12] SIRI is a parameter that reflects the host's immune and inflammatory status quite effectively. It has been reported to predict survival in various malignancies, such as pancreatic cancer, gallbladder cancer, oral squamous cell carcinoma, and cervical cancer. However, data regarding the prognostic role of SIRI in lung cancer are quite limited.[13]

This study aims to predict the patient group with a 12-month survival using the SIRI parameter in DNBM SLCL patients who have a median survival of less than 6 months, as reported in the literature.

METHODS

The study was carried out with the permission of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Researches Ethics Committee (Date: 21.12.2022, Decision No: 2022-12/2203). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between December 2014 and August 2021, patients aged 18 and over who were diagnosed with DNBM SCLC in the Medical Oncology Unit of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital were included. The study was prepared in accordance with the Helsinki Declaration. Patient information was retrospectively scanned and recorded from the hospital database. Patients who did not meet the inclusion criteria were excluded.

SIRI was calculated from pre-treatment laboratory parameters in the included patients using the method of monocyte count x neutrophil count / lymphocyte count. The analyses evaluated the impact of the SIRI variable on the prognosis of DNBM SCLC patients.

All patients underwent staging evaluations with brain MRI and PET-CT. All causes, apart from malignancies that could affect the SIRI value, were excluded from the patients.

Statistical analyses were conducted using SPSS version 24.0. Survival analyses were compared using the Kaplan-Meier test. The role of the SIRI variable in predicting OS12 in DNBM SCLC patients was assessed using the Receiver Operating Characteristic (ROC) curve. In univariate analyses, variables with a p-value <0.250, which could contribute to survival clinically, were evaluated in multivariate logistic regression analysis. A significance level of $p<0.05$ was considered statistically significant in all statistical tests.

RESULTS

Out of the 256 registered SCLC patients in the database, 42 patients diagnosed as DNBM were included in the study. Among the patients, 36 were male (85.7%), and 6 were female (14.3%), with age of 19 patients (45.2%) were 60 years or younger, while 23 (54.8%) were over 60 years old.

Cases were evaluated according to the Eastern Cooperative Oncology Group (ECOG) performance score, with 1 patient (2.4%) having a score of 0, 27 patients (64.3%) having a score of 1, and 14 patients (33.3%) having a score of 2.

Out of the patients, 34 (80.9%) had metastases in distant organs in addition to brain metastasis either at the time of diagnosis or during follow-up. In 8 patients (19.1%), de novo brain metastasis was the only distant organ metastasis observed.

Among the patients, 32 (%76.2) received only first-line platinum-etoposide combination chemotherapy (CT) , while 10 (%23.8) patients received 2 or more lines of systemic CT after progression based on their treatment history. Additionally, all 42 (100%) patients received whole-brain radiotherapy (WBRT) before CT.

SVCS was observed in 3 patients (7.1%) at the time of diagnosis, and hyponatremia was observed in 11 patients (26.2%).The median OS of the patients included in the study was determined to be 5.6 months. Demographic and clinical characteristics of the patients are summarized in **Table 1**.

In the survival analysis conducted based on age, no statistically significant difference was observed between patients aged 60 and below compared to those aged over 60 (6.5 months vs. 5.3 months; p = 0.32) (**Figure 1.**).

At the time of diagnosis, SIRI values were calculated for each patient before initiating any treatment based on the laboratory parameters obtained. ROC analysis demonstrated that when the SIRI marker was ≤ 1.79, the OS12 of the patients was statistically significantly predicted (AUC: 0.751, sensitivity: 66.7%, specificity: 66.7%; p=0.022) (**Figure 2**).

Table 1. Clinicopathological features of the patients Total n:42/(%)	
Gender	
Female	6 (14.3)
Male	36 (85.7)
Age median (min-max)	61 (39-81)
≤60	19 (45.2)
>60	23 (54.8)
Ecog	
0	1 (2.4)
1	27 (64.3)
2	14 (33.3)
Smoking	
No	1 (2.4)
Yes	41 (97.6)
Presence of other distant organ metastases at diagnosis or during follow-up	
No	8 (19.1)
Yes	34 (80.9)
Superior vena cava syndrome (SVCS) at diagnosis	
No	39 (92.9)
Yes	3 (7.1)
Number of lines of chemotherapy	
<2	32 (76.2)
≥2	10 (23.8)
Palliative WBRT	
No	0 (0.0)
Yes	42(%100)
Hyponatremia	
No	31 (73.8)
Yes	11 (26.2)
*Median OS (Overall Survival)	
≤60 years	6.5 months
>60 years	5.3 months
Total	5.6 months
*Kaplan-Meier survival analysis	

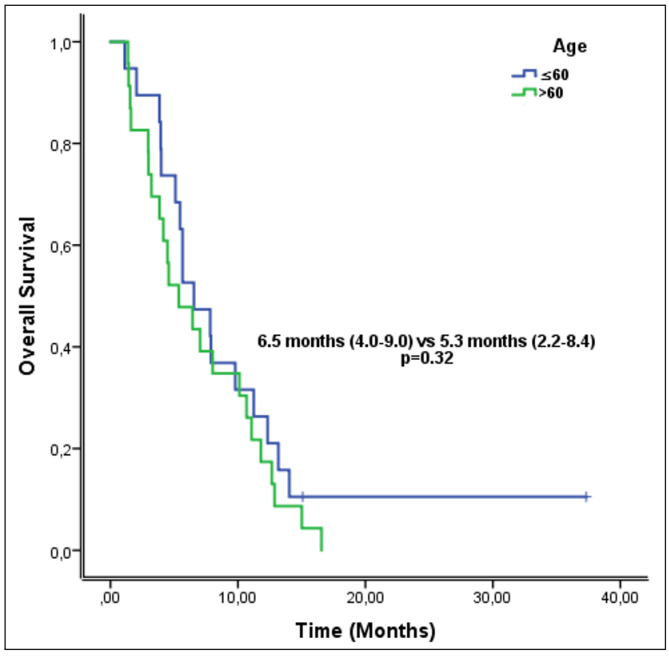

Figure 1. Overall survival by age

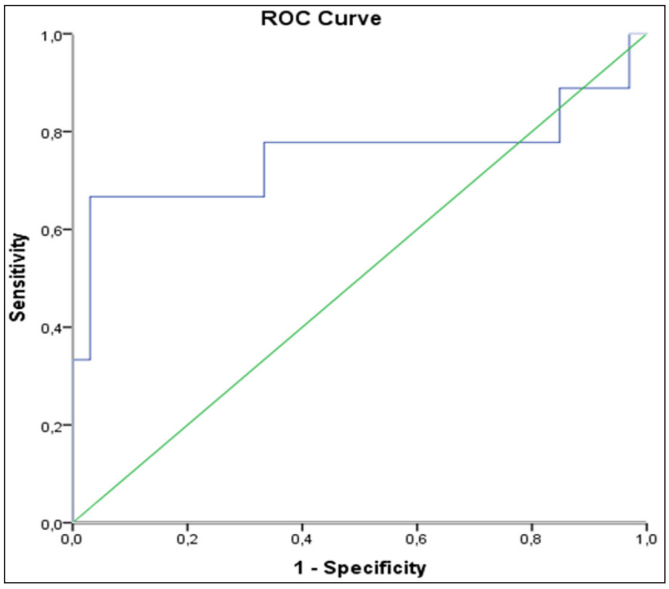

Figure 2. Evaluation of SIRI variable with the ROC curve in DNBM SCLC patients for predicting OS12

OS 12-month	AUC	95% CI	Cut-Off	Sensitivity (%)	Specificity (%)	p
SIRI	0.751	0.507-0.995	≤1.79	66.7	66.7	0.022

In the univariate analysis, among the laboratory factors, hemoglobin (Hb), Total Bilirubin (T.bil.), Calcium (Ca), and SIRI were found to be effective on OS12 in DNBM SCLC patients. Multivariate logistic regression analysis indicated that having SIRI ≤ 1.79 was a statistically significant positive independent predictor for OS12 compared to SIRI >1.79 (odds ratio: 8.00, 95% confidence interval: 1.08-58.90, p=0.04) (Table 2).

Table 2. 12-month overall survival*	univariate logistic regression		multivariate logistic regression	
	or (CI 95%)	p value	or (CI 95%)	p value
Hb	0.60 (0.36-1.01)	0.05	0.69 (0.40-1.19)	0.18
Total bilirubin	0.21 (0.01-2.38)	0.21	0.35 (0.02-5.78)	0.46
Calcium	0.36 (0.10-1.27)	0.11	0.24 (0.04-1.38)	0.11
SIRI >1.79 SIRI ≤1.79	1 4.00 (0.83-19.10)	0.08	1 8.00 (1.08-58.90)	0.04
			r2 = 0.38, -2loglikelihood= 31.57	
*Logistic regression analysis				

DISCUSSION

Treatment delays incancer patients can increase mortality.[14] For predicting the prognosis of SCLC, various factors have been investigated, but the lack of a standardized marker highlights the need for new biomarkers in this regard.[15] Inflamation markes are practical in many solid tumors.[16] Various inflammation and immune-based

prognostic indices such as the neutrophil-lymphocyte ratio (NLR) , monocyte-lymphocyte ratio (MLR) , and platelet-lymphocyte ratio (PLR) have been developed to predict patients' recurrence and survival rates.[17] SIRI is a newly defined index, calculated as the neutrophil count × the monocyte count / the lymphocyte count, which better reflects the host's immune and inflammation balance. Furthermore, it has been reported to predict survival in various cancer types, although studies on its role in lung cancer are rare.[13] The aim of this study is to evaluate the prognostic and predictive significance of the pre-treatment calculated SIRI index in SCLC patients with DNBM who received palliative WBRT and systemic CT in the first-line treatment.

Similar to LC in general, SCLC is more common in men, but the proportion of cases in women has increased worldwide in the last 50 years when compared to men, which also reflects trends in tobacco consumption. Additionally, the elderly population among SCLC patients is on the rise, with the proportion of elderly patients (>70 years old) in the United States increasing from 23% in 1975 to 44% in 2010.18 Of the 42 patients included in our study, 36 were male (85.7%), 23 patients were aged 60 or older (54.8%), and 41 patients (97.6%) had a history of smoking.

Superior vena cava syndrome (SVCS) occurs due to the compression of the mass, tumor invasion, and/or thrombosis of the superior vena cava (SVC). It encompasses a wide clinical spectrum, ranging from asymptomatic cases to life-threatening emergencies.[19] SVCS is observed in approximately 10% of SCLC patients at the time of diagnosis.CT and/or radiotherapy (RT) can alleviate the symptoms of SVCS in these patients.[20] Electrolyte disturbances are common in cancer patients and can worsen the prognosis. Among these disorders, hyponatremia is the most common, with a prevalence of 11% in limited-stage SCLC patients and 24% in extensive-stage patients.[21] In our study, SVCS was observed in 3 patients (7.1%) at the time of diagnosis, and hyponatremia was observed in [11] patients (26.2%). These findings are consistent with the data in the literature, indicating that the patient population in our study is similar to the literature data.

At the time of diagnosis, DNBM is detected in 10% of SCLC patients.[6] The median OS in extensive-stage SCLC is 5 months.[7] In this study, DNBM was detected in 16% of 256 retrospectively scanned SCLC patients, and the mean median OS of the cases was determined to be 5.6 months, showing similarity to the data in the literature.

Cancer-related studies comparing the prognostic capacity of SIRI and NLR in similar cohorts have shown that SIRI is a stronger predictive marker than NLR.[22] In a meta-analysis that included 10,754 cases encompassing all cancer patients conducted by Zhou et al.[23] it was demonstrated that high pre-treatment SIRI levels were associated with a poor prognosis. In the study conducted by Yılmaz et al.[15] SIRI was identified as an independent prognostic factor for both progression free survival (PFS) and OS in extensive-stage SCLC. It was noted that a high SIRI level was significantly associated with shorter PFS and OS. In our study, ROC analysis demonstrated that when the SIRI marker was ≤1.79, it significantly predicted OS12 in patients (AUC: 0.751, sensitivity: 66.7%, specificity: 66.7%; p=0.022). Furthermore, in univariate analysis, among the laboratory parameters effective for OS12 in DNBM SCLC patients, and in multivariate logistic regression analysis, where these parameters were evaluated, it was found that SIRI ≤1.79 was a statistically significant positive independent predictor for OS12 compared to SIRI >1.79 (OR: 8.00, 95% CI: 1.08-58.90, p=0.04).

In a study encompassing patients with advanced-stage melanoma, gastrointestinal, lung, and head-neck cancer who received immunotherapy, it was demonstrated that a high baseline or early increase in the measured NLR, PLR, and MLR markers during treatment were associated with poor clinical outcomes.[24] Furthermore, in another study investigating the relationship between the pretreatment calculated high systemic immune inflammation index (SII) based on circulating blood platelet, neutrophil, and lymphocyte counts (platelet × neutrophil/lymphocyte) and immunotherapy response, it was demonstrated that a high SII value before treatment was independently associated with poor PFS and OS in patients with metastatic renal cell carcinoma treated with nivolumab-ipilimumab in the first-line setting.[25] Adding atezolizumab to platinum-etoposide chemotherapy as shown in the IMpower 133 trial and adding durvalumab to the treatment regimen as shown in the CASPIAN trial were both demonstrated to contribute approximately 2-2.5 months to the statistically significant median OS in extensive stage SCLC, and PD-L1 has no predictive value for immunotherapy in SCLC.[3] Based on the analyses in our study and considering the studies conducted on immunotherapy and inflammatory index parameters, it can be suggested that low SIRI in pre-treatment DNBM SCLC patients predicts longer OS12 when immunotherapy is added to the treatment. Furthermore, there is a need for extensive studies to investigate the independent role of SIRI as a predictor for immunotherapy in extensive-stage SCLC. In the future, parameters based on systemic inflammation may not only identify the risk but also serve as target markers for clinical treatments in cancer patients.[22]

CONCLUSION

The findings of this study, given that the patient group in the study population had clinical and pathological characteristics similar to the literature, are valuable in predicting independently lower SIRI markers for patients with DNBM SCLC who live longer than the expected average overall survival. However, for the practical application of this information in real-world scenarios, further comprehensive research is needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Researches Ethics Committee (Date: 21.12.2022, Decision No: 2022-12/2203).

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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An evaluation of spinal anesthesia results in pediatric patients undergoing pilonidal sinus surgery: a retrospective study

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ABSTRACT

Aims: The aim of this retrospective study was to evaluate the efficacy, side-effects, and complications of spinal anesthesia (SpA) in children undergoing pilonidal sinus surgery with SpA.

Methods: The records of pediatric patients who underwent pilonidal sinus surgery with SpA from January 2019 to March 2023 were retrospectively evaluated from the database in the Samsun University Samsun Maternity & Children's Training and Research Hospital, Department of Anesthesiology and Reanimation, Türkiye. Children's sociodemographic characteristics, clinical and vital signs, motor block duration, operative time, and complications were recorded.

Results: Eighty-one patients underwent pilonidal sinus surgery with SpA, 54 (66.7%) boys and 27 (33.3%) girls, with a mean age of 14.38±1.29 years. The patients' mean body mass index was 26.83±1.1 $kg.m^{-2}$, and the success rate was 96.3% (n=78). Eleven (13.6%) patients received supplemental anesthesia among the 78 procedures completed using SpA. The incidence of complications was 5.1% (n=4). Intraoperative hypotension developed in two cases and postoperative vomiting in two, all of which resolved with no sequelae.

Conclusion: Our retrospective analysis suggests that pediatric SpA is a safe and effective technique for children undergoing pilonidal sinus surgery. However, further prospective studies are warranted to confirm these findings.

Keywords: Anesthesia, children, spinal anesthesia, surgery, pilonidal sinus

INTRODUCTION

Spinal anesthesia (SpA) provides safe and effective anesthesia and analgesia for surgical procedures without the need for airway intervention.[1] It has a number of advantages over general anesthesia and lowers the risk of cardiorespiratory events (such as hypoxemia, bradycardia, and hypotension) associated with general anesthesia in neonates and young infants, as well as smaller adults during the course of minor surgical procedures. The advantages of SpA in pediatric patients include a rapid onset, the provision of adequate motor and sensory block, and reducing pain and the stress response to surgery.[2,3]

However, both anesthesiologists and surgeons have traditionally been reluctant to apply SpA in the pediatric population.[4] A survey study revealed that the unwillingness to apply SpA for routine pediatric surgical procedures is multifactorial in nature. One factor that possibly contributes to such reluctance among surgeons may be the idea that SpA is technically difficult and entails a longer preoperative time.[5] The technique also has a number of disadvantages, particularly the fact that as many as 10% of SpAs in very young children will require conversion to general anesthesia due to various unanticipated events. Other limitations include its limited effect duration (90 min) and the potential need for additional anesthetics.[3,6,7]

The aim of this retrospective study is to share our experiences with SpA in children undergoing pilonidal sinus surgery and to evaluate the side-effects and complications associated with the procedure. This paper also discusses our hypothesis was concerning whether or not SpA is safe and effective in pediatric patients. Our primary aim is to evaluate our results for pediatric SpA performed by us due to pilonidal sinus surgery and the complications thereof. Our secondary aim is to discuss our clinical findings in the light of the current literature.

METHODS

This retrospective study was carried out with the permission of Samsun University Clinical Researches Ethics Committee (Date: 15.02.2023, Decision No: 2023/3/2). All procedures were carried out in accordance with ethical rules and the principles of the Declaration of Helsinki.

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Study Population

Data from patients who underwent pilonidal sinus surgery with SpA at the Samsun University, Samsun Maternity and Children's Training and Research Hospital, Department of Anesthesiology and Reanimation, Türkiye, between January 2019 and March 2023 were examined retrospectively. Patients with histories of pilonidal sinus surgery under SpA were included in the study. Individuals aged over 18, receiving general anesthesia, or undergoing additional procedures together with pilonidal sinus surgery (appendectomy, tonsillectomy, herniorrhaphy, orchiopexy, circumcision, etc.) were excluded.

SpA procedure

Appropriate hydration was performed prior to SpA. The children undergoing SpA were kept in the lateral decubitus position by a technician, particular attention being paid to lumbar kyphosis to ensure optimization of the puncture conditions (Figure 1). Patients were sedated when needed. The intrathecal space was accessed at the L4-L5 or L5-S1 levels via median puncture under sterile conditions by means of 25 mm, 25-gauge, or 26-gauge Quincke spinal needles (Figure 2). Once return of the cerebrospinal fluid was observed, a mixture of 0.5% hyperbaric bupivacaine (0.3 mg per kg body-weight) was administered. The needle was then extracted, after which the patient was placed in position for surgery. The success of SpA (in terms of loss of autonomic or motor response to external stimuli) was confirmed through gentle tactile stimulation of the thigh by means of a forceps before the procedure commenced. The Modified Bromage scale was applied to assess the motor block component, a value of 0 representing no motor block present, 1 an inability to stand unassisted, 2 the ability to flex the ankle, but not the knee, and 3 complete motor block in a fully awake child.[8] Surgery was performed on patients with block levels of T10 or higher.

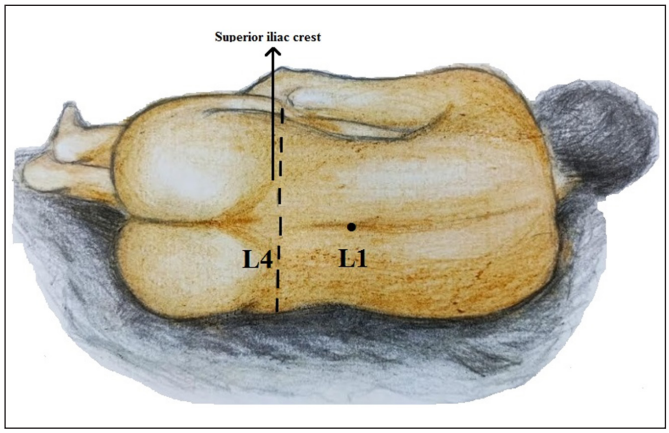

Figure 1. The lateral decubitus position for spinal anesthesia in children

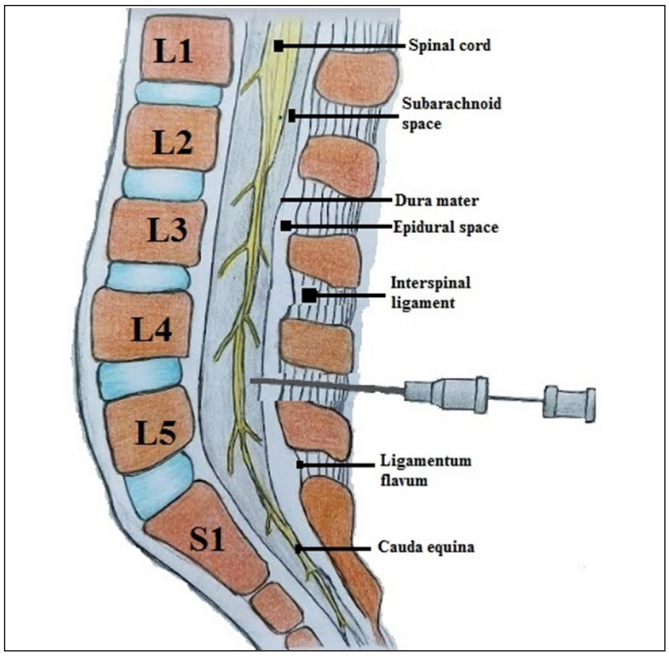

Figure 2. The spinal anesthesia technique using the L4-L5 segment

The procedure was discontinued in case of failure following two punctures. SpA was regarded as unsuccessful in these cases, and general anesthesia was performed instead.

All SpAs were performed by anesthetists with at least three years' experience in this area. The technique was not performed by anyone other than a specialist physician in our center.

Sedation for Spinal Puncture

Children who were agitated, fearful, or hyperactive in the preoperative period were given intravenous midazolam (0.05 mg per kg body weight) to ensure the reliability and success of the spinal block.[9]

Supplemental Anesthesia

Supplemental anesthesia was defined as the additional use of intravenous anesthetics throughout the perioperative period following an initially successful spinal puncture. Children who were agitated, fearful, or hyperactive in the intraoperative period received continuous intravenous infusion of remifentanil (0.05 µg per kg body-weight at the beginning of the operation and 0.025 µg per kg body weight for maintenance).

Perioperative Care

All the children in this study were routinely monitored throughout the procedure and up to discharge. All cases' vital signs were recorded every 5 min in the operating room and also in the recovery room. Hypotension was defined as 30% decrease of baseline systolic blood pressure, or mean arterial pressure (MAP) less than 60 mm-Hg as described by Santana et al.[9] Fluid bolus or vasoactive medication use and respiratory adverse event rates were investigated from the perioperative

care records. The medical staff closely monitored all the patients in terms of apnea. Postoperative oxygen supplementation requirements were defined as any requirement for non-invasive oxygen delivery, such as via nasal oxygen cannula, to ensure that oxygen saturation levels were maintained above 92%.

Data Collection

Clinical data including sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, number of punctures, time to complete block, supplemental anesthesia, blood pressure values, rescue analgesia, duration of operation, complications of SpA, and length of hospital stay were analyzed.

All parents/guardians provided detailed, signed forms agreeing to the use of their children's clinical details for scientific purposes, a formal requirement in our hospital.

Statistical Analysis

Data analysis was performed on SPSS version 25 software (Statistical Package for Social Sciences- IBM Corp., Armonk, NY, USA). Nominal variables were expressed as frequencies and percentages, and continuous variables as mean±standard deviation.

RESULTS

Eighty one patients with a mean age of 14.38±1.29 years were included in the study. Fifty-four (66.7%) of the patients were boys and 27 (33.3%) were girls, with a mean BMI in the total patient group of 26.83±1.1 $kg.m^{-2}$.

SpA was initially attempted for all 81 procedures. Spinal needle placement failure occurred in three (3.7%) patients who subsequently received general anesthesia. Seventy-eight cases were completed using SpA, 18 (22.2%) of which were briefly sedated to permit successful spinal puncture. Lumbar puncture was successfully achieved at the first attempt in 75 (96.2%) patients, and at the second attempt in three (3.8%).

Mean operative time was 75.8±8.96 min, mean motor block development time 7.68±1.01 min, and the time for the motor block to fade was 63.93±6.03 minutes (Table 1). Motor block developed in all patients.

Eleven (13.6%) of the 78 children who underwent SpA received additional anesthesia with the application of a laryngeal mask during surgery due to early returning motor block or autonomic responses. Four of these children were girls and seven were boys (p=0.819). The mean age of the girls was 13.5±0.57 years and that of the boys was 13.57±0.78 years. There was no significant age difference between the boys and girls (p=0.878). Clinical data for the patients who received additional anesthesia are shown in Table 2.

Table 1. Detailed information of patients in the study

Clinical variables	Values
Total number	81
Age (years, mean±SD)	14.38±1.29
Sex, girl (N, %)	27, 33.3%
Body mass index (kg/m², mean±SD)	26.83±1.1
ASA classification (N, %)	
ASA 1	64, 79%
ASA 2	17, 21%
Sedation for spinal puncture (N, %)	18, 22.2%
Number of puncture (mean±SD)	1.02±0.21
Motor block development time (min, mean±SD)	7.68±1.01
Motor block duration (min, mean±SD)	63.93±6.03
Supplemental anesthesia (N, %)	11, 13.6%
Operative time (min, mean±SD)	75.8±8.96
Hospital stay (day, mean±SD)	1.07±0.26

ASA: American Society of Anesthesiologist, SD: standard deviation

Table 2. Clinical data for the patients who underwent additional anesthesia

Clinical variables	Values
Total number	11
Age (years, mean±SD)	13.54±0.68
Sex, girl (N, %)	4, 36.3%
Body mass index (kg/m², mean±SD)	27.25±0.69
ASA classification (N, %)	
ASA 1	8, 72.7%
ASA 2	3, 27.3%
Sedation for spinal puncture (N, %)	6, 54.5%
Number of puncture (mean±SD)	1
Motor block development time (min, mean±SD)	7.75±1.24
Motor block duration (min, mean±SD)	63.9±5.95
Operative time (min, mean±SD)	79.54±7.77
Hospital stay (day, mean±SD)	1.09±0.3

ASA: American Society of Anesthesiologist, SD: standard deviation

Hemodynamic parameters were evaluated in terms of normal limits for all age groups. Hypotension was defined as a decrease in MAP below 35 mm-Hg. Hypotension was determined in two patients (aged 12 and 16 years) during observation and postoperative vomiting in two (aged 13 and 14), and our overall complication rate was 5.1%. No postoperative apnea, bradycardia, desaturation, or post-dural puncture headache (PDPH) was observed in any case.

DISCUSSION

This study evaluated the effectiveness of spinal anesthesia in children undergoing pilonidal sinus surgery. A success rate of 96.3% and a complication rate of 5.1% were determined. Sedation was applied to 18 (22.2%) patients before SpA. Mean time to motor block development was 7.68±1.01 min, mean duration of motor block was 63.93±6.03 min, and the supplemental anesthesia rate was 13.6%. SpA has previously been used effectively in pediatric pilonidal sinus surgery and has

numerous clinical advantages over general anesthesia. These include less intraoperative desaturation and bradycardia, higher minimum systolic blood pressure with fewer intervention requirements, less heat loss, a lower incidence of postoperative early apnea, shorter anesthesia times from the conclusion of surgery to leaving the operating room, and shorter times to first feed.[3,11]

An examination of the literature shows that pediatric SpA enjoys a high success rate. Studies with a similar design to the present research have reported success rates of 97.5-100%.[3,10-12] The success rate in the present study was 96.3%, a figure compatible with previous research in the literature.

While pediatric SpA may entail complications such as hypotension, vomiting, bradycardia, desaturation, PDPH, or postoperative apnea, the rates are low. Desaturation, one of the most important complications, was reported at a rate of 2% by Eizaga Rebollar et al.[3] Caliskan et al.[12] reported a complication rate of 3.4%, PDPH being the major complication. Kantekin et al.[13] reported a rate of 4.8%, the most important complication being foot drop. The complication rate in the present study was 5.1%. These included hypotension in two children and postoperative vomiting in two, but no bradycardia, desaturation, or postoperative apnea were observed. In terms of complication rates, this study is consistent with the previous literature.

The incidence of PDPH is lower in children than in adults due to increased production and turnover of cerebrospinal fluid, low cerebrospinal fluid pressure, and highly elastic dura.[11] Previous studies have reported an overall incidence of 4-5% (similar to that in adults) in the 2-15 year age group, with symptoms being generally mild and severe headache being highly unusual (0.1%).[10,14,15] Imbelloni et al.[16] detected PDPH in three (1%) children in their extensive study of 307 patients. Caliskan et al.[12] reported mild headache not fully compatible with PDPH criteria in one case (1.1%). Kantekin et al.[13] encountered no PDPH in their study. No PDPH was also observed in the present research, and this is also consistent with the literature and other studies from Türkiye.

Remifentanil infusion was initiated as an additional anesthetic agent for maintenance of anesthesia in 13.6% of patients with laryngeal masks. Figures of 35% were reported by Caliskan et al.[12] 17.4% by Kantekin et al.[13] and 22% by Baltrak and Soyalp.[14] The figure for supplemental anesthesia in this study was thus slightly lower than in other research from Türkiye.

SpA can be performed on children in either the seated or lateral decubitus positions.[17,18] In the present study, SpA was performed with all patients in a seated position. Varying local anesthetic agents and doses have been reported in SpA applications in pediatric cases.[19,20] Isobaric or hyperbaric bupivacaine (0.5%) are still the most popular agents for pediatric SpA.[11] Eizaga Rebollar et al.[3] determined differing local anesthetic doses in different age groups depending on the length of surgery based on their seven-year experience. According to that study, hyperbaric 0.5% bupivacaine may be recommended as a local anesthetic with an operative time of <60 min, isobaric 0.5% bupivacaine or levobupivacaine with an operative time of 60-75 min, and isobaric 0.5% bupivacaine with epinephrine 1:200,000 in case of operative times of 75-90 min. Local anesthetic doses of 0.5 mg/kg for <5 kg body weight, 0.4 mg/kg for 5-15 kg, 0.3 mg/kg for >15 kg were also recommended. Similarly in their review study, Gupta and Saha[11] described 0.3 mg/kg hyperbaric bupivacaine (0.5%) as an appropriate dose in children weighing >15 kg. In the present study, hyperbaric 0.5% bupivacaine was employed at a dose of 0.3 mg/kg, a figure within the clinical dose range reported for pediatric cases in the previous literature.

This retrospective study has a number of limitations. One involves the retrospective and single-center nature of the research. It was also not possible to evaluate children's pain levels in the postoperative period due to missing data. Another limitation of this study in terms of determining the true complication rate is that patients only presented to us in case of a problem after the second day postoperatively. However, we also think that this study is particularly valuable due to the limited number of existing publications concerning pediatric SpA.

CONCLUSION

With a high success rate of 96.3% in the present study, an acceptable mean motor block development time of eight minutes, its permitting a comfortable procedure over a mean 75 minutes, and low complication rate, SpA represents an alternative general anesthesia method in pediatric patients undergoing pilonidal sinus surgery. However, further prospective studies with larger populations and longer follow-up times are now needed to validate such findings.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Samsun University Clinical Researches Ethics Committee (Date: 15.02.2023, Decision No: 2023/3/2).

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Relation between impaired coronary microvascular circulation and plasma atherogenic index in patients with ankylosing spondylitis

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ABSTRACT

Aim: The coronary flow reserve (CFR) is a sign of endothelial dysfunction and early-stage coronary artery disease (CAD). Plasma atherogenic index (PAI) is related to subclinical CAD and may be used as a predictor of cardiovascular mortality. Our aim is to determine CFR and PAI in patients with AS and to investigate whether PAI can be used in the detection of early stage CAD.

Methods: The study population comprised 48 patients, who were diagnosed with AS based on modified New York criteria and 35 healthy volunteers. PAI values were calculated with the formula log 10 triglyceride (TG) / high-density lipoprotein (HDL).

Results: No difference was detected between the two groups for the demographic variables, including age, sex and BMI. The comparison of the groups for PAI and CFR demonstrated that PAI levels were observed to be significantly higher and CFR levels were observed to be significantly lower in the AS patients ($p=0.01$, $p<0.001$, respectively). Correlation analysis revealed that CFR and PAI were negatively correlated (PAI- $p<0.0001$ $r=-0.661$). When two groups were formed, one below CFR level 2 and the other above CFR level 2, only PAI was found to increase significantly from the new lipid indices ($p=0.004$).

Conclusion: There is an independent negative correlation between PAI and CFR values. PAI may be useful in identifying AS patients facing high risk of adverse cardiovascular events, and may also enable the early diagnosis of subclinical atherosclerosis.

Keywords: Ankylosing spondylitis, plasma atherogenic index, atherosclerosis, coronary flow reserve

INTRODUCTION

Ankylosing spondylitis (AS) is a rheumatic disease, which is characterized by chronic inflammation that severely affects the axial skeleton. Sacroiliitis being its distinguishing feature, this disease causes spinal ankyloses as a result of both inflammations at tendon attachment points and syndesmophyte formation. Known to vary among populations, the prevalence of this disease ranges between 0.1-2%.[1]

AS may also affect extra-articular structures, including the eyes, lungs and heart. Of all AS patients, 2-10% present with cardiac signs, including early-stage atherosclerosis. While the risk of cardiovascular disease associated with autoimmune diseases is considered to be multifactorial, accelerated atherogenesis caused by systemic inflammatory response is considered to have a significant place among the underlying physiopathological mechanisms.[2,3]

The coronary flow reserve (CFR) is defined as the ratio of the hyperemic diastolic peak flow velocity to baseline diastolic peak flow velocity, and is considered to be a basic indicator of coronary microvascular function. Reduced CFR is a sign of endothelial dysfunction, atherosclerosis and early-stage coronary artery disease (CAD). CFR has been shown to have prognostic value in the assessment of cardiovascular events associated with various systemic diseases.[4-6] CFR can be measured by transthoracic echocardiography. This method is preferred due to its high diagnostic accuracy, versatility, low cost and particularly avoiding exposure to radiation.[7]

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While conventional atherogenic lipid parameters are still used for the assessment of CAD risk, many large-scale epidemiological studies have demonstrated that novel lipid indices, such as the plasma atherogenic index (PAI), offer a better estimation for atherosclerotic CAD risk, compared to conventional parameters.[8-10] The recently popular PAI is a novel lipid index, which is the logarithmically converted ratio of the molar concentrations of triglyceride to high-density lipid cholesterol (HDL-C). Research has shown that PAI is related to atherosclerosis and subclinical coronary artery disease, and may be used as a predictor of cardiovascular mortality.[11,12]

The present study was aimed at determining CFR, as an indicator of subclinical atherosclerosis, and PAI, for the assessment of CAD risk, in patients diagnosed with AS. Furthermore, it was aimed to investigate whether PAI could be used in the detection of early-stage CAD.

METHODS

The study was carried out with the permission of İstanbul Medeniyet University, Göztepe Training and Research Hospital Ethics Committee (Date: 22.07.2020, Decision No: 2020/0459). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All patients, who participated in the study, were informed prior to their registration, and both their written and verbal consent were obtained.

Study Population

The study population comprised 48 patients, who were admitted to the rheumatology polyclinic of our hospital and were diagnosed with AS based on modified New York criteria. After their detailed medical history was recorded, the AS patients underwent physical examination. Thirty-five healthy volunteers, who matched the AS patients for age, sex and body mass index (BMI), were included in the study as control subjects.

Individuals under the age of 18, those with a medical history of stroke, and persons with congestive heart failure, CAD, dilated/hypertrophic or restrictive myopathies, severe valvular heart disease, hypertension (HT), diabetes/impaired glucose tolerance, obstructive sleep apnoea, dyslipidaemia, and morbid obesity (BMI >35 kg/m²), as well as smokers, alcoholics (with an excessive alcohol consumption >120 g/day), and individuals with diseases such as renal and hepatic failure that may affect the coronary blood flow, and those with associating systemic diseases were excluded from the study. Furthermore, asthma patients were excluded for safety reasons, and individuals with cardiac arrhythmia and those, for whom it was not possible to perform CFR measurements due to images of suboptimal quality, were also excluded from the study. Persons with a medical history of vasoactive drug use, and those with abnormal basal electrocardiographs (i.e., showing the presence of Q-waves and left branch blockage, an altered ST-segment or myocardial ischaemia-specific T-wave alterations) were also excluded from the study.

Biochemical Parameters and Plasma Atherogenic Index

Venous blood samples were taken from both the AS patients and controls in the morning, after a fasting period of 10-12 hours. Fasting glucose, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol and triglyceride (TG) levels were measured. High-sensitivity C-reactive protein (hsCRP) plasma levels were detected. Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald formula (TC=LDL+HDL+TG/5). PAI values were calculated with the formula log10 TG/HDL. Non-HDL cholesterol levels were calculated by subtracting the HDL level from the TC level. The Castelli risk indices (CRI) I and II were calculated with the formulae TK/HDL and LDL/HDL, respectively. The atherogenic coefficient (AC) was calculated by dividing the non-HDL level by the LDL level. When calculating the PAI, the TG and HDL levels were firstly converted to their molar equivalents, and then the formula log (TG/HDL-C) was applied.

Echocardiographic and Coronary Flow Reserve Assessments

Assessments were made using a Vivid-6 (GE Medical Systems, Horten-Norway) ultrasound device and with secondary harmonic imaging. All data were stored digitally and were analysed by a cardiologist, who was known to be experienced in echocardiography and was blinded to the clinical and laboratory data. The conventional echocardiographic assessment of the AS patients and healthy controls was made according to the standards described by the American Echocardiography Association. The left ventricular mass was calculated with the Devereux formula, using the end-diastolic left ventricular wall thickness and left ventricle diameter. The ejection fraction of the left ventricle was calculated using the modified Simpson's method and apical views.

For the assessment of the CFR, the transducer was positioned at the level of the fourth and fifth intercostal spaces, near the midclavicular line, such that the left anterior descending (LAD) artery was imaged through modified two or four chamber windows while the patients were in the left lateral position. The patients were continuously monitored, both echocardiographically and for heart rate. B mode and Doppler imaging were performed at transducer frequencies of 8 MHz and 1.00-2.50 kHz, respectively. All individuals were given an

infusion of dipyridamole, at a dose of 0.56 mg/kg for 4 minutes. Individuals, for whom the targeted heart rate was not achieved, were administered with an additional dose of 0.28 mg/kg. In the AS patients and healthy controls, CFR was measured with the pulse wave Doppler method, using the basal diastolic current velocity and the peak current velocity after dipyridamole infusion. To determine the diastolic peak flow velocities (DPFV), measurements were performed during at least 3 cycles, more specifically, at rest, during maximal dipyridamole infusion, and 3 minutes after the dipyridamole infusion was terminated. Subsequently, the average was calculated. CFR was defined as the ratio of the hyperaemic diastolic peak velocity to the baseline diastolic peak velocity, and CFR values ≥2.0 were considered to be normal. All echocardiographic procedures were performed by a single researcher. The observer variability of our laboratory was as indicated in previous study.[13]

Statistical Analysis

Statistical analyses were performed using the SPSS software (Version 26, Chicago, IL, USA). The homogenous distribution of the groups was assessed with the Kolmogorov-Smirnov test.

Group comparisons of the variables, for which the groups were determined to display a homogenous distribution, were made with Student's t-test. The results are given as mean±standard deviation. The comparison of the variables, for which the groups did not display a homogenous distribution, was made with the Mann-Whitney U test. These results are given as minimum-maximum values.

Correlations were analysed with Pearson's correlation analysis. For all analyses, a p<0.05

value was considered statistically significant. In bivariate correlation analyses, while an r value <0.30 indicated the absence of a correlation or the presence of a very weak correlation, an r value <0.50 indicated a weak correlation, and r values ≥0.50 indicated a moderate or strong correlation between the variables.

RESULTS

The basal demographic data and clinical and laboratory findings of the AS patients and healthy controls are shown in Table 1. No difference was detected between the two groups for the demographic variables, including age, sex and BMI. CRP levels were significantly higher in the diseased group, whilst CFR levels were significantly lower (Figure 1). While the groups did not differ for the conventional lipid parameters, such as TC, HDL, LDL and non-HDL levels, the AS patients were observed to display significantly higher TR levels (p=0.01).

Table 1. Comparison of demographic, clinical and laboratory values of patient and control groups

	Patients n=48	Control n= 35	p
Age (years)	39.6±9.7	37.7±6.4	0.33
Gender (F, n)	31	21	0.78
BMI (kg/m²)	25.9±3.2	26.3±2	0.32
Glukoz (mg/dl)	93.7±7.3	91.3±5.8	0.11
TC (mg/dl)	184.3±37	180.4±27.5	0.60
TG (mg/dl)	142.4±74	105.2±50.6	0.01
HDL (mg/dl)	42.6 (26-105)	45.14 (30-63)	0.06
LDL (mg/dl)	109.9±29.9	114.6±25	0.45
Non-HDL (mg/dl)	141.8±39	135.2±25.8	0.38
PAI	0.49±0.3	0.32±0.26	0.01
CCI-1	4.6±1.43	4.11±0.86	0.07
CCI-2	2.77±1.01	2.61±0.69	0.43
AC	3.61±1.44	3.11±0.87	0.07
CFR	2.21±0.45	3.01±0.5	<0.001
hsCRP (mg/dl)	7.36 (0.45-19)	2.18 (0.5-6.0)	<0.001

TC; Total cholesterol, HDL; High-density lipoprotein cholesterol, TG; triglyceride, LDL; Low-density lipoprotein, PAI; Plasma atherogenic index, CRI; Castelli risk indice, AC; Atherogenic coefficient, CFR; Coronary flow reserve, hsCRP; High-sensitivity C-reactive protein

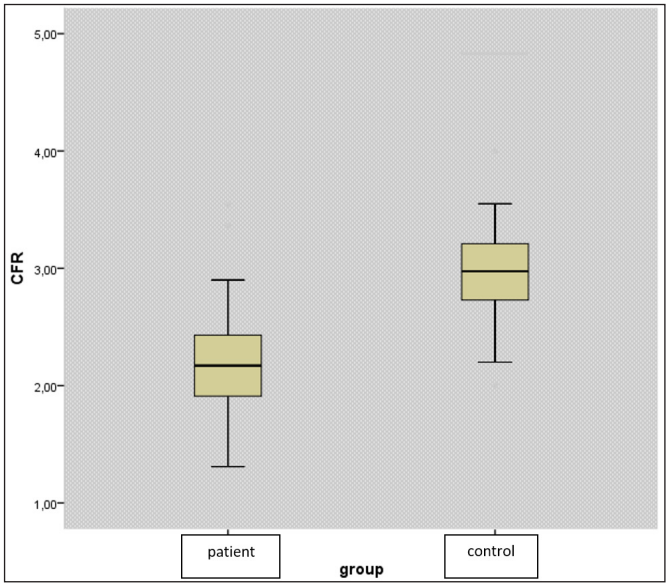

Figure 1. Comparison of CFR levels of AS patients and control groups. CFR; Coronary flow reserve, AS; Ankylosing spondylitis

The comparison of the groups for the novel lipid indices demonstrated no difference to exist for CCI-1, CCI-2 and AC, whilst PAI levels were observed to be significantly higher in the AS patients (p=0.01) (Figure 2).

Correlation analysis revealed that the novel lipid indices, including CFR and TRG, as well as non-HDL and PAI, were negatively correlated, whilst CFR and HDL were positively correlated with each other (PAI - p<0.0001 r=-0.661; CCI-1 - p=0.001 r=-0.483; CCI-2 - p=0.011 r=-0.0362; AC - p=0.001 r=-0.481) (Table 2). The correlation between CFR and PAI is shown in Figure 3.

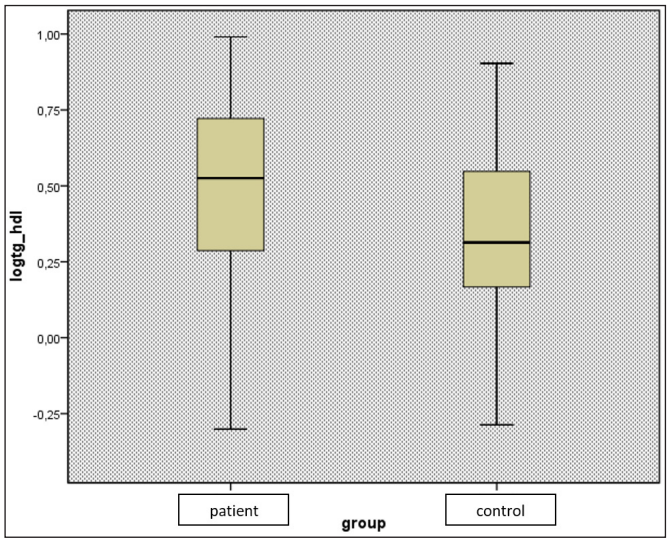

Figure 2. Comparison of PAI levels of AS patients and control groups. PAI; Plasma atherogenic index, AS; Ankylosing spondylitis

Table 2. Correlation analysis of non-CFR parameters between CFR in AS patients

	CFR	
	r values	p values
PAI	-0.661	<0.0001
AC	-0.481	0.001
CCI-1	-0.483	0.001
CCI-2	-0.362	0.011
CRP (mg/dl)	0.299	0.131
TC (mg/dl)	-0.187	0.204
TG (mg/dl)	-0.529	<0.0001
HDL (mg/dl)	0.477	0.002
LDL (mg/dl)	-0.164	0.266
Non-HDL (mg/dl)	-0.347	0.016

CFR; Coronary flow reserve, AS; Ankylosing spondylitis, PAI; Plasma atherogenic index, AC; Atherogenic coefficient, CRI; Castelli risk indice, hsCRP; High-sensitivity C-reactive protein TC; Total cholesterol, TG; triglyceride, HDL; High-density lipoprotein cholesterol, LDL; Low-density lipoprotein

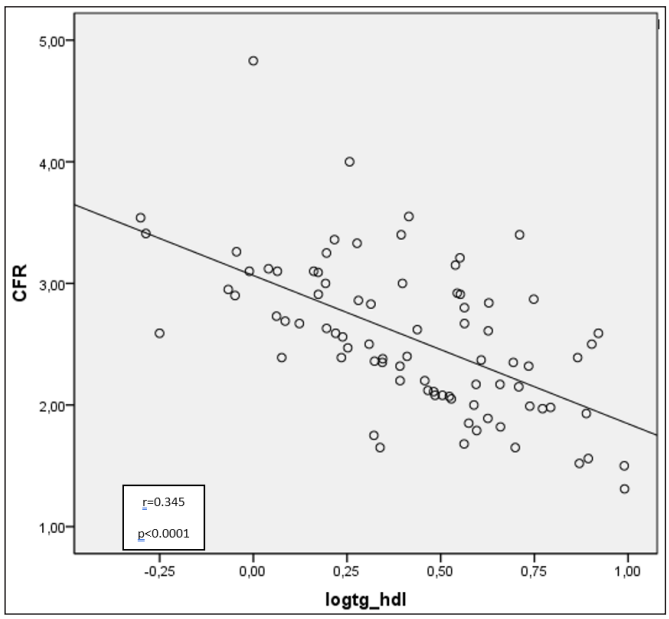

Figure 3. Relationship between PAI and CFR in patients with AS. CFR; Coronary flow reserve, PAI; Plasma atherogenic index, AS; Ankylosing spondylitis

Two groups were established, based on the measurement of the level of CFR as an indicator of atherosclerosis, one including individuals with a CFR level below 2 and the other including those with a CFR level above 2. TR levels were significantly higher and HDL levels were significantly lower in the group with lower CFR levels (p=0.03, p=0.02 and p=0.04, respectively). Of the novel lipid indices only PAI was determined to have significantly increased (p=0.004). No difference was detected for the other demographic parameters, examination findings or lipid parameters/indices (Table 3).

Table 3. Comparison of demographic, clinical and laboratory values between subgroups with low and high CFR levels (cut-off value 2 for CFR)

	CFR <2 (n=16)	CFR >2 (n=32)	p
Age (years)	36.3±11.1	41.2±8.6	0.09
Gender (F n=31)	9	22	0.39
BMI (kg/m²)	25.9±3.7	25.8±2.8	0.94
SBP (mmHg)	127.6±8.2	131.3±5.6	0.09
DBP (mmHg)	78.2±4.1	80.3±4.2	0.13
TC (mg/dl)	187.1±38.2	182.8±36.4	0.70
TG (mg/dl)	188.4±75.4	119.3±62.5	0.02
HDL (mg/dl)	37.1 (26-47)	45.7 (30-105)	0.04
LDL (mg/dl)	110.5±29.5	109.5±30.7	0.91
Non-HDL (mg/dl)	150.9±38.2	137.3±39.2	0.25
PAI	0.66±0.23	0.40±0.30	0.004
AC	4.09±1.13	3.37±1.54	0.10
CCI-1	5.06±1.09	4.37±1.54	0.11
CCI-2	2.97±0.74	2.67±1.12	0.33
hsCRP (mg/dl)	7.99 (0.45-17.9)	5.43 (0.6-19)	0.03

CFR; Coronary flow reserve, SBP; Systolic blood pressure, DBP; Diastolic blood pressure, BMI; Body mass index TC; Total cholesterol, HDL; High-density lipoprotein cholesterol, TG; Triglyceride, LDL; Low-density lipoprotein, PAI; Plasma atherogenic index, CRI; Castelli risk indice, AC; Atherogenic coefficient, CFR; Coronary flow reserve, hsCRP; High-sensitivity C-reactive protein

DISCUSSION

The present study demonstrated that PAI values and CFR levels were higher in the AS patients, compared to the healthy controls. Based on a correlation analysis, PAI values and CFR levels were found to be positively correlated with each other in the AS patients. The results of this study suggest that the PAI values of AS patients could be used as an indicator of subclinical atherosclerosis.

AS is the most common type of spondyloarthropathy with a prevalence ranging from 0.2% to 0.9%. Apart from the skeletal system, this disease is known to affect the cardiovascular system also, and in the event of cardiovascular involvement, the rate of mortality ranges from 20% to 40%.[14] Although increased mortality has not been precisely linked to coronary artery disease, it has been demonstrated that, in AS patients, endothelial functions are impaired and risk factors involved in the pathogenesis of atherosclerosis are altered, these alterations being correlated with the increase observed in

inflammation markers.[15,16] Owing to these mechanisms, the risk of developing atherosclerotic coronary heart disease is high in AS patients.

Endothelial dysfunction is considered to be the first step in the pathogenesis of atherosclerosis. Several mechanisms underlying endothelial dysfunction during inflammatory reactions have been demonstrated. One of these mechanisms is associated with the strong stimulatory effect of oxidised lipoproteins on the expression of cytokine-induced vascular adhesion molecules (VCAM-1), which mechanically links inflammation to the atherogenic process.[17,18] In fact, Gaydukova et al.[19] reported that the plasma levels of vascular adhesion molecules were higher in AS patients, compared to healthy control subjects. Another mechanism is related to the vascular endothelium being a target of tumour necrosis factor alpha (TNF-α), which has a major role in the pathogenesis of chronic inflammatory diseases. Activated endothelial cells are responsible for the secretion of intrinsic chemotactic molecules, and also establish autocrine/paracrine signal cycles localised to the vascular wall and/or of intercellular nature.[20] Furthermore, the genetic regulation of the endothelium reduces the bioavailability of nitric oxide (NO). Thus, the correlation between TNF-α and endothelial dysfunction is associated with a reduced NO level, which is considered to be a critical step.[21] In this respect, it is highly probable that an increased plasma TNF-α level would induce endothelial dysfunction and atherosclerosis. Indeed, Caliskan et al.[22] demonstrated that TNF-α levels significantly increased with AS. A third mechanism involves oxidative stress. It is known that the level of reactive oxygen species (ROS), generated by neutrophils that are related to TNF-α and infiltrate the diseased area, increases in the event of chronic inflammatory diseases.[23] It has been shown in several in vivo animal models that high levels of ROS are associated with reduced NO bioavailability.[24] In previous research conducted by Feijoo et al.[25] and Karakoc et al.[26] oxidative stress markers were determined to have increased in AS patients. A fourth mechanism involves dyslipidaemia, which is an independent determinant of endothelial dysfunction. Although studies are available on the correlation among conventional cardiovascular risk factors, such as endothelial dysfunction and dyslipidaemia, in patients with chronic inflammatory diseases, the results of previous investigations on altered lipid levels are controversial.[27] Nevertheless, it has been reported that while chronic inflammation causes structural changes in lipoproteins, which cannot be detected by standard blood lipid measurements, it also converts LDL into small, dense and pro-atherogenic particles.[28] Moreover, TNF-α contributes to increasing the oxidative modification of LDL. Cure et al.[29] and Caliskan et al.[22] reported that, excluding differences observed in TR levels, TC, HDL and LDL levels did not differ between healthy individuals. In addition, in their meta-analysis by Masi et al.[30] HDL was found to be lower in patients with AS, and no difference was found in other cholesterol levels between patients with AS and healthy individuals. Another fifth mechanism is related to autoantibodies. The production of autoantibodies is involved in the pathogenesis of multiple chronic inflammatory diseases. In patients with such diseases, autoantibodies against normal endothelial and plasma components have been determined, and these auto-antibodies are considered to be involved in the pathogenesis of endothelial dysfunction and atherosclerosis. While this involvement has been clearly demonstrated in systemic lupus erythematosus (SLE), it remains uncertain in some other chronic inflammatory diseases.[24] The present study was aimed at assessing the correlation between endothelial dysfunction and lipid parameters. In this study, we detected that TR levels were significantly higher in the AS patients, compared to the healthy controls. These results were in agreement with those previously reported by Cure et al.[29] and were contradictory to those reported by Caliskan et al.[22] and Masi et al.[30] Despite some controversial results, we ascertained that, in agreement with available literature reports, the TC, HDL and LDL levels of the diseased and control groups were similar.[31] Based on these results, it can be said that there are changes in cholesterol levels of AS patients compared to healthy controls, as in other chronic inflammatory diseases.[27]

Several different methods can be used for the assessment of early-stage atherosclerosis. These methods enable the assessment of the various aspects of the disease as well as the different regions of the arterial tree, and involve the measurement of the intima-media thickness (IMT) of the carotid artery, the flow-mediated dilation (FMD) of the brachial artery, the aortic sclerotic index (AoSI), and the CFR level etc. While each of these parameters can be used as a predictor of cardiovascular events, Gullu et al.[32] claimed that the measurement of the CFR level alone would suffice to determine the treatment to be applied and to follow up the results of treatment. While CFR is used to assess microvascular endothelial functions, it is still not common to use the aforementioned method in the assessment of endothelial function in patients with chronic inflammatory diseases. CFR can be used to assess moderate to severe coronary artery lesions, whilst following a sudden impairment of coronary circulation after stent implantation or acute myocardial infarct, the assessment of the regulation of coronary blood circulation significantly contributes to the determination of prognosis.[33-35] While an impairment of the capacity of the coronary blood circulation to increase indicates the severity of the disease affecting the epicardial arteries, this could also be related to microvascular

dysfunction, as when there is no hemodynamically severe coronary stenosis, maximal increase in blood flow is predominantly determined by the resistance vasculature of the coronary microcirculation. Impaired CFR in the epicardial coronary arteries which appear either normal or mildly diseased in angiographs, have been shown to serve as a predictor for the progression and prognosis of cardiovascular disease.[5] Furthermore, impaired CFR levels have been demonstrated to be associated with bad prognosis in patients diagnosed with coronary microvascular dysfunctions, such as dilated cardiomyopathy and hypertrophic cardiomyopathy.[36, 37] Research on chronic inflammatory diseases and COVID-19 has pointed out to reduced CFR.[38,39] Caliskan et al.[22] determined that CFR decreased in AS patients. Cure et al.[29] reported that, the carotid intima-media thickness, another early-stage predictor of coronary atherosclerosis, was greater in AS patients, compared to the control group. Poddubnyi et al.[40] ascertained that, when compared to controls, reactive hyperaemia of the brachial artery significantly decreased in AS patients. In the present study, we too used the measurement of CFR levels to assess the coronary microvasculature in AS patients and aimed to detect early-stage atherosclerosis in these individuals. Literature reports are available, which indicate impaired CFR levels in AS patients, in agreement with the results of the present study.[22] Our results suggest that AS patients face the risk of developing coronary artery disease.

Impaired lipid parameters predispose individuals to atherosclerosis. The conventional atherogenic lipid profile consists of increased TC, LDL and TG levels, and decreased HDL levels. Some studies suggest that novel lipid indices, including PAI, Framingham's risk scoring, CCI I-II and AC, serve better in the prediction of cardiovascular events, compared to conventional lipid parameters.[41] Owing to its smaller particle size, small dense low-density lipoprotein (sdLDL) penetrates the arterial wall much easier than LDL, forms deposits and undergoes oxidation to generate oxLDL. Several recent studies suggest that sdLDL serves better in predicting atherosclerosis, compared to LDL, and thus, recommend its clinical use.[42] It has been reported that the sdLDL level is correlated with PAI, the measurement of which is both costly and technically complicated.[43] While lipid concentrations may vary during the course of chronic inflammatory diseases such as rheumatoid arthritis (RA), different cholesterol fractions appear to fluctuate in the same direction. PAI is reported to be less affected by fluctuations associated with RA.[44] Recent studies have indicated that PAI could be used as an indicator for the early diagnosis of subclinical atherosclerosis in patients with rheumatic diseases, such as Behçet's syndrome, RA, SLE and familial Mediterranean fever.[29] It is indicated that while PAI values ranging between -0.3 and 0.1 are associated with low cardiovascular risk, a range of 0.1-0.24 indicates moderate risk, and values above 0.24 indicate high risk.[45] In the present study, we detected significantly high PAI values (0.49±0.3). The other lipid indices were also high, but these elevated levels were of no statistical significance. Cure et al.[29] also determined significantly high PAI values in AS patients. The PAI levels detected in the present study showed that the AS patients faced a high risk of developing atherosclerotic cardiovascular disease.

Research conducted on early-stage atherosclerosis in patients diagnosed with chronic inflammatory diseases has revealed a correlation with PAI values. In their research on patients with inflammatory bowel disease, Kul et al.[46] determined that PAI values and CFR levels were inversely correlated with each other. In their study on patients with Behçet's syndrome, Cure et al.[47] determined a strong independent correlation between PAI and carotid intima-media thickness (cIMT) values. In a study carried out in SLE patients, Uslu et al.[48] ascertained that PAI was an independent risk factor for cIMT. Cure et al.[29] assessed early-stage atherosclerosis in AS patients by measuring cIMT, and also investigated the correlation of this parameter with PAI. Based on their results, they revealed a strong independent correlation between PAI and cIMT values, and suggested that PAI would serve as a better indicator for the diagnosis of subclinical atherosclerosis in AS patients, when compared to the TC/HDL ratio. In the present study, we ascertained that the CFR level was correlated with all of the novel lipid indices. Considering levels ≥2 to be normal, the AS patients were assigned to two groups based on CFR measurements, and the group with lower CFR levels was ascertained to display significantly higher levels of the novel lipid indices, excluding PAI. Our results suggest that, compared to the other lipid indices, PAI could serve as a better indicator of early-stage atherosclerosis. It is known that, in individuals under the age of 40, the possibility of predicting early-stage atherosclerosis with cIMT values is lower.[49] Thus, in relatively young individuals, similar to those included in the present study, CFR could serve as a better marker for the diagnosis of early-stage atherosclerosis. In this context, we consider the results of the present study to offer a stronger statement.

PAI appears to be superior to conventional lipid parameters and other novel lipid indices in predicting cardiovascular risk. This is attributed to logarithmically transformed PAI values eliminating distribution irregularity. Furthermore, the determination of PAI values is simple and inexpensive, and PAI values can be used indirectly to assess sdLDL levels.

The present study has some limitations, the first being the enrolment of a small number of AS patients. Secondly, despite the predictive value of CFR in determining the risk of CAD, as a result of the patients enrolled in this study not having been followed up in the long-term, the extent to which the findings of the present study may contribute to daily clinical practice is uncertain. Thirdly, CFR measurements were made only from the LAD. Even if there are low levels of CFR in other arteries, these may be mislabelled as normal values. Fourthly, CRP alone was used as an indicator of inflammation, and this indicator may not represent the whole spectrum of inflammatory activity. Finally, conditions that have the potential to affect CFR in AS patients, such as disease activity, disease duration, and medications used, were not evaluated in this study. This may have caused bias in the study results.

CONCLUSION

A high PAI may be useful in identifying AS patients facing high risk of adverse cardiovascular events, and may also enable the early diagnosis of subclinical atherosclerosis. Nonetheless, further research is required to elucidate the exact mechanisms of early-stage atherogenesis in AS patients and to demonstrate the full impact of atherogenic dyslipidaemia on cardiovascular results in these patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Medeniyet University, Göztepe Training and Research Hospital Ethics Committee (Date: 22.07.2020, Decision No: 2020/0459).

Informed consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Employment status, presence of chronic disease and daily screen time are determinants of healthy diet literacy

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ABSTRACT

Aims: While it has become easier for consumers to reach information with the developments in technology, however, to be able to find the right resources for the information has become difficult. It is known that this situation is related to the health and nutrition literacy of individuals. In this study, it was aimed to determine health literacy, digital healthy diet literacy and healthy eating attitudes of adult individuals.

Methods: Study data were collected with the help of a questionnaire form from 150 individuals (106 females and 44 males, mean age 32.1±10.62 years) who live in Türkiye and voluntarily agreed to participate in the study between January and June 2023.

Results: More than half of the participants (56%) were found to have more than six hours of daily screen time. The most common sources of information on health and nutrition are reported as academic databases and Instagram (both 30.7%). In both genders, individuals' eating attitudes towards healthy eating were found to be high. When the factors affecting health literacy and digital healthy diet literacy were examined, it was seen that daily screen time, working status and having chronic diseases were statistically important factors ($p<0.05$).

Conclusion: These data have drawn a general framework about the individuals living in Turkey, but there is a need for more extensive research on other demographic groups of the society.

Keywords: Health literacy, nutrition literacy, screen time, body mass index

INTRODUCTION

In recent years, the prevalence and mortality of non-communicable chronic diseases such as cardiovascular diseases, certain types of cancer, obesity, and type 2 diabetes have been observed to increase worldwide. According to the analysis conducted by the World Health Organization (WHO), unhealthy eating habits, defined as a diet high in refined carbohydrates, sodium, saturated fat, and calories, are associated with 71% (41 million people) of total deaths each year and the risk of non-communicable chronic diseases and premature death.[1,2] Being healthy is not merely the absence of illness or disability; it encompasses complete physical, social, and mental well-being. Among the determinants of "being healthy," individuals' access to health services and the recently emerged digital technology have also been recognized.[3] Health literacy, considered one of the most important factors influencing health, is defined as 'the degree to which individuals have the capacity to obtain, process, and understand basic health information and services required to make appropriate health decisions.[4] Achieving higher literacy rates and levels in a population is highly valued because it is associated with a range of health outcomes both directly and indirectly.[5] The WHO Commission on Social Determinants of Health has identified 'the critical importance of education for health equity' in both low-income and high-income countries.[6] Low levels of health literacy negatively affect health professional-patient communication.[7] From the perspective of the healthcare community, this situation also impacts preventable diseases and effective disease management because adults with poor health literacy skills face difficulties in interpreting and acting upon health information that could reduce their risk of diseases and related symptoms.[8]

In order to protect and prevent non-communicable chronic diseases, the WHO has set six fundamental targets in its global action plan for the period of 2013-2030 and nine targets aimed to be achieved globally by 2025. To achieve these goals, the WHO has developed global, regional, national, and social action plans to reduce the risk factors of diseases, explain the effects of nutrition and physical activity on health, and raise awareness on

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this matter. Education, communication, and increasing public awareness are among the significant objectives of these plans.[9,10] In order to attain these goals, health authorities emphasize the importance of nutritional literacy level, which is defined as 'nutrition literacy applied in the field of nutrition' or 'the capacity of an individual to access, understand, interpret, and apply basic nutritional information and services to improve their health' during the prevention and treatment of non-communicable chronic diseases, as a subset of health literacy.[11]

Nutrition is the process of taking in and utilizing essential nutrients from birth to sustain vital functions, promote growth and development, and enable individuals to live healthy and productive lives for an extended period.[12] Healthy eating, on the other hand, refers to consuming all necessary nutrients in sufficient quantities, in a balanced and diverse manner, and at appropriate times.[13] Achieving healthy eating behaviours requires accessing accurate information, evaluating it, and making informed decisions. It necessitates both knowledge and skills for individuals to implement specific dietary recommendations and guidelines. Having such knowledge and skills requires a good level of nutrition literacy.[14] Consequently, there has been an increasing global interest in topics such as "health, healthy living, and healthy eating" to enhance awareness of the importance of nutrition, understanding the relationship between nutrition and disease, and recognizing food and food groups.[15] This study aims to understand the health and nutrition literacy levels of adult individuals in Türkiye (formerly known as Turkey) and their attitudes toward healthy eating.

METHODS

The study was carried out with the permission of Çukurova University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 06.01.2023, Decision No: 129-73-64). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants and Setting

This study aimed to evaluate the attitudes of adult individuals towards healthy eating and their digital healthy diet literacy. The study was conducted with 150 participants aged between 19 and 65 living in Turkey, including 106 women and 44 men. Data were collected through an online survey prepared by the researchers between January 2023 and June 2023. Before filling out the survey, participants were provided with information about the study, and their written consent was obtained. The following ethical considerations were taken into account when including participants in the study: respecting the privacy of the participants, avoiding pressure on participants to complete the survey, providing an accurate and clear description of the study, and presenting the study in an unbiased manner by avoiding words that may invite specific responses.

Scales

An online survey form was used as the data collection tool in the study. The survey form consisted of three sections: i) sociodemographic characteristics, ii) health literacy scale and digital healthy diet literacy scale, iii) attitude scale for healthy nutrition (ASHN). Validity and reliability studies specific to the use of the scales (health literacy scale, digital healthy diet literacy scale, and attitude scale related to healthy eating) in Turkish adult individuals were conducted and the evaluation was made using intersection values/classification methods specific to these scales. In addition, permission for the use of the scales was obtained from the authors via email. The digital healthy diet literacy scale with four items was an extended domain of a comprehensive health literacy framework.[16,17] This scale was found to be a valid and reliable tool for the quick assessment of participants' ability to access, understand, appraise, and apply healthy diet information found on the internet.[18] The health literacy scale consisted of 12 items, the digital healthy diet literacy scale consisted of four items 18 and the attitude scale related to healthy eating consisted of 21 items and had a structure with four factors. The index values calculated by the formula for the scales ranged from 0 to 50. The attitude scale related to healthy eating had a minimum score of 21 and a maximum score of 105.[19] The validity and reliability study of the Turkish version of both scales was conducted to evaluate the health literacy and digital healthy diet literacy of individuals aged 18-65.[20] Participants' reported body weight and height information were used to calculate body mass index (BMI) using the formula body weight/height^2 (kg/m^2). The classification of BMI was based on the WHO classification, where BMI categories were defined as follows: <18.5 underweight, 18.5-24.9 normal weight, 25.0-29.9 overweight, and ≥30.0 kg/m2 obesity.[21]

RESULTS

In the present study, 70.7% of the participants in the study were female, and 29.3% were male. **Table 1** presents the distribution of individuals' demographic characteristics and health information by gender. Regarding marital status, 51.3% of the individuals are married, with 54.5% of male participants and 50% of female participants being married. The majority of individuals (87.6%) have a high school education or above (although not shown in the **Table 1**), 61.3% are employed, and 54.6% have an income level above 10.000 Turkish Lira.

Table 1. Characteristics of individuals

Characteristics	Males (n:44)		Females (n:106)		Total (n:150)		p**
	n	%	n	%	n	%	
Marital status							0.720
Married	24	54.5	53	50	77	51.3	
Single	20	45.5	53	50	73	48.7	
Employment status							0.139
Employed	31	70.5	61	57.5	92	61.3	
Unemployed	13	29.5	45	42.5	58	38.7	
Presence of chronic disease							0.650
Yes	7	15.9	22	20.8	29	19.3	
No	37	84.1	84	79.2	121	80.7	
Chronic disease							
Digestive system diseases	1	14.3	6	28.6	7	25.0	
Thyroid diseases	-	-	7	33.3	7	25.0	
Other (prostate, genetic factor deficiencies, kidney diseases, and glaucoma)	2	28.6	4	19.0	6	21.4	
Cardiovascular diseases	2	28.6	2	9.5	4	14.3	
Mental/psychological disorders	-	-	2	9.5	2	7.1	
Diabetes	1	14.3	-	-	1	3.6	
Eating disorders	1	14.3	-	-	1	3.6	
Income (per month, TLa)							0.192
0 - 5000	7	15.9	30	28.3	37	24.7	
5001 - 10.000	10	22.7	21	19.8	31	20.7	
Above 10.000	27	61.4	55	51.9	82	54.6	
Daily screen time (hour)							0.037
0-2	9	20.5	16	15.1	25	16.7	
2-4	10	22.7	31	29.2	41	27.3	
4-6	13	29.5	24	22.6	37	24.7	
Above 6	12	27.3	35	33.0	47	31.3	

a TL: Turkish Lira, b p<0.05

In terms of health information, 19.3% of individuals, with 15.9% of males and 20.8% of females, have been diagnosed with a chronic illness. Among those with a diagnosis, 14.3% have cardiovascular disease (28.6% of males and 9.5% of females), 25% have digestive system disease (as shown in Table 1) (14.3% of males and 28.6% of females), 14.3% of males have diabetes and eating disorders, and 33.3% of females have thyroid disease. Additionally, 21.4% of individuals have various other diseases such as prostate issues, genetic factor deficiencies, kidney diseases, and glaucoma.

When examining the distribution of individuals' daily screen time, it is determined that 27.3% of male individuals and 33% of female individuals spend 6 hours or more in front of screens. Additionally, 29.5% of male individuals and 22.6% of female individuals spend 4-6 hours, 22.7% of male individuals and 29.2% of female individuals spend 2-4 hours, and 20.5% of male individuals and 15.1% of female individuals spend less than 2 hours per day in front of screen.

The distribution of sources for acquiring nutrition and health-related information by gender is presented in Figure 1. It is found that 30.7% of individuals, including 20.5% of male individuals and 34.9% of female individuals, obtain information from academic websites such as PubMed. Additionally, 20.7% of individuals, with 25% of males and 18.9% of females, acquire information from news websites. Furthermore, 48.6% of individuals, including 25% of male individuals and 33% of female individuals, obtain information on nutrition and health from various social media platforms such as Instagram, Twitter, WhatsApp, Telegram, and Facebook.

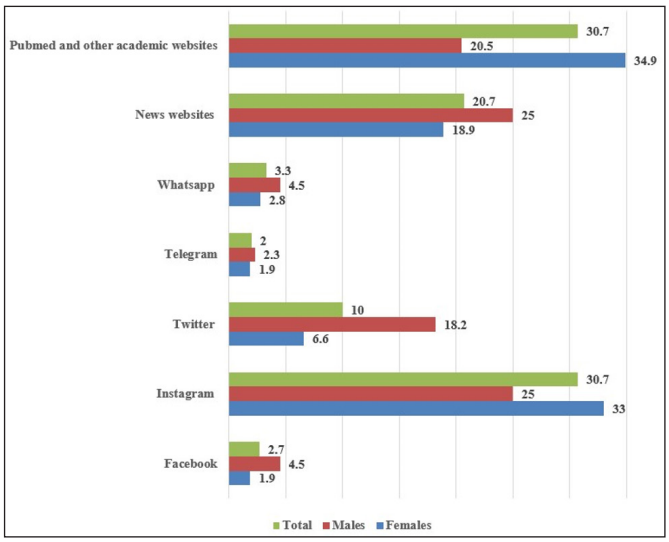

Figure 1. Sources of information on nutrition and health

Figure 2 presents the distribution of individuals' BMI according to WHO criteria. Among male individuals, 40.9% are overweight, 38.6% have a normal BMI, 15.9% are obese, and 4.5% are underweight. Among female individuals, 61.3% have a normal BMI, 18.9% are overweight, 16% are obese, and 3.8% are underweight.

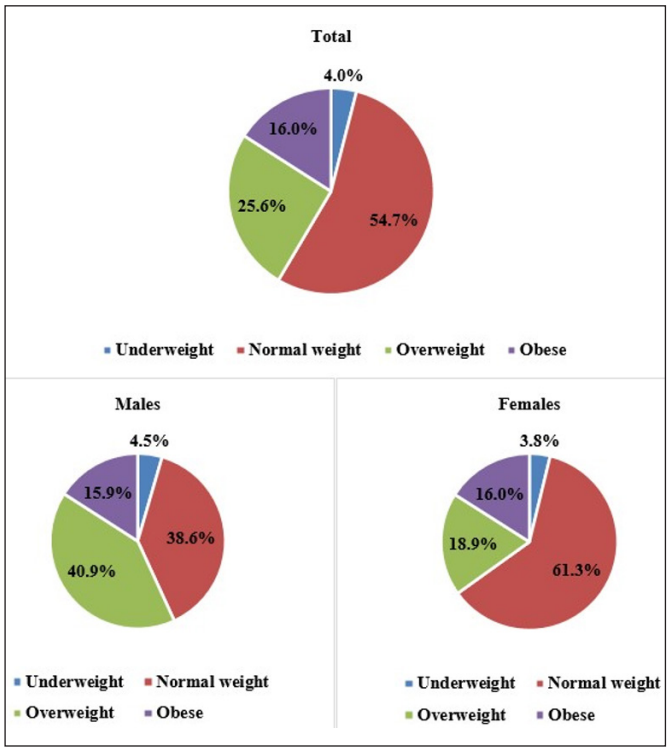

Figure 2. Distribution of individuals' body mass index according to WHO criteria

The evaluation of individuals' attitudes towards healthy eating using the ASHN by gender is presented in Table 2. According to the table, 69.3% of individuals, including 65.9% of males and 70.8% of females, have high scores indicating a positive attitude towards healthy eating. Furthermore, 21.3% of individuals, including 18.2% of males and 22.6% of females, have moderate scores. Additionally, 5.4% of individuals, including 7.3% of males and 3.8% of females, have very high scores, while 8.4% of individuals, including 12.6% of males and 5.1% of females, have low scores indicating a less healthy eating attitude. The difference in ASHN scores between genders was not found to be statistically significant (p>0.05).

Table 2. Attitude scale for healthy nutrition scores according to the gender

ASHNa Score	Males (n:44)		Females (n:106)		Total (n:150)		pb
	n	%	n	%	n	%	
Very poor healthy eating (21-22 points)	-	-	-	-	-	-	
Low healthy eating (23-42 points)	2	4.5	2	1.9	4	2.7	
Moderate healthy eating (43-63 points)	8	18.2	24	22.6	32	21.3	0.583
High healthy eating (64-84 points)	29	65.9	75	70.8	104	69.3	
Very high healthy eating (84-105 points)	5	11.4	5	4.7	10	6.7	

a ASHN: Attitude scale for healthy nutrition, b p<0.05

The evaluation of ASHN according to BMI is given in Table 3. According to this; 83.3% of underweight individuals, 67.1% of normal-weight individuals, 71.1% of overweight individuals and 70.8% of obese individuals had a healthy diet with high ASHN scores; It was determined that 7.3% of normal-weight individuals, 2.6% of overweight individuals and 12.5% of obese individuals had ASHN scores in the very high healthy diet range.

In Table 4, the analysis of determinants of the digital healthy diet literacy scale, which is considered the dependent variable, is shown using multivariate linear regression models. The regression model incorporates variables such as age, gender, marital status, education, employment status, monthly income level, presence of chronic illness, daily screen time, sources of health and nutrition information, BMI and ASHN. The variables that were found to be statistically significant (p<0.05) in the regression model are employment status, presence of chronic illness and daily screen time.

DISCUSSION

It is expected that individuals who have higher nutrition and health literacy might have better eating behaviors as well as attitudes towards healthy nutrition depending on the characteristics such as age, gender, BMI, profession and health status. In this study, using a multivariate linear regression model, we have shown that screen time, presence of chronic diseases and employment status were the main determinants of digital healthy diet literacy.

Table 3. Attitude scale for healthy nutrition scores according to the body mass index

	Underweight (n:6)		Normal weight (n:82)		Overweight (n:38)		Obese (n:24)		Total (n:150)	
ASHN Score	n	%	n	%	n	%	n	%	n	%
Very poor healthy eating (21-22 points)	-	-	-	-	-	-	-	-	-	-
Low healthy eating (23-42 points)	-	-	3	3.7	1	2.6	-	-	4	2.7
Moderate healthy eating (43-63 points)	1	16.7	18	22.0	9	23.7	4	16.7	32	21.3
High healthy eating (64-84 points)	5	83.3	55	67.1	27	71.1	17	70.8	104	69.3
Very high healthy eating (84-105 points)	-	-	6	7.3	1	2.6	3	12.5	10	6.7

ASHN: Attitude scale for healthy nutrition

Table 4. Determinants of digital healthy diet literacy scale via multivariate linear regression models

	β1 (%95 CI)	SE	β2	t	p	Zero	Partial	Part	VIF
(Constant)	-12.614	8.629	-	-1.462	0.168	-	-	-	-
Age (year)	0.043	0.046	0.240	0.949	0.369	0.100	0.255	0.129	3.478
Gender	-0.509	0.912	-0.094	-0.558	0.360	-0.083	-0.153	-0.076	1.544
Marital status	2.837	1.106	0.564	2.565	0.586	0.099	0.580	0.348	2.629
Employment status	1.284	1.141	0.247	1.125	0.023	-0.228	0.298	0.152	2.624
Education	1.771	0.580	0.575	3.056	0.281	0.426	0.647	0.414	1.925
Presence of chronic diseases	-4.205	2.339	-0.335	-1.798	0.009	-0.358	-0.446	-0.244	1.888
Monthly income status	0.636	0.235	0.642	2.708	0.953	0.373	0.600	0.367	3.066
Screen time (hour)	-0.295	0.154	-0.373	-1.910	0.018	-0.182	-0.468	-0.259	2.082
Sources of information on nutrition and health	0.039	0.092	0.035	0.431	0.079	0.035	0.035	0.035	1.000
BMI (kg/m2)	-1.448	1.695	-0.479	-0.854	0.409	0.099	-0.230	-0.116	17.161
ASHN score	0.099	0.623	0.028	0.159	0.876	0.322	0.044	0.022	1.649

*SE: Standard error; CI: Confidence interval; VIF: Variance inflation factor; BMI: Body mass index; ASHN: Attitude scale for healthy nutrition, Dependent variable: Digital healthy diet literacy scale; β1 Non-standard coefficient; β2: Standard coefficient; F 3.190; p<0.05; Adj. R2=0.761.

On the other hand, ASHN, a score for attitudes towards healthy nutrition, was not found to be a statistically significant determinant after the digital healthy diet literacy determinants were examined.

Dietary intake may change based on the presence of chronic diseases due to the fact that individuals with one or multiple chronic diseases are more tend to have healthier choices. A relationship between dietary patterns and chronic diseases has been shown in the literature.[22] However, it is also known that adults who have multiple chronic disease risk factors reported poorer diet quality.[23] Taylor et al.[24] have reported that nutrition literacy may predict adherence to a healthy or an unhealthy diet pattern in adults who have a nutrition-related chronic condition. Considering the long-term impacts of adherence to an unhealthy diet, it is highly possible to see a relationship between the presence of chronic diseases and diet patterns. Hence, having low healthy diet literacy scores might be the cause of the presence of chronic disease. In our study, we have found a reverse relationship between having chronic diseases and digital healthy diet literacy. Digital healthy diet literacy was found to be 4.205 units lower in those who had one/multiple chronic diseases (p=0.009). This result indicates that lower healthy diet literacy scores might have caused poor dietary intake, which could be the reason why those who have chronic diseases had lower digital healthy diet literacy scores.

The association between BMI/body weight status and nutrition/healthy diet literacy has been reported in many studies and different results have been shown.[24-26] It is possible to say that BMI might have either a positive or negative relationship with nutrition literacy. Some studies showed that individuals with higher BMI had lower nutrition literacy, while in some others positive association between BMI and nutrition literacy has been reported.[24,25] Even though BMI has been shown to be an important determinant of both healthy eating behavior and healthy diet literacy, in some studies authors did not find any relationship.[26,27] Similarly, in the present study, BMI was not associated with healthy diet literacy in adults (p>0.05). This inconsistency in findings may be due to several factors related to the participants, including the age and gender as well as the methods used for measuring body weight. There are many scales which are used to measure nutrition literacy. The health literacy scale and digital healthy diet literacy scales, which are suggested to be used together, were used in the present study. The health literacy scale and digital healthy diet literacy scale are relatively recent scales and a validity and reliability study have been recently done in the Turkish population.[20] Hence, it is also important to indicate that although the main aim of the literacy scales is the same, however, different scales might be a reason why studies have reported different results from each other.

A large body of research has shown that there is a socioeconomic gradient in diet quality. In other words, people with higher socioeconomic status tend to have healthier diets than people with lower socioeconomic status. This is likely due to a number of factors, including access to healthy foods, knowledge about healthy nutrition, and time and resources.[28] It is known that energy-dense foods, such as processed snacks and sugary drinks, are relatively inexpensive, while nutrient-dense foods, such as fruits and vegetables, are more expensive.[29] The present study tried to explore the association between diet literacy and employment status of the participants. As expected, similar results have been found in the present study. Employment status was positively related to healthy diet literacy. Digital healthy diet literacy was 1.284 units higher in those who were employed (p=0.023). It can be concluded that people with limited financial resources are more likely to consume energy-dense foods and have poor diet quality which can lead to weight gain and other health problems such as insulin resistance and obesity.

It has been very well documented that screen time causes poor diet quality, greater adiposity/obesity and poorer life quality in different age groups. Studies on children, adolescents and adults reported that higher screen time is closely associated with psychosocial development, physical health and cognitive skills, depression and anxiety symptoms, insomnia, eye-related problems (myopia and dry eye syndrome) and higher energy and sweetened foods intake.[30-32] Adult individuals who spend 2.5 to 4 hours per day watching television have twice the likelihood of being overweight, while those who watch more than 4 hours per day are four times more likely to be overweight than those who watch less than 1 hour per day.[33] On the other hand, following the recommended amount of screen time was linked to a higher chance of having healthy eating habits. Girls who watched up to 2 hours of screen time were more likely to eat breakfast and have fresh produce and fish in their diet while boys who followed the screen time recommendation had a greater likelihood of eating breakfast, fresh fruit, and fish.[31] In the present study, the screen time of more than half of the participants was above 6 hours. Additionally, those who reported higher screen time had lower healthy diet literacy scores. Overall, high screen time is a problem across all age groups and it is significant to stick to the screen time guideline to be able to decrease the likelihood of consuming unhealthy foods and drinks, the risk of noncommunicable diseases.

CONCLUSION

This study has shown that BMI and ASHN were not determinants of health literacy and digital healthy diet literacy while employment status, presence of chronic illness and screen time were significant determinants. It is clear that the use of electronics has increased drastically in recent years and it is expected to see even higher use of electronics in future. Availability of information has become effortless; however, it is still a challenge for individuals to reach reliable information sources. Hence, despite having easy access to information cannot be translated that individuals would have higher health and nutrition literacy. It is recommended to conduct larger studies on different groups in the population as well as to increase the awareness of the individuals via reliable sources.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Çukurova University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 06.01.2023, Decision No: 129-73-64).

Informed consent: All participants were informed consent form before they participated in the study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Pctx1 venom in the treatment of vasospasm due to experimental subarachnoidal hemorrhage

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ABSTRACT

Aims: We aimed to investigate the role of neuron damage in experimental animals following vasospasm, by increasing perfusion of neuronal tissue through vasodilation using the venom of PcTx1, and to determine its effectiveness in reducing neuron damage after vasospasm.

Methods: Thirty adult male Wistar albino rats weighing between 300 and 400 grams were used and divided into three groups: the Sham group (Group 1, n=10), to which no application was made; the SAH (control) group (Group 2, n=10), in which a double SAH model was created and 1 cc of saline was administered intraperitoneally; and the SAH+PcTx1 group (Group 3, n=10), in which a double SAH model was created and 1 cc/kg of PcTx1 venom was administered intraperitoneally daily. Basilar artery diameter and immunochemical measurements were performed histopathologically, and neurohistopathological findings were scored semiquantitatively in terms of vascular changes, neuron degeneration, gliosis, and bleeding criteria using a scale of 0 (none), 1 (mild), 2 (moderate), or 3 (severe). eNOS immunopositivity was also evaluated. The detection of apoptosis in the brain was performed by evaluating the effector enzyme caspase-3 immunoreactivity of the exogenous apoptosis pathway.

Results: The most severe vascular spasm and degeneration-necrosis of brain tissue gray matter neurons were seen in Group 2, whereas the vascular narrowing was less severe in Group 3. Brain parenchyma and neuron and neuroglial reactions were milder in Group 3. eNOS expression was detected at a higher level in Group 1, Group 2, and Group 3, respectively. For apoptosis and caspase-3 immunoreactivity of the exogenous apoptosis pathway, no immunopositive reactions were observed in Group 1.

Conclusion: For the occurrence and formation mechanisms of vasospasm after subarachnoid hemorrhage, this pathological condition is thought to result from multifactorial and various biochemical reactions. In our study, it was found that psalmotoxin effectively prevented vasospasm and significantly reduced tissue damage after vasospasm.

Keywords: Experimental subarachnoidal hemorhage, psalmotoxin, venom, vasospasm

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a condition in which blood spreads to the subarachnoidal space due to various pathologies. The first condition of vasospasm-related mortality and morbidity reduction is to take preventive measures in the patient who has had aneurysmal SAH and whose aneurysm has been successfully clipped with surgical intervention , to monitor the patient very closely on the most risky days in terms of vasospasm and to intervene with the least suspicious energetic treatment.[1-8]

Cerebral vasospasm is the main cause of focal cerebral ischemia after subarachnoid hemorrhage. The vasospasm is most risky complication for subarachnoid hemorrhage in terms of mortality and morbidity.[9-11]

Although the physiopathology of cerebral vasospasm is not conclusive, there is no doubt that blood reaching subarachnoid distance causes the development of cerebral vasospasm. Experimental studies have shown that blood injected to subarachnoid distance causes vasospasm.

Vasoactive substances are released as a result of hemolysis of erythrocytes reaching subarachnoid distance. In vitro and in vivo studies have shown that oxyhemoglobin is the main culprit in the development of vasospasm among these substances. Oxyhemoglobin causes the secretion of vasoconstrictor prostaglandins from endothelial cells. It has been shown in various experimental models that vasoactive prostaglandins of PGF2-alpha, PGD2, PGE2 and thromboxane A2 increase in vasospasm, which are products of arachidonic acid metabolism.[12-17]

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The effect of free radicals in the etiology of cerebral vasospasm has also been investigated in experimental and clinical studies. Superoxide anion radical emerges during methemoglobine autoxidation of oxyhemoglobin.[18] In addition, iron compounds emitted into the environment during the destruction of hemoglobin catalyze the Haber-Weiss reaction, resulting in the emergence of hydroxyl radical (OH) from the most reactive radicals. Many drugs are still being tried in the treatment of symptomatic vasospasm, which is defined as a syndrome caused by ischemic signs and symptoms associated with progressive narrowing of cerebral vessels. Acid detection ion channel 1a (ASIC1a) is the basic acid sensor in the mammalian brain and plays an important role in neuronal damage after cerebral ischemia. Evidence of neuroprotective effect of ASIC1a inhibition was obtained by using "PcTx1 venom" from tarantula Psalmopoeus cambridgei before. The observed neuron protective effect of this ASIC1a selective inhibitor PcTx1 has been shown in the literature that PcTx1 is due to hundreds of ASIC1a ion channel blockades or blocking of other ion channels and receptors.[19-23] (**Figure 1**).

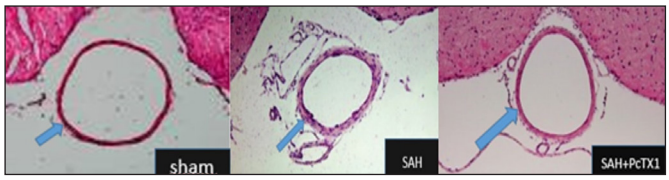

Figure 1. Induced vasospasm after experimental SAH. The hematoxylin-eosin-stained sectional pictures of the basilar artery indicated by the blue arrow group 1, group 2 and group 3 are shown. In rats with SAH treated with PCTx1 venom, the basilar artery lumen area appears to be dilated. (Scale bars=200 μm).

For this reason, it was thought that PcTx1 venom may be effective in vasospasm through direct inhibition of ASIC1a. Severe oxygen depletion that occurs during ischemic stroke causes acidosis through increased lactate levels in order. Anaerobic glycolysis oxidative phosphorylation causes brain damage. pH drops and this severe ischemia occurs.[13-15] In vivo studies show that acidosis increases ischemic brain injury and has been shown to have a direct correlation between brain acidosis and infarct size. Acidosis caused by decrease in cerebral pH can be activated by acid-sensing ion channels (ASIC) and this activation has been suggested to play a critical role in stroke caused by neuronal damage.[24] (**Figure 2**).

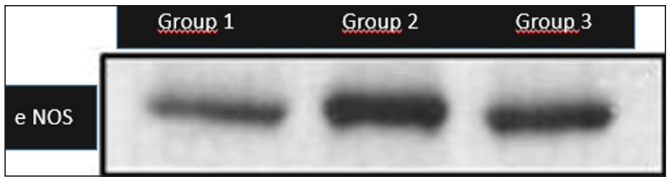

Figure 2: The picture shows a representative Western blots investigating endothelial nitric oxide synthase levels (eNOS) in brain tissue.

ASIC has been observed to be depolarized with sensory neurons in response to a sudden drop in pH for almost 20 years. 13 Although ASICs are belong to the sodium canal of the epithelial tissue, it is also associated with a decrease in extracellular pH and calcium channels. 5 PcTx1, the most powerful and selective inhibitor of ASIC1a, is a 40-residue peptide isolated from the tarantula psalmopoeus cambridgei venom.[20] In studies in ischemic stroke models, PcTx1 has been proven to be neuroprotective.[21-23] In a rat model with transient focal ischemia (middle cerebral artery occlusion), 30 minutes ago and after ischemia induction, PcTx1 venom injection alleviates infarction by 60% and PcTx1 venom has an effect via ASIC1a.[14] These observations have improved our understanding of stroke pathophysiology and made it a therapeutic candidate for the development of neuron preservatives for stroke treatment. We wanted to investigate this activity by vasodilating through ASIC1a inhibition in the treatment of vasospasm after experimental cerebral subarachnoidal hemorrhage. For the occurrence and formation mechanisms of vasospasm after subarachnoid hemorrhage, this pathological condition is thought to result from multifactorial and various biochemical reactions.

In the present study, investigated the role of neuron damage in experimental animals after vasospasm in preventing neuron damage by increasing the perfusion of neuronal tissue by vasodilatation with venom of PcTx1 and its effectiveness in reducing neuron damage after vasospasm.

METHODS

This study was carried out between 2016-2019 in Kırıkkale University Faculty of Medicine Laboratory of Experimental Animals after the approval of Kırıkkale University Animal Experiments Local Ethics Committee (Date: 02.02.2016, Decision No:16/01-16/18). The materials were evaluated in the Laboratory. All animals received humane care in compliance with the principles of laboratory animal care developed by the National Academy of Sciences.

In Vivo Rat Model

In our study, apart from the neuron protective effect, the effect of PcTx1 venom on vasospasm was investigated by applying an experimental subarachnoidal hemorrhage model in Wistar albino rats weighing 300-400 g. Rats were housed in ad libitum environment at least 1 week and after that the experiment began.

Thirty adult male Wistar albino rats weighing between 300 and 400 grams were used and were divided into three groups:

Sham group (Group 1, n: 10): No application was made to the control-sham group.

Experimental SAH control group (Group 2, n: 10): Experimental SAH (autologous blood injection into cisterna magna of rats in this study) was created in the control group. After the first hemorrhage, a double SAH model was used at 48th hour and 1 cc normal saline was administered intraperitoneally.[23]

Experimental SAH+PcTx1 group (Group 3, n: 10): Experimental group underwent a double SAH model repeated at 48 hours after the creation of experimental SAH and first bleeding. Then, 1 cc / kg PcTx1 venoma (Tarantula D6, Richter Pharma AG, Austria) was administered intraperitoneally daily.[23]

On the 14th day, all groups were sacrificed. The brain of the rats was excised and basilar artery diameter and immunochemical measurements were performed histopathologically. Neurohistopathological findings were scored semiquantitatively in terms of vascular changes, neuron degeneration, gliosis and bleeding criteria and 0=None; 1=Mild, 2=Moderate and 3=Severe.

Double Sah Model

Ketamine Hydrochloride (Ketalar flacon,Pfizer) 60 mg/kg and Xylazine (Rhompun 2% injectable flacon, Bayer) 12 mg /kg intraperitoneal (i.p.) were applied to all rats after twelve hours of starvation to provide general anesthesia. The prone position was detected and operation site cleaning was performed with 10% povidone iodine solution (Batticon 10%, Adeka Pharmaceutical Industry). Subarachnoid space was reached by puncture with 23G cannula from occipito-atlantal distance by bringing head flexion. Autologous blood injection was performed to Cisterna magna and experimental subarachnoid hemorrhage (SAH) was created. 48-hour after the first bleeding, the dual SAH model was used by repeating the same procedure.[23] On the 14th day, high dose ketamine hydrochloride (Ketalar flacon,Pfizer) 100 mg/kg and Xylazine (Rhompun 2% injectable flaconi, Bayer) were administered as 12 mg/kg i.p. The rats underwent bilateral fronto-parieto-occipital craniectomy. The cerebrum, cerebellum and brainstem remaining on the foramen magnum have been removed to preserve their total anatomical integrity. Then the rats were sacrificed.

Histopathological Examination

After euthanasia, each rat's brain was removed and detected for 48 hours in 4% buffered paraformaldehyde. After 24 hours of washing under running water, the fixed tissues were treated for routine follow-up after being treated with alcohol (50%, 60%, 70% ,90% and absolute alcohol) and xylol, and paraffin burial was performed. Sections with a thickness of 5 µm were obtained from each block.The sections taken were stained with hematoxylin-eosin and analyzed by immunohistochemical staining for eNOS and apoptosis (eNOS and apoptosis) procedures.

Immunoperoxidase Examination

In order to determine the presence of the relevant antigen in the tissues under examination, a streptavidin-biotin immunoperoxidase kit was used in accordance with the kit's procedure. The sections were deparaffinized in xylene and then kept in distilled water for 5 minutes before being rehydrated in a graded alcohol series. The tissues' hydrogen peroxidase activity was eliminated by holding them in 3% peroxide for 15 minutes. After a 20-minute boiling in sodium citrate (pH 6.0), the antigen retrieval process was performed. The tissues were then held in protein blocking serum for 7 minutes and incubated in 1/200 dilution prepared eNOs and Caspase-3 antigen-specific monoclonal antibodies at room temperature for 1 hour. After 15 minutes of secondary antiserum labeled with biotin, the tissues were exposed to the enzyme streptavidin peroxidase for 15 minutes. The Aminoethyl Carbazole (AEC) chromogen was dripped for the color process, and Mayer's hematoxylin was used for 1-2 minutes for counter-staining. After this process, the painted tissues were covered with water-based adhesive.

Basillary Artery Diameter Measurement

The sections obtained from each rat were evaluated by light microscope. Among the series sections taken for the measurement, the section with the most appropriate viewing was selected. By examining the preparations, the basillary artery diameters were evaluated in the BAB Bs200pro program using the Olympus BX 51 (Japanese) computer-aided microscope system and photographed. In the basillary artery images, image-processing and system analysis measured by an impartial observer who did not know the groups. 10 measurements extending from four sections of each subjects to the vascular lumen were made and their standard deviations and averages were calculated (**Figure 1**).

Statistical Analysis

SPSS 20 (IBM SPSS Incorporated, Chicago, IL, USA) were used for the analysis. Kruskal-Wallis variance analysis and Mann Whitney U test with Bonferroni adjustment were used. A p value <0.05 was considered for significance. When Bonferroni adjustment was performed, padjusted<0.0175 was considered for significance.

RESULTS

Neurohistopathological findings, vascular changes, neuron degeneration, gliosis and bleeding criteria were scored semicantatively and accordingly 0=None; 1=Mild, 2=Moderate and 3=Severe.

eNOS, apopitosis, vascular changes, neuronal degeneration, gliosis scores and basillar artery diameter measurement results were shown on Table 1. The difference between groups were statistically significant ($p<0.05$). To find the values which caused difference, Pairwise comparisons by Mann Whitney U Test with Bonferroni Adjustment were performed and p adjusted <0.0175 is considered as statistically significant.

- eNOS values of the Group 1 was statistically higher than those in Group 2; and Group 3 (padjusted<0.0175) (Table 2).
- Apopitosis values of Group 3 was significantly lower than those in Group 1 and Group 2 (padjusted<0.0175) (Table 2).
- Vascular changes, neuronal degeneration, gliosis scores were found as group 2>group 3 (Experimental PcTx1 group) >group 1 (padjusted<0.0175) (Table 2).
- Basillar artery diameter values of Group 3 was significantly higher than those in Group 1 and Group 2 (padjusted<0.0175) (Table 1). Basillar artery diameter of Group 2 was also lower than group 1 (padjusted<0.0175) (Table 1).

Histopathological Findings

According to histopathological findings obtained in the study, the most advanced vascular spasm and degeneration-necrosis in brain tissue gray matter neurons are seen in the experimental SAH group 2. Whereas in the brains of the group 3, vascular contraction is milder and consequently neuron and neuroglial reactions appear to be slightly shaped. The group 1 had minimal pathological changes among all groups, and histological findings are limited to bleeding only in the meningeal tissues surrounding the brain root.

Group 1 (Sham): In brain tissues of healthy rats, in addition to minimal hyperemia in the meningeal tissues surrounding cudex cerebri, cerebellum, pons and medulla oblongata, hemorrhage areas were observed in 3 cases, limited to the meningeal region. Neuron and neuroglial tissues had a normal histological appearance. These histopathological changes were interpreted as changes after meningeal damage during the extraction of brain tissue (Figure 1).

Group 2 (SAH-control): The common finding of the brain tissues examined was characterized by free erythrocyte piles compatible with bilateral hematoma, partly around the cerebellum meninx tissues with pons and medulla oblongata. In the brain gray substance close to these areas; advanced vasospasm (contraction), neuronal degeneration, necrosis, multifocal gliosis and focal hemorrhages were observed in the capillaries. It was found that the lumen narrowed as unselectable and the lumen structures were not selected in the capillaries contained in the gray matter and in other veins; and in partially healthy ones, there was a significant contraction. In neurons, in mildly degenerated neuron groups, while central chromatolysis and satellitosis were common, some neurons were found to shrink and take spindle shape and their cytoplasm was homogeneous and dark eosinophilic. In this group of rats' brain tissues, common findings were hematoma pressing on the meninx and brain gray matter in the region where the operation is performed and degenerative changes (Figure 1).

Table 1. Neurohistopathological findings and Basillar artery diameter measurement results of the group

	Group 1 (n=10)			Group 2 (n=10)			Group3 (n=10)			P*
	Median	Min	Max	Median	Min	Max	Median	Min	Max	
eNOS	15.50	11.00	21.00	17.00	8.00	23.00	20.00	16.00	24.00	0.000
Apopitosis	21.00	16.00	27.00	84.50	68.00	102.00	13.50	8.00	20.00	0.000
Vascular changes	0.00	0.00	1.00	3.00	2.00	3.00	1.00	1.00	2.00	0.000
Neuronal degeneration	0.00	0.00	1.00	3.00	2.00	3.00	1.00	1.00	2.00	0.000
Gliosis	0.00	0.00	0.00	2.50	1.00	3.00	1.00	1.00	2.00	0.000
Basillar artery diameter	87.00	76.85	92.38	74.37	65.34	80.29	83.40	74.78	89.38	0.000

*p value shows the results of Kruskal Wallis Test

Table 2. Pairwise comparisons by Mann Whitney U Test with Bonferroni Adjustment

	Group 1-Group 2		Group 1-Group 3		Group 2-Group 3	
	z	padjusted*	z	padjusted*	z	padjusted*
eNOS	-3.565	0.000	-3.195	0.001	-1.878	0.060
Apopitosis	-3.784	0.000	-3.408	0.001	-3.782	0.000
Vascular changes	-3.963	0.000	-3.342	0.001	-3.527	0.000
Neuronal degeneration	-4.038	0.000	-3.827	0.000	-3.527	0.000
Gliosis	-4.091	0.000	-4.147	0.000	-3.022	0.003
Basillar artery diameter	-3.628	0.000	-3.780	0.000	-3.780	0.000

*padjusted<0.0175 is considered as statistically significant

Group 3 (SAH + PcTx1): In this group of rat brains, unlike the histological changes described in the previous study group (Group 2), much milder meningeal hematoma, vasodilatation in vascular structures and adjacent degenerative changes in gray matter were recorded. However, the capillary lumens are open and the inside of them, smaller amounts of erythrocytes were present. Some medium-sized vessels have a normal lumen appearance and appearance of vascularisation were detected. In neurons, degenerative changes were moderate in the form of satellitosis, chromatolysis and cytoplasmic contraction in two cases, while in other cases mild chromatolysis was characterized (**Figure 1**).

Immunohistochemistry Findings

In immunopathological examinations; eNOS immunoreactivities was observed in rat brains, especially in the capillaries contained in the gray substance of the brain root and in the medium-sized muscular vessels in the meninx. In general, immunoreactivities were selectively limited to endothelial cells, whereas in some cases eNOS showed homogeneous pattern in vascular lumens. Group 3 had the highest eNOS immunopositivity, followed by group 2 and then group 1.

For the purpose of detecting apoptosis in the brain; caspase-3 immunoreactivity (the effector enzyme of the external apoptosis pathway) were examined in the groups. There were no immunopositive reactions in the group 1, whereas apoptotic activity was generally low in group 3. Apoptotic cells were slightly higher in group 2 (**Figure 2**).

DISCUSSION

Vasospasm is a complex pathophysiological process that can occur following subarachnoid hemorrhage (SAH), potentially leading to severe neuronal damage and neurological deficits. In this study, we investigated the role of PcTx1 venom in the treatment of vasospasm induced by experimental SAH in Wistar albino rats. Our objective was to determine whether PcTx1 venom administration could mitigate vasospasm and reduce neuronal damage, shedding light on potential therapeutic avenues for this challenging condition.

Clinical symptoms typically manifest around the 7th day, while radiological findings are usually identified around the 9th day on average. CT plays a crucial role in identifying ischemic areas and ruling out other potential causes, such as intracranial hematoma and hydrocephalus, particularly in patients experiencing clinical deterioration. Among a series of 135 cases studied following SAH, angiographic vasospasm was observed in 68% of cases, while 21% exhibited CT evidence of infarction.[20] Preliminary studies suggest that positron emission tomography (PET), single photon emission CT (SPECT), and perfusion-weighted CT and MRI examinations may be beneficial for early diagnosis in the evaluation of vasospasm-induced hypoperfusion and ischemia.[21]

Preventing the development of vasospasm is crucial in patients who have undergone successful closure of aneurysmal subarachnoid hemorrhage (SAH) in order to minimize mortality and morbidity associated with this condition. In the SAH (control) group, we observed the most severe vascular spasm and degeneration-necrosis of gray matter neurons. These findings are consistent with the well-established notion that vasospasm can result in reduced cerebral blood flow, ischemia, and subsequent neuronal damage. The narrowing of cerebral vessels and associated hemodynamic changes play a pivotal role in the pathogenesis of SAH-induced neuronal injury.[25]

In contrast, in the SAH+PcTx1 group, we noted significantly less severe vascular narrowing and milder brain parenchyma and neuron reactions. This suggests a potential neuroprotective effect of PcTx1 venom in preventing vasospasm-induced neuronal damage. The mechanism underlying this protective effect may involve the venom's ability to induce vasodilation, thereby increasing perfusion to neuronal tissue. Previous studies have highlighted the vasodilatory properties of certain venom components, supporting our observations.[26,27]

Our analysis of endothelial nitric oxide synthase (eNOS) expression revealed interesting findings. eNOS is an enzyme responsible for the production of nitric oxide (NO), which is a potent vasodilator.[28] We observed that eNOS expression was higher in both the SAH (control) group and the SAH+PcTx1 group compared to the sham group. This suggests a compensatory response to the vascular changes induced by SAH, where the endothelium attempts to counteract vasospasm by increasing NO production. However, in the SAH+PcTx1 group, the increase in eNOS expression was more pronounced, possibly reflecting the venom's direct influence on endothelial function and NO release.

Origitano et al.[22] identified three H treatments consisting of hypertension, hypervolemia, and hemodilution. In the following years, this treatment was routinely applied after surgery in many centers where aneurysm surgery was performed, but the suggestion of phlebotomy for hemodilution mentioned in the original article was not widely adopted. Complications of this treatment, which is used to restore symptomatic vasospasm in addition to prophylaxis, include pulmonary edema, myocardial infarction, delusional hyponatremia due to fluid loading, cerebral edema, hemorrhagic cerebral infarction, and cardiac arrhythmias. Due to these complications,

which can be considered quite severe, there has been an increasing argument in recent years that this application should be reserved for vasospasm cases that require treatment rather than prophylaxis.

To take measures to prevent the development of vasospasm in the patient who has suffered aneurysmal subarachnoid hemorrhage and whose aneurysm has been successfully clipped surgically, especially during the most risky days for vasospasm, to monitor the patient very closely and to interfering with an energetic treatment is the first condition for reducing vasospasm-induced mortality and morbitidy.

In a study conducted by Farabi et al.[29] it was observed that ASIC channels are abundantly expressed in various brain regions, including neuronal structures, and they can cause major changes in arteriolar diameter by affecting the microvascular wall structures. Therefore, it was suggested that the inhibition of ASIC1A channel could theoretically be effective in preventing vasospasm after subarachnoid hemorrhage.These findings support the idea that ASIC1A channel could be targeted to prevent vasospasm after subarachnoid hemorrhage. However, they also provide information about the potential effects of ASIC channels on cerebral circulation.

In the study conducted by Koehn et al.[30] it was shown that PcTx1, used as an ASIC1A inhibitor, had neuroprotective effects within the first 24 hours on mice with spinal cord injuries (both mechanical and hemorrhagic). Additionally, histological examinations performed at 24 hours and 6 weeks after the injury showed that the dorsolateral white matter of mice treated with PcTx1 was better preserved. These results indicate the potential use of PcTx1 as a therapeutic agent against spinal cord injuries.

Furthermore, we investigated apoptosis using caspase-3 immunoreactivity. In the sham group, no immunopositive reactions for apoptosis were observed, indicating the absence of apoptotic cell death in normal conditions. However, in the SAH (control) group, where vasospasm was severe, it is plausible that ischemia-induced cell death pathways, including apoptosis, were activated, contributing to neuronal damage.31 Importantly, the SAH+PcTx1 group exhibited reduced neuronal apoptosis, suggesting a potential anti-apoptotic effect of PcTx1 venom.

The underlying mechanism by which psalmotoxin exerts its vasospasm-preventive effects is thought to involve its ability to modulate specific cellular pathways involved in vascular tone regulation. By targeting these pathways, psalmotoxin may effectively inhibit the constriction of cerebral blood vessels and subsequent development of vasospasm.[32] Moreover, the observed reduction in tissue damage suggests that psalmotoxin may also have neuroprotective properties, which could further contribute to its therapeutic potential in preventing vasospasm-induced neuronal injury.

Our findings have significant clinical implications. Vasospasm remains a challenging and often devastating complication of SAH, with limited treatment options. The neuroprotective effects of PcTx1 venom demonstrated in this study warrant further investigation as a potential therapeutic intervention for vasospasm management. However, it is essential to acknowledge that translating these findings from an animal model to clinical practice will require extensive research and safety evaluations.

To fully establish the clinical utility of psalmotoxin in the treatment of vasospasm and its associated neuronal damage, additional experimental studies are required. These studies should focus on elucidating the optimal dosage, administration route, and treatment duration of psalmotoxin. Furthermore, investigations into potential adverse effects and drug interactions should be conducted to ensure the safety and tolerability of psalmotoxin in clinical settings.

Limitations

We conducted experiments on a rat model, and the translation of these findings to human patients may differ due to species-specific variations. Additionally, the mechanisms underlying PcTx1 venom's effects on vasospasm and neuronal damage require further elucidation. Future research should focus on in-depth molecular and cellular investigations to understand the precise mechanisms involved.

CONCLUSION

As a result of clinical and laboratory studies on the occurrence and formation mechanisms of vasospasm after subarachnoid hemorrhage, this pathological condition occurs as a result of many multifactorial and intercomposed biochemical reactions. In our study, it was observed that psalmotoxin effectively prevented vasospasm and significantly reduced tissue damage after vasospasm. Therefore, the efficacy of psalmotoxin in the treatment of vasospasm and neuronal damage improvement is needed to be investigated in other experimental studies. Additionally clinical trials are also needed to evaluate new treatment methods to prevent vasospasm and to help neurological recovery.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Kırıkkale University Animal Experiments Local Ethics Committee (Date: 02.02.2016, Decision No:16/01-16/18).

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Real-life data of azacitidine-venetoclax combination in acute myeloid leukemia patients: a single center experience

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ABSTRACT

Aims: To evaluate real-life data on the efficacy and safety of Venetoclax (Ven) therapy used in combination with hypomethylating agent (HMA) in patients with acute myeloid leukemia (AML).

Methods: The records of newly diagnosed, relapsed or refractory (RR) AML patients over 18 years of age who were planned to be treated with Azacitidine (AZA) combined with Ven because they were not suitable for intensive chemotherapy and patients who received AZA combined with Ven maintenance therapy after achieving remission were retrospectively analyzed. The standard protocol for patients is subcutaneous or intravenous AZA 75 mg/m2 on days 1-7/ every 28 days + oral Ven treatment 100-400 mg/day for 28 days. The treatment response rates, survival times, and side effect profiles of 18 newly diagnosed patients, 12 RR patients, and 4 patients receiving AZA+Ven as maintenance treatment between January 2021 and March 2022 were evaluated.

Results: It was found that 8 of the 34 patients (23.5%) who were examined in the present study died before the first response could be evaluated. When the response rates were evaluated, complete response (CR) or complete remission with incomplete blood count recovery (CRi) (CR+CRi) was found to be 61% in the group receiving AZA+Ven in the first line, and CR+CRi was 50% in the group receiving AZA+Ven because of RR AML. In the group receiving AZA+Ven in the first line, the average Overall Survival (OS) was 8.00 months (95% CI: 1.58-14.41), and 7.00 months in the RR group (95% CI: 1.78-12, 21). All patients in the group receiving AZA+Ven for maintenance purposes were alive and the median follow-up period was 12.50±6.02 months in this group (Mean±SD). The most common side effect was neutropenia, and the most common cause of death was disease progression.

Conclusion: In AML patients ineligible for intensive treatment due to advanced age or comorbidities, real-life data of AZA+Ven therapy with effective CR+CRi rates and a manageable spectrum of side effects promise hope.

Keywords: Acute myeloid leukemia, azacitidine, hypomethylating agent, venetoclax

INTRODUCTION

Targeted agents act specifcally in regions that are overexpressed in cancer cells, thereby they increase the effectiveness of antineoplastic therapy and significantly reduces the adverse effects (AEs), presented by conventional chemotherapy.[1] As one of the targeted treatments, Ven is an oral, highly selective inhibitor used against B-cell lymphoma 2 (BCL-2), which is an antiapoptotic protein and directs cells to apoptosis. Its use in acute myeloid leukemia (AML) has come to the agenda because BCL-2 is overexpressed in the leukemic stem cell population.[2] The incidence of AML, which is the most common type of acute leukemia in adults, is 3.5/100.000 per year.[3]

Since the median age at the time of AML diagnosis is 68, and a significant rate of patients are not suitable for intensive treatment because of accompanying comorbidities and low physical performance, fragile AML patients have been treated with HMA because of its tolerability and relatively safe profile for many years. The rates of complete remission with HMA alone are approximately 25-30% and the median OS is approximately 10 months.[4] Response with HMAs is achieved in a median of 3-4 months, however, only 2%-4% of patients aged ≥60 years who cannot undergo stem cell transplantation can maintain their disease-free status for 10 years after their treatment.[5]

Although a rapid response was achieved in monotherapy studies on Ven in AML, the fact that response rates were not permanent and that higher response rates were obtained in the group previously received HMA led to a tendency towards combination therapies.[6]

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The aim of this study was to evaluate real-life outcomes regarding efficacy and safety by analyzing the data of patients who received HMA-combined Ven therapy because they were not eligible for intensive chemotherapy and to compare them with the data obtained in clinical trials.

METHODS

The study was granted ethical approval by the University of Health Sciences Gülhane Scientific Researches Ethics Committee (Date: 27.06.2022, Decision No: 2022-249). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The file records of the patients who were followed up with a diagnosis of AML in the Adult Hematology Clinic of Gülhane Training and Research Hospital and received combined Ven treatment with AZA between January 2021 and March 2022 because they were not suitable for intensive chemotherapy were examined retrospectively. Those who received combined treatment in the first line, those who received treatment for RR AML, and those who received as AML maintenance treatment after achieving remission were assessed separately.

Responses were evaluated per the International Working Group criteria for AML. CR designation requires that the patient achieve the morphologic leukemia-free state and have an absolute neutrophil count (ANC) more than 1,000/L, platelets (plt) more than 100,000/L and the bone marrow would have less than 5% blasts and no Auer rods. For the definition of CRi, all other criteria must be met of CR except ANC >1,000/L or plt count >100,000/L. Partial remission (PR) designation requires all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.[7] Efficacy was assessed as rate of objective response (CR + CRi + PR). Duration of response (DOR) for patients who achieved a CR or CRi and OS was evaluated. Investigator-assessed adverse events (AEs) were summarized according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 6.0.[8]

Sattistical Analysis

Statistical analyses were made by using the IBM SPSS Statistics for Windows Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). The descriptive statistics were presented as n and % for categorical variables and as Mean±SD or Median (Min-Max) for continuous variables. The Wilcoxon Test, which is one of the nonparametric tests, was used for before and after comparisons of some numerical parameters. The Kruskal Wallis Test, which is one of the nonparametric tests, was used for triple comparisons. The Bonferroni Test was used as the post-hoc test. Finally, the Kaplan-Meier method was used to determine the survival durations, and $p<0.05$ was considered statistically significant.

RESULTS

A total of 34 patients were evaluated in the study, including 18 newly diagnosed patients, 12 RR patients, and 4 patients receiving AZA+Ven as maintenance treatment. Aside from age, these patients had very fragile characteristics because of accompanying comorbidities, and 28 out of 34 patients (82.3%) had at least 1 chronic disease (diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, congestive heart failure, cerebrovascular disease, bullous pemphigoid, sarcoidosis, asthma, cholelithiasis, hypothyroidism, osteomyelitis) and the presence of a hip prosthesis was noted in 1 patient. Also, as well as these chronic diseases, 1 patient had a history of breast cancer, 1 had prostate cancer, 1 larynx cancer, 1 sarcoma, and 1 non-hodgkin lymphoma (NHL), and 1 patient had a history of lung cancer together with the diagnosis of AML. Baseline demographic and clinical characteristics of the patients are given in **Table 1**.

Two patients who received AZA+Ven in the 1st line and whose progression status was stated as "undetermined" were reported in this way because they died before the response evaluation could be made during the 2nd cycle (cause of death was determined as febrile neutropenia (FEN) in 1 patient and COVID-19 in the other). 5 patients in RR group whose progression status was stated as "undetermined" were clinically and laboratory compatible with progression but they were recorded in this way because bone marrow (BM) examination was not performed to reveal progression. Following the AZA+Ven treatment, 1 out of 12 patients (8.3%) in the RR group and 1 out of 4 patients (25%) in the maintenance group underwent Allogeneic stem cell transplantation (ASCT).

ANC, hemoglobin (Hb), and plt values that were monitored after initiation of AZA+Ven treatment were found to be lower in the 3 groups when compared to the values before treatment. Although the decrease in all 3 series was statistically significant in the first line and RR groups ($p<0.001$), these values were not statistically significant in the maintenance group ($p>0.05$).

The grades of cytopenias are more important rather than the occurrence of cytopenias. The degrees of cytopenia under AZA+Ven were determined as follows.

Grade 3-4 thrombocytopenia was 77.8%/75%/50% in the first line/RR and maintenance groups, respectively.

Grade 3-4 neutropenia was 66.7%/75%/100% in the first line/RR and maintenance groups, respectively.

Grade 3-4 anemia was 44.5%/58.3%/25% in the first line/RR and maintenance groups, respectively.

Rapid apoptosis occurs and leukemic cells are rapidly removed from the BM after AZA+Ven treatment. BM blast rates before starting AZA+Ven, number of cycles completed before response evaluation, and BM blast rates after the treatment are given in **Table 2**.

Table 1: Baseline demographic and clinical characteristics of the patients

	First Line (n=18)
Age: Median (min-max)	77 (43-89)
Gender: F/M (n/%)	6/12 (33.3/66.7)
ECOG PS: 1/2/3/4 (n/%)	1/9/6/2 (5.6/50/33.3/11.1)
AML type:De-Novo /Seconder (n/%)	11/7 (61.1/38.9)
MDS history: Yes/No (n/%)	3/15 (83.3/16.7)
Cytogenetic risk category: Fav/Int /Adv (n/%)	0/14/4 (0/77.8/22.2)
Median total number of Ven cycles: (min-max)	3.0 (1-15)
Relapse /Progression: Yes/No/Undetermined (n/%)	4/12/2 (22.2/66.7/11.1)
Median time to Relapse/Progression: month (min-max)	7.0 (6.0-12.0)
Median follow-up:month (min-max)	5.0 (1.0-19.0)
Alive / Exitus (n/%)	6/12 (33.3/66.7)
RR (n=12)	
Age: Median (min-max)	62 (25-79)
Gender: F/M (n/%)	5/7 (41.7/58.3)
ECOG PS: 1/2/3/4 (n/%)	4/5/3/0 (33.3/41.7/25/0)
AML type:De-Novo /Seconder (n/%)	8/4 (66.7/33.3)
MDS history: Yes/No (n/%)	2/10 (16.7/83.3)
Cytogenetic risk category: Fav/Int /Adv (n/%)	0/8/2 (0/80/20)
Median number of treatment lines prior AZA+Ven:(min-max)	3.0 (1.0-6.0)
Median DOR maintained with last treatment prior AZA+Ven:month (min-max)	8.5 (2.0-28.0)
Prior hypomethylating agent, Yes/No (n/%)	10/2 (83.3/16.7)
Median total number of Ven cycles: (min-max)	2.5 (1.0-14.0)
Relapse /Progression: Yes/No/Undetermined (n/%)	4/2/5 (33.3/25/41.7)
Median time to Relapse/Progression (min-max)	6.0 (1.0-10.0)
Median follow-up:month (min-max)	2.0 (1.0-15.0)
Alive / Exitus (n/%)	3/9 (25/75)
Maintenance (n=4)	
Age: Median (min-max)	44 (31-61)
Gender: F/M (n / %)	2/2 (50/50)
ECOG PS: 1/2/3/4 (n/%)	3/1/0/0 (75/25/0/0)
AML type:De-Novo /Seconder (n / %)	3/1 (75/25)
MDS history: Yes/No (n/%)	1/3 (25/75)
Cytogenetic risk category: Fav/Int /Adv (n/%)	0/3/1 (0/75/25)
Median total number of Ven cycles: (min-max)	8.5 (2-19)
Relapse /Progression: Yes/No/Undetermined (n/%)	0/40 (0/100/0)
Median follow-up:month (min-max)	12.5 (6.0-19.0)
Alive / Exitus (n/%)	4/0 (100/0)

F:Female. M:Male. DOR:Duration of Remission AML:Acute Myeloid Leukemia, Fav:Favorable Int:Intermediate Adv:Adverse MDS: Myelodysplastic Syndrome, ECOG PS:Eastern Cooperative Oncology Group Performance Score, Genetic risk classification is based on the European Leukemia Network (ELN) 2022 criteria

Table 2. Bone marrow results before/after AZA+Ven

	First Line (Mean±SD)	RR (Mean±SD)	Maintenance (Mean±SD)
Number of Ven cycles prior to 1st BM assessment (n)	2.14±1.51	2.62±2.06	2.00±1.00
Number of Ven cycles prior to 2nd BM assessment (n)	4.83±2.92	9.00±1.41	2.00±
Number of Ven cycles prior to 3rd BM assessment (n)	5.50±2.12	-	-
BM blast rate prior Ven (%)	57.27±21.37	58.90±22.24	1.50±0.88
BM blast at the 1st assessment after Ven (%)	9.50±15.04	31.12±34.39	0.66±0.57
BM blast at the 2nd assessment after Ven (%)	6.66±9.22	11.00±12.72	-
BM blast at the 3rd assessment after Ven (%)	16.00±19.79	-	-

Ven:Venetoclax. BM:Bone Marrow

In the present study, 4 of 18 patients (22.2%) who received AZA + Ven in the first line and 4 of 12 patients (33.3%) who received AZA + Ven for RR AML died before the first response evaluations. Although it seems that sufficient blast clearance was not achieved in the BM examinations performed for 1st response evaluation (Table 2), when the sub-analyses were examined, remission was achieved in 10 out of 14 patients (71.4%) in first-line group and in 3 out of 8 patients (37.5%) in the RR group . Despite the high remission rates obtained in the 1st response evaluation, the reason for the high mean value of the BM blast rate is the high amount of BM blasts in patients in whom remission was not achieved.

No tumor lysis was detected in any patient. Other AEs of the patients are listed in Table 3.

Table 3. Adverse effects of the patients

Adverse Effect	First Line n (%)	RR n (%)	Maintenance n (%)
Neutropenia	13 (72.2)	10 (83.3)	4 (100.0)
Anemia	10 (55.5)	10 (83.3)	2 (50.0)
Thrombocytopenia	10 (55.5)	8 66.6)	1 (25.0)
Pneumonia	7 (38.9)	1(8.3)	-
FEN	6 (33.0)	4 33.3)	-
Vomiting	3 (16.6)	-	-
Fatigue	1 (5.5)	-	-
Nausea	1 (5.5)	1(8.3)	-
None	2 (11.1)	1(8.3)	1 (25.5)

FEN: Febrile neutropenia

Since Ven is metabolized by Cytochrome P450 3A4 (CYP3A4), dose reduction is needed when it is used with antifungals that cause CYP3A4 inhibition. The prophylactic antifungal use status of the patients who were evaluated in the present study and the distribution of their fungal infection history under AZA+Ven treatment is given in Table 4.

When evaluated with Fisher's Exact test, there was no statistically significant difference between prophylactic antifungal use and history of fungal infection under AZA+Ven (p=0.545)

The best response degree achieved by the patients under AZA+Ven treatment and the time to reach the best response are given in Table 5.

The OS data of the patients who were evaluated in the present study is given in Figure 1.

In the group receiving AZA+Ven in the first line, the average OS was 8.00 months (95% CI: 1.58-14.41), and was 7.00 months in the RR group (95% CI: 1.78-12, 21).

All patients in the maintenance group are alive and the median follow-up period was 12.50±6.02 months in this group (Mean±SD).

Table 4. Prophylactic antifungal use and history of fungal infection under AZA+Ven

First Line	n (%)
Prophylactic antifungal	
None	1 (5.6)
Fluconazole	13 (72.2)
Posaconazole	3 (16.7)
Caspufungin	1 (5.6)
History of fungal infection under AZA+Ven	
No	14 (77.8)
Yes	4 (22.2)
RR	
Prophylactic antifungal	
None	6 (50.0)
Fluconazole	5 (41.7)
Posaconazole	1 (8.3)
History of fungal infection under AZA+Ven	
No	8 (66.7)
Yes	4 (33.3)
Maintenance	
Prophylactic antifungal	
None	3 (75.0)
Fluconazole	0 (00.0)
Voriconazole	1 (25.0)
History of fungal infection under AZA+Ven	
No	4 (100.0)
Yes	0 (0.0)

Table 5. Best response and time to reach best response

Best Response	First Line n (%)	RR n (%)	Maintenance n (%)
CR	4 (22.2)	3 (25.0)	4 (100)
CRi	7 (38.8)	3 (25.0)	0
Refractory	3 (16.6)	2 (16.7)	0
NA	4 (22.2)	4 (33.3)	0
Time to best response (months) Mean±SD	3.18±1.32	3.00±1.41	
Median (min-max)	4.0 (1.0-5.0)	3.0 (2.0-4.0)	

CR:Complete Response. Cri:Complete Remission with Incomplete Blood Count Recovery, NA (Not Available): Patients who died before response assessment could be performed

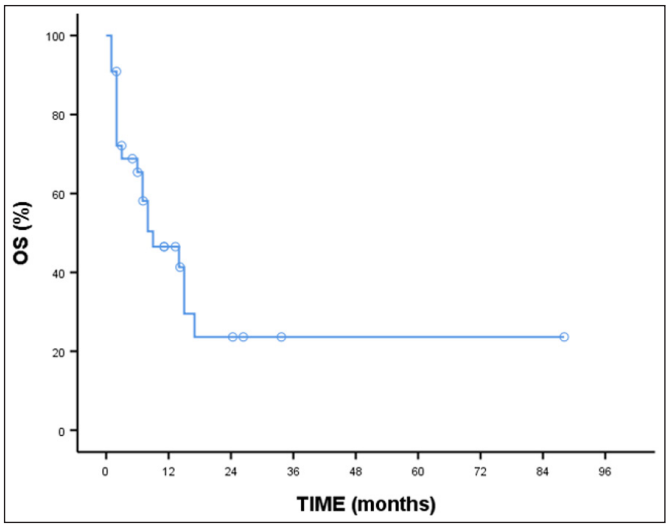

Figure 1. Overall survival data for patients. OS: Overall survival

Of the 34 patients evaluated in the study, 13 (38.2%) were alive and 21 (61.8%) were exitus. Among the causes of death of the patients in our study were COVID-19, FEN, progression, sepsis were defined and in 19% of patients, the cause of death could not be determined. The most common cause of death in both groups was COVID-19. The 2nd most common cause of death was FEN in the first line group, while it was progression in the RR group.

DISCUSSION

Various studies report that the HMA+Ven combination increases the response rates and OS in AML patients when compared to HMA monotherapy and is tolerated well.[9-12]

Combination therapies raise concerns regarding increased AE rates. Cytopenias are the most common AEs in hematological diseases. Although the risk of cytopenias is higher with the addition of Ven to HMA, it is generally managed easily.[9,13]

In the present study a significant deepening of cytopenias under AZA + Ven treatment was detected in patients with active leukemia, but the decrease in the maintenance group was not found to be statistically significant. The possible reason for this is that although leukemic cells are removed from the BM and peripheral blood through rapid apoptosis with the addition of Ven, BM recovery cannot occur at the same rate in patients with active leukemia. For this reason, cytopenias are detected more frequently in active leukemia patients, but the drug-induced suppression process is less common in the group receiving maintenance treatment and own intact BM.

In a Phase 3 study that compared patients receiving AZA+Ven Treatment with those receiving AZA monotherapy, it was reported that myelosuppression increased with the addition of Ven to AZA, but it did not deteriorate clinical outcomes.[14] In our study, despite cytopenias deepened at statistically significant levels in patients except the maintenance group and cytopenias levels reached Gr 3-4 in >50% of them, 23.5% of 34 patients died because of infectious reasons.

If the hematological recovery process under AZA + Ven treatment exceeds 2 weeks, a BM examination must be performed to evaluate whether the cytopenia is leukemia-related or drug-induced.[15] If blast increase is not detected, not every cytopenia might cause concerns. Especially in cases with a transformation from MDS to AML, cytopenias might continue after HMA + Ven treatment as evidence of reversion to the previous low-grade MDS.

The most common AE's observed in our study are shown in **Table 3**.When drug doses need to be reduced because of AEs, Jonas et al.[16] recommend shortening the duration of Ven or reducing the dose of HMA instead of reducing the dose of Ven, except in cases of drug-drug interaction.

Neutropenia due to the nature of the disease or drug effects is a common finding in AML. Even antibacterial, antifungal, and antiviral prophylaxis are used widely in AML, it is still not universally accepted.[17] But there are also publications arguing that mold-active antifungal agents should be mandatory for prophylaxis, especially in high-risk patients.[18] However, the intense drug-drug interaction between Ven and Azole-group antifungals, which are moderate-strong inhibitors of CYP3A4, caused that azoles were not allowed in many clinical studies in which HMA+Ven was evaluated.[9,19] In the study conducted by DiNardo et al.[9] in which Azoles were not allowed and routine antifungal prophylaxis was not used, prophylaxis was performed with alternative antifungals (e.g., Echinocandin) in 46% of the patients, and a low rate of clinically significant fungal infection was detected (8%). Considering the invasive fungal infection rates of around 4.1% under HMA monotherapy, these rates are acceptable.[20] For this reason, antifungal prophylaxis is generally recommended to be administered during severe neutropenia and for short periods, and prophylaxis with Echinocandins that have anti-aspergillus activity and do not require a reduction in the dose of Ven seem reasonable for these patients.[16,20,21] However, if Echinocandins are not preferred because of unavailability, high costs, and the necessity of intravenous administration, the use of Azole-group antifungals must not be avoided. Since Ven is metabolized by CYP3A4, dose reduction must be made when needed with antifungals that cause CYP3A4 inhibition. In light of some sub-studies in which drug interactions were evaluated, recommendations were made regarding the dose reduction that must be made in the Ven dose in case of azole use. Posaconazole is a strong CYP3A4 inhibitor and causes a 7.1-8.8-fold increase in the effectiveness of Ven when used together as a result of the increase in Cmax and decrease in its clearance.[22] If the use of antifungals that inhibit CYP3A4 strongly (e.g., voriconazole/posaconazole) is absolutely necessary, it is recommended to reduce the Ven dose by 75%, and if it is to be used with moderate CYP3A inhibitors (e.g., fluconazole and isavuconazonium sulfate) it is recommended to reduce the Ven dose by 50%. In patients whose treatment is interrupted because of toxicity that results from concurrent use with CYP3A4 inhibitors, Ven can be restarted 2-3 days after the discontinuation of the inhibitor.[23] In our study, no statistically significant difference was found between the history of fungal infection in patients who used prophylactic antifungals under AZA+Ven and those who did not. (**Table 4**)

It was reported in the study of Abishek et al.[10] that 43% of the patients were RR to the frontline HMA+Ven combination, refractoriness was detected in 5 patients in our study (14.7%), but it must be taken into consideration that 8 of 34 patients (23.5%) died before the first response evaluation.

When the response rates of the patients were evaluated in our study, CR+CRi was found to be 61% in the 1st line group and 50% in the RR group (**Table 5**). In the study of Abishek et al.[10] the CR+CRi rate was found to be 73% and was reported to be 60% in the study by DiNardo et al.[9] in high-risk subgroups such as secondary AML or with poor cytogenetics.

The time to reach the best response was determined as a median of 4 months (minimum 1 month - maximum 5 months) for the patients who could be evaluated for response and achieved CR/CRi in the 1st line group and a median of 3 months (minimum 2 months - maximum 4 months) in the RR group. In the study of Pollyea et al.[24] the median time to achieve the first response with the AZA + Ven Combination was reported as 1.2 months. The longer time to reach the best response in our study was found to have occurred because the routine of evaluating the response after the first cycle was not established in the early periods when the HMA+Ven combination was introduced into our center. The fact that the first response evaluations of the patients were made after the median 2.2 cycles (minimum 1-maximum 6 cycles) in our study might have caused the failure to identify patients who achieved responses in earlier cycles.

Concerns might be raised if morphological remission is not achieved after the first cycle because a very rapid response is expected from HMA+Ven treatment. However, if a significant decrease in the leukemic population is detected according to the baseline blast percentage after the 1st cycle and if Ven-based therapy is continued; BM examination is recommended again after the 2nd cycle. There are publications in the literature suggesting that if remission is still not achieved after the second cycle, success cannot be expected from the treatment and another treatment must be initiated.[10,11] However, there are also publications reporting that the time to reach the best response might be delayed under AZA+Ven treatment. In the study conducted by Winters et al., it was reported that the patients receiving AZA+Ven treatment in the off-trial group had the best response even after the 7th cycle. These results might be encouraging for patients who are frail and do not have many treatment options should not immediately despair at the lack of response in early cycles.

Routine BM control must be performed after the 4th cycle for patients with a response after the 1st or 2nd cycle of HMA+Ven treatment and every 6 months if there is no suspicion of relapse.[15,16]

In the management of myelosuppression in patients who achieved remission after the first cycle but neutropenia persists; recovery should be waited until the ANC reaches ≥500/µl, with a maximum of 14 days from day 29. In case of recurrent neutropenia, it was recommended to reduce the duration of Ven for subsequent cycles to 21 days and/or to reduce the dose of AZA, rather than to reduce the Ven dose.

A 20.5-month follow-up in the Viale-A study showed a significant increase in OS with combination therapy, with a median OS was 14.7 months in the AZA+Ven group and 9.6 months in the AZA+Placebo group (P <.001).[19] It was considered that the poor clinical history of the patients might be among the reasons why OS was found to be lower than the literature in our study. Five of 34 patients (14.7%) had a history of solid malignancy and 1 had a history of NHL. The fact that approximately 1/3 of patients have secondary AML is thought to lead to poor response to treatment and poor OS outcomes. In addition, the mean number of previous treatment lines received by the patients in the RR group was 3 (min 1-max 6) and 41.7% patients had a history of ASCT. A decrease in survival is an expected result as the risk factors of the patients increase. In the study of Abishek et al.[10] in which 29% of the patients were secondary AML and 81% of the patients were in the adverse risk group according to ELN Criteria, the median OS was 1.7 months in patients who were primary refractory to HMA+Ven and 2.3 months in relapsed patients.

Among the reasons why the response and survival rates demonstrated by real-life data were inferior to the results of clinical trials is the inclusion of patients with secondary AML, prior HMA history, advanced cardiovascular disease / heart failure, chronic obstructive pulmonary disease requiring regular oxygen use, advanced renal failure, active viral hepatitis, metabolic / immunological disease or other active malignancy in the off-trial group.

We think that another possible reason for the low OS found in our study is related to our tendency to use 200 mg dose of Ven in combination with antifungals in the early years when AZA+Ven combination was included in our clinical practice. The fact that only 9 (26.5%) of the 34 patients whose data were evaluated in our study were able to receive 400 mg Ven, might have led to low efficacy and results below the expected survival times. We think that if the number of patients is larger and if the Ven dose is not reduced unless absolutely necessary, it is possible to observe increased survival rates.

Limitations of the Study

The limitations of the present study were the small number of patients, the fact that the data were collected retrospectively, the lack of standardization in the use of antifungal prophylaxis, Ven doses and periods of follow-up BM biopsies because the patients were followed by different hematologists despite being in the same center.

CONCLUSION

HMA+Ven combination appears to be a candidate to become the standard treatment in the group of patients who are not suitable for intensive treatment, with its rapid-onset and sustainable efficacy and manageable AE spectrum.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was granted ethical approval by the University of Health Sciences Gülhane Scientific Researches Ethics Committee (Date: 27.06.2022, Decision No: 2022-249).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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The value of albumin-related ratios in predicting disease severity and mortality in acute cholangitis

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ABSTRACT

Aims: Acute cholangitis is a potentially fatal bacterial illness that poses a significant risk to patients if not promptly addressed, despite the progress made in the field of diagnosis and treatment. Multiple laboratory and clinical data are employed in assessing the severity and fatality rates associated with acute cholangitis. This study aimed to assess the predictive utility of the ratio between elevated laboratory results and albumin levels in determining the severity of disease and mortality rates in patients with cholangitis.

Methods: The study comprised a cohort of 471 individuals diagnosed with acute cholangitis, alongside a control group of 150 individuals without acute cholangitis. The patients' information was acquired by conducting a retrospective search of the computerized database. The study collected data on the age, gender, routine laboratory parameters, concomitant disorders, etiology of cholangitis, and outcomes (discharge or death) of all patients. The patients were categorized into three grades, namely grade 1, grade 2, and grade 3, based on the severity of cholangitis, using the Tokyo 2018 standards as a reference.

Results: The study comprised a sample size of 621 people. Out of the whole sample size, 53.1% (330 individuals) were identified as male. The study observed a broad range of ages (23-98) with a median age of 67 years, which was found to be greater in the cholangitis group. Among the patients in the cholangitis group, a mortality rate of 6.8% (32 individuals) was observed. A notable disparity was seen in all laboratory parameters between the two groups. The cholangitis group had greater levels of albumin-related ratios, and there was a positive correlation observed between all ratios and the severity of the condition. In deceased individuals, there were greater rates observed for variables other than the γ-glutamyl transferase/albumin ratio (GAR). The results of both univariate and multivariate regression analyses demonstrated a significant correlation between the ratios of direct bilirubin to albumin (DBAR), international normalized ratio to albumin (IAR), neutrophil to albumin (NAR), and mortality. Additionally, the study revealed that the mortality and severity of cholangitis could be predicted by all the albumin-related ratios examined, particularly the INR/albumin ratio (IAR), as indicated by the ROC analysis.

Conclusion: It is posited that the utilization of albumin-related ratios, obtainable through routine laboratory testing, may serve as an effective means to assess the severity of acute cholangitis and predict mortality rates associated with the condition. Immediate biliary drainage is recommended for patients with elevated ratios.

Keywords: Acute cholangitis, albumin-related ratios, severity, mortality

INTRODUCTION

Acute cholangitis refers to a bacterial infection that affects the biliary system, presenting a spectrum of severity that may range from moderate symptoms like jaundice, stomach discomfort, and fever to potentially life-threatening complications such as septic shock.[1] It continues to be a common clinical presentation worldwide. Previously associated with fatality rates above 50%, despite improvements in diagnosis and treatment, acute cholangitis remains a significant and potentially life-threatening condition in the absence of intervention.[2,3] A bile and biliary tract blockage that results in systemic inflammation is the cause of acute cholangitis, also defined as ascending cholangitis. Stones, pancreatic and biliary cancers, stents, and strictures may induce biliary tract obstruction.[3,4] The most common cause of acute cholangitis is choledocholithiasis.[5] Again, it has been reported that 1% to 5% of this picture develops following endoscopic retrograde cholangiopancreatography (ERCP).[6] An obstruction in the biliary tract leads to impaired bile flow to the small intestine and causes bile stasis. This bile stasis causes the proliferation of bacteria that either enter the biliary tract from the intestine or reach the biliary

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tract via the portal venous system.[7] The key elements of treatment in acute cholangitis are antimicrobial therapy and biliary decompression.[2,5] Early intervention is crucial in the management of grade 3 cholangitis in order to minimize the risk of catastrophic consequences.[2] However, cholangitis occurs for a wide variety of reasons and with different severity, and many factors may influence survival in patients with acute cholangitis.[8]

Although the severity of cholangitis has been assessed using a variety of criteria up to this point, a systematic method was not established until the Tokyo guidelines were released. The Tokyo Guidelines were produced in 2007 and were the first published set of diagnostic criteria backed by clinical, laboratory, and imaging research. Imaging results showing blockage as well as observations related to cholestasis and systemic inflammation were taken into account while formulating these criteria. Furthermore, using laboratory data such as white blood cells (WBC), c-reactive protein (CRP), international normalized ratio (INR), and albumin, a system evaluating the severity of the condition was devised using the Tokyo standard.[2]

WBC, neutrophils, and CRP increase in the presence of an infection. When the biliary tract is obstructed, bilirubin and glutamyl transferase (GGT) levels increase. On the other hand, albumin levels, which is a negative acute-phase reactant, decrease in the presence of inflammation.[9] In this study, we investigated the predictive value of the ratio of increased laboratory parameters to albumin in terms of the severity of cholangitis and mortality. Many studies have been conducted on the clinic, diagnosis, and treatment of cholangitis. With this study, we would like to contribute to the accumulation of knowledge in this field.

METHODS

The study was carried out with the permission of Batman Training and Research Hospital Scientific Researches Ethics Committee (Date: 24.01.2023, Decision No: 336). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 471 patients who underwent ERCP with the diagnosis of cholangitis at Batman Dünya Hospital between January 2010 and December 2022, and as a control group, 150 patients who underwent ERCP for biliary stent revision and did not have a cholangitis clinic in the same period. Information about the patients was obtained through a retrospective search of the electronic database. Age, gender, routine laboratory parameters, comorbid diseases, etiology of cholangitis, and discharge or death of all patients were recorded. Urea/albumin (UAR), INR/albumin (IAR), GGT/albumin (GAR), neutrophil/albumin (NAR), CRP/albumin (CAR), and direct bilirubin/albumin (DBAR) ratios were calculated by formulating in the SPSS program. In the Tokyo guideline, acute cholangitis is classified as grade 1, grade 2, and grade 3, and early bile drainage is recommended as the severity increases. In the present study, the Tokyo 2018 guideline was taken as a reference. Therefore, patients were grouped into grade 1, 2, and 3 according to the severity of cholangitis.

All patients older than 18 years of age, male and female, of both sexes, diagnosed with acute cholangitis and with routine laboratory parameters, were included in the study. Exclusion criteria were the absence of routine laboratory parameters, the presence of concomitant pancreatitis, a focus of infection other than cholangitis, the presence of any acute or chronic disease that would prolong the INR value other than cholangitis, and/or a history of drug use. Patients who had elevated WBC and CRP levels without cholangitis findings and underwent stent revision were excluded from the control group.

Statistical Analysis

The patient data obtained during the investigation were analyzed using the IBM Statistical Package for the Social Sciences (SPSS 25.0-IBM, NY, USA) software for Windows version 25.0. Descriptive statistics were provided in the form of frequency and percentage for categorical data, and median, minimum, and maximum for continuous data. The data's adherence to the Gaussian distribution was assessed using the Kolmogorov-Smirnov test. Intergroup comparisons were conducted using the Mann-Whitney U-Test for two groups, the Kruskal-Wallis H-Test for more than two groups, and the Chi-Square or Fisher's Exact Test for comparing categorical variables. A logistic regression analysis was employed to ascertain whether the escalation in rates constituted a risk factor for mortality. A receiver operating characteristic (ROC) analysis was conducted to evaluate the discriminatory potential of the ratio values in relation to disease severity and survival. Subsequently, a ROC curve was generated to visually represent the results. Spearman's correlation analysis was employed to assess the association between ratio values and disease severity. Statistical significance was attributed to the results when the p-value was below the threshold of 0.05.

RESULTS

A total of 621 participants, including 471 with cholangitis and 150 in the control group, were included in the study. Of these, 53.1% (330) were male. There was a wide age distribution (23-98), with a median age of 67 years. In the cholangitis group, 6.8% (32) of patients died. The distribution of demographic and clinical findings among the participants is given in **Table 1**. No statistically significant relationship is found between the groups in terms of gender distribution (p>0.05). There was a

statistically significant difference between the two groups in terms of age distribution (p<0.05). The mean age of the cholangitis group was higher than the mean age of the individuals in the control group. There was a statistically significant difference between the two groups in all laboratory parameters (p<0.05).

The results of the analyses evaluating whether there was a difference between albumin-related ratios according to the severity of cholangitis in the patients included in the study are shown in Table 2. A statistically significant difference was found between the groups in terms of ratios (p<0.001).

Table 1. Distribution of demographic and clinical findings of the patients

Characteristics (N=621)	Total (N=621) n (%) or Median (Min-Max)	Control (n=150) n (%) or Median (Min-Max)	Cholangitis (n=471) n (%) or Median (Min-Max)	p-value
Gender				0.147
Male	330 (53.1)	72 (48)	258 (54.8)	
Female	291 (46.9)	78 (52)	213 (45.2)	
Age, year	67 (23-98)	61 (23-87)	69 (26-98)	<0.001
Cholangitis Severity				NA
Control	150 (24.2)	150 (100)	NA	
Grade 1 (Mild)	200 (32.2)	NA	200 (42.5)	
Grade 2 (Moderate)	112 (18)	NA	112 (23.8)	
Grade 3 (Severe)	159 (25.6)	NA	159 (33.7)	
Cholangitis Source				
Hospital related	NA	NA	183 (38.9)	
Community-sourced	NA	NA	288 (66.1)	
Cholangitis Etiology				<0.001
Benign	500 (80.5)	141 (94)	359 (76.2)	
Malignant	121 (19.5)	9 (6)	112 (23.8)	
Comorbidity				0.001
Yes	536 (86.3)	117 (78)	419 (89)	
No	85 (13.7)	33 (22)	52 (11)	
Latest Status				<0.001
Alive	589 (94.8)	150 (100)	439 (93.2)	
Deceased	32 (5.2)	0 (0)	32 (6.8)	
Lab				
Glucose (mg/dl)	113 (25-795)	99 (65-321)	117 (25-795)	<0.001
Urea (mg/dl)	36 (10-232)	30 (10-73)	39 (12-232)	<0.001
Creatinine (mg/dl)	0.89 (0.36-5.90)	0.76 (0.48-1.90)	0.95 (0.36-5.90)	<0.001
AST (U/L)	99 (7-2235)	25 (7-728)	122 (7-2235)	<0.001
ALT (U/L)	108 (5-1359)	31.5 (5-899)	134 (6-1359)	<0.001
GGT (U/L)	340 (9-2374)	77 (9-1514)	419 (16-2374)	<0.001
ALP (U/L)	246 (21-2066)	120 (21-867)	287 (45-2066)	<0.001
Total Protein (g/dl)	6.60 (3.69-9.10)	6.90 (4.80-8.60)	6.50 (3.69-9.10)	<0.001
Albumin (g/dl)	3.90 (1.90-5.00)	4.30 (3.20-5.00)	3.70 (1.90-4.90)	<0.001
Total Bilirubin (mg/dl)	3.60 (0.20-30.36)	0.80 (0.2-17.76)	4.40 (0.40-30.36)	<0.001
Direct Bilirubin (mg/dl)	2.50 (0.07-23.23)	0.30 (0.07-15.11)	3.10 (0.1-23.23)	<0.001
INR	1.14 (0.89-3.13)	1.02 (0.89-2.20)	1.2 (0.90-3.13)	<0.001
WBC (µl)	9820 (2310-54770)	6870 (3550-9920)	11850 (2310-54770)	<0.001
Neutrophil (µl)	7730 (1560-50150)	4010 (1800-7510)	10000 (1560-50150)	<0.001
Lymphocyte (µl)	1100 (90-9970)	1860 (960-3900)	800 (90-9970)	<0.001
Hemoglobin (g/dl)	12.7 (7.1-17.6)	13.1 (9.4-16.0)	12.6 (7.1-17.6)	0.001
PLT (µl)	230 (20-723)	273.50 (65-512)	216 (20-723)	<0.001
CRP (mg/L)	62.30 (0.8-400.80)	3.20 (0.80-9.75)	91.00 (3.00-400.80)	<0.001
UAR	9.25(2.10-110.53)	7.17 (2.10-18.72)	10.54 (2.55-110.53)	<0.001
GAR	93.80 (2.08-629.45)	19.70 (2.08-344.09)	114.73 (4-629.45)	<0.001
DBAR	0.66 (0.02-9.16)	0.06 (0.02-3.46)	0.86 (0.02-9.16)	<0.001
IAR	3.00 (1.86-15.81)	2.37 (1.86-4.49)	3.28 (1.88-15.81)	<0.001
NAR	2.08 (0.42-20.90)	0.97 (0.42-1.72)	2.73 (0.43-20.90)	<0.001
CAR	16.68 (0.16-200.64)	0.83 (0.16-2.73)	24.18 (0.64-200.63)	<0.001

UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

Table 2. Distribution of rates according to cholangitis severity

	Control	Cholangitis Severity			p
		Grade 1 Median (Min-Max)	Grade 2 Median (Min-Max)	Grade 3 Median (Min-Max)	
UAR	7.17 (2.10-18.72)	8.31 (2.71-29.38)	11.02 (2.55-42.29)	17.09 (4.13-110.53)	<0.001
GAR	19.70 (2.08-344.09)	114.88 (4-629.45)	137.77 (4.65-560.24)	94.57 (9.46-558.33)	<0.001
DBAR	0.06 (0.02-3.46)	0.55 (0.002-9.16)	1.09 (0.14-6.85)	1.10 (0.14-9.13)	<0.001
IAR	2.37 (1.86-4.49)	2.82 (1.88-6.32)	3.22 (2.17-5.86)	4.50 (2.22-15.81)	<0.001
NAR	0.97 (0.42-1.72)	1.90 (0.58-8.24)	3.43 (0.43-11.03)	3.86 (0.64-20.9)	<0.001
CAR	0.83 (0.16-2.73)	15.08 (0.73-23.5)	23.99 (0.64-93.08)	45.17 (0.80-200.63)	<0.001

UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

The analysis, which evaluated the relationship between the rates of patients and disease severity, is presented in Table 3. It is seen that there is a positive linear relationship between ratios and disease severity. A low-level positive correlation was found for GAR, a moderate level for UAR, DBAR, and IAR, and a strong positive correlation for NAR and CAR.

Table 3. Correlation analysis results between ratios and disease severity

	UAR	GAR	DBAR	IAR	NAR	CAR
Spearman's Correlation						
Severity						
r	.517**	.356**	.628**	.696**	.706**	.749**
p	0.000	0.000	0.000	0.000	0.000	0.000
N	621	621	621	621	621	621

UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

The analysis comparing albumin-related ratios between discharged and exited patients is shown in Table 4. It was found that there was a statistically significant difference between the groups for UAR, DBAR, IAR, NAR, and CAR (p<0.001), but not for GAR (p = 0.344).

Table 4. Distribution of ratios by outcome variable

	Alive	Exitus	p
	Median (Min.- Maks.)	Median (Min.- Maks.)	
UAR	10.00 (2.55-110.53)	25.66 (4.17-86.98)	<0.001
GAR	117.50 (4.00-629.45)	105.06 (15.65-558.33)	0.344
DBAR	0.82 (0.24-9.16)	2.48 (0.24-9.13)	<0.001
IAR	3.23 (1.88-9.90)	5.48 (2.80-15.81)	<0.001
NAR	2.66 (0.43-13.76)	5.31 (0.63-20.90)	<0.001
CAR	23.40 (0.64-200.63)	43.64 (4.51-142.61)	0.001

UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

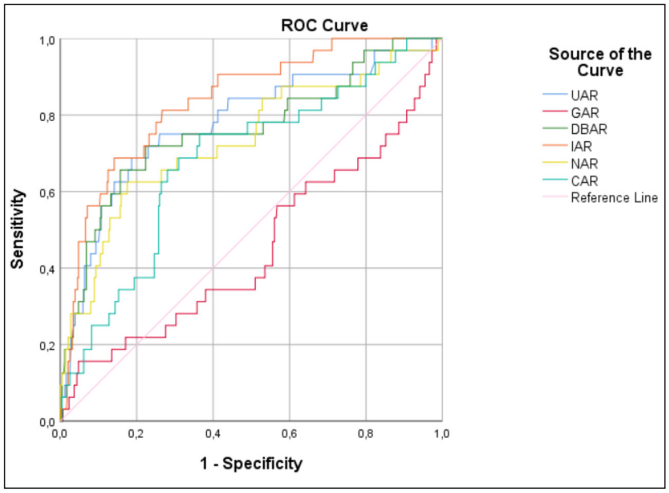
The results of the analysis evaluating whether high rates are a risk factor for mortality in patients with cholangitis are shown in Table 5. It was determined that high UAR, DBAR, IAR, NAR, and CAR were risk factors for mortality in univariate analysis. When the parameters that showed a significant difference in univariate analysis were re-evaluated in multivariate analysis, it was determined that a 1-unit increase in DBAR, IAR, and NAR increased mortality by 1.36, 1.45, and 1.16 times, respectively (p<0.05).

Table 5. Univariate and multivariate analysis of rates as mortality risk factors

	Univariate			Multivariate		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
UAR	1.053	1.032-1.075	<0.001	1.019	0.994-1.045	0.141
GAR	1.000	0.997-1.004	0.897			
DBAR	1.660	1.396-1.975	<0.001	1.363	1.108-1.676	0.003
IAR	1.785	1.487-2.143	<0.001	1.458	1.123-1.892	0.005
NAR	1.353	1.213-1.510	<0.001	1.165	1.008-1.345	0.038
CAR	1.017	1.007-1.027	0.001	0.897	0.972-1.002	0.095

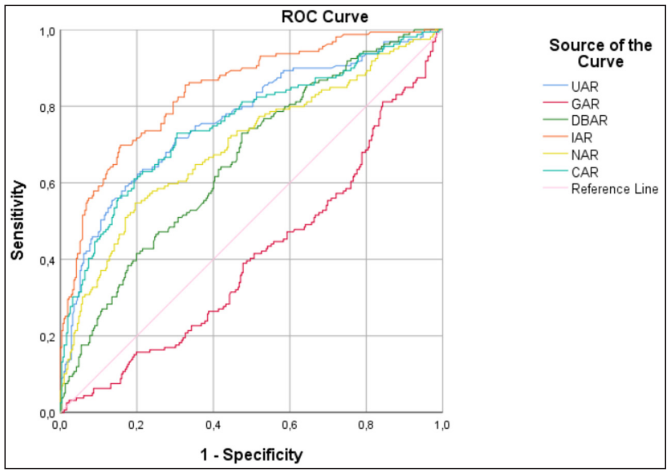
UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

The results of the ROC analysis performed to examine the differential effect of the ratios according to the mortality status of the patients are shown in Graphic 1. The area under the curve shows the statistical significance of the discrimination ability of the diagnostic test. In the present study, the highest value was found for IAR (84%), and an IAR >3.89 predicts mortality at a good level.



Graphic 1. ROC Analysis of Ratios by Mortality. UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

The results of the ROC analysis performed to examine the differential effect of the ratios according to severe cholangitis are shown in **Graphic 2**. The highest area under the curve was found for IAR (84%), and an IAR >3.46 was a good predictor of severe cholangitis.



Graphic 2. ROC Analysis of Ratios by Severe Cholangitis. UAR: Urea/albumin ratio, GAR: GGT/albumin ratio, DBAR: Direct Bilirubin/albumin ratio, IAR: INR/albumin ratio, NAR: Neutrophil/albumin ratio, CAR: CRP/albumin ratio

DISCUSSION

Acute cholangitis is a potentially fatal bacterial illness that poses a significant risk to patient health if not promptly addressed, notwithstanding the progress made in the field of diagnosis and treatment.[2] Biliary blockage can arise from several benign and malignant etiologies, encompassing pancreatic and biliary cancers, biliary stents, biliary strictures, and notably, the presence of stones.[3] Numerous research investigations have been undertaken to ascertain the extent of severity and fatality associated with cholangitis.[10-14] The Tokyo Guideline is extensively employed in the management of acute cholangitis. The Tokyo guidelines classify acute cholangitis into three grades: grade 1, grade 2, and grade 3. As the severity of the condition escalates, the guidelines advocate early biliary drainage.[2]

In the assessment of acute cholangitis, laboratory indicators such as bilirubin, alkaline phosphotase (ALP), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) are employed to detect cholestasis-related elevations. These parameters are utilized alongside systemic inflammation markers including fever, elevated white blood cell count, and C-reactive protein (CRP) levels. Furthermore, the grading of cholangitis severity also takes into account elevated levels of bilirubin, decreased levels of albumin, increased white blood cell count, and indications of systemic organ failure. Patients diagnosed with acute cholangitis are deemed to have hepatic failure if their International Normalized Ratio (INR) exceeds 1.5. Similarly, renal failure is established if the patient's creatinine levels surpass 2 mg/dl. The individuals in question are classified as having severe cholangitis.[2] Individuals diagnosed with acute cholangitis who do not undergo biliary drainage will experience elevated levels of systemic inflammatory markers and cholestasis measures, irrespective of the plasma half-life. Furthermore, there is an elevated probability of experiencing organ failure. This study aimed to assess the ability of laboratory parameter ratios, including CRP, direct bilirubin, GGT, neutrophils, urea, and INR, to predict disease severity and death in patients with cholangitis. These laboratory parameters are known to increase in individuals with cholangitis, while albumin, a negative acute phase reactant, is expected to decrease.

The rates pertaining to albumin have been investigated in various pathological conditions. The association between disease activation and the CRP/albumin ratio was demonstrated in a study including individuals diagnosed with inflammatory bowel disease.[15] In a study conducted by Behera et al.[16] it was discovered that there exists an association between the ratio of C-reactive protein (CRP) to albumin and the prognosis of patients with acute pancreatitis. In their study, Şahiner et al.[17] investigated the relationship between mean platelet volume/albumin (MAR) and the severity of cholangitis. Their findings revealed a significant link between the severity of cholangitis and MAR. The findings of our investigation indicate a notable correlation between the CRP to albumin ratio (CAR) and both illness severity and fatality rates. Similarly, a significant association was identified between the urea-to-albumin ratio (UAR) and both the disease severity and mortality rate. In the literature, UAR was evaluated as a promising marker for predicting 28-day mortality in a study supporting our finding.[18] Despite the identification of a statistically significant association between GAR and the severity of acute cholangitis, our correlation analysis revealed a poor link between these variables. There was no statistically significant link seen between the variable of interest, GAR, and the outcome measure of mortality.

While there is a lack of existing literature examining the specific relationship between the DBAR and the severity and mortality of acute cholangitis, there is data suggesting that the bilirubin/albumin ratio is correlated with mortality in patients admitted to intensive care units.[19] Similarly, IAR and NAR have not been studied in acute cholangitis. According to a study conducted by Çekmen et al.[20] it was shown that NAR has potential utility in the diagnostic assessment of acute appendicitis. The present investigation revealed a notable association between the three ratios and both the severity of acute

cholangitis and death. Furthermore, regression analysis demonstrated that DBAR, IAR, and NAR were associated with a 1.36-fold, 1.45-fold, and 1.16-fold increase in mortality, respectively.

In the current investigation, a ROC analysis was conducted to assess the varying impact of the ratios on mortality and severe cholangitis. The results revealed that the IAR exhibited the highest area under the curve (AUC), indicating its superior predictive ability. Specifically, an IAR value greater than 3.89 was associated with mortality, while a value exceeding 3.46 was indicative of severe cholangitis, both at a satisfactory level of accuracy.

Despite certain limitations, such as its retrospective nature and the absence of healthy volunteers in the control group, the current investigation is believed to possess notable merits. These include a substantial sample size and the novel assessment of various albumin-related parameters in the context of acute cholangitis. As a result, these strengths are expected to make a valuable contribution to the existing body of literature.

CONCLUSION

Upon comprehensive examination of the present study data in conjunction with existing research, it is our contention that the utilization of albumin-related ratios derived from fundamental laboratory tests (namely UAR, DBAR, IAR, and NAR in the context of the present study) is warranted to assess the severity of acute cholangitis and predict mortality rates associated with this condition. Immediate biliary drainage should be administered to patients with elevated ratios.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Batman Training and Research Hospital Scientific Researches Ethics Committee (Date: 24.01.2023, Decision No: 336).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Anthropometric analysis of Turkish fetuses' face

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ABSTRACT

Aims: This study aims at collecting data on the morphology of the face during its development in order to get detailed information on the neighboring structures and its variations using anatomical dissections and obtain normal morphometric values of the face growth and human fetuses during the 1st, 2nd and 3rd trimester.

Methods: This study was performed on spontaneously aborted 97 fetuses (49 males, 48 females) (11 first trimester, 63 second trimester and 24 third trimester) that have no observable congenital malformations or maternal history of risky pregnancy. The fetuses were taken from a Gynecology Department of a School of Medicine and a Maternity Hospital in Konya. Thirteen direct facial anthropometric measurements were performed on 97 volunteers. The data obtained were compared with the data of previous studies.

Results: Means and standard deviations of the parameters in regard to gestational weeks and trimesters were calculated. A significant correlation was observed between all parameters and gestational age ($p<0.05$). There were also significant differences between sexes for any of the parameters ($p<0.05$). All measurements were determined to be greater in male fetuses than female fetuses except for en-gn, sn-gn, sa-sba and ex-en.

Conclusion: The data acquired in this study is expected to help other studies on face anomalies, pathologies and variations in addition to diagnoses and treatments of such conditions conducted in anatomy, pathologic anatomy (feto pathology), forensic medicine, medical imaging, obstetrics and pediatrics.

Keywords: Face, development, morphometry, fetus

INTRODUCTION

Chantal index and circumference-interorbital index acquired from the measured parameters are also essential tools for anatomists and cranio facial surgeons.[1,2] Craniofacial dimensions may be identified by a single gene, gene groups or environmental factors.[3] For diagnosis of certain anomalies and syndromes, abnormal facial features such as telechantus, ocular hypertelorism or hypotelorism are taken into account by many clinicians, geneticists and maxillofacial surgeons. The measurement becomes stable by the time it reaches adult levels in the mid-to late twenties.[4,5]

The face is separated into three parts; upper, middle and lower thirds. The basic aesthetic feature of the lower third is created by lips, especially the upper lip has a significant effect mainly on the aesthetic judgment of the face.[6] The size and curvature of the exposed red lip surface is liable to substantial individual, gender and ethnic variations.[7] Lips and their relationship with the position of anterior teeth have a significant effect on a person's smile and overall facial aesthetics.[8] The lips become thinner as people age and the wet line moves caudally, oral commissure also begins to downturn with advancing age.[9] Almost all measurements demonstrate a downward trend after the fifth or sixth decade of life.[10]

Since there was no systematic study on facial morphometric measurements, this study was desired to be performed. The study is expected to provide valuable information to the forensic odontologists, plastic surgeons and the forensic experts. That is, it can be beneficial for cosmetic correction and identification.

METHODS

The study was carried out with the permission of Selçuk University Meram Faculty of Medicine Clinical Researches Ethics Committee (Date: 27.06.2008, Decision: 2008/171). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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This study was conducted on human fetuses aged between 7 and 37 weeks of gestation (crown rump length [CRL]). Measurements were made on 97 fetuses. The fetuses were detected with immersion method using %10 formalin in the fetus collection of Necmettin Erbakan University, Meram Faculty of Medicine, Anatomy Department in 2016-2017.

Fetuses were grouped in accordance with their gestational ages: Group1 (first trimester), group 2 (second trimester) and group 3 (third trimester) included fetuses aged 7-12 weeks, 13-25 weeks and 26-37 weeks, respectively. A digital compass sensitive to 0.01 mm was used for the measurements.

The vertical measurements are as follows[19] (Figure 1):

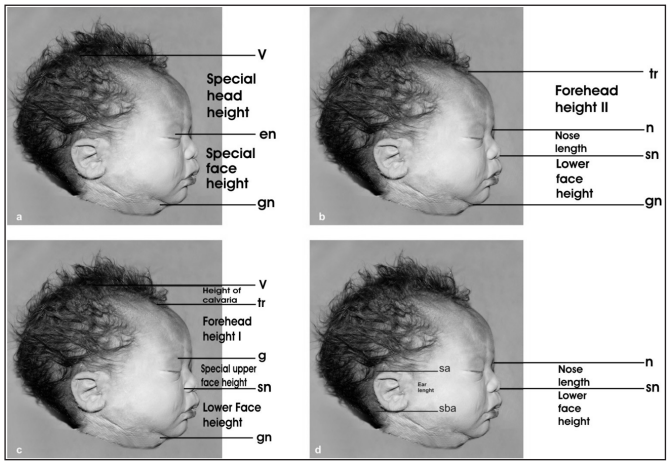

Figure 1. Vertical measurements (11): a; special head height [vertex-endocanthion (v-en)], special face height [endocanthion-gnathion (en-gn)], b; forehead height II [trichion-nasion (tr-n)], nose length [nasion-subnasale (n-sn)], lower face height [subnasale-gnathion (sn-gn)], c; height of calvaria [vertex-trichion (v-tr)], fore head height I [trichion-glabella (tr-g)], special upper face height [glabella-subnasale (g-sn)], lower face height [subnasale-gnathion (sn-gn)], d; nose length [nasion-subnasale (n-sn)], ear length [supraaurale-subaurale (sa-sba)].

The head:

- Height of calvaria (vertex-trichion) (v-tr),
- Forehead height I (trichion-glabella) (tr-g),
- Forehead height II (trichion-nasion) (tr-n),
- Special head height(vertex-endocanthion) (v-en),

The face:

- Special face height (endocanthion-gnathion) (en-gn),
- Special upper face height (glabella- subnasale) (g-sn),
- Lower face height (subnasale-gnathion) (sn-gn),

The ear:

- Ear length (supraaurale-subaurale) (sa-sba),

The horizontal measurements are as follow (Figure 2):

The orbits:

- Left eye fissure length (exocanthion-endocanthion) (ex-en),
- Intercanthal distance (endocanthion-endocanthion) (en-en),

The nose:

- Nose width (alare-alare) (al-al),
- The labio-oral region:
- Mouth width (cheilion-cheilion) (ch-ch).

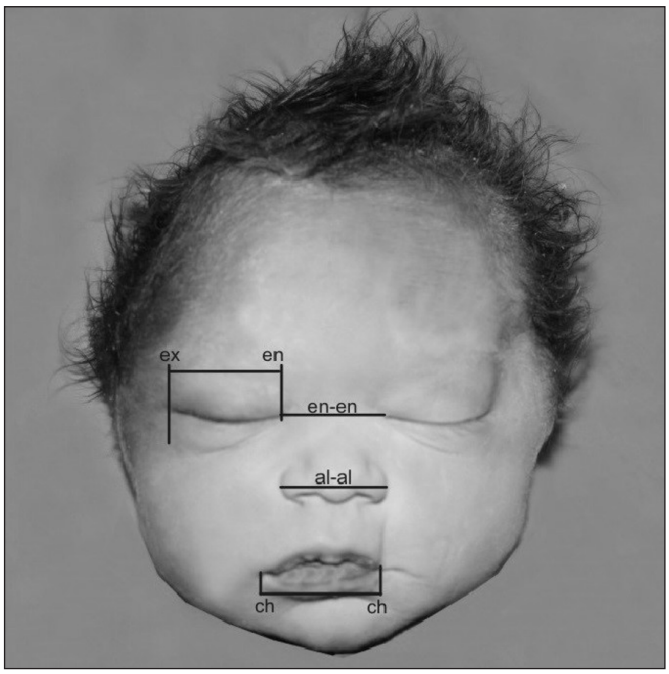

Figure 2. Horizontal measurement (11): right eye fissure length [exocanthion-endocanthion (ex-en)], intercanthal distance (endocanthion-endocanthion (en-en)], nose width [alare-alare (al-al)], mouth width [cheillion-cheillion (ch-ch].

Statistical Analysis

SPSS 20.0 (IBM Inc., Chicago, IL, USA) software was used for the analyses of the study. Descriptive statistics were presented as frequencies and percentages for categorical variables, and mean±SD for numerical variables in addition to percentile values. Continuous variables were examined for normality by Kolmogorov-Smirnov method. Student t-test was employed for two independent samples, and the analysis of variance was employed for several independent samples. Pearson correlation coefficients were calculated between measurements and gestational age. $P<0.05$ was considered statistically significant as 5% Type-I error.

RESULTS

A total of 98 fetuses were included in the study. The sex ratios were close to each other and the proportion of males was 51% (n=50). Trimester rates for fetuses were 2nd trimester (64.3%), 3rd trimester (24.5%) and 1st trimester (11.2%), respectively. Gestational ages were between 8 and 28 weeks. The average age in male fetuses was 19.67±7.29 weeks, 16.66±5.85 weeks in female fetuses and 18.18±6.75 weeks in general.

Values measured from fetuses were compared between genders. En-gen (p=0.013) and tr-r (p=0.012) were found to differ significantly between genders. Both measured values

were significantly higher in male fetuses. However, although the measurement result of r-sn was higher in male fetuses, the difference between genders was not statistically significant (p=0.115). Sn-gn, tr-g, g-sn and ex-en measurement results were also significantly higher in male fetuses. Sa-sba, en-en, al-al and ch-ch measurement results did not differ significantly between gender groups (Table 1).

Table 1. Measurement results according to gender

Measurements		Male (n=50)	Female (n=48)	p
		Mean±SS		
en_gn	mm	29.15±12.36	23.79±8.33	0.013*
tr_r	mm	22.58±9.79	17.97±7.42	0.012*
r_sn	mm	15.05±6.0	13.26±5.58	0.115
sn_gn	mm	20.46±7.93	16.8±5.25	0.008*
tr_g	mm	19.17±7.87	14.77±5.8	0.002*
g_sn	mm	16.59±6.1	14.11±5.68	0.041*
sa_sba	mm	17.58±9.07	15.13±6.31	0.109
ex_en	mm	13.08±5.88	10.67±3.87	0.020*
en_en	mm	13.29±5.12	11.6±4.15	0.076
al_al	mm	12.98±4.99	11.53±5.09	0.140
ch_ch	mm	16.03±5.98	14.58±5.65	0.231

*: significant at 0.05 level according to Independent Sample t-test

Comparisons of measurement for trimester periods are presented in Table 2. All measurements differed significantly between periods (p <0.001). All of the measurements increased in proportion to the trimester period (Figure 3). Comparing all measurements with respect to trimester periods in terms of gender difference, all mean values between the periods were found to be significantly different. Measurement values of the face increased in both male and female fetuses in proportion to trimester periods (p <0.001). In addition, the mean, minimum, maximum and quartile (25th, 50th and 75th percentile) values for all morphometric measurements in terms of gender difference are presented in Table 3. All morphometric measurement values correlated positively and significantly with gestational age (week) in terms of gender difference. The highest correlation in male fetuses belonged to sa-sba (r=0.973). The lowest correlation was found between al-al and gestational week (r=0.746). In female fetuses, the highest correlation was found to be r-0903 with en-gn and the lowest correlation was r=0.750 with al-al measurements.

Table 2. Measurement results for Trimester periods

	1st trimester (n=11)	2nd trimester (n=63)	3rd trimester (n=24)	p
	Mean±SS			
en_gn	12.31±2.81	23.76±5.25	40.31±10.23	<0.001*
tr_r	10.14±1.97	18.18±5.7	30.6±8.83	<0.001*
r_sn	5.6±1.42	13.2±3.92	20.67±4.42	<0.001*
sn_gn	9.38±2.25	17.23±3.94	26.7±6.81	<0.001*
tr_g	8.78±1.59	15.25±4.6	25.43±6.96	<0.001*
g_sn	5.99±1.9	14.47±3.85	22.05±4.4	<0.001*
sa_sba	7.35±1.69	14.15±4.56	26.39±6.96	<0.001*
ex_en	5.48±1.05	10.87±2.6	17.53±6.0	<0.001*
en_en	7.02±1.55	11.37±3.16	17.81±4.34	<0.001*
al_al	4.75±1.27	11.77±3.98	17.03±3.66	<0.001*
ch_ch	7.43±1.61	14.33±3.62	21.34±5.64	<0.001*

*: significant at 0.05 level according to One-way ANOVA test with Tukey HSD post-hoc test showing that every trimester period is significantly different from others

Table 3. Descriptive measures according to trimester periods according to gender

	1st trimester	2nd trimester	3rd trimester	p	Min-Max	P25-P50-P75
	Mean±SS					
Male						
en_gn	9.95±0.92	23.18±5.0	43.51±10.11	<0.001*	9.3- 56.7	20.47-26.6-36.8
tr_r	11.7±0.42	18.14±5.17	32.8±9.43	<0.001*	11.0- 50.5	14.97-20.4-28.8
r_sn	6.15±1.2	12.37±3.64	21.54±4.38	<0.001*	5.3- 26.6	10.02-13.6-20.27
sn_gn	7.4±0.57	16.84±3.64	29.34±6.58	<0.001*	7.0- 38.7	14.7-19.4-24.2
tr_g	10.1±1.13	15.42±4.0	27.8±6.98	<0.001*	7.0- 39.3	13.0-18.55-22.9
g_sn	6.95±0.07	13.97±3.7	23.03±4.7	<0.001*	6.9- 28.6	11.35-15.85-20.02
sa_sba	7.05±0.07	13.13±4.44	27.8±7.73	<0.001*	6.7- 39.1	10.92-15.0-22.47
ex_en	5.8±0.57	10.64±2.09	18.86±6.96	<0.001*	5.4- 31.0	9.3-11.9-14.5
en_en	7.35±0.49	11.12±3.18	18.38±4.73	<0.001*	6.7- 24.1	9.5-12.5-17.0
al_al	5.5±1.13	11.01±3.45	17.86±3.93	<0.001*	4.7- 23.7	8.97-11.8-16.8
ch_ch	8.4±1.7	13.37±3.24	21.97±5.65	<0.001*	7.2- 32.0	12.1-14.75-18.7
Female						
en_gn	12.83±2.84	24.35±5.51	33.9±7.36	<0.001*	8.9- 47.1	17.47-24.4-28.02
tr_r	9.79±2.02	18.23±6.28	26.19±5.71	<0.001*	5.8- 37.6	12.3-15.8-22.3
r_sn	5.48±1.49	14.06±4.08	18.91±4.21	<0.001*	3.6- 28.9	9.05-12.8-17
sn_gn	9.82±2.25	17.63±4.25	21.43±3.44	<0.001*	6.6- 26.2	12.45-16.0-21.82
tr_g	8.49±1.57	15.07±5.21	20.68±4.02	<0.001*	6.0- 29.0	9.52-13.0-17.95
g_sn	5.78±2.06	14.99±4.0	20.1±3.1	<0.001*	3.4- 26.0	10.1-14.8-18.2
sa_sba	7.41±1.89	15.19±4.51	23.58±4.2	<0.001*	4.9- 32.3	10.0-14.6-21.3
ex_en	5.41±1.15	11.11±3.06	14.89±1.56	<0.001*	4.0- 17.9	7.1-10.55-14.2
en_en	6.94±1.71	11.64±3.18	16.65±3.43	<0.001*	4.0- 19.7	8.55-11.2-14.3
al_al	4.59±1.3	12.55±4.37	15.39±2.51	<0.001*	2.4- 21.2	7.65-11.8-14.7
ch_ch	7.21±1.61	15.4±3.77	20.09±5.79	<0.001*	5.0- 29.0	10.0-14.45-17.85

*: significant at 0.05 level according to One-way ANOVA test with Tukey HSD post-hoc test showing that every trimester period is significantly different from others

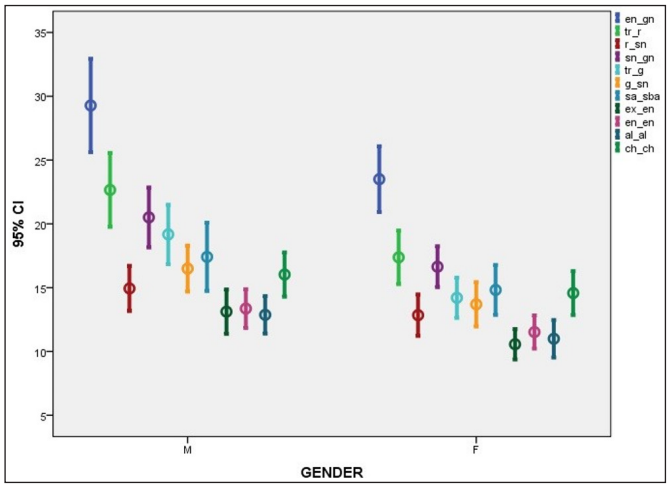

Figure 3. Fetus face measurements according to gender

DISCUSSION

Age, gender, race, climate and regional conditions cause body sizes to vary. The most important part of this variation is the facial area. The eyes are the parts of the face that have the most distinctive characteristics. Parameters related to the eyes play an important role in the diagnosis and the treatment of some anomalies and syndromes, in treatment of abnormal appearance such as hypertelorism, hypotelorism and telecanthus by many clinicians, geneticists and the plastic surgeons, in eyeglasses production and in setting physical anthropologic standards.[11,12]

Lately, craniofacial anthropometry has developed into a crucial tool benefitted by geneticists, opticians, anthropologists, forensic medicine specialists and reconstructive surgeons. Direk, Deniz Uslu et al.[13] observed a significant decrease in the nasoprontal angle with age in measurements of the orbital region. When the studies on different races were compared, the narrowest nasofrontal angle was identified as 134.[3] in North American Caucasians and the widest nasofrontal angle was identified as 149.2 in Direk, Deniz Uslu et al.[13-16] study.

As in other parts of the body, the external nose, head and face develop rapidly during adolescence. Knowing the pattern of development and timing of maturity are of great importance to set the best time for the reconstruction nasal deformities. Farkas, Hreczko, Koral et al. (1981) observed that the width and height of the nose basically stopped growing at the age of 12 in women and 14 or 15 in men, and that the size and shape of the external nose changed less after maturity.[19] We conducted an anthropometric study on selected normal young Han Chinese between 17 and 24 years old in order to provide reliable reference data during reconstruction of secondary nasal deformity after cheiloplasty, nasal reconstruction and repair of nasal defects and rhinoplasty in adults for Chinese population.

Anthropologists have stated that various nasal shapes and sizes emerged from the evolutionary adaptation of the nose to climate. According to Negus, populations adjusted to dry environments are inclined to have wide and protruding external noses, downwardly directed nostrils, and narrower skeletal apertures.[17] It is believed that these features induce turbulence to nasal airflow and that they maximize filtration and humidification of air within nasal passages. On the contrary, the ones who have smaller and flatter external nares, more anteriorly directed nares and shorter pyriform apertures are more effectively adapted to humid environments. These findings are also in line with our study conducted on people from West India mostly involving subjects from Rajasthan who have large external nares with downwardly directed nasal tips and subjects from the Himalayan region who have flatter noses with more anteriorly directed nares and shorter nasal apertures.

To consider objective factors in external nose reconstruction, systematic anthropometric methods are commonly used for measuring the soft tissue of the external nose before surgery. Preoperative evaluation and surgical planning should be carried out according to the shapes of face, mouth, eyes and body, while also referring to the measurement values of the normal population in the same gender and ethnic to decide the degree of reconstruction and the morphology of implant and objectively guide the actual surgery.[18]

Faces with four equal sections of the profile canon were not found in either of the populations. Among the variations of this canon, the height of the calvaria was smaller than the special upper and lower face heights in the majority of the other study group.[19] However, in our population the height of the calvaria while also smaller than the upper face height was greater than the lower face height. The upper face height was smaller than the lower face height in both populations. The most striking difference was that the forehead height I was smaller than the upper and lower face heights in high percentages of the other data.[19] In our measurements, although the forehead height I was smaller than the lower face height it was greater than the upper face height. The last vertical canon was equal in 2.9% and 2.2% of our women and men respectively. The literature data are similar to our results.[19] In both populations the most common variation reported was the nose length smaller than the ear length.

The interpretation of reference anthropometric data of the orbital region is both a fundamental phase for the quantitative specification of normal individuals and it can also be effectively used in the diagnostic procedures (treatment of traumas, chromosomal, and single gene alterations; teratogenically induced conditions such as fetal alcohol syndrome).[20-22] In fact, measurements are important to distinguish different pathologies and individual morphological variations.

CONCLUSION

The facial growth of the fetus is crucial in terms of anatomic and anthropologic perspective as well as oral and maxillofacial surgery. It plays a vital role in lower jaw surgery and intervention. Awareness of the facial position will help identify chromosomal deviations, genetic syndromes and other facial defects so that the anesthesia implemented in the lower jaw intervention and surgical interventions is achieved.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Meram Faculty of Medicine Clinical Researches Ethics Committee (Date: 27.06.2008, Decision: 2008/171).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Prognostic significance of albumin-to-alkaline phosphatase ratio for overall survival in metastatic lung adenocarcinoma patients

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ABSTRACT

Aims: This study aims to determine the prognostic significance of the pretreatment albumin/alkaline phosphatase ratio (AAPR) for overall survival in patients diagnosed with metastatic lung adenocarcinoma (MLA).

Methods: The medical records of 459 patients diagnosed with MLA between 2010 and 2021 were retrospectively reviewed. The AAPR was calculated using blood test results obtained at the time of diagnosis.

Results: The study identified the optimal threshold value for AAPR as 0.314. Patients with a high AAPR (AAPR>0.314) demonstrated significantly longer median survival and overall survival time compared to those with a low AAPR (AAPR ≤ 0.314) (p<0.001). Specifically, the median survival time for the low AAPR group was 2.13±0.29 (95% CI: 1.56-2.70) months, while the high AAPR group had a median survival time of 4.1±0.59 (95% CI: 2.90-5.23) months (p<0.001). The 1-year survival rates were 27.3% and 5.3% for the high and low AAPR groups, respectively (p<0.001). Additionally, an AAPR ≤ 0.314 increased the risk of death by 1.96 times at 1 year.

Conclusion: The AAPR was significantly reduced in MLA patients, making it a significant biomarker for forecasting prognosis and directing treatment options for these patients.

Keywords: Metastatic lung adenocarcinoma, albumin-to-alkaline phosphatase ratio, prognostic factor, survival

INTRODUCTION

Adenocarcinoma (ADC) accounts for approximately 40% of lung tumours and is often diagnosed at a late metastatic stage.[1] Survival rates for lung cancer are significantly affected by the presence of distant organ metastases. Detecting metastases at diagnosis remains a challenge and a reliable biomarker for this purpose has not yet been established. The process of carcinogenesis and tumour progression often results in abnormal serum enzyme synthesis before the clinical manifestation of the disease.[2] It is worth noting that inflammation and nutritional status are significant factors that influence the onset, development, treatment response, and clinical outcomes in cancer patients, as indicated by numerous recent studies.[3,4]

Assessing nutritional status often involves utilizing albumin (ALB), which also serves as a crucial indicator of the inflammatory response. Disease progression, malnutrition, and inflammation may hinder the synthesis of ALB, leading to a notable reduction in ALB levels.[5] Such a reduction in ALB levels has been associated with reduced survival and increased mortality in cancer patients.[6,7] Due to its association, albumin level has also been included in various scoring systems predicting the survival of patients with lung cancer.[8,9] Furthermore, elevated serum levels of alkaline phosphatase (ALP) are detected in liver, kidney, and bone diseases. Numerous studies have shown that elevated serum ALP levels are associated with a poorer prognosis in cancer patients.[10,11] The ratio of serum ALB to ALP level, known as the ALB/ALP ratio (AAPR), has gained popularity as a possible indicator of inflammatory and nutritional status in cancer patients. In 2015, Anthony et al.[12] reported on the prognostic value of AAPR and identified it as a significant predictor in hepatocellular carcinoma (HCC). Recent evidence further corroborates the observation that low pretreatment AAPR is linked to unfavorable outcomes in various malignancies, including non-small cell lung cancer.[13-15] A 20-year meta-analysis of 5951 patients with 10 different types of cancer in China found that those with a higher AAPR had a better OS than those with a

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lower AAPR. The integration of the AAPR-TNM system with the AAPR produced better results than the current TNM system.[16]

However, the prognostic significance of AAPR for survival in metastatic lung adenocarcinoma has not been extensively investigated. Therefore, this study aims to evaluate the impact of AAPR on the prognosis of patients with metastatic adenocarcinoma.

METHODS

The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.04.2023, Decision No: 2012-KAEK-15/2699). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was designed retrospectively, no written informed consent form was obtained from patients.

Patients

The study included MLA patients diagnosed and followed-up at Health Sciences University Ankara Atatürk Sanatorium Training and Research Hospital between January 2010 and January 2021.

The inclusion criteria were as follows: (I) Patients over 18 years old with histologically or cytologically confirmed metastatic lung adenocarcinoma diagnosed in the hospital's pulmonology departments, (II) patients with sufficient imaging data (such as computed tomography, magnetic resonance imaging, and PET-CT) for tumor staging, (III) patients who had not received any prior antitumor treatment (including radiotherapy, chemotherapy, immunotherapy, and targeted therapy), and (IV) patients with routine complete blood count and blood biochemistry results.

Exclusion criteria from the study were as follows: (I) Patients younger than 18 years old, (II) patients with non-adenocarcinoma non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC), (III) patients with secondary cancer, (IV) patients with concomitant hepatitis, liver cirrhosis, cholecystitis, nephrotic syndrome, inflammatory diseases, and lymphoproliferative diseases, (V) patients with concomitant infections, (VI) patients with known bone fractures and bone disease, and (VII) patients whose information could not be accessed in the hospital records and computer database.

The study retrospectively included 459 patients with pathologically diagnosed adenocarcinoma and distant metastases. Overall survival was determined by assessing disease-free survival and time to death. AAPR at the time of diagnosis were calculated by obtaining the mean value. Patients were then categorized into low and high AAPR groups based on this value, and statistical analyses were performed to compare the two groups.

Clinical Data

The clinical data collected for this study included age, gender, smoking history, sites of metastasis, and pre-treatment AAPR values. The pretreatment AAPR was calculated as follows: AAPR=Serum ALB level (g/L) / Serum ALP level (IU/L).

Observation Indicators

Median overall survival (OS) was defined as the time interval between the initiation of therapy and the last follow-up and/or death.

Tumor Staging

Tumor staging was conducted based on the eighth edition of the staging criteria published by the International Association for the Study of Lung Cancer.[17]

Statistical Analysis

All statistical analyses were performed using SPSS 22.0 software (Inc., Chicago, IL). The normality of the data was assessed using the Kolmogorov-Smirnov Test. Descriptive statistics were presented as median and min-max for normally distributed data. The relationship between AAPR level and categorical or continuous variables was analyzed using the chi-square test or Mann-Whitney U test, respectively. Prognosis based on overall survival (OS) was analyzed using Kaplan-Meier and log-rank tests. Univariate and multivariate Cox regression analyses were conducted to identify independent prognostic factors. Hazard ratios (HRs) along with bilateral p-values and corresponding 95% confidence intervals (CIs) were reported. All variables with a p-value <0.05 in the univariate analysis were included in the multivariate model. A p-value of <0.05 was considered statistically significant.

RESULTS

In our study, we included 459 patients who had pathological diagnoses of adenocarcinoma and distant metastasis (MLA), along with their pretreatment values. 80.2% (n=368) were male, 9.8% (n=91) were female, and the median age was 64 years (min 28-max 89). 353 (76.9%) patients had a smoking history. In terms of frequency, bone (59.9%, n=275) was the most commonly detected site of metastases, followed by the opposite lung (37.9%, n=174), pleura (36.4%, n=167), pleural effusion (29.9%, n=137), adrenal (28.8%, n=132), brain (18.8%, n=86), and liver metastases (15.3%, n=70).Spleen (n=11), skin (n=4), and vocal cord (n=1) metastases were classified as metastases in other sites.

The cut-off value for AALP was determined by analyzing ROC curves and the Youden index (Youden index=sensitivity + specificity-1). Among 459 MLA patients, an AALP value of 0.314 corresponded to the maximum Youden index value. Therefore, 0.314 was adopted as the proposed threshold for AALP. Of the patients, 308 had AALP >0.314, and 151 had AALP≤0.314.

Since ALP values were found to be higher in patients with liver and bone metastases, this particular group was analyzed separately. The analysis included a total of 283 patients with liver, bone, or both metastases, out of which 62 patients had both liver and bone metastases. The optimal subgroup cut-off for AAPR was found to be 0.335 when a separate cut-off was established for this group (with a sensitivity of 93.3%, specificity of 48.7%, AUC: 0.722; 95% CI 0.651-0.794; p<0.001). Both ROC curves are shown in Figure 1.

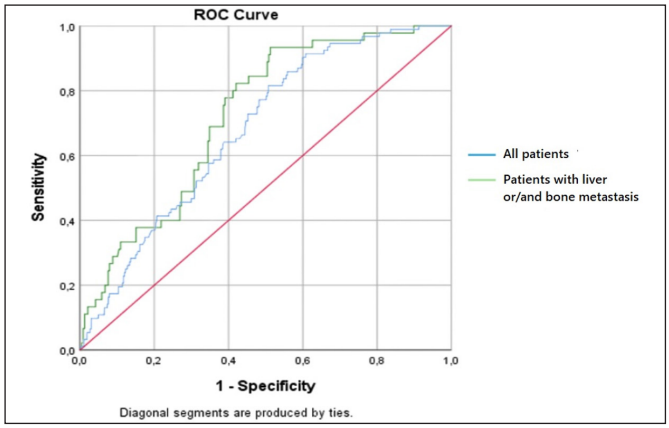

Figure 1. ROC analysis curves to predict 1-year survival in all ADC patients and only those withbone/kc mets.

Results showed that patients with a high AAPR greater than 0.314 had significantly longer median survival and overall survival than patients with a low AAPR of 0.314 or less (p<0.001). Specifically, median survival was 2.13±0.29 (95% CI: 1.56-2.70) months for the low AAPR group and 4.1±0.59 (95% CI: 2.90-5.23) months for the high AAPR group (p<0.001). The one-year survival rates were 27.3% for the high AAPR group and 5.3% for the low AAPR group (p<0.001; Figure 2). An AAPR of ≤0.314 increased the risk of death by 1.96 times within one year.

According to ROC analysis anticipating 1-year mortality, 283 patients diagnosed with ADC and liver and/or bone metastases were grouped into high (AALP >0.335; n=164) and low (AALP≤0.335; n=119) categories using an optimal cut-off value of 0.335. The low AALP group had a median survival of 1.97±3.67 (95% CI 1.47-2.53) months, which was statistically significantly lower (p<0.001) compared to the high AALP group of 3.48±10.31 (95% CI 2.0-4.97) months. In this cohort, the 1-year survival rate was 2.5% and 25.6% in the lower and higher categories, respectively (p<0.001).

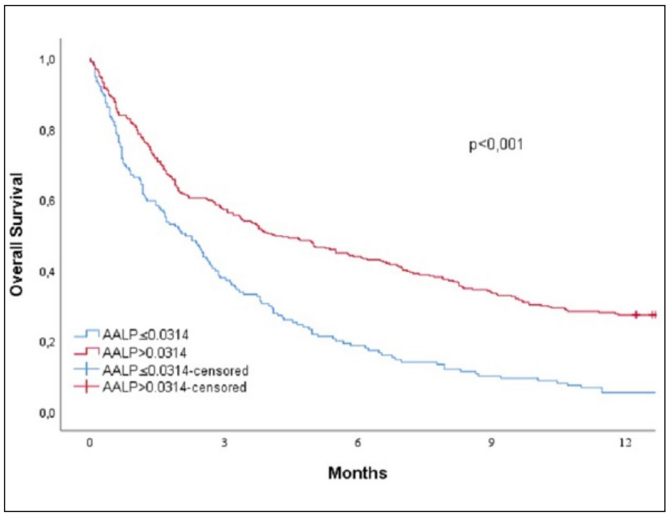

Figure 2. Kaplan-Meier curve illustrating the relationship between AALP and overall survival in patients diagnosed with ADC. The p-value was calculated using the log-rank test.

Table 1. The relationship between clinical characteristics and distant metastasis regions with AALP

		AALP≤ 0,314 (n=151)	AALP> 0,314 (n=308)	p
Gender	Male Female	124 (33.7%) 27 (29.7%)	244 (66.3%) 64 (70.3%)	0.464
Smoking Status	No Yes	30 (28.3%) 121 (34.3%)	76 (71.7%) 232 (65.7%)	0.251
Contralateral Lung	No Yes	91 (31.9%) 60 (34.48%)	194 (68.1%) 114 (65.52%)	0.572
Bone	No Yes	46 (25%) 105 (38.18%)	138 (75%) 170 (61.82%)	0.003
Liver	No Yes	115 (29.56%) 36 (51.43%)	274 (70.44%) 34 (48.57%)	<0.001
Brain	No Yes	121 (32.44%) 30 (34.88%)	252 (67.56%) 56 (65.11%)	0.664
Pleura	No Yes	97 (33.22%) 54 (32.34%)	195 (66.78%) 113 (67.66%)	0.846
Malignant pleural effusion	No Yes	103 (31.99%) 48 (35.04%)	219 (68.01%) 89 (64.96%)	0.525
Adrenal	No Yes	99 (30.28%) 52 (39.4%)	228 (69.72 80 (60.6%)	0.06
Other	No Yes	111 (29.9%) 40 (45.5%)	260 (70.1%) 48 (54.5%)	0.005

Mann Whitney-U test, AALP: Albumin/Alkalen fosfataz

ALB and ALP levels were not included in the multivariate model in the univariate and multivariate Cox regression analyses predicting 1-year survival, as they influenced AAPR. However, in the univariable analysis, ALB and ALP levels were also identified as significant factors affecting one-year survival (p<0.001). According to the results of the multivariate analysis, an AAPR of 0.314 or less, male gender, smoking history, bone metastases and cranial metastases all had a significant effect on survival at one year. (Table 2).

Table 2. Univariate and multivariate analysis results for 1-year survival in ADC patients.

	Univariate Analysis Results			Multivariate Analysis Results		
	HR	CI	p	HR	CI	p
AALP (≤0,314, >0,314)	0.672	1.58 - 2.42	<0.001	0.584	1.44-2.23	<0.001
Age	0.009	0.99-1.02	0.78	-	-	-
Gender(male, female)	0.476	1.22-2.12	0.001	0.327	1.08-1.91	0.045
Smoking History(no, yes)	0.477	1.24-2.09	<0.001	0.301	1.004-1.82	0.047
Contralateral metastasis	0.192	0.98-1.49	0.072	-	-	-
Bone metastasis	0.402	1.21-1.85	<0.001	0.308	1.087-1.70	0.007
Liver metastasis	0.426	1.16-2.01	0.002	0.099	0.82-1.48	0.517
Cranial metastasis	0.344	1.09-1.82	0.008	0.285	1.03-1.72	0.032
Pleural metastasis	0.095	0.89-1.35	0.378	-	-	-
Malignant pleural effusion	0.113	0.89-1.39	0.317	-	-	-
Adrenal metastasis	0.267	1.05-1.62	0.018	0.101	0.88-1.39	0.39
Metastasis in other regions	0.441	1.21-1.99	0.001	0.239	0.97-1.67	0.086

HR: Hazard ratio, CI: confidence interval, AALP: Albumin/alkalen fosfataz.

DISCUSSION

Serum levels of ALB and ALP are two key liver function test parameters that can reflect biochemical and pathological changes in a number of medical conditions and are used as a cost-effective and readily available laboratory test. However, the use of the AAPR for prognosis in malignant disease is limited. Compared to traditionally used biomarkers such as tumor stage, the AAPR appeared to provide additional information, including tumor burden, inflammation, and nutritional status.[18]

This may clarify the prognostic influence of AAPR across different cancers, different stages of the same tumour, and different treatments for cancer patients. It is therefore possible that AAPR could be an independent indicator for many different types of cancer. In NSCLC, it is critical to perform the necessary assessments in newly diagnosed patients to select the most appropriate treatment plan that will improve survival. In planning the optimal treatment for a patient with metastatic NSCLC, patient and tumour characteristics are critical. This is particularly true for adenocarcinoma, where targeted therapies are being developed and prognostic markers are needed to guide treatment decisions.

In the present study, it has been shown that AALPR may serve as a promising prognostic indicator in clinical applications and that a decreased level of AALPR is associated with a poor OS in patients with MLA.

In a 20-year meta-analysis of a total of 5951 patients with 10 different types of cancer in China, cut-off values in the studies ranged from 0.35 to 0.68. Patients with higher AAPR had better OS when divided into two categories according to the median value of 0.44 (HR: 0,50; %95 GA: 0,43-0,58; p <0,001). In a subgroup analysis by tumour type, a higher AAPR was associated with a better OS in NSCLC (HR: 0.45; 95% CI: 0.26-0.78; p<0.001), SCLC (HR: 0.60; 95% CI: 0.44-0.82; p<0. 001), HCC (HR: 0.49; 95% CI: 0.34-0.69; p<0.001), pancreatic ductal adenocarcinoma (PDC) (HR: 0.47; 95% CI: 0.31-0.71; p<0.001) and nasopharyngeal carcinoma (NPC) (HR: 0.42; 95% CI: 0.21-0.85; p=0.016). In a subgroup analysis by tumour type in this meta-analysis, a higher AAPR was associated with a better OS in NSCLC (HR: 0.45; 95% CI: 0.26-0.78; p<0.001), SCLC (HR: 0.60; 95% CI: 0.44-0. 82; p<0.001), HCC (HR: 0.49; 95% CI: 0.34-0.69; p<0.001), PDC (HR: 0.47; 95% CI: 0.31-0.71; p<0.001) and NPC (HR: 0.42; 95% CI: 0.21-0.85; p=0.016). They showed that pre-treatment AAPR can be used as a prognostic indicator in NSCLCs, SCLCs, HCCs, PDACs, and NPCs. They have also shown that correlating the AAPR-TNM system with the AAPR gives better results than the current TNM system.[16]

Li D et al, in a study of 290 metastatic NSCLC patients, of whom 215 (74.1%) had adenocarcinoma, found that patients with AAPR >0.36 had longer survival than those with AAPR ≤0.36 (13 vs 7 months, p<0.001). Patients without liver/bone metastases had higher AAPR and lower ALP than those with liver/bone metastases (0.47 vs. 0.40, p<0.001; 80.17 vs. 95.40 U/L, p<0.001, respectively). LDH and ALB levels were not significantly different in these two groups (both p>0.05).[18]

Our study group was comprised solely of patients with adenocarcinoma within the NSCLC category. All patients were metastatic and had not undergone any previous treatment. In our study, similar to the meta-analysis by Tian et al.[16] and the research by Li et al.[18] the high AALP group had a significantly longer median survival time than the low AALP group, reflecting a positive disease prognosisAgain, as in the study by Li et al.[18] we looked at 283 patients with ADC and bone metastases separately and found that the median survival of the high AALP group (>0.335; n=164) was significantly higher than that of the low AALP group. The 1-year survival rates

in the low and high AALP groups were 2.5% and 25.6%, respectively.

In their study, Zhou et al.[19] examined 224 patients with advanced NSCLC and established the threshold value for AAPR as 0.35. Kaplan-Meier analysis revealed a median OS of 9.73 months (95% CI=8.6-12.33) for AAPR <0.35 and 13.7 months (95% CI=11.43-16.37) for AAPR ≥0.35 (log-rank p <0.0001). The Cox regression analysis further demonstrated that AAPR <0.35 increased the risk of death (HR=1.65, 95% CI=1.11-2.46). They also found that the risk of dying was 71% higher when comparing those with bone metastases to those without.

Furthermore, another study conducted by Zhou et al.[20] focused on 808 patients with advanced NSCLC. They classified the patients into three groups based on their AAPR levels: low (AAPR<0.34, n=266), moderate (AAPR=0.34-0.47, n=259), and high (AAPR>0.47, n=283). The results showed that moderate and high AAPR levels were associated with better outcomes, with hazard ratios (HR) of 0.77 (95% CI=0.58-1.03) and 0.59 (95% CI=0.45-0.78), respectively. The median OS for low, moderate, and high AAPR groups was 9.3, 11.8, and 16.9 months, respectively (p<0.001). Similar results were seen in subgroup analyses in almost all subgroups.

A study of AAPR in patients with advanced NSCLC was conducted by Liu et al.[21] their results showed a noteworthy decrease in AAPR levels. Patients with elevated AAPR had a median progression-free survival (PFS) and OS of 17 months and 23 months, respectively, whilst those with diminished AAPR had a median PFS and OS of 8 months and 13 months, respectively. The area under the curve (AUC) of AAPR for both PFS and OS was higher than that of ALB and ALP (p<0.05). Low AAPR was associated with significantly shorter PFS and OS compared to high AAPR, with a median PFS of 8 months vs. 25 months and a median OS of 12 months vs. 36 months.

In our study, similar to the results of the aforementioned articles, we found that the high AAPR group (AAPR>0.314) had a significantly longer median survival and overall survival than the low AAPR group (AAPR ≤ 0.314), indicating a better disease prognosis. In the present sturdy, we also found that an AAPR ≤ 0.314 was associated with a 1.96-fold increase in the risk of death within one year.

CONCLUSION

Our study represents the initial evaluation of AAPR in patients diagnosed with the adenocarcinoma subtype, in contrast to other studies in the relevant literature that concentrate on advanced-stage NSCLC.

The findings demonstrate a considerable reduction in AAPR levels amongst patients diagnosed with metastatic lung adenocarcinoma (MLA) and therefore, indicate its utility as a valuable biomarker that can aid in predicting prognosis as well as guiding treatment decisions among these patients.

However, it is important to note that the study has some limitations. The study was conducted retrospectively at a single centre. In order to establish the independent prognostic potential of the AAPR value and to gain a deeper understanding of its relationship with median survival, prospective studies are needed which encompass all factors that could influence the AAPR value.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.04.2023, Decision No: 2012-KAEK-15/2699).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Impact of the COVID-19 pandemic on mode of delivery

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ABSTRACT

Aims: The first case of COVID-19 was reported on March 11th, 2020, in Turkey, and the measures taken by the state to prevent the spread of the virus were put on hold by March 2022. The purpose of this study is to present information with special focus on mode of delivery among pregnant women during COVID-19 pandemic. We aimed to assess the effect of pandemic on the rates of normal vaginal delivery and C-section.

Methods: This is a restrospective cohort study including all pregnant women at more than 20 weeks of gestation admitted to labour and delivery unit in an academic tertiary care hospital. Records of patients two years before the pandemic and two years of the pandemic were extracted. The number of pregnants admitted to the labour and delivery, the mode of delivery, selected method of anesthesia, total expenses of the patients, the length of hospital stay, indications for cesarian section were compared between the two periods.

Results: A total of 9048 patients were identified, of which 4745 were before the pandemic and 4303 during the pandemic. The most striking finding was the decrease in C-section rates during pandemic which was mostly due to decrease in number of primary C-sections. The length of hospital stay was shorter during pandemic as well. The mean age, route of anesthetics, surgery length did not differ between the two groups.

Conclusion: The available evidence on COVID-19's potential impact on C-section rates is conflicting. Some suggest that there might be evidence indicating a possible link between COVID-19 and increased rates of C-section. However, this study showed that when all the deliveries are included pandemic caused a significant decrease in the rates of primary C-section which might be due to decreased interventions of the healthcare professionals.

Keywords: COVID-19, cesarean rate, vaginal delivery, birth outcomes, maternal health

INTRODUCTION

In December 2019, the novel coronavirus SARS-CoV-2 made its initial appearance in Wuhan, demonstrating both the potency and transmissibility to trigger a global pandemic. Within the first 6 months, there were over 6 million confirmed infections worldwide.[1] On March 11, 2020, Turkey reported its first case of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). By April 2020, due to increasing numbers of cases strict regulations were applied to prevent the spread of the disease. Our hospital was selected as a pandemic hospital as being one of the biggest medical facilities in Istanbul. Most of the elective medical services were put on hold and all the units were rapidly adapted to care for patients with COVID-19. However, obstetric and delivery units continued to provide care to their patients. In response to the exponential increase in COVID-19 cases in Turkey, Ministry of Health adopted universal testing of all patients admitted to the hospitals, including pregnant patients regardless of the existence of the symptoms. Therefore, Turkey's obstetric population is unique in that virtually all were tested thereafter.

In March 2020, the Journal of the American Medical Association published the initial case report regarding potential vertical transmission of COVID-19 infection.[2] This report described the situation of a newborn born to a mother with COVID-19. Conversely, prior to the publication of this case report, all of the limited studies released had indicated the lack of vertical transmission.[3,4] Amidst this period of uncertainty, numerous associations issued statements on this matter. National and international scientific communities responded in line with this.[5,6] The International Federation of Gynecology and Obstetrics (FIGO) and the Royal College of Obstetricians and Gynaecologists (RCOG) both emphasize that the presence of COVID-19 should not impact the choice of delivery method,

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unless there is an urgent need due to severe respiratory issues.[7,8] Significantly, there was a lack of substantial evidence indicating any reasons to avoid vaginal delivery. The consensus among experts has echoed this discovery.[9,10] However, data on the impact of COVID-19 on pregnancy outcomes demonstrated an increase in the rate of caesarean delivery and prematurity.[11-13] A national cohort study from United Kingdom showed an increase in morbidity due to COVID-19 among pregnant women with medical comorbidities or ethnic minorities.[14] In addition, the rate of prematurity and caesarean delivery were greater compared to the control group.

We report our results of a retrospective study among all the pregnant women admitted to labour and delivery unit from 2018 to 2022 in a tertiary center. The results of obstetric outcomes during the two years of pandemic were compared with the results before the pandemic.

METHODS

The study was carried out with the permission of İstanbul Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 27.07.2022, Decision No: 2022/514/222/29). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We conducted a retrospective cohort study of consecutive pregnant women at more than 20 weeks of gestation admitted to labour and delivery unit in an academic tertiary care hospital. Because the study was designed retrospectively, no written informed consent form was obtained from patients. Medical records were subtracted starting from March 2018 to March 2020. We aim to compare the obstetric outcomes of deliveries during the two years before pandemic and during the two years of COVID-19 pandemic. Universal testing for SARSCoV-2 was implemented starting from 24 March 2020. A nasopharyngeal (NP) swab for SARS-CoV-2 testing using a reverse transcription polymerase chain reaction (RT-PCR) assay was performed to all the women admitted to labour and delivery.

After the COVID-19 outbreak, upon presentation to the labour and delivery unit, women were evaluated for symptoms of disease including self-reported fever, cough, sore throat, rhinorrhea, shortness of breath or myalgias. The ones with a confirmed SARS-CoV-2 test were admitted to a special unit within labor and delivery. Our hospital was selected as one of the pandemic hospitals. All the elective interventions were put on hold and mainly served in the units that were converted to COVID-19 units. Ministry of Health did not indicate early discharge during the pandemic. For women and neonates with clinical stability, our hospital system offered discharge at 24 hours after vaginal delivery and 48 hours after caesarean delivery.

Upon approval of the Local Ethics Committee (Local Ethics Committee protocol number:2022/514/230/3), demographic (age, ethnicity, insurance status), clinical, obstetric data were abstracted from the electronic medical record for each woman. Data was collected starting from March 2018 to March 2022. The first two years represent the time before pandemic. The last two years include the time of COVID-19 pandemic. We compared the number of pregnants admitted to the labour and delivery before and during the pandemic. The mode of delivery, selected method of anesthesia, total expenses of the patients, use of antibiotics, the length of hospital stay, indications for cesarian section were compared between the two periods. The primary question of the study was whether obstetric management of the patients was altered based on outbreak of COVID-19 pandemic.

We used descriptive statistics to examine the differences between the two groups (before COVID-19 pandemic and during the pandemic). T test was used to compare means for numerical variables, and chi-square test was used to compare ordinal and nominal categorical variables. All data were analysed using SPSS 20.

RESULTS

A total of 9048 patients were identified, of which 4745 were before the pandemic and 4303 during the pandemic. The mean age in both groups were similar; 28,65 years old before the pandemic and 28.20 during the pandemic. Even though, women who did not have any insurance constitutes a small fraction of the patients, number of pregnant women who had no insurance were doubled during the pandemic.

The mean operation time before the pandemic and during pandemic did not show any significant difference. The length of stay in the hospital was longer before the pandemic. The mean time for hospital stays before and during the pandemic were 1.84±1.64 days and 1.76±0.92 days, respectively (p=0.004). When the route of administration of anesthetic were compared, we did not find any significant difference in both groups. Finally, the hospitalization expenses were significantly different between the groups (**Table 1**).

The rates of C-sections in our hospital were between 40-50%, irrespective of the COVID-19 pandemic (**Figure 1**). Of 4745 deliveries before the pandemic 2212 were C-section and 2533 were vaginal deliveries. Primary C-section rates were also extracted. C-section rates were 46.6% and within these patients 29.76 % of them were primary C-section.

During the first wave of pandemic in April 2020, the number of the deliveries were decreased by almost five folds which might be contributed to the recognition of our center as a pandemic hospital and the excessive anxiety among the pregnant women. During the first wave, the number of C-sections exceeded the number of vaginal deliveries (Figure 2).

However, during the pandemic, rates of vaginal deliveries were found to be significantly higher than the C-section rates except the first wave as mentioned before. The rates of primary C-sections were also decreased during the pandemic (21.9%) compared to data from 2018 and 2019 (29.76%). Among the pregnant patients who had a confirmed COVID-19 infection primary and total C-section rates were higher, 15.52% and 61.6%, respectively. Of 9048 patients, there were 5 maternal deaths, all of them due to critical COVID-19 infection. During the pandemic, emergency C-section rates decreased compared to pre-pandemic period (Table 2).

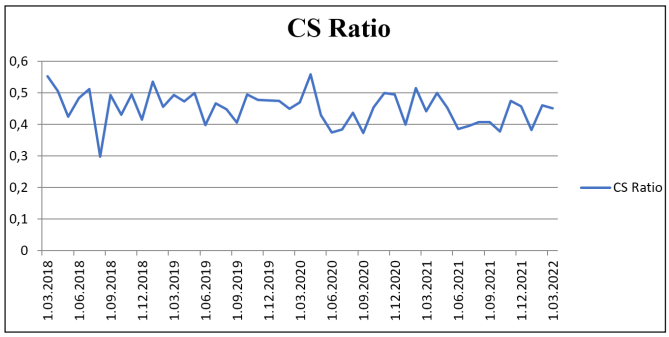

Figure 1. The trend in the CS ratio by time. The CS ratio has fluctuated almost between 0.4 and 0.5 during the period of 2018-2022 (the mean is 0.45).

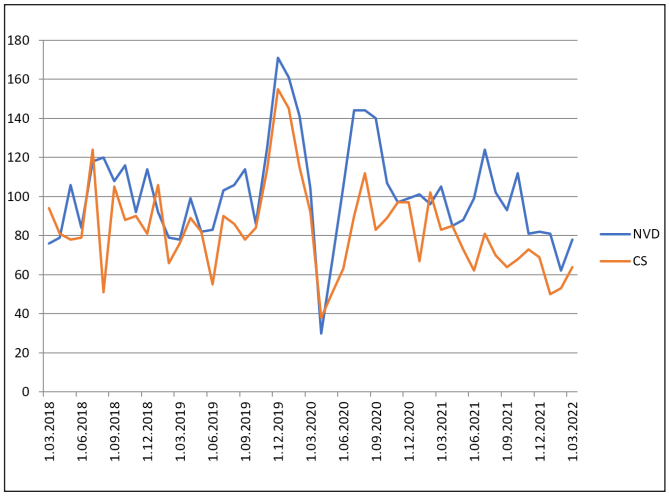

Figure 2. The trend of NVD and CS between March 2018 and March 2022. The number of NVDs were generally higher than the number of C-sections, regardless of pandemic. During the pandemic, the gap between the NVD and C-section increased in terms of numbers.

Table 1. Baseline Demographics. Data are mean±SD or n (%) unless otherwise specified.

Characteristic	Before COVID-19 (n=4.745)	During COVID-19 (n=4.303)	Total (n=9.048)	p-value
Age (y)	28.65±5.93	28.20±5.99	28.4±5.97	
Insurance				< 0.000
No Insurance	17 (0.36)	36 (0.84)	53 (0.59)	
Public Insurance	4.353 (91.74)	4.027 (93.59)	8380 (92.62)	
Private Insurance	375 (7.90)	240 (5.58)	615 (6.80)	
Operation time	47.59±84.96	44.88±129.90		0.237
Hospitalization after delivery	1.84±1.64	1.76±0.92		0.004
Total Expense	901.27±2.534.31	1.386.86±1.507.95	1.132.22±2.123.09	< 0.000

Table 2. Mode of Delivery. Data are mean±SD or n (%) unless otherwise specified.

Characteristic	Before COVID-19 (n=4.745)	During COVID-19 (n=4.303)	Total (n=9.048)	p-value
Previous cesarean birth	1545	1458	3003	
Anesthesia				0.077
General	531 (11.2)	371 (8.6)	902 (9.97)	
Epidural	7 (0.1)	12 (0.3)	19 (0.21)	
Spinal	1513 (31.9)	1182 (27.5)	2695 (29.78)	
No anesthesia	2694 (56.8)	2738 (63.6)	5432 (60.04)	
CS Emergency				< 0.000
Emergency	3649 (76.90)	2945 (68.44)	6594 (72.88)	
Elective	1096 (23.10)	1358 (31.56)	2454 (27.12)	
Delivery Type				< 0.000
NVD Primipar	691 (14.6)	644 (15)		
NVD	1841 (38.8)	1771 (41.2)		
C-section Primipar	652 (13.7)	405 (9.4)		
C-section Primipar	1539 (32.4)	1444 (33.6)		
Multiple	21 (0.4)	27 (0.6)		

DISCUSSION

In the present study, we investigated the impact of COVID-19 pandemic on labor and delivery. Among the 4303 pregnant persons presenting to labor and delivery during the pandemic period the prevalence of COVID-19 infection was 5,09% in our study. There was a slight decrease in the number of deliveries during the COVID-19 pandemic compared to the same months before the pandemic. We found that during the pandemic the number of vaginal deliveries had a higher ratio than the C-sections. However, within the group of women who had infection C-section rates were 62.6%. Interestingly, the number of emergency C-section rates were higher before the pandemic.

The prevalence of COVID-19 infection among the women presenting the labor and delivery reported in this study were somewhat coherent with the previous studies. In a recent review, Jamieson et al.[15] reported a prevalence of COVID-19 ranging from 3-20% . Mutlu et al.[16] reported that the total number of births and vaginal birth rates decreased in the first wave in a tertiary hospital in Turkey. Our results also revealed that during the first wave of the pandemic there was a dramatic decrease in the number of deliveries and rates of vaginal deliveries. This might be contributed to the patients' choice of hospital, since the virus had caused enormous anxiety and patients probably did not prefer a tertiary center for delivery.

Curiously, during the two years of COVID-19 pandemic, when the total number of patients were put in account, rates of vaginal deliveries were higher compared to before pandemic. Primary C-section rates also decreased during the pandemic. Our study showed that, initially, the choice of the hospital was affected by the infection. The decrease in C-section ratios revealed that there might be an alteration in the behavior of the health workers, as well. Healthcare professionals were also anxious because of the infection, which might have resulted in less intervention causing decreased rates of C-sections. This suggests that, during the pandemic, health professionals might prefer vaginal births over cesareans to reduce infection risk. Several studies with conflicting results have been published on this matter.[17-20] Nevertheless, more research is needed to confirm this hypothesis.[21] Since we did not study the behavioral changes of the healthcare professionals in our hospital during the pandemic, our results are certainly not eligible to draw a conclusion on this subject.

This study was conducted in a tertiary hospital in Istanbul, Turkey. During the four years examined in this study, the same group of healthcare professionals were working in the hospital. Standardized healthcare is an important aspect of this study. Moreover, our study covered the longest time of COVID-19 pandemic in Turkey, which results in more reliable comparisons.

Limitations of the study are the fact that the data of the study was collected from a single center which was converted to a pandemic hospital. However, considering the decreased access to healthcare services during pandemic and the size of the sample in this study, our results would still provide insights of the general population.

CONCLUSION

This study aimed to investigate the effect of COVID-19 pandemic on pregnant patients accepted to labor and delivery. Most of the papers in the literature compared the C-section rates within the pregnant patients who had a confirmed positive COVID-19 test. We tried to understand the impact of a pandemic on a special group of patients; pregnant women admitted to the labor and delivery. We found that pandemic caused a decrease in both C-section rates and primary C-section rates. We believe this might be explained in part by the decreased intervention during labor.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 27.07.2022, Decision No: 2022/514/222/29).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Assessment of sonication-based culture in diagnosing orthopedic implant infections: a comparative analysis with microbiological diagnostic approaches

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ABSTRACT

Aims: This study aimed to investigate the diagnostic advantages of microbiological culture, histopathological examination, and the management of sonication in the diagnosis of infections related to orthopedic implants and prostheses.

Methods: The study included 21 patients suspected of orthopedic implant or prosthesis-related infections. The classification of implant and prosthesis-related infections and the choice of treatment were based on the Infectious Diseases Society of America diagnostic and treatment guidelines. During the operations, samples were taken from the implant and inflamed tissue around the implant for each patient, and these samples were evaluated using standard culture, histopathological examination, and sonication methods.

Results: The sonication method exhibited a higher sensitivity in comparison to both tissue cultures and cultures acquired from implants and prostheses without the application of sonication (61.1% vs. 38.8% vs. 27.7%, $P < 0.05$, respectively). The count of isolated microorganisms was greater in the sonication method when compared to both tissue cultures and conventional cultures taken from implants and prostheses (16 vs. 10 vs. 6, $P < 0.05$, respectively). The sensitivity of the sonication method was found to be higher compared to conventional cultures, even among patients who had been administered preoperative antibiotics ($p<0.05$).

Conclusion: In the diagnosis of orthopedic implant and prosthesis infections, the sonication method was more effective as a diagnostic approach compared to conventional methods. A greater number of agents can be identified using the sonication method in infected tissues.

Keywords: Prosthesis, implant, infection, sonication

INTRODUCTION

The frequency of orthopedic prosthesis and implant applications has increased over the past two decades. It has been reported that in the United States, approximately one million people undergo total hip and knee arthroplasty surgery each year, and this number is projected to reach four million annually by 2030.[1,2] While complications are infrequent after orthopedic implant and prosthesis procedures, the growing number of patients undergoing these surgeries leads to a higher overall incidence of complications. One of the most serious complications after surgery are prosthetic and implant-related infections. These infections result in increased morbidity and mortality rates, as well as longer hospitalization, long-term antibiotic use and more surgical interventions.[3-5]

In diagnosing implant-induced infections, the best approach is to culture the tissues near the implant during an operation and isolate the responsible microorganism. However, in patients with suspected orthopedic implant infections (SOII), isolating the causative microorganism from the surrounding tissue cultures is not always feasible. The reason for this is that the bacteria hide under the biofilm layer they form on the implant. On the other hand, most of the patients take antibiotics before and during surgery and the likelihood of isolating the causative microorganism in culture decreases.[6] In addition, the likelihood of isolating the causative microorganism in culture may vary among diagnostic methods.

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One of the diagnostic methods for prosthesis and implant infections is the sonication of the extracted implant or prosthesis. Sonication is the decomposition of the biofilm layer on the implant with ultrasonographic sound waves. It is suggested that the sonication method increases the likelihood of isolating the the infection-causing microorganism relative to the tissue culture near the implant, and that this also applies to patients who undergo antibiotic treatment prior to the surgery.[7] Therefore, this study aimed to compare the microbiological culture, histopathological, and sonication methods to identify the causative agents in patients who had their implants or prostheses removed due to SOII or suspected joint prosthesis infection (SJPI).

METHODS

This prospective cross-sectional study was conducted at the Gülhane Training and Research Hospital Orthopedics and Traumatology Clinic from July 2015 to December 2015, in accordance with the Helsinki Declaration and the Good Clinical Practice Guidelines. The study received approval from the Gülhane Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.06.2015, Decision No: 1491-88-14/1648.4-467). Informed consent was obtained from all cases included in the study.

The study included 21 patients who admitted with SOII or SJPI and subsequently had an implant or prosthesis removal procedure. The Infectious Diseases Society of America (IDSA) guidelines were employed for classifying and determining treatment options for these infections.[1] Eligibility criteria for the study inclusion encompass patients meeting at least one of the following: the identification of the same microorganism from cultures taken during two or more surgeries or from both preoperative aspiration and intraoperative cultures; the observation of purulent fluid in the prosthesis area without any other known cause; detection of acute inflammation in the peri-prosthetic tissue or on the prosthesis during histopathological examination after surgical debridement or prosthesis removal; and the presence of an externally opening sinus tract associated with the prosthesis. Additionally, patients who did not meet any of the aforementioned criteria but exhibited at least two of the following symptoms in the implant or prosthesis area-pain, limited motion, increased temperature, swelling, or necrosis at the incision site-were also included in the study, considering they might have a prosthesis infection. Patients with ongoing pain following prosthesis placement, who reported restricted movement and, irrespective of elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) values, exhibited indications of non-union, pseudoarthrosis, or implant loosening in radiographic examinations, were also included in the study due to suspected implant or prosthesis infection. Patients with contamination in any extracted sample such as peri-prosthetic tissue or implant or an infection originating from another source were excluded from the study.

Antimicrobial therapy was described as the use of antibiotics within the 14 days before the extraction of the implant or prosthesis. Demographic, clinical, microbiological, pathological, and laboratory findings were recorded for each patient. The implant age was defined as follows: the median time elapsed from the initial surgery to the point when infection was suspected. The reference ranges for laboratory parameters were as follows: For leukocytes, 4-10×10^9/L; for ESR, 0-20 mm/h; and for CRP, 0-5 mg/L.

Sample Collection

All surgical procedures were conducted in an environment with clean laminar airflow. In appropriate cases, joint fluid was aspirated preoperatively, and leukocyte count and microbiological examination were performed. The extracted implants were taken aseptically and stored in sterile polypropylene containers with screw caps. Every sample was transported to the microbiology lab within a two-hour window after surgery. Tissue cultures surrounding the implant or prosthesis were taken from all patients. Removed implants and prostheses were evaluated both by conventional culture and through sonication. Additionally, tissue samples from around the implant or prosthesis, as well as the sonication fluids of the removed implants or prostheses, were sent to the pathology laboratory for histopathological and cytological examination.

Conventional Culture

During the operation, for each patient, four tissue samples were taken from the implant and the inflamed tissue surrounding the implant. The samples were dispatched to laboratories under sterile conditions for both histopathological and microbiological analyses.

Procedures on the Implant

Fifty ml of sterile distilled water was added to the implants inside the sterile polypropylene tubes, followed by 30 seconds of vortexing. At this stage, 100 microliters from the obtained liquid was inoculated onto 5% sheep blood agar, chocolate agar, and eosin methylene blue (EMB) agar (Salubris, Istanbul, Turkey), both in aerobic and anaerobic environments. After the inoculation, the implant sample was sonicated at 50 kilohertz for five minutes (Elma D-78224 Singen/Htw, Germany), and then vortexing was repeated for 30 seconds. The sample was centrifuged at 13,000 G force

for 15 minutes. The supernatant was discarded, and 100 microliters from the remaining liquid at the bottom was inoculated onto 5% sheep blood agar, chocolate agar, and EMB agar, in both aerobic and anaerobic environments. Aerobic cultures were incubated at 37°C for 48 hours in an incubator containing 5% CO_2. Anaerobic cultures were incubated for 7 days in an anaerobic chamber incubator (Bactron, Sheldon Manufacturing Inc. OR, ABD), with conditions being checked every other day.

Tissue Cultures

Tissue specimens, harvested under sterile conditions and shipped to the lab in sterile vessels, were placed into sterile mortars. They were then mixed with 1 ml of tryptic soy broth and crushed. From the crushed specimen-broth blend, 100 microliters were sampled and cultured on 5% sheep blood agar, chocolate agar, and EMB agar under both aerobic and anaerobic conditions. Aerobic cultures were incubated for 48 hours in an incubator containing 5% CO_2, while anaerobic cultures were incubated for 7 days in an anaerobic chamber incubator, with daily checks.

Colony counts of the microorganisms grown on the plates were determined and noted as colony forming units (cfu)/ml. The proliferating microorganisms were identified using conventional methods and the Phoenix 100 automated phenotypic identification device (BD, Maryland, USA). Antibiotic susceptibility tests were conducted using the Phoenix 100 automated phenotypic identification device (BD, Maryland, USA) and the Kirby-Bauer disk diffusion test, in accordance with the Clinical and Laboratory Standards Institute (CLSI) criteria. Results were evaluated quantitatively as cfu/ml in categories of pre-sonication and post-sonication of the implant, as well as in the tissue category. Bacterial typing was conducted at the genus and species level, together with the results of antibiotic susceptibility tests.

Statistical Analysis

All data were analyzed with IBM SPSS Statistics for Windows 20 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean±standard deviation values, while non-normally distributed variables are given as median (min-max) values. Accordingly, Student t-test and Mann-Whitney U test were used for comparisons between two groups. Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using Chi-square and Fisher exact tests. The sensitivity values was determined using the formula: True positives / (True positives + False negatives).8 Significance was accepted at $p<0.05$ (*) for all statistical analyses.

RESULTS

The study population consisted of 21 cases, including 11 cases with SJPI (mean age: 60.9±16.0 years) and 10 cases with SOII (mean age: 38.6±12.1 years). The median implant age was higher in the SJPI group compared to the SOII group (19 months vs. 7 months, $p < 0.001$). The rate of preoperative antibiotic use was higher in the SOII group compared to the SJPI group (100% vs. 45.5%, p=0.007). In the SJPI and SOII groups, at least two of the symptoms such as pain, limited mobility, increased temperature, discharge, swelling, and necrosis in the incision area were present. In both groups, the ratio of patients with leukocyte values within normal limits was similar, while the ratio of patients with elevated CRP was higher in the SJPI group compared to the SOII group (72.7% vs. 10%, p=0.005). Demographic and clinical characteristics of patients with SOII and SJPI are presented in Table 1.

Table 1. Demographic and clinical findings of the patients suspected of prosthesis and implant infection

Variables	SJPI n=10	SOII n =11	p value
Age, years	61 (21-83)	39 (20-83)	<0.001*
Median implant age, months	19 (1-60)	7 (1-18)	<0.001*
Preoperative antibiotic use, n (%)	10 (100)	5 (45.5)	0.007*
Female gender, n (%)	8 (80.0)	5 (45.5)	0.113
Symptom duration, month	2 (1-3)	1.5 (0.5-2.0)	0.035*
Pain-Limited mobility	7 (70.0)	10 (90.9)	0.235
Drainage	0	5 (45.5)	0.017*
Increased temperature	9 (90.0)	8 (72.7)	0.325
Necrosis	0	5 (45.5)	0.017*
Leukocytosis	2 (20.0)	1 (9.0)	0.482
Elevated ESR	8 (80.0)	6 (54.5)	0.227
Elevated CRP	10 (10.0)	8 (72.7)	0.005*
Time between infection suspicion and surgery, days	22 (16-32)	14 (13-27)	0.015*
Follow-up time, months	11 (1-12)	10 (1-12)	0.863

Data are shown as mean ±SD or median (min-max) or number and percentage (%). * p <0.05 shows statistical significance. Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SJPI, patients who suspected of joint prosthesis infection; SOII, patients who suspected orthopedic implant infection.

In the histopathological examination, active or chronic inflammation findings were detected in the tissues surrounding the implants and prostheses and in sonication fluids of the implants and prostheses in 18 out of 21 patients. In the remaining three patients, no signs of inflammation were found in the histopathological examination, and no pathogens were isolated in the microbiological cultures. In these three patients, there were complaints of pain in the implantation area prior to surgery. Additionally, they had elevated ESH or CRP levels and showed signs of loosening in direct radiography. Consequently, these patients underwent surgical procedure based on suspicions of infection. Given that no pathogens were detected in the microbiological

cultures and there were no indications of inflammation in the histopathological analysis for these patients, the possibility of implant infection was ruled out, and they were evaluated as cases of aseptic loosening.

In the 18 patients with positive histopathological results, the sonication method exhibited higher sensitivity in detecting pathogens compared to the tissue and conventional culture methods (61.1% vs. 38.8% vs. 27.7%, p<0.05, respectively). Similar findings were also detected in the SJPI and SOII subgroups (Table 2).

Table 2. Comparison of sensitivity between conventional, tissue, and sonication fluid cultures.

Variables	Culture Identified / Total	Sensitivity (%)
All population		
Tissue culture	7 / 18	38.8
Conventional culture	5 / 18	27.7
Sonication fluid culture	11 / 18	61.1*
SJPI group		
Tissue culture	3 / 10	30.0
Conventional culture	2 / 10	20.0
Sonication fluid culture	5 / 10	50.0*
SOII group		
Tissue culture	4 / 8	50.0
Conventional culture	3 / 8	37.5
Sonication fluid culture	6 / 8	75.0*

Data are shown as number for cultures. * p< 0.05 for sonication fluid culture method vs. tissue and conventional culture methods. Abbreviations: SJPI, patients who suspected of joint prosthesis infection; SOII, patients who suspected orthopedic implant infection.

Identified Microorganisms

A total of 32 microorganisms were identified from all the cultures. The microorganisms most commonly identified were Staphylococcus species and *Ralstonia pickettii*. In the three separate cultures taken from the patients, similar microorganisms were identified, excluding *Acinetobacter baumannii*, *Peptoniphilus assaccharolyticus*, and *Pseudomonas aeruginosa*. The number of detected microorganisms was higher in the sonication method compared to other cultures (Table 3).

Table 3. Distribution of the isolated bacteria according to tissue, conventional, and sonication culture methods.

Microorganisms	Cultures		
	Tissue	Conventional	Sonication fluid
Acinetobacter baumannii	-	-	1
Enterococcus species	1	-	1
Escherichia coli	-	1	1
Enterobacter cloacae	1	-	1
Peptoniphilus assaccharolyticus	1	-	-
MRCNS	5	1	4
Corynebacterium striatum	1	1	1
Ralstonia pickettii	-	1	4
MSSA	1	1	1
Pseudomonas aeruginosa	-	-	1
Serratia marcescens	-	1	1
Total	10	6	16

Data are shown as number for cultures. Abbreviations: MSSA, Methicillin-sensitive *Staphylococcus aureus*; MRCNS, Methicillin-resistant coagulase-negative staphylococci

Inconsistencies between tissue culture results around the implant or prosthesis and sonication culture results were detected in seven patients. In four patients, while the tissue culture around the implant or prosthesis was negative, growth was detected in the sonication. In one patient, discrepancies were detected between the tissue culture results from the implant or prosthesis area and the results obtained through the sonication method. In two cases, in addition to the microorganisms obtained from the tissue culture around the implant or prosthesis, polymicrobial agents were isolated using the sonication method (Table 4). In two cases within the SOII group, a greater number of bacteria were detected using the sonication method in addition to the bacteria or bacteria isolated from tissue cultures.

In three out of 15 patients who continued antibiotic treatment before surgery, no signs of inflammation were found in the histopathological examination, and no agents were detected in microbiological cultures. In three patients, pathogens were detected using the sonication method despite the tissue cultures around

Table 4. Patients with discrepancy between tissue culture and implant-prosthesis sonication fluid culture.

No	Tissue culture	Polymicrobial	Sonication fluid cultre	Polymicrobial	Preoperative antibiotic use
1	MRCNS *Enterococcus* species	Yes	MRCNS *Enterococcus* species *Acinetobacter baumannii*	Yes	Yes
2	Negative	No	Esherichia coli	No	Yes
3	MRCNS	No	*Ralstonia pickettii*	No	Yes
4	Negative	No	*Ralstonia pickettii*	No	No
5	MSSA	No	MSSA *Ralstonia pickettii*	Yes	Yes
6	Negative	No	*Ralstonia pickettii* *Pseudomonas aeruginosa*	No	Yes
7	Negative	No	*Serratia marcescens*	No	Yes

Abbreviations: MSSA, Methicillin-sensitive *Staphylococcus aureus*; MRCNS, Methicillin-resistant coagulase-negative staphylococci

the implant and prosthesis being negative. In two cases, more microorganisms were detected with the sonication method compared to tissue cultures. For the other patients, results from conventional cultures matched those from the sonication method. The sonication technique identified pathogens at a higher rate irrespective of antibiotic utilization. In patients who received antibiotic treatment, the sonication method exhibited a sensitivity of 66.6%. In contrast, the conventional or prosthesis culture technique had a 33% sensitivity, and the tissue culture method recorded a sensitivity of 46%.

DISCUSSION

The results of this study indicate that the sonication method is a more effective diagnostic approach compared to conventional methods in patients with orthopedic implant and prosthesis infections. The sonication method allowed for the detection of a greater number of pathogens in infected tissues.

In orthopedic implant and prosthesis infections, making a definitive diagnosis is of great importance for initiating appropriate antimicrobial treatment.[9,10] Although the examination of preoperative synovial fluid is considered the gold standard for diagnosis, standard cultures exhibit limited sensitivity.[11] This may be related to the microorganisms generally being of low virulence, the use of antibiotics prior to surgery, and the biofilm layer that forms on the implant. Therefore, several methods, including the sonication technique which targets the separation of the biofilm layer, have been identified for more effective diagnosis.[12,13]

Symptoms such as necrosis and discharge, as well as signs of acute inflammation, were higher in the SOII group compared to the SJPI group, while the age of the implant was lower. These findings suggest that bacterial agents in early-onset prosthesis/implant infections have higher virulence and this might lead to more dominant clinical symptoms in these patients.[14,15] However, the age of the SJPI group was higher. This difference may be associated with primary osteoarthritis and, consequently, joint replacement surgeries being performed at older ages.[16] Additionally, the fact that implantations for bone fixation, typically due to fractures, are frequently performed in the physically active younger age group might explain the age difference.[17]

In previous limited studies, the sonication technique has been demonstrated to be more effective than conventional methods for identifying infections caused by prosthetic or orthopedic implants.[7,17] It is known that pre-operative antibiotic use adversely affects the isolation of the pathogen.[18,19] Despite this, it has been reported that the sonication method displayed a more effective diagnostic performance even in the patient group receiving antibiotic treatment.[7,17] Besides, in a study where the sonication fluid was evaluated with the PCR method, the sonication method displayed higher sensitivity in antibiotic-treated patients than in those without antibiotic treatment.[20] In the present study, even though all of the SJPI patients and approximately 50% of the SOII patients were receiving antibiotic treatment, the sonication method detected microorganisms with higher sensitivity compared to other methods in both the SOII and SJPI groups. Additionally, in three out of the 15 patients who used antibiotics, while conventional culture results were negative, bacteria were only identifiable via the sonication method. Moreover, the detection of polymicrobial etiology with sonication in two cases who had received antibiotic treatment, compared to standard tissue cultures, further underscores the effectiveness of the sonication method even in the presence of antibiotic use.

Staphylococcus was the most frequently isolated microorganism via the sonication method, consistent with existing literature.[7] This was followed by *Ralstonia pickettii*, a bacterium that can cause serious infections, especially in immunosuppressed patients. Out of the four patients in whom *Ralstonia pickettii* was detected, two had osteosarcoma, while the other two were elderly and diagnosed with diabetes. These findings suggest that the types of proliferating microorganisms might vary in immunosuppressed patients

This study had some significant limitations. First, it was a single-center study. Second, the sample size was small. Third, a majority of the patients had used antibiotics before surgery. These factors might affect the sensitivity of the culture methods.

CONCLUSION

Orthopedic implant and prosthetic infections are commonly encountered nowadays and can pose challenges in achieving a definitive diagnosis. The sonication method has a high sensitivity in these infections. Its diagnostic efficacy remains superior to conventional microbiological diagnostic methods, even in patient groups using antibiotics. Therefore, the sonication method can be a significant screening tool in determining the causative agents in SOII and SJPI patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gülhane Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.06.2015, Decision No: 1491-88-14/1648.4-467).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Mesenteric panniculitis clinical presentations, management, and outcomes: a single institute experience of 89 patients

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ABSTRACT

Aims: Mesenteric panniculitis is a rare, non-specific, chronic inflammatory disease with a reported incidence of 0.16-3.3% that primarily involves the mesenteric adipose tissue. We aimed to retrospectively analyze the clinical features of patients diagnosed with mesenteric panniculitis.

Methods: We retrospectively analyzed the reports of 941 patients who were examined in the Gastroenterology Clinic of Lokman Hekim Hospital and underwent abdominal computerized tomography (CT) between January 2019 and December 2021.

Results: Among CT scan reports of 941 patients, the diagnosis of mesenteric panniculitis was present in 89 (9.45%) patients (55 male and 34 female). The reasons for obtaining a CT scan in those patients were as follows: severe abdominal pain in 53 (59.6%) patients, weight loss in 16 (17.9%) patients, bloating, distention, and suspicion of sub-ileus in 12 (13.5%) patients, and alterations in abdominal movements (constipation or diarrhea) in 8 (8.9%) patients. Among patients with mesenteric panniculitis, autoimmune diseases were also analyzed 21 were having Hashimoto thyroiditis, 2 were having vitiligo, 2 were having Sjögren's disease, 1 was having primary biliary cholangiopathy, and 1 was having a diagnosis of celiac disease.

Conclusion: Mesenteric panniculitis is not a very rare disease, diagnosed with mainly CT findings. Although the disease may be associated with some autoimmune diseases and malignancies, the disease outcomes are generally fine. However, there are still many unknown points, especially about the etiology and outcomes of the disease.

Keywords: Mesenteric panniculitis, chronic inflammatory disease, autoimmune diseases, computerized tomography, inflammation

INTRODUCTION

Mesenteric panniculitis is a rare, non-specific, chronic inflammatory disease with a reported incidence of 0.16-3.3% that primarily involves the mesenteric adipose tissue. In some rare conditions, inflammation may extend through the omentum and mesocolon.[1] The patients are usually asymptomatic and mesenteric panniculitis is diagnosed incidentally in some imaging techniques, especially computerized tomography (CT), performed for another reason. However, mesenteric panniculitis may also cause some symptoms such as abdominal pain, a palpable abdominal mass, nausea, vomiting, or rarely bowel perforation or obstruction.[2]

There are two main forms of mesenteric panniculitis; the classical inflammatory type and retractile panniculitis. In the classical form, there is inflammation, necrosis, and degeneration of fat tissue. On the other hand, in the retractile form, there is a prominent fibrosis of mesentery with retraction of the adjacent structures. Mesenteric panniculitis was mainly associated with some etiological conditions such as abdominal surgery, abdominal cancer, mainly lymphoma, colon cancer or genitor-urinary cancers, previous abdominal trauma, and/or some autoimmune diseases.[3]

In previous literature, the data regarding the clinical presentation, management, and outcomes of mesenteric panniculitis is limited. Our study aimed to retrospectively examine the clinical features of patients diagnosed with mesenteric panniculitis.

METHODS

This is a retrospective observational study. The study was carried out with the permission of Lokman Hekim University Scientific Researches Ethics Committee (Date: 21.12.2022, Decision No: 2022/194). All procedures were carried out in accordance with the ethical rules

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and the principles of the Declaration of Helsinki. All of the patients had given written informed consent to participate in the study.

A total of 996 patients were planned to be included in the study. However, after excluding patients who did not accept to participate in the study, 941 patients were included. We retrospectively analyzed the reports of CT scans of 941 patients who were followed up and treated in our Gastroenterology Outpatient Clinic of Lokman Hekim Hospital and underwent abdominal tomography between January 2019 and December 2021.

The abdominal region of all patients was scanned with a 64-slice CT device. Scanning parameters; tube voltage, 120 kV; tube current, 250 MAS; matrix, 512 × 512; the section thickness 5 mm. Multiplanar reconstruction (MPR) images were created from these images.

The diagnosis of mesenteric panniculitis was defined by the same radiologist. The radiological diagnosis of mesenteric panniculitis was determined according to the typical CT findings in Coulier's study.4 The five hallmarks of the Coulier's study were as follows: (1) mesenteric fat mass lesions, (2) mesenteric fat tissue density being higher than the surrounding abdominal tissue, (3) vascular and perimesenteric soft tissue nodules, (4) fat ring, and (5) annulus fibrosus. If 3 of these findings were positive, mesenteric panniculitis was diagnosed. The patients diagnosed with mesenteric panniculitis were determined and their demographic and clinical data were recorded from the hospital's electronic data recording system. Concomitant diseases, medications given for this disease, and the outcomes of the disease were obtained from the patient records. Before reporting the study, all patients diagnosed with mesenteric panniculitis were called by telephone and asked about the long-term outcomes of the disease.

Statistical Analysis

All statistical analysis were performed with SPSS statistics software version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were performed for analyses. Quantitative data were expressed as mean±standard deviation (SD), median, and range. Categorical data were expressed as a percentage.

RESULTS

Among CT scan reports of 941 patients, the diagnosis of mesenteric panniculitis was present in 89 (9.45%) patients (55 male and 34 female). The male/female ratio of the patients diagnosed with mesenteric panniculitis was 1.61. The mean age of the patients was 57.71± 13.30 years (range: 29-84 years). The mean body mass index (BMI) of the patients was 30.78±6.14 kg/m² (range: 23.86 -38.42) (Table 1).

Table 1. Demographic features of the study participants

Male/female	55/34
Age (mean)	57.71± 13.30 (range: 29-84 years)
Body mass index (BMI) (mean)	30.78±6.14 kg/m² (range: 23.86 -38.42)
The reasons for obtaining a CT scan	Severe abdominal pain: 53 (59.6%) Weight loss: 16 (17.9%) Suspicion of sub-ileus: 12 (13.5%) Alterations in abdominal movements: 8 (8.9%)
The concomitant diseases	Malignancies: 27 (30.3%) Autoimmune diseases: 27 (30.3%) Abdominal surgery: 38 (42.7%)

The reasons for obtaining a CT scan in those patients were as follows: severe abdominal pain in 53 (59.6%) patients, weight loss in 16 (17.9%) patients, bloating, distention, and suspicion of sub-ileus in 12 (13.5%) patients, and alterations in abdominal movements (constipation or diarrhea) in 8 (8.9%) patients. We retrospectively analyzed the patient records and determined the concomitant diseases in those patients. Concomitant malignancies were present in 27 (30.3%) patients (colorectal cancer in 13 patients, pancreas cancer in 9 patients, ovarian cancer in 2 patients, ovarian cancer in 1 patient, gastric cancer in 1 patient, cholangiocellular cancer in 1 patient). Among patients with mesenteric panniculitis, autoimmune diseases were also analyzed 21 were having Hashimoto thyroiditis, 2 were having vitiligo, 2 were having Sjögren's disease, 1 was having primary biliary cholangiopathy, and 1 was having a diagnosis of celiac disease. Among participants, 4 (4.5%) had a new diagnosis of cancer in concurrence with their CT. Abdominal surgery history was present in 38 (42.7%) patients.

When CT images were evaluated according to the Coulier classification. All patients had mesenteric fat mass lesions and mesenteric fat tissue density being higher than the surrounding abdominal tissue.Vascular and perimesenteric soft tissue nodules were detected in 80 of the patients. Fat ring (65 patients), and annulus fibrosus (48 patients) were detected in fewer numbers. The findings are summarized in Table 2.

Table 2. CT findings of mesenteric panniculitis

Signs	Fat mass lesions	Higher tissue density	Vascular and perimesenteric soft tissue nodules	Fat rings	Annulus fibrosus
Percentage of patients (%)	89 (100 %)	89 (100%)	80 (89.8%)	65 (73%)	48 (53.9%)

The medications given to the patients for the treatment are summarized in Table 3. The mostly prescribed treatment for those patients was antibiotics. And some patients obtained combination treatments such as antibiotics and anti-inflammatory medicines. It was determined that 22 patients did not get any treatment for this disease. CT scans of a patient's in our study are shown in Figures 1A-B and C.

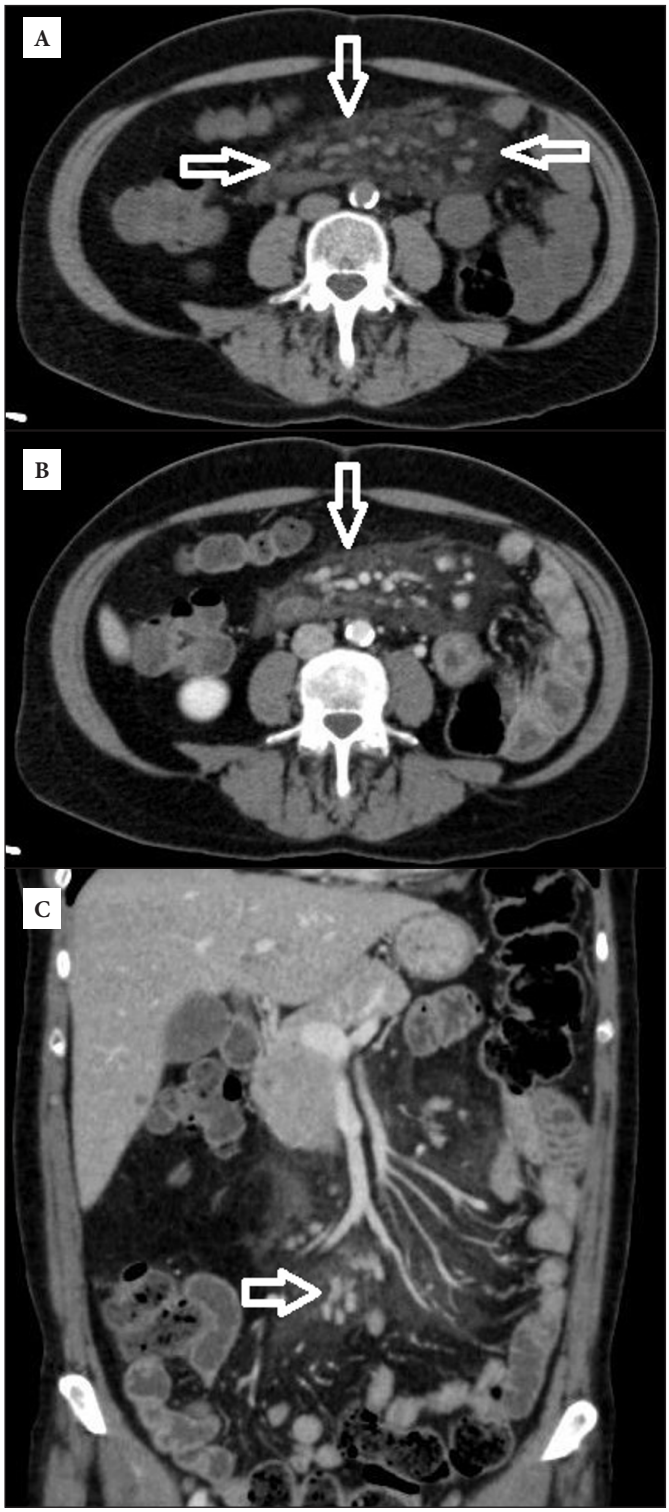

Figure 1. 57-year-old male patient complaining of abdominal pain. Contrast and pre-contrast CT images show a fat mass lesion in the mesentery (A), increased mesenteric fat tissue density (B) and mesenteric lymph nodes in the perivascular region (C).

Table 3. Treatments were given for the mesenteric panniculitis

Medications	Number of patients (%)
Antibiotics (Ciprofloxacin, metronidazole, or a combination of both)	54 (60.7)
Non-steroidal anti-inflammatory drugs (NSAIDs)	11 (12.4)
Steroid treatment	7 (8.5)
Colchicines	2 (2.2)
No treatment	22 (24.7)

The mean follow-up period was 9.42±4.32 months (6-14 months). When the patients were asked about the outcomes of the disease; all of them reported that with or without treatment all their symptoms healed in a few weeks. Seven patients told that after this CT scan obtained in our hospital reporting mesenteric panniculitis, they again had an abdominal CT in one year and 2 of them having mesenteric panniculitis also reported in their new CT scan. None of the patients were diagnosed with a new malignancy or autoimmune disease, in this last year.

DISCUSSION

In the present study, we reported the clinical presentations, management, and treatment outcomes of 89 patients diagnosed with mesenteric panniculitis. We determined that; the main symptom of the patients was severe abdominal pain or discomfort, and the main concomitant diseases present were intraabdominal malignancies and autoimmune diseases. Although most of the patients were prescribed some medications, all patients, treated or untreated, got well in a few weeks. The disease did not re-occur in most of the patients in approximately 9 months follow-up.

In the present study, mesenteric panniculitis was more common in males, the patients were in their mid-to-late adulthood, with the main symptom of abdominal pain or discomfort which were similar to the previous literature.[5,6]

Etiological factors associated with mesenteric panniculitis include some malignancies, autoimmune diseases, abdominal trauma, and some infections.[9] Autoimmune diseases and autoimmune etiology are mostly accused factors in etiology.[10,11] In the present study, compatible with the previous literature, the most common concomitant diseases were malignancies and autoimmune diseases. Even though an association between intraabdominal malignancies and mesenteric panniculitis was questioned before, a direct association between mesenteric panniculitis and subsequent malignancy could not be confirmed before.[12,13] In a recent study, on 716 patients diagnosed with mesenteric panniculitis, concomitant malignancy was present in 354 (49.4%) patients and a history of abdominal surgery was present in 179 (25%) patients.[14] Our findings were also compatible with the previous data. Although CT is often the best choice for the diagnosis of mesenteric panniculitis, diagnosis can also be made with US and MRI. US finding is often an increase in volume along with a fat mass at the root of the mesentery. Oval-shaped or fatty mesenteric mass with convex anterior border is centrally located and has focal mesenteric increased echogenicity. Displacement of the intestinal loop and lymph nodes may also be observed.[15] On MRI, mesenteric fat tissue appears as a mass with medium signal intensity on T1-weighted

images and high signal intensity on T2-weighted images.[2] CT also results in a mass-like area of heterogeneously enhanced fat attenuation that may displace local bowel loops but typically do not displace surrounding mesenteric vascular structures Mesenteric lymph nodes often occur in the region of segmental mesenteric banding, and in a small percentage of cases the nodes may enlarge more than 1 cm. Fat ring (65 patients), and annulus fibrosus (48 patients) were detected in fewer numbers. Expansion, tortuosity and wall thickening may be observed in the mesenteric vascular structures. Additionally, thrombosis may occur in the mesenteric vascular structures. No thrombosis was detected in any of our patients. In a study by Wang and Li,[16] CT findings of mesenteric panniculitis were similar to our study. While mesenteric fat mass, increased density of fat mass, soft tissues consisting of vascular and perimesenteric fat tissue and lymph nodes were the most common findings, fat rings and annular fibrosis were less common.

In this study, mostly prescribed medications were antibiotics and NSAIDs. Although approximately a quarter of the patients did not get any treatment, all patients improved in a few weeks. In previous literature, antibiotics, NSAIDs, and corticosteroids were also mostly prescribed medications and the patients were responsive to these medications. The overall prognosis was usually good.[17-19] Sahin et al.[17] reported the treatment outcomes in 36 patients diagnosed with mesenteric panniculitis and reported that approximately 60% of the patients were treated with antibiotics and again approximately 60% of patients were treated with NSAIDs. Regarding these data, the role of antibiotics in treatment of mesenteric panniculitis should be evaluated in larger studies.

We can list the limitations of this study that should be noted as follows. The first of these was that it was a retrospective study. Secondly, the follow-up period was not long enough. Third, the study was single-center and may have some biases.

CONCLUSION

Mesenteric panniculitis is not a very rare disease, diagnosed with mainly CT findings. Although the disease may be associated with some autoimmune diseases and malignancies, the disease outcomes are generally fine. However, there are still many unknown points, especially about the etiology and outcomes of the disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Lokman Hekim University Scientific Researches Ethics Committee (Date: 21.12.2022, Decision No: 2022/194).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Our data on detailing metastasis localization and subtype characteristics in metastatic colorectal cancer patients treated with Bevacizumab

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ABSTRACT

Aims: Our aim in this study was to determine the relationship between metastasis types and mutation subtypes in patients who were followed up in our center and received bevacizumab treatment, to determine the survival rates according to metastasis types, and to contribute to the literature on this subject.

Methods: In our study, we retrospectively evaluated 42 consecutive metastatic colorectal cancer patients who were admitted to our hospital and diagnosed with colorectal cancer, thorax-abdominal CT scans were performed in our clinic to detect possible metastases, and the presence of metastases in one or more localizations was detected and treated with Bevacizumab.

Results: The majority of colorectal cancers included in our study had the histopathological subtype of adenocarcinoma (90.5%). Genetic analyses revealed that 47.6% (20 patients) had mutant KRAS gene types, while 52.4% (22 patients) had wild type. The distribution of metastases was as follows; 31 (73.8%) cases with liver involvement, 12 (28.6%) with peritoneal involvement and 24 (57.1%) with lung involvement. In our study, median overall survival was 19 months and median disease-free survival was 7 months.

Conclusion: The results of studies to date will be useful to help predict prognosis and to select appropriate regimens for treatment. We aimed to contribute to this process by presenting our own data in our own study. However, the true role of RAS genes as prognostic markers continues to be questioned, and multicenter studies are needed on the predictive and prognostic factors of colorectal cancers.

Keywords: Colorectal cancer, kras, metastasis, prognosis

INTRODUCTION

Colorectal cancer is the third most common cancer in the world, and although mortality rates have decreased in recent years, it is still a major cause of morbidity and mortality in both men and women worldwide. Although colorectal cancers are known to be cancers of advanced age, the incidence of early-onset colorectal cancer diagnosed in patients younger than 50 years of age is increasing worldwide and is becoming a cancer affecting a younger patient population. In addition, due to the absence of obvious symptoms in the early stages of colorectal cancer, distant metastasis rates accompanying the primary tumor diagnosis are high, and fifty percent of metastatic patients die within 5 years of diagnosis, usually as a result of metastatic disease.[1-3] This reality is another source of concern for colorectal cancers and has led to an increased interest in the epidemiology of colorectal cancers and the determinants of the treatment process. Today, traditional prognostic factors have been replaced by new outcome predictors, including those defined according to the molecular origin of the primary tumor. In particular, RAS or BRAF mutation status and biomarkers have recently been introduced into clinical scoring systems and are increasingly becoming an integral part of oncosurgical treatment algorithms.[4,5]

METHODS

The study was carried out with the permission of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Researches Ethics Committee (Date: 21.12.2022, Decision No: 2022-12/5). All procedures were performed in accordance with ethical rules and the principles of the Declaration of Helsinki.

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Forty-two consecutive patients who were diagnosed with metastatic colorectal cancer in our clinic and underwent thorax-abdominal CT scanning to detect possible metastases were evaluated retrospectively. After the detection of one or more metastases, adjuvant chemotherapy followed by bevacizumab treatment was administered. The patients included in our study received fluorouracil, leucovorin, and oxaliplatin (FOLFOX), fluorouracil, leucovorin, irinotecan (FOLFIRI), and fluorouracil, leucovorin (FUFA) as adjuvant chemotherapy agents. FOLFOX was administered to 67% (28), FOLFIRI to 23%, FOLFOX+FUFA to 5% (2), and FUFA to 5% of the patients. The maximum treatment regimen was six cycles, and the minimum treatment regimen was one cycle. In our patient population, bevacizumab was administered as monoclanal anicor for etastatic colorectal cancers. Bevacizumab was given alone in ten patients; bevacizumab + FOLFOX combination in ten patients; bevacizumab + FOLFIRI combination in 11 patients; bevacizumab + FUFA combination in 9 patients; and bevacizumab was accompanied by Xelox and Capecitabine in only one patient. Bevacizumab, the component of complementary therapy, was administered for a maximum of 30 cycles and a minimum of 5 cycles.

Statistical Analysis

In this study, patient data collected was analyzed using IBM Statistical Package for the Social Sciences (SPSS 23.0-IBM, NY, USA) and MedCalc statistical software version 12.7.0.0 (MedCalc Software, Ostend, Belgium) package programs. Frequency and percentage were provided as descriptive statistics for categorical variables, while median, minimum, and maximum values were used to describe continuous variables. Kaplan-Meier curves were plotted for overall survival and disease-free survival, and the Log-rank test was used to compare the groups. Results were considered statistically significant when the p-value was less than 0.05.

RESULTS

A total of 42 patients, 26 (61.9%) males and 16 (38.1%) females, were included in the study. The age of the patients ranged between 21 and 81 years with a median age of 59 years. Tumor localization was 50% (21 patients) in the colon, 45.2% (19 patients) in the rectum and 4.8% (2 patients) in the colorectal region. The majority of tumor subtypes were adenocarcinomas (90.5%). When the KRAS gene types of the patients were analyzed, 47.6% (20 patients) had mutant type and 52.4% (22 patients) had wild type. There were 31 (73.8%) with liver involvement, 12 (28.6%) with peritoneal involvement, and 24 (57.1%) with lung involvement. The overall median survival was 19 months, and the median disease-free survival was 7 months. In our study, we also looked at the relationship between metastasis foci and survival. In peritoneal metastases, we found that the median overall survival was 12 months in patients with peritoneal involvement and 23 months in patients without peritoneal involvement, and there was a statistically significant difference between these two groups ($p=0.041<0.05$). In our disease-free survival analysis, the median progression-free survival of patients with and without peritoneal involvement was equal at 7 months, and no statistically significant difference was observed ($p<0.05$) **Figure 1**. When we looked at patients with liver involvement as another important metastasis focus, we found that the median overall survival was 22 months in patients with liver involvement and 15 months in patients without liver involvement, and there was no statistically significant difference between them ($p=0.399>0.05$) **Figure 2**. The median progression-free survival was 9 months in patients with liver involvement and 7 months in patients without liver involvement, and there was no statistically significant difference between them ($p=0.396>0.05$). When we looked at survival according to mutations, survival was 15 months in the KRAS mutant type and 23 months in the wild type. However, progression-free survival was the same in both groups and was 7 months. However, we did not find a statistically significant difference between the two genes in terms of overall survival ($p=0.438>0.05$). In terms of disease-free survival, the median progression times of both mutant and wild-type were equal at 7 months, and no statistically significant difference was observed between them ($p<0.05$). In our study, we went one step further and looked at the survival relationship between the KRAS mutation and metastasis localization. In terms of overall survival, the median survival was 13 months for mutants and those with liver involvement and 28 months for those without, while it was 16 months for wild-types and those with liver involvement and 18 months for those without. However, no statistically significant difference was observed between them ($p=0.533>0.05$). In terms of disease-free survival, the median progression time was 4 months for the mutant type and those with liver involvement and 7 months for those without, while it was 2 months for the wild type and those with liver involvement and 7 months for those without, and no statistically significant difference was observed between them ($p: 0.405>0.05$). Similarly, when the presence of peritoneal involvement was analyzed according to KRAS gene types, the median overall survival was found to be 18 months in patients with mutant type and peritoneal involvement and 28 months in patients without peritoneal involvement. The median survival was 11 months in patients with wild-type peritoneal involvement and 18 months in patients without peritoneal involvement. However, no statistically significant difference was observed between the groups ($p<0.05$). In disease-free

survival, the median progression-free survival was 7 months in patients with mutant gene and peritoneal involvement and 9 months in those without, while the median progression-free survival was 9 months in patients with wild-type gene and peritoneal involvement and 7 months in those without, and no statistically significant difference was observed (p:0.748>0.05) **Figure 3**. In terms of overall survival, the median survival time for patients with mutant type and lung involvement was 12 months and 28 months for those without, while the median survival time for patients with wild type and lung involvement was 13 months and 18 months for those without. There was no statistically significant difference between the groups (p=0.100>0.05). In disease-free survival, the median progression time was 7 months for the wild type and those with lung involvement and 8 months for those without lung involvement. The median time to progression was 7 months for mutants and those with lung involvement and could not be calculated for those without lung involvement because the progression rate did not reach 50%. No statistically significant difference was observed (p=0.804>0.05) **Figure 4**.

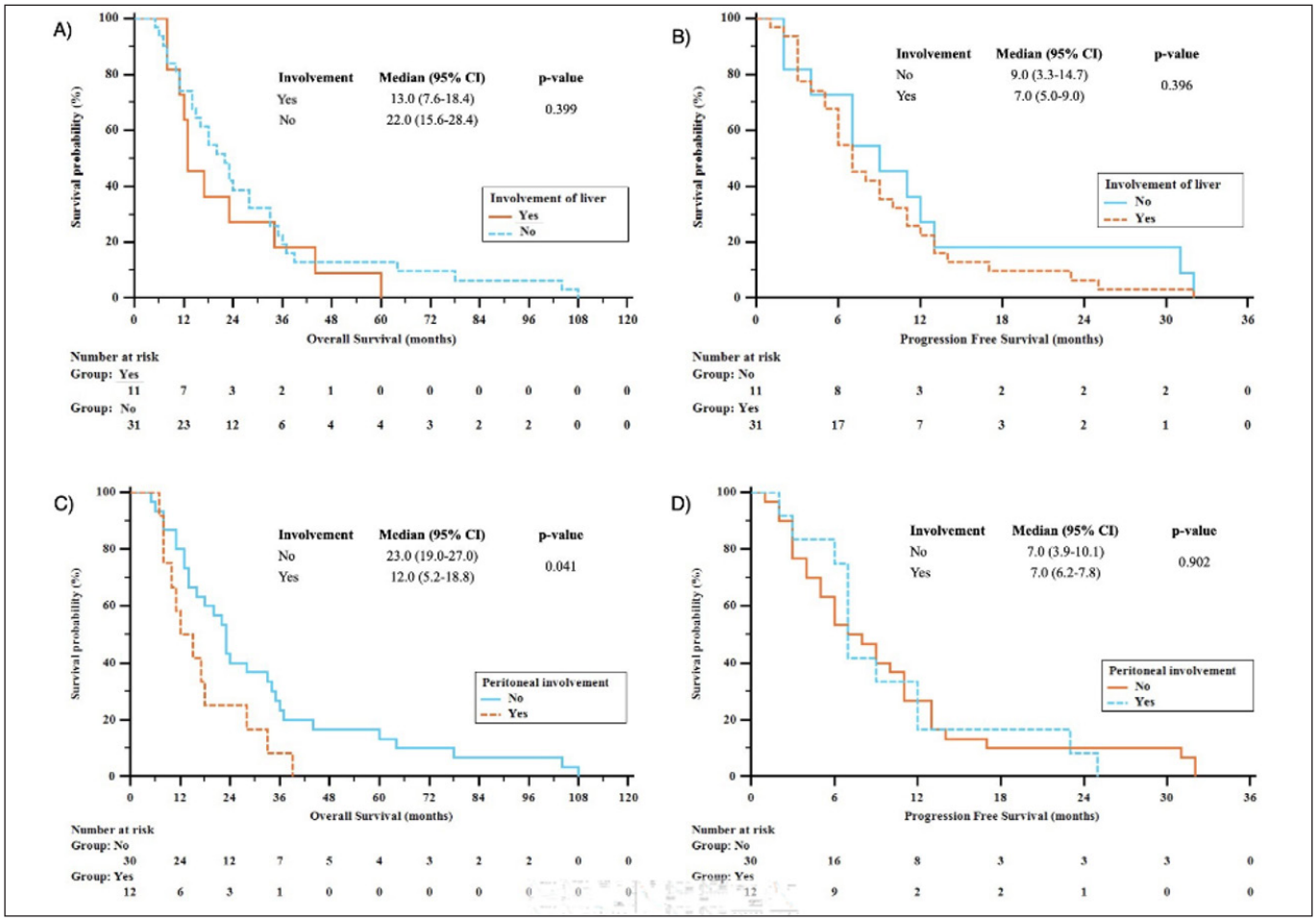

Figure 1. Liver involvement and peritoneal involvement

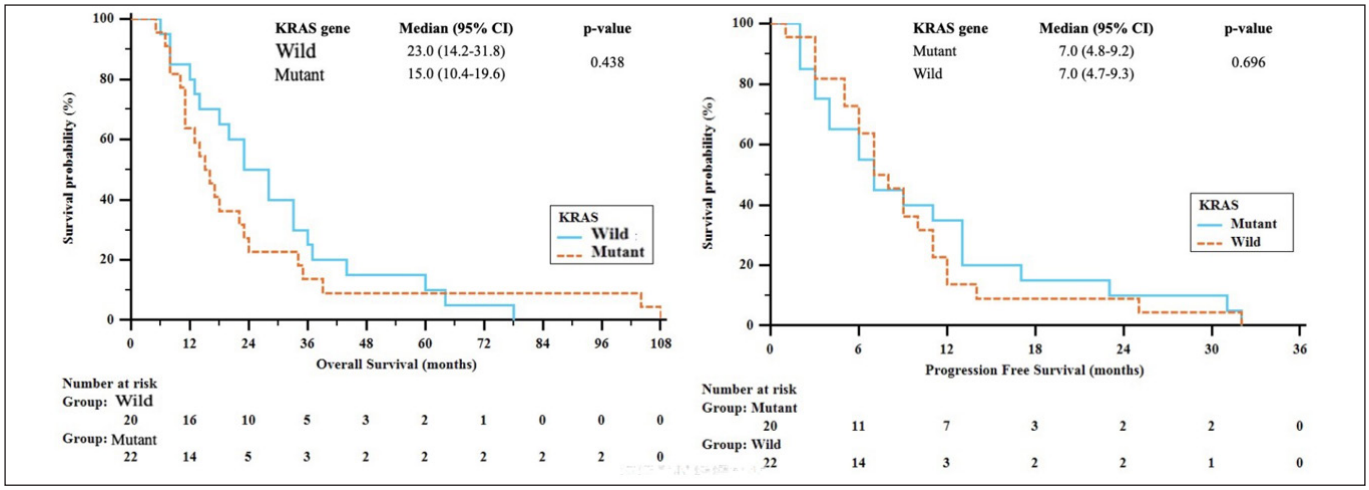

Figure 2. KRAS gene

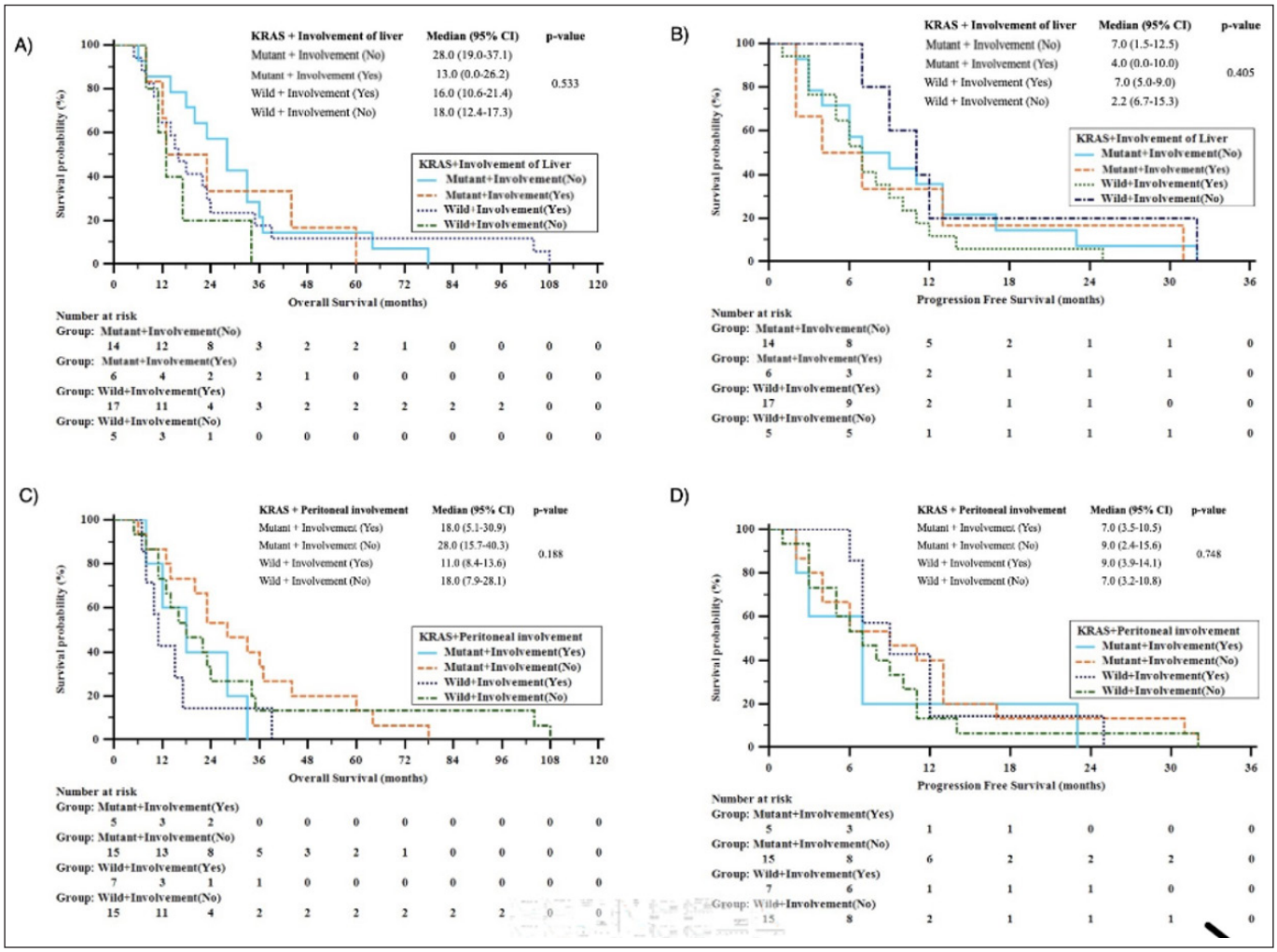

Figure 3. KRAS+ liver involvement and peritoneal involvement

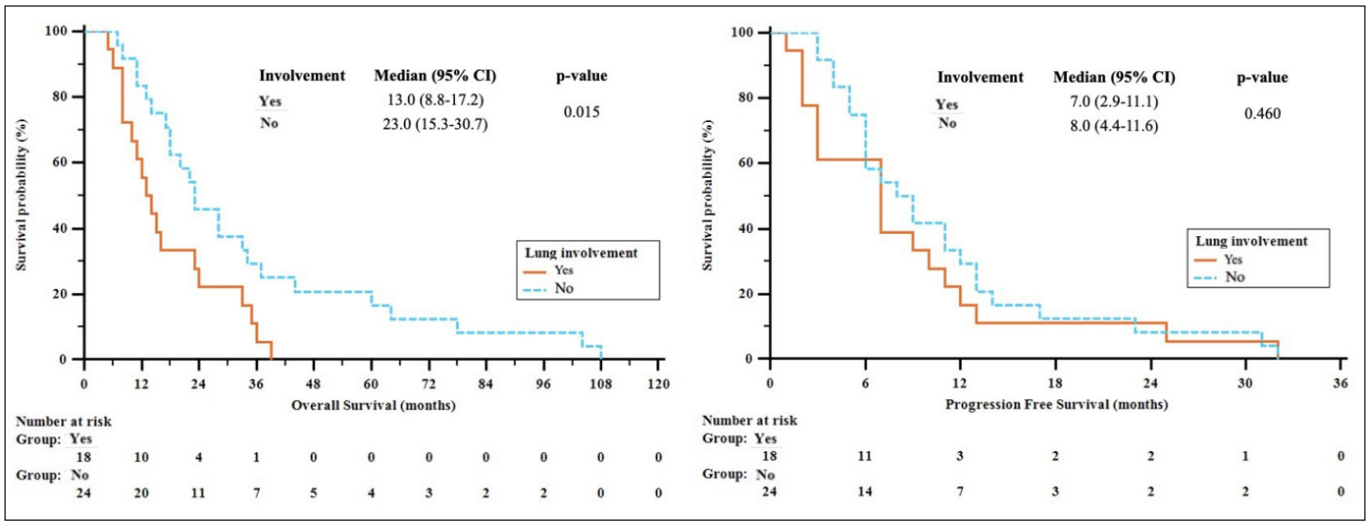

Figure 4. KRAS+ lung involvement

DISCUSSION

Despite the advantages provided by the development of imaging technology in diagnosis and follow-up processes and the success rates achieved in treatment, the incidence of colorectal cancer, like all other cancers, is gradually increasing all over the world with the increasing population.[2] This situation has led to an increased interest in the epidemiology of colorectal cancers and the factors determining the treatment process and prognostic and predictive factors in recent years. Since concomitant metastases determine morbidity and mortality as well as primary cancer, studies determining cancer treatment processes aim to understand possible metastasis mechanisms. When we look at colorectal cancer and its

concomitant metastases, we see that approximately 20% of patients have concomitant metastases at the time of diagnosis, since no obvious symptoms are observed in the early stages of colorectal cancer.[3] Half of patients die, usually in the first years after diagnosis, mostly due to the consequences of metastatic disease.[6] Large population studies have shown that approximately one-third of patients diagnosed with colorectal cancer develop liver metastases during follow-up. In our study, 73.8% of patients had liver metastases, 57.1% had lung metastases, 28.6% had peritoneal metastases, and 28.7% had other metastases (**Table**). There is a strong correlation between survival in colorectal cancer and the site of metastasis. Deaths due to colorectal cancer are usually due to metastatic spread to distant sites. In general, peritoneal metastases are less frequently diagnosed. Therefore, the true incidence of peritoneal metastases is uncertain but has been reported to be as high as 40-80% in autopsy series. Patients with peritoneal metastases have the worst prognosis of all patient groups.[7] Many studies have found that patients with peritoneal metastases have poorer survival rates than those with metastases to other sites, with untreated patients dying within months.[8-11] Studies showing that the median survival rate of colorectal cancer patients with peritoneal metastases decreased by 30% were supported by subsequent studies and reported median survival times between 10.4 and 23.9 months. Another prospective study reported a median survival of 21.5 months and a median time to progression of 4.4 months.[12,13] Our own study also supports previous studies, and we found the median overall survival to be 12 months in patients with peritoneal involvement and 23 months in patients without peritoneal involvement, and there was a statistically significant difference between the two groups (p: 0.041<0.05). According to our analysis, patients with peritoneal involvement survived less than those without. In our disease-free survival analysis, the median progression-free survival of patients with and without peritoneal involvement was equal at 7 months, and no statistically significant difference was observed (p<0.05) **Figure 1**.

The liver is the most common site of colorectal cancer metastasis, followed by other metastatic sites. Since most mesenteric venous drainage drains into the hepatic portal vein system, more than 50% of patients present with liver metastases.[14] In the relationship between colorectal cancer and liver metastases, studies have shown that approximately 15-25% of patients have distant metastases at the time of initial diagnosis, and the remaining 18-25% of patients develop distant metastases within 5 years of initial diagnosis, resulting in approximately 50%-70% of patients with colorectal cancer developing metastases in the liver. In colorectal cancer patients with liver metastases, median survival without treatment is 5 to 20 months, and the 5-year survival rate is 11%, which is the best prognosis for patients presenting with local metastases.[15,16] However, over the years, improved resection and treatment protocols have resulted in favorable outcomes in liver metastatic cases, resulting in median survival times of over 30 months (19-50 months) and progression-free survival times ranging from 6-12 months.[17] In our patient population, we found that the median overall survival was 22 months in patients with liver involvement and 15 months in patients without liver involvement, and there was no statistically significant difference between them (p=0.399>0.05). The median progression-free survival was 9 months in patients with liver involvement and 7 months in patients without liver involvement, and there was no statistically significant difference between them (p=0.396>0.05). The overall median survival time and progression-free survival times in our study are consistent with other studies. The overall and disease-free survival curves according to the presence of liver and peritoneal involvement in our study participants are shown in **Figure 1**.

Tabel. Distribution of demographic and clinical characteristics of participants

Characteristics (N=42)	n (%) or Mean (Min-Max)
Gender	
Male	26 (61.9)
Female	16 (38.1)
Age year	59 (21-81)
Localization	
Colon	21 (50)
Rectum	19 (45.2)
Kolorectal	2 (4.8)
Subtype	
Adenocarsinoma	38 (90.5)
Mucinous	4 (9.5)
KRAS gen	
Mutant	20 (47.6)
Wild	22 (52.4)
Liver involvement	31 (73.8)
Peritoneal involvement	12 (28.6)
Lung involvement	24 (57.1)
Other involvement	
Overall Survival, month	19 (5-108)
Progression- free Survival, Month	7 (1-32)

To date, various hypotheses have been put forward regarding the development of colorectal cancer. As in other cancer types, many genetic and environmental factors are responsible for the development of colorectal cancers. Kirsten rat sarcoma viral oncogene (KRAS) is a small proto-oncogene that binds to a protein involved in the regulation of cellular responses to many extracellular stimuli.[18,19] It is now widely accepted that sporadic colorectal cancers usually arise from preneoplastic lesions through inactivation of tumor suppressor genes

and activation of oncogenes.[20] Colorectal cancers are predominantly KRAS mutant types. In mutant types, the tumor is more aggressive, and survival is less likely. In addition, the presence of mutations develops resistance to treatment. Therefore, the determination of KRAS mutation status is valuable in the treatment of patients with this condition.[21,22]

Compared with KRAS wild-type colorectal cancer, KRAS mutant colorectal cancer has a different biological behavior and therapeutic approach.[21] Although the proven predictive value of KRAS mutations has long been accepted, the prognostic value of these mutations is still under evaluation. Since colorectal cancer continues to be an important public health problem, it is of great importance to determine the parameters affecting its prognosis. To mention some important studies, the RASCAL study has shown that the presence of mutations increases the likelihood of recurrence and death.[23] Many studies have shown that stage III patients with KRAS mutations exhibit significantly worse disease-free survival than those with wild-type KRAS, which may be partly explained by the effect of KRAS mutations on prognosis.[24-28] Another study found that patients with any gene mutation may develop resistance to anti-EGFR therapy and have worse outcomes and different metastatic patterns compared to those with wild-type genes.[29] Foltran and colleagues showed that patients with any oncogene mutation had worse survival rates compared to those with wild-type.[30] However, there are also studies with different results. Dinu and colleagues found that the status of the KRAS gene had no prognostic significance.The overall and disease-free survival curves according to the KRAS gene type included in our study are shown in **Figure 2**. In our study, the median overall survival of mutant genes was 15 months, while the median survival of wild-type genes was 23 months, which is consistent with a recent study.[31] However, we did not find a statistically significant difference between the two genes in terms of overall survival in our study (p=0.438>0.05) **Figure 2**. In terms of disease-free survival, the median progression times of both mutant and wild-type were equal at 7 months, and no statistically significant difference was observed between them (p<0.05). There are studies that have found that patients with KRAS mutations are more likely to have peritoneal metastases, liver-peritoneal metastases, and multiple organ metastases compared to all wild-type Kang and colleagues found that in tumors with any gene mutation, the KRAS mutation metastasized more frequently to the peritoneum and liver-peritoneum compared to all wild-type.[3] Furthermore, KRAS or BRAF mutations associated with a poor prognosis compared to their wild-type counterparts were also reported by Liu and colleagues.[32] Ucar and colleagues have shown that multiple KRAS mutations are associated with a better prognosis compared to single mutations.[33] There are many studies on the median survival and progression-free survival times in the presence of KRAS mutations.[34-36] However, to the best of our knowledge, our study is the first to investigate the median survival and progression-free periods in the presence of liver, peritoneal, and lung metastases in patients with KRAS mismatch. The overall and disease-free survival curves of the participants in our study according to the presence of liver and peritoneal involvement according to KRAS gene type are shown in **Figure 3**. In terms of overall survival, the median survival was 13 months for those with mutant type and liver involvement and 28 months for those without, while it was 16 months for those with wild type and liver involvement and 18 months for those without. However, no statistically significant difference was observed between them (p=0.533>0.05). In terms of disease-free survival, the median progression time was 4 months for mutant type and those with liver involvement and 7 months for those without, 2 months for wild type and those with liver involvement and 7 months for those without, and no statistically significant difference was observed between them (p: 0.405>0.05). Similarly, when the presence of peritoneal involvement was analyzed according to KRAS gene types, median survival was found to be 18 months in patients with mutant type and peritoneal involvement and 28 months in patients without peritoneal involvement. While the median survival was 11 months in patients with wild-type and peritoneal involvement, it was 18 months in patients without peritoneal involvement. However, no statistically significant difference was observed between the groups (p<0.05). In disease-free survival, median progression-free survival was 7 months in patients with mutant gene and peritoneal involvement and 9 months in those without, while median progression-free survival was 9 months in patients with wild-type gene and peritoneal involvement and 7 months in those without, and no statistically significant difference was observed (p:0.748>0.05). If we look at the frequency of lung involvement according to the KRAS gene type of the participants, the overall and progression-free survival curves are shown in **Figure 4**. In terms of overall survival, the median survival time for patients with mutant type and lung involvement was 12 months and 28 months for those without, while the median survival time for patients with wild type and lung involvement was 13 months and 18 months for those without. There was no statistically significant difference between the groups (p=0.100>0.05). In disease-free survival, the median progression time was 7 months for patients with wild-type lung involvement and 8 months for patients without lung involvement. The median time

to progression was 7 months for mutants and those with lung involvement and could not be calculated for those without lung involvement because the progression rate did not reach 50%. No statistically significant difference was observed (p=0.804>0.05).

Study Limitations

The patients selected in this study were conducted with a limited number of patients in a single center, and since it is a retrospective study based on the data in their files, the study was limited to these two factors.

CONCLUSION

Our study is consistent with other studies showing that the KRAS mutation has a negative effect on overall survival results. However, in the retrospective analysis we conducted on the relationship with metastatic foci to investigate the value of KRAS genes as a prognostic factor, median survival and progression-free survival times were shortened in the liver metastatic group, the group with periteneal involvement, and the group with lung involvement in KRAS mutant patients, but the results were not statistically significant. Therefore, although the predictive and treatment-guiding contribution of KRAS genes has been proven many times, its prominent role as a prognostic factor could not be proven in our study as in some other studies. In this sense, our study aims to contribute to studies questioning the real role of KRAS genes as prognostic markers. Multicenter studies are needed to diversify the predictive and prognostic factors of colorectal cancers and to clarify the contribution of KRAS genes in this regard.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Researches Ethics Committee (Date: 21.12.2022, Decision No: 2022-12/5).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The psychosocial status of siblings and mothers of children with cancer from the perspective of mothers

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ABSTRACT

Aims: In the low/middle income countries (LMIC), a few of health centers provide psychological support to siblings and mothers of children with cancer. The aim of study was to draw attention to psychosocial status of siblings and mothers of children with cancer in a LMIC.

Methods: The study was a case-control study which was conducted at a tertiary center in Mersin, Turkey. The sample consisted of two groups as follows; siblings of children with cancer (n=39) were included as study group and children without cancer diagnosis in family (n=49) were included as control group. Behavioral problems of the children were evaluated with the Child Behavior Checklist 4-18. Beck Depression Inventory (BDI) and Multidimensional Perceived Social Support Scale (MSPSS) were used for maternal depressive symptoms and maternal perceived social support.

Results: In contrast to what was expected, there was no statistical difference in behavioral problems among two groups. Maternal BDI was higher and MSPSS was lower in the study group compared to the control group. Study group had more school difficulties such as absenteeism ($p<0.001$) and poor school performance ($p=0.011$). Grandmother caregiving, less maternal social support from her spouse, poor school performance, less knowledge about the cancer diagnosis, mother's depressive symptoms, longer hospital stay for cancer treatment, being female and being older were found to be risk factors for behavioral problems of study group.

Conclusion: Mothers of children with cancer had more depressive symptoms and lower social support. Behavioral problems of siblings of children with cancer may be related to school adaptation, maternal mental health, maternal social support, and socio-demographic characteristics. The intervention of maternal mental health should provide to optimize well -being of mother and siblings. School absenteeism and poor school performance should be investigated for intervention programs for behavior problems of siblings of children with cancer.

Keywords: Behavioral problems, mothers of children with cancer, siblings of children with cancer, low/middle income countries

INTRODUCTION

The diagnosis of childhood cancer and experiences during cancer treatment is an important psychosocial stress factor for the whole family. The diagnosis and treatment of process may lead to change family dynamics, affect parental relationships, and cause reorganization of roles and responsibilities within the family.[1] Siblings witness the suffering of their siblings with cancer, are worried about losing a sibling and stay away from their parents and siblings due to prolonged hospitalization. During this period, they may face many problems such as experiencing family, school, and social problems.[2,3] Adaptation of parents and siblings to such events may range from resilience to clinically significant psychopathology.[4]

Psychosocial care standards have been developed through multidisciplinary studies to evaluate and meet the psychosocial needs of children with cancer and their families.[5] According to psychosocial care standards, it is recommended that siblings ("SCC") and parents of children with cancer be considered a psychosocially high-risk group and included in support programs.[5]

In our country, this issue is not given enough attention, and only a few health centers have a family-centered approach that provides psychosocial support to children diagnosed with cancer and their families6. Although studies in this area are mostly from high-income western countries, there are limited studies in the literature investigating the behavioral problems and

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experiences of SCCs in low/middle income countries (LMIC).[1,7] The period of adaptation to cancers differs between culture.[8] So, in this study, we aimed to assess the behavioral needs of a sample of school-aged SCC compared to a control group without a family history of cancer in a LMIC. And to identify risk factors (maternal mental health, maternal social support, parental relationship, difficulties in their lives such as having to move, school difficulties and caregivers) for behavioral problems of school-aged SCC.

METHODS

The study was a case-control study conducted at Mersin City and Training and Research Hospital, a tertiary care hospital, between August and December 2022. The study was carried out with the permission of Toros University Clinical Researches Ethics Committee (Date: 27.05.2022, Decision No: 109).

Participants

Mothers who had a child diagnosed with childhood cancer for at least one year in the Pediatric Hematology and Oncology Service of Mersin City and Training and Research Hospital and also had a healthy child aged between 4-18 years without chronic diseases were included in the study. A total of 41 mothers were interviewed to participate in the study. Two mothers could not participate in the study due to language problems.

The control group consisted of mothers who applied to pediatric outpatient clinics, did not have a family history of cancer, had healthy children between the ages of 4 to 18, and were willing to participate in the study. In the control group, 54 mothers were interviewed and the aim of the study was explained. Since five mothers did not want to participate due to lack of time, a total of 49 mothers were included in the control group.

67 SCCs were included in the study. Having more than one sibling in a family may lead to biased findings. Therefore, only one healthy sibling was included in the study. Siblings were randomly selected. As a result, 39 children were included in the study group and 49 children were included in the control group.

The cancer diagnoses included hematologic malignancies (50%); solid tumors (25%); brain tumors (15%); and other (10%).

Procedure

The data form filled out by the mothers included sociodemographic data, the caregiver of the healthy child, the healthy child's school life (school achievement, absenteeism, the effect of cancer diagnosis on school achievement), and changes in the child's life after the diagnosis. Sociodemographic data included maternal and paternal education levels (less than or more than nine years of education), monthly income (below minimum wage, minimum wage and above minimum wage), children's school achievement (grouped as good, fair and poor). Recurrence, remission status and duration of hospitalization during cancer treatment were obtained from hospital medical records. Duration of hospitalization was categorized as less than 1 year, one to two years, more than two years. Duration of cancer diagnosis was categorized as 1-2 years, 2.1-4 years, >4 years.

The mothers in the study group were asked open-ended questions about important changes [about their address, job, marriage) that they experienced during the treatment of their children with cancer. Examples of open-ended questions are "How did your marriage change after your child was diagnosed with cancer?", "How did your professional life change after your child was diagnosed with cancer? "How did your healthy children learn about their siblings' cancer diagnosis?" "Did you change your address for cancer treatment?".

In addition, all participants were asked to complete three validated tools: Beck Depression Inventory (BDI) for mother's depressive symptoms, the Multidimensional Scale of Perceived Social Support (MSPSS) for maternal social support, and the Child Behavior Checklist/4-18 (CBCL/4-18) for children behavior assessment.

Assessment Tools

Beck depression inventory: It is a 21-item self-assessment scale developed by Beck et al and used to evaluate depressive symptoms.[9] Each item is scored between 0-3. Higher scores indicate more depressive symptoms. Turkish validity and reliability study was performed by Hisli et al.[10]

Multidimensional scale of perceived social support (MSPSS): It is a widely used social support scale that developed by Zimet et al.[11] In Turkey, adaptation, validity and reliability studies were conducted by Eker and Akar.[12] It includes social support perceived from family, friends and a special person (spouse, fiancé, etc.). Total score obtained from the 12-item scale, where each item is graded between 0-7 points. High score indicates a high level of support.

Child behavior checklist/4-18 (CBCL/4-18): It was used in the study to evaluate the behavioral problems of children. CBCL was developed by Achenbach[13] and the validity and reliability study was performed by Erol et al.[14] The questions are three Likert-type questions answered by parents. "Not true"; 0, "sometimes or

somewhat true"; 1 and "very or often true"; 2. It consists of eight subgroups: withdrawn, somatic complaints, anxiety/depression, social problems, thought problems, attention/hyperactivity problems, delinquent behaviors, aggressive behaviors and other problems. The sum of the scores of withdrawn, somatic complaints, and anxiety subgroups includes internalizing behavior problems; the sum of the scores of the aggression and delinquent subgroups constitute externalizing behavior problems, and the sum of the scores of all subgroups constitutes the total problems. Higher scores indicate more behavioral problems.

Statistical Analysis

Normality control of continuous variables was evaluated with the Shapiro Wilk test. Since the variables did not fit the normal distribution, nonparametric methods were used in the comparisons. The Mann Whitney U test was used to compare two independent groups and Kruskal Wallis test was used to compare more than two groups. Spearman Rho correlation coefficients were used to examine the linear relationship between continuous variables. Chi-Square and Fisher Exact tests were used to analyze categorical data. Multiple Linear Regression models were created with the variables that could affect the problem scores in the study group. Data analysis was performed in IBM SPSS 21 package program.

RESULTS

The mean age of the study group was 10.03±3.98 years, 43.5% (n=17) were female and the mean age of the control group was 10.59±3.95 years, 39% (n=19) were female. There was no statistically significant difference between the two groups in terms of age and gender (p=0.507, p=0.648, respectively). The median duration of cancer diagnosis (IQR) was 3 years (2.5-5 years). Sociodemographic and disease-specific data are summarized in Table 1. In addition, changes in family life during cancer diagnosis and treatment are shown in Table 1.

The maternal BDI score was statistically higher (p=0.005) and the MSPSS score was lower (p<0.001) in the study group compared to the control group. Maternal BDI was found to be positively associated with internalizing and total problems in the study group (r=35.3, p=0.027; r=32.3 p=0.045). However, the study showed that there was no relationship between the social support perceived by the mothers and the behavioral problems of the sibling in the study group.

There was no statistically significant difference between the two groups in terms of behavioral problems (Table 2).

Table 1 Descriptive sociodemographic and cancer-related parameters

	Case group (n=39)	Control group (n=49)	p value
Age*	10.03±3.98	10.59±3.95	0.507
Maternal age*	37.46±7.55	38.61±7.70	0.484
Paternal age*	43.03±9.40	42.47±7.33	0.756
Age of children with cancer*	9.98±4.56		
Maternal educational level <9years n(%)	33 (84.6)	28 (57.1)	0.006
Paternal educational level <9years n (%)	30 (76.9)	26 (53.1)	0.021
Non-employee mother n (%)	35 (89.7)	32 (65.3)	0.008
Monthly family income n (%)			
Above than minimum wage	8 (20.5)	11 (22.4)	<0.001
Minimum wage	14 (35.9)	34 (69.4)*	
Below than minimum wage	17 (43.6)*	4 (8.2)	
School absenteeism n (%)	11 (35.5)	1 (2.3)	<0.001
School achievement n (%)			
Good	16 (51.6)	28 (65.1)	0.011
Fair	9 (29)	15 (34.9)	
Poor	6 (19.4)*	0	
During cancer treatment negatively impact of school achievement n (%)	13 (41.9)	NA	
Birth of order n (%)			
Older than children with cancer	19 (48.7)		
Younger than children with cancer	20 (51.2)		
Drop out of school n (%)	5 (16.1)		
Duration of diagnosis, year, median (IQR)	3 (2.5-5)		
Duration of diagnosis, year, n (%)			
1-2 years	13 (33.3)		
2.1-4 years	14 (35.9) 12 (30.8)		
>4.1 years			
Recurrence n (%)	8 (20.5)		
Remission n (%)	27 (66.7)		
Duration of stay at hospital n (%)			
<1year	22 [56.4)		
1-2 years	11 [28.29)		
>2.1 years	6 [15.4)		
Talking about cancer diagnosis n (%)			
Hidden	18 (50)		
Face to face talking	18 (50) 18(46.2)		
Negatively impact of partner relationship n (%)			
Changing in address n (%)			
Had to move another city	9 (23.1)		
Going another city for cancer treatment	5 (12.8))		
None changed	25 (64.1)		
Negatively impact in job n (%)	8 (20.5)		
Caregiver of healthy children during cancer treatment, n (%)		NA	
Mother	7 (17.9)		
Father	9 (23.1)		
Older sister	9 (23.1)		
Grandmother	14 (35.9)		

*: mean±SD

p valueComparison of sociodemographic data, cancer treatment parameters and behavioral problems of the study group are summarized in Table 3.

In the study group, the externalizing problems of children with good school achievement were found to be lower (p=0.036). According to the statements of the mothers, the externalizing and total problem scores of children whose school achievement was negatively affected during the cancer period were found to be higher than those whose school achievement was not affected (p=0.028 and p=0.01, respectively). No significant relationship was found between change of address and marriage and behavioral problems. When the caregivers of healthy children were examined, the internalizing and total problem scores of children who were cared for by their grandmothers were higher than those of children who were cared for by their mothers, fathers and older sisters (Table 4).

In multiple linear regression analysis, caregiver, change of address, mother's perceived social support, school achievement, the way of learning the diagnosis, mother's BDI score, duration of hospitalization for cancer treatment, being a girl, being older than children with cancer, and children's age were found to be risk factors for behavioral problems in siblings of children with cancer (see Table 5).

DISCUSSION

The study examined the behavioral problems of school-age SCC to comprehensively compare with the control group. We examined multifactorial independent variables potentially associated with behavioral problems, such as social, school and family functioning. The study found several important implications for developing cost-effective and feasible intervention programs.

In the study, it was found that the lives of the majority

Table 3. Descriptive the Relationship Between Sociodemographic Parameters and Behavioral Problems of Siblings of Children with Cancer

	Internalizing Problems	Externalizing Problems	Total Problems
Sex*			
Female (n=17)	9 (1.5-18.5)	5(2-11)	25 (13-41.5)
Male (n=22)	8 (2-12.5)	7.5 (2.75-12.25)	26 (13.25-46.75)
p value	0.798	0.609	0.989
Birth of Order*			
Older Than Children with Cancer (n=20)	6.5 (1-12)	5.5(2.25-10.5)	23 (11-41.5)
Younger Than Children with Cancer (n=19)	8 (2-24)	7 (2-28)	26 (15-101)
p value	0.242	0.317	0.439
Maternal Educational Level*			
<9 Years (n=33)	8 (2-12.5)	6 (2.5-12)	26 (14.5-44.5)
≥9 Years (n=6)	7 (2-23)	4.5 (0-20.75)	24.5 (3.75-72.5)
p value	0.740	0.640	0.830
Paternal Educational Level*			
<9 Years (n=30)	8 (2-12)	5.5 (2-11.25)	24.5 (14.75-43.75)
≥9 Years (n=9)	10 (1.5-18)	8 (1.5-14.5)	33 (7.5-54)
p value	0.867	0.828	0.790
Family monthly income*			
Above than minimum wage (n=8)	5 (1.25-12.5)	8 (0.75-12.75)	25 (5.75-41.5)
Minimum wage (n=14)	9 (1.75-12.25)	5.5 (2-10.5)	27.5 (14-38.5)
Below than minimum wage (n=17)	9 (2.5-20)	5 (2.5-9.5)	25 (14.5-50)
p value	0.612	0.944	0.826
Duration of Cancer Diagnosis*			
1-2 Years (n=13)	9 (2.5-19.5)	8 (4-23.5)	26 (19-72)
2.1-4 Years (n=14)	9 (1.75-12.5)	5.5 (1.75-11.25)	30.5 (10.75-46)
>4.1 Years (n=12)	5.5 (1.25-9.75)	4 (2-13.5)	17.5 (12-43.25)
p value	0.458	0.425	0.698
Remission*			
Yes (n=27)	8 (2-13)	7(2-12)	26 (15-43)
No (n=12)	6 (2-19.5)	4.5(2.25-13.5)	18.5 (11-48.25)
p value	0.855	0.594	0.749
Recurrence*			
Yes (n=8)	8 (2-14)	6 (3-10)	26 (15-39)
No (n=31)	7 (1-12)	4 (2-12)	18 (9-34)
P-value	0.232	0.589	0.376
Duration of Hospitalization *			
<1 Year (n=22)	9 (1.75-22.5)	6.5 (1.75-13.75)	26 (9.25-50)
1-2 Years (n=11)	8 (2-10)	6 (3-13)	20 (16-34)
>2.1 Years (n=6)	5(1.75-10.5)	4 (1.75-65)	20 (9-39.25)
p value	0.698	0.413	0.822

*: median (IQR)

of families were negatively affected after the diagnosis of cancer. Approximately half of the mothers stated that their marriages were negatively affected,[15] 23.1% stated that they had to move to another city due to cancer treatment and 20% stated that their jobs were negatively affected.[16] Most of the mothers accompanied the sick child during hospitalization. Only 17.9% (n=7) of the mothers were able to take care of their healthy children during treatment. This finding is similar to the literature.[17] The results of previous studies on family adaptation and experience are similar to the present findings.[15,16]

Certainly, the diagnosis of cancer in their child is one of the worst experiences for parents. Maternal depressive symptoms are still higher and maternal perceived social support is lower than the control group. Consistent with our study, a previous study by Howard showed that maternal depressive symptoms may persist for 5 years after diagnosis.[18] In the literature, previous studies have shown that maternal perceived social support was lower, consistent with this study.[19,20]

SCC can lead to severe acute and long-term difficulties. The results of various studies on sibling behavior in the literature are inconsistent.[6,7,21] Contrary to our expectation, this study showed that there was no significant difference between the siblings of the children and the control group in terms of behavioral problems. In our study, the duration of diagnosis was approximately 3 years, at least one year. In parallel with the studies by Houtzager and Alderfer, we thought that the psychosocial adjustment of the sibling improved over time.[2,22,23] However, school problems may become apparent approximately 2 years after the diagnosis.[2,7] In this study, in line with the literature, siblings of children with cancer experienced more school-related difficulties than the control group according to maternal reports (16.1% siblings dropped out of school, could not attend preschool education, were absent from school and had poor school achievement).[7,17] Siblings may experience academic problems and school absenteeism due to lack

Table 4. To demonstrate the relationship between changes in family life and behavioral problems

	Internalizing problems	Externalizing problems	Total problems
School absenteeism*			
Yes (n=11)	10 (3-14)	8 (2-13)	29 (17-52)
No (n=20)	2 (1-9)	4 (2-9.75)	15.5 (7.25-27.5)
P-value	0.023	0.279	0.079
School achievement*			
Good (n=16)	3 (2-8.75)	2.5 (0.25-7.75)a	15.5 (4-27.5)
Fair (n=9)	9(1.5-18)	8 (3-14.5)b	33 (12-54)
Poor (n=6)	6 (0.75-13.75)	8.5 (4.75-20.75)ab	23 (16.75-65.75)
P-value	0.621	0.036	0.095
The impact of school achievement*			
None change	2.5 (2-9)	3 (0.73-7.5)	15 (5.5-26.5)
Negatively impact	10 (2-23.5)	8 (3.5-14.5)	33 (16.5-57)
p-value	0.068	0.028	0.010
Talking about cancer diagnosis*			
Hidden (n=18)	8 (2-16.75)	6 (2.75-12.25)	26 (16.5-43.75)
Face to face talking (n=18)	6.5 (1.75-12)	5 (2-10.25)	18 (10.75-37.75)
p-value	0.389	0.563	0.323
The impact of marriage relationship*			
None (n=21)	8 (2-14)	6 (2.5-12.5)	25 (12.5-44.5)
Negatively affect (n=18)	8.5 (2.5-12.5)	5.5 (2-11.5)	27.5 (14-47.5)
p-value	1.000	0.910	0.683
Changing in address*			
Changing city (n=9)	8 (2.5-18.5)	6 (2.5-31)	26 (13.5-78)
Going another city only during treatment (n=5)	2 (0.5-20.05)	12(1-20.5)	26 (7.5-66.5)
None (n=25)	9 (2-13.5)	5(2-10.5)	25 (12.5-44.5)
p-value	0.528	0.706	0.848
Caregiver of healthy children during cancer treatment*			
Mother (n=7)	4 (1-8)[d]	3(0-12)	17 (4-28)[g]
Father (n=9)	7(0.5-9.5)[c]	6 (3-9.5)	24 (13-34.5)[f]
Sister (n=9)	3 (2-12)	4(1-7)	16 (7-31)[e]
Grandmother (n=14)	13 (8-25.25)[cd]	13 (4.5-34.25)	40.5 (28.25-104.25)[efg]
p-value	0.017	0.055	0.016

*: median (IQR)

Table 5. To demonstrate the risk factors of behavioral problems for sibling of children with cancer

Model	Standardized Coefficients	Sig.	95.0% Confidence Interval for B	
	Beta		Lower Bound	Upper Bound
Internalizing problems R2:0,879 F:11,238 p<0,001				
(Constant)		0.007	-17.460	-3.221
Age of children with cancer	0.914	0.000	0.842	1.616
Changing city	-0.546	0.002	-13.224	-3.729
Going another city only for treatment	-0.865	0.000	-23.588	-12.146
Grandma caregiving	0.613	0.000	4.644	12.041
Sister caregiving	-0.304	0.009	-7.683	-1.257
Being female	0.287	0.035	0.276	6.940
Talking about diagnosis	-0.544	0.000	-9.803	-3.885
Poor school achievement	0.308	0.008	1.409	8.163
School absenteeism	0.273	0.095	-0.685	7.775
Social support from family	0.619	0.000	0.288	0.746
Social support from spouse	-0.425	0.003	-0.475	-0.115
Externalizing problems R2:0,884 F:7,657 p<0,001				
(Constant)		0.025	-26.137	-2.036
Being older than children with cancer	2.636	0.000	-20.070	-8.764
Duration of stay at hospital	0.335	0.047	0.005	0.730
Remission	0.609	0.003	4.393	16.778
Changing city	0.475	0.043	0.362	18.987
Going another city only for treatment	-1.039	0.000	-39.366	-16.974
Mother caregiving	0.605	0.001	6.452	20.020
Grandma caregiving	0.822	0.000	8.028	21.313
Talking about diagnosis	-0.714	0.000	-16.551	-7.055
Poor school achievement	1.134	0.000	16.882	29.356
Fair school achievement	0.627	0.001	5.814	17.349
School absenteeism	-0.890	0.003	-24.283	-5.992
Maternal Beck Depression inventory	0.593	0.001	0.239	0.684
Social support from family	0.769	0.000	0.490	1.197
Social support from spouse	-0.522	0.004	-0.775	-0.176
Total problems R2:0,801 F:8,488 p<0,001				
(Constant)		0.349	-17.578	47.343
Maternal age	-0.372	0.015	-1.773	-0.214
Age of children with cancer	0.854	0.000	2.472	5.366
Changing city	-0.362	0.014	-34.043	-4.331
Going another city only for treatment	-0.682	0.000	-69.611	-26.470
Grandma caregiving	0.636	0.000	15.641	43.338
talking about diagnosis	-0.532	0.000	-33.855	-11.811
Poor school achievement	0.537	0.000	15.000	41.934
Social support from family	0.405	0.010	0.312	1.995
Social support from spouse	-0.260	0.067	-1.279	0.048

of concentration and lack of parental attention and supervision.

Studies have indicated that being older and female may be risks factor for behavioral problems.[21] This may be related to taking more responsibility in the family.[2] In the study, depressive symptoms of the mother, less social support from the spouse, caregiving by the grandmother, longer duration of hospitalization and talking about the cancer diagnosis were found to be associated with the sibling's behavior. According to a review by Long, family functioning plays an important role for psychosocial adjustment of school-age SCC.[7] Family is a very important social support system for children.[24] Better family functioning supports better sibling adjustment.[25] Consistent with our study, low level of knowledge about the diagnosis of cancer has been shown to be a risk factor for sibling adjustment in a previous study.[26]

School is another important social support system for children. Many studies in the literature have shown that school adjustment plays an important role for the psychosocial status of the sibling.[7,27] According to the findings of the present study, poor school performance may be a risk factor for behavioral problems.

The study has some limitations. The study is a cross-sectional study. The psychosocial status of siblings and

mothers were examined once. We do not have any information about the first time of diagnosis. The study was conducted in a single center and only one sibling from a family participated in the study to avoid bias. Therefore, the sample size is small. Therefore, the results should be interpreted with caution. The questions were answered only by mothers, so the psychosocial situation was analyzed from the mother's perspective.

Despite these limitations, the study also has strengths. As mentioned above, the first step for intervention programs for high-risk groups is to identify risk factors. In Turkey, this issue has been less studied and the awareness on the subject is low compared to high-income countries.

CONCLUSIONS

The study found several important implications for developing cost-effective and feasible intervention programs. The results showed that mothers of children with cancer had more depressive symptoms and had lower social support. Mothers should have speedy and permanent assessment for depressive symptoms and social support.

School-aged SCC did not exist more behavior problems compared to control groups. However, parents of SCC reported poor school achievement and higher school absenteeism than the control group. Poor school achievement, family functioning (caregiver, mother's mental health, change of address, style of learning the cancer diagnosis), mother's perceived social support from her partner, and sociodemographic parameters (being female and being older than children with cancer) were associated with the behavior of siblings with cancer.

Maternal mental health and lower maternal social support from her partner may impact sibling's adjustment. To arrive intervention for parent mental health should be provided for optimize parent and sibling's well-being.

In additional school adjustment can play important role in sibling's behavioral adaptation. Attention should be paid to school absenteeism and school success. School and family-based intervention may be effective for behavioral problems of siblings. School social services and school guidance and psychological counseling units should be included in intervention programs.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Toros University Clinical Researches Ethics Committee (Date: 27.05.2022, Decision No: 109).

Informed Consent: Written informed consent forms were obtained from the parents of all patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Exploring occupational safety and health in future workscapes

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ABSTRACT

Aims: The aim of this manuscript is to address the evolving dynamics of work, which are placing increasing demands on current occupational safety and health (OSH) protocols. It emphasizes the need for a more adaptable approach to ensure safe and efficient work environments. The primary objective is to introduce new frameworks capable of handling the uncertainties of the future in OSH.

Methods: To tackle the challenges posed by the changing landscape of work, the U.S. National Institute for Occupational Safety and Health (NIOSH) has adopted a strategic foresight approach. This approach is rooted in future studies and strategic planning, allowing NIOSH to anticipate future challenges in OSH. It involves creating well-structured and informed scenarios of potential futures, enabling organizations to prepare effectively for upcoming challenges and capitalize on emerging opportunities.

Results: This manuscript represents NIOSH's inaugural foray into strategic foresight. The results showcase the integration of strategic foresight methods to enhance institutional readiness in the realm of OSH. The study delves deep into the anticipated trajectories of OSH research and protocols, offering valuable insights into the future of OSH.

Conclusion: In conclusion, the evolving nature of work necessitates a more adaptable approach to occupational safety and health. NIOSH's strategic foresight venture marks a significant step towards achieving this goal. By proactively preparing for future challenges and opportunities, organizations can ensure safer and more efficient work environments. This manuscript provides a foundation for enhancing institutional readiness and navigating the evolving landscape of OSH research and protocols.

Keywords: Future of work, strategic foresight, occupational safety and health, envisioned futures, changing dynamics, data protection, mental wellness, collaboration, remote work

INTRODUCTION

Swift transformations in social, technological, environmental, economic, and political domains, often denoted by the STEEP framework, are reshaping the landscape of work, influencing both the workforce and the workspace in profound ways.[1-5] This evolution is distinctly evident in its effects on occupational safety and health (OSH) practices, with prevailing trends suggesting a continuous evolution in the foreseeable future.[6-9] Scholars and practitioners have posited that a broader perspective on OSH will be imperative to adeptly navigate and adapt to these unfolding changes.[10.] This encompasses a widened understanding of the determinants impacting worker well-being and the recalibration of outcomes pertinent to the OSH spectrum.[9,10] The urgency to redefine OSH frameworks to stay ahead of these evolving dynamics, with emphasis on transitioning from the OSH 4.0 model to the more advanced OSH 5.0, is gaining momentum.[11] Moreover, earlier studies underscore the instrumental role of predictive scenarios in flagging emerging threats or compounding risks in the work environment.[12]

As we rethink OSH concepts, innovative research and proactive strategies become vital to ensure the long-term safety, health, and wellness of workers. In our past discourse, we championed the role of strategic foresight as a holistic, system-centric methodology uniquely suited for the burgeoning OSH framework.[13] Grounded in the principles of futures studies and strategic management, strategic foresight employs a repertoire of proven methods to draft comprehensive anticipatory scenarios, enabling organizations to preempt challenges and leverage upcoming prospects.[13,14] These scenarios are not just conjectures but are anchored in evidence,

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offering insights in a more relatable narrative format as opposed to conventional charts or policy summaries.[15-17] They serve as a lens to visualize nascent trends, offering a glimpse into the interplay of various determinants shaping the future work ecosystem. Notably, the primary objective of these foresight scenarios is not to provide a precise projection of the future but to canvas a spectrum of plausible futures, each brimming with its set of opportunities and challenges.[18,19]

Though foresight doesn't offer a crystal ball into the future, its integration into strategic planning can be instrumental in sidestepping unforeseen adversities and sculpting desired future trajectories.[13,19-21] Many global corporate giants, including the likes of Shell, General Electric, Siemens, and Daimler AG, have harnessed strategic foresight to bolster resilience during tumultuous phases and market upheavals.[22,23] Additionally, the U.S. federal administration, with agencies such as NIOSH at the forefront, is increasingly leaning towards foresight-driven strategies to future-proof their research and operational frameworks.[24,25]

In this manuscript, we delve into NIOSH's maiden strategic foresight initiative, a venture aimed at bolstering institutional acumen in strategic foresight and honing readiness to the impending shifts influencing OSH research and service paradigms. The discourse presented is the cumulative effort of a cross-functional team from NIOSH, representing a broad spectrum of its divisions, under the stewardship of authors SF, JS, and NE.

METHODS

The study was carried out with the permission of Ethics Committee of Faculty of İstinye University (Date:16.07.2023, Decision No: 2023-07). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Foresight Paradigm for Occupational Safety and Health

We employed a modified version of the scenario-centric Foresight Framework, originally conceived at the Kent University, to envision diverse futures pertinent to occupational safety and health.[13,26] This model, illustrated in Figure 1, delineates a systematic procession of tasks leading to the conception of congruent and credible future scenarios. These scenarios, derived from research findings, are then critically assessed to unearth their strategic ramifications, subsequently informing proactive strategy formulation and futuristic decision-making.

While this structure suggests a step-by-step progression, it's crucial to note that the journey isn't strictly linear. After completing each phase, revisiting previous stages to ascertain if further refinement or elaboration is warranted can be essential. At every juncture of our current endeavor, we meticulously assessed the prior phase's deliverables to decide if more efforts were required before advancing, thus shaping an iterative cycle akin to a feedback mechanism often seen in logical frameworks. Detailed elaboration of our methodological application, forming the crux of this paper, has set the stage for the comprehensive strategic foresight procedure.

Establishing the Framework

The inception of the foresight structure hinges upon the delineation of the domain, often synonymous with the focal subject (as shown in Figure 1. Phase 1). This initial framing demarcates the project's breadth, elucidates the core parameters affiliated with the topic, and scrutinizes the prevailing domain circumstances to differentiate the prospective future from the extant present.

Territorial Blueprint

Our endeavor aimed to untangle the intricate question: In what ways will forthcoming developments shape NIOSH's research and service endeavors? The project's epicenter revolved around the imminent landscape of occupational safety and health in the U.S. An illustrative domain blueprint, directed our pursuit of both overt and subtle harbingers that could potentially redefine OSH's future trajectory, bifurcated into primary and ancillary domain themes. The chief domain areas were demarcated as: Infrastructure, Regulatory Frameworks, OSH Talent Pool, Assets, OSH Endeavors, and the STEEP framework. Each pivotal domain was further broken down into auxiliary topics to sharpen our information scouring precision. Infrastructure entailed an examination of

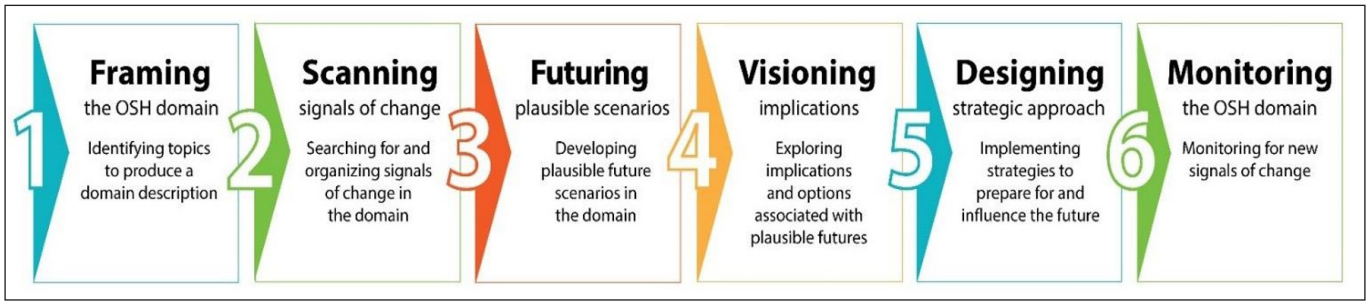

Figure 1. The OSH Foresight Structure, first introduced by Streit et al.[13]

labs, administrative hubs, and apparatus. Regulatory Frameworks delved into tech policies, human capital management, and scientific regulations. The OSH Talent Pool spotlighted aspects like talent equilibrium, segregation of research-centric and non-research staff, and talent cultivation. Assets emphasized datasets, research milieu accessibility, participant demographics, and collaboration. OSH Endeavors comprised both research and service facets. The STEEP domain encapsulated socio-cultural, technological, economic, ecological, and political dimensions. Given NIOSH stood as this initiative's epicenter, the narrative was predominantly sculpted by the U.S. context.

Temporal Perspectives

The Three Horizons Framework (as illustrated in Figure 2) serves as a bridge, seamlessly linking our current realities with potential futures. This structure allows us to deeply reflect on prevailing assumptions, nascent shifts, and envision possible preferred futures.[27,28] The Three Horizons model equips OSH with an analytical lens, facilitating a comprehensive understanding of how transformations materialize. This is achieved by acknowledging the simultaneous existence of three distinct future perspectives within our current context.[13,28]

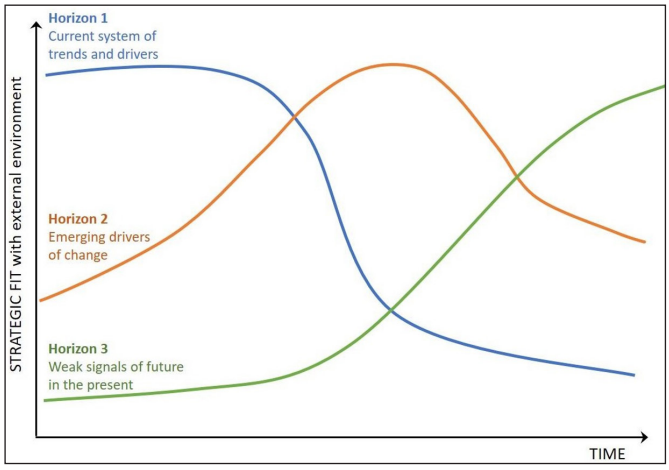

Figure 2. The visual diagram of the Three-Horizon Foresight

Horizon 1 (H1) represents the contemporary modus operandi. As time progresses and various shifts come into play, it's natural for H1's practices to be deemed obsolete or inefficient, thereby losing their strategic alignment with evolving external environments. In stark contrast, what may currently be perceived as 'peripheral' or 'alternative' solutions and practices gradually gain prominence, forging the path for the distant future, termed Horizon 3 (H3). Interspersed between these two extremes lies Horizon 2 (H2). This intermediate phase is emblematic of tumultuous times, marked by significant upheavals and transformations. This period witnesses a gradual phasing out of H1's principles, simultaneously laying down the foundational stones for H3's emergence.

Time Scales in Planning

The visual diagram of the Three-Horizon Foresight, as depicted in Figure 3, offers an insightful perspective on planning for change over time 28, as articulated in Streit et al.[13]

		Driver Y								
		Advanced Technology	Virtual Workplace	Data Security	Knowledge Generation	Social Credit	Climate and Energy	Workforce	Work Arrangements	Total Reinforcing Score
Driver X	Advanced Technology	-----	5	5	5	4	5	4	5	33
	Virtual Workplace	5	-----	5	4	5	5	4	5	33
	Data Security	5	3	-----	5	4	4	3	4	28
	Knowledge Generation	5	3	5	-----	4	4	4	3	28
	Social Credit	3	5	5	2	-----	5	4	4	28
	Climate and Energy	5	4	3	4	5	-----	3	3	27
	Workforce	4	5	2	4	4	3	-----	5	27
	Work Arrangements	4	5	1	4	3	3	5	-----	25

Figure 3. Cross-impact matrix for drivers of change

In the realm of strategic foresight, time horizons are frequently correlated with an organization's standard operational and business cycles.[28,29] In our project's context, we meticulously synchronized the time horizons with the strategic planning intervals of NIOSH. The immediate future, represented by H1, spanned from 2021 to 2026. H2, symbolizing the medium-term future, encompassed the timeframe between 2027 to 2036. Lastly, H3, depicting the distant future, extended to 2037 and subsequent years. This delineation offers a structured template for envisaging the immediate, medium, and distant futures of OSH in the American context.

Evaluating the Present Landscape

Prior to embarking on our investigative journey into the future, it was imperative to delineate the contemporary influential factors within the domain. An in-depth analysis of the prevailing conditions, pivotal stakeholders, and the recent chronology was conducted to set the stage for our exploration into the forthcoming times. This wasn't a quest to create an exhaustive account of the present OSH landscape. Instead, our evaluation is a distillation of insights furnished by the team and veteran NIOSH leadership, with their expertise spanning the realm of OSH right from NIOSH's foundational days in 1970. This evaluation, detailed in Tables 1-3, has been structured around the principal categories delineated in the domain map (refer to Figure 2). Concise interpretations of our discoveries are bolstered by references offering in-depth insights. The appended segment incorporates a comprehensive list of abbreviations employed in these tabulations and across the manuscript (refer to Supplement Table S1).

Current Landscape of Occupational Safety and Health (OSH)

Present Conditions

Activities: The NIOSH Strategic Plan, together with the Burden, Need, and Impact (BNI) framework, predominantly drives OSH research.[30,31] This is complemented by service-oriented endeavors that hinge on essential partnerships addressing myriad mandates and the requirements of stakeholders. Emphasizing the role of employee well-being, it is deemed pivotal not only to OSH but also to the economic health of organizations.[6]

Facilities: With its research centers scattered geographically, NIOSH has recently amplified its capabilities, notably in places like Cincinnati, OH.[32] However, the COVID-19 pandemic posed challenges, restricting access to these centers due to safety measures.[33] In response, both CDC and NIOSH championed the inception and realization of wholesome remote working paradigms.[34]

Policies: A contemporary shift towards heightened privacy and security has redefined how data usage and interpretation occur in OSH.[35-38] Additionally, there's a growing emphasis on inclusivity, touching upon aspects like diversity, equity, and evolving employment dynamics, coupled with a surging focus on mental health and holistic well-being.[39-41]

Resources: With technological evolution, data management and linkages are undergoing transformations, albeit with amplified security apprehensions. The pandemic-induced restrictions affected human subject research projects and access to U.S. worksites. Collaboration with key stakeholders, although indispensable for NIOSH, often presents establishment and maintenance challenges.[42]

STEEP: The dynamic flux within Social, Technological, Economic, Environmental, and Political domains casts direct ramifications on OSH research, service facets, stakeholder dynamics, and funding allocations.

Workforce: NIOSH currently grapples with an aging workforce, with significant retirement projections looming.43 Addressing this multigenerational work milieu demands unwavering adaptability, underscored by collaborative endeavors, rigorous training, and a drive for enhanced productivity.

Crucial Stakeholders

Academia: NIOSH finds support from university-centric bodies, both funded and otherwise, that bolster current research trajectories while spotting opportunities for seamless integration and practical implementation.

Employer organizations: These comprise both individual employers and conglomerate trade associations that partake in research, translating findings into actionable workplace transformations.

Federal entities: Advisory committees, and partner agencies like EPA, OSHA, NIH, and DOT, play pivotal roles, offering guidance, recommendations, and partnering in research, services, and information dissemination.

International collaborators: World-renowned bodies like WHO, ILO, and WTO collaborate with NIOSH, turning to it as a reliable beacon for OSH-centric research, services, data, and advisories.

The domain also witnesses active involvement from insurance organizations, labor bodies, lobbyists, media (notably during the COVID-19 crisis), national academies, OSH professional associations, standardization committees, state and local health departments, and the U.S. Congress.

Historical Milestones

From its inception in 1970 through the Occupational Safety and Health Act[44] to the significant strides in the following decades, OSH has witnessed notable milestones. The relocation of NIOSH's headquarters in 1994 aimed to bolster partnerships.[44,45] The 1990s were characterized by regulatory shifts, evolving workforce demographics, and declining union memberships. The post-9/11 era marked an emphasis on security, both physical and cyber.[46,47] With the dawn of the 2000s, technological revolutions like AI began redefining work.[48,49] The 2010s heralded changes in employment dynamics, with the gig economy's resurgence.[50] Recently, concerns regarding data security became prominent, with significant cyberattacks targeting sensitive research data.[51-52]

RESEARCH

Recognizing the importance of foreseeing and preparing for the future, our research endeavors embarked on the exploration of potential change signals. The scanning process, as depicted in **Figure 1**. Stage 2, draws from a wide array of information sources to identify deviations from the established norms, focusing on emerging trends and signals.[20,53,54] Both conventional and unconventional sources, such as blogs, social media, and publicly available reports, were tapped into to discern these weak signals.[55,56]

Scanning

In our scanning phase, we curated a substantial list of 240 hits, providing valuable insights across all established timeframes and categorized according to the domain

map, as illustrated in Figure 2. This library of scanning hits was pivotal for our research.

A thorough synthesis of the scanning hits was performed. Each hit was classified based on various criteria, such as trends, issues, plans, and projections, to understand how the future may diverge from the present. This framework, known as TIPPS, is instrumental in shaping strategic foresight research.[26] To streamline the data and maintain a manageable dataset, overlaps were condensed. As an instance, all trends indicating a shift towards a holistic approach to OSH were compiled into a singular trend statement.[6,57]

Drivers of Change

Our subsequent step involved pinpointing the drivers of change. Synthesized from thematic clusters of the scanning results, these drivers highlight evidence-backed developments projected to mold the future.[26.] Eight principal drivers were identified, as depicted in Table 1.

Cross-Impact Matrix

After defining the drivers, we ventured into developing a cross-impact matrix, a proven foresight tool used to explore the interplay of drivers in the future.[26] This matrix helps distinguish neutral drivers, which may be considered for exclusion in the scenario development stage.[56,57]

In Figure 2, the matrix illustrates the influence of one driver over another. The matrix should be understood as, "Given the occurrence of Driver X, the impact on Driver Y will be either reinforcing, neutral, or contradictory." We adopted a 5-point scoring mechanism to represent the relationships, with 5 indicating a strong reinforcement and 1 symbolizing a strong contradiction.

Our evaluation failed to identify any neutral drivers. Each of the eight drivers was impactful enough to be integrated into the scenario-building process. Particularly noteworthy was the interplay between Advanced Technologies and the Virtual Workplace, which displayed a reinforcing score of 33, indicating their significant role in future scenario development.

RESULTS

For the current study, we employed four generic future archetypes, serving as foundational frameworks for our scenarios. This research discerned that globally prevalent future visions can be grouped into four predominant categories. Figure 2 provides detailed descriptions and essential developmental questions related to each archetype.

As part of the next phase in scenario development (refer to Figure 1. Stage 3), our comprehensive project team was segmented into four groups. Each group was tasked with drafting a preliminary 400-600 word future scenario aligned with their designated archetype. To ensure a holistic exploration of the future scenario, teams were encouraged to thoroughly analyze all eight drivers during the draft phase, highlighting those deemed most influential for their assigned scenario. Each driver unfolded a unique narrative across the four futures, playing a vital role in at least one scenario. After drafting, the narratives were cross-examined for uniqueness and cohesiveness, with the authors of this paper harmonizing the writing styles for a unified presentation. Section 4.1 lists the title, abstract, and chief drivers for the finalized four scenarios.

Table 1. Key drivers and descriptions

Driver	Description	Keywords from TIPPS	Supporting TIPPS
Advanced Technology	Evolution in technology, notably AI, augments work productivity and customization, though introduces challenges related to worker retraining and hazard management.	Advanced tech, Robots, AI, Cybernetics	Numerous
Climate and Energy	Rising awareness of climate change prompts a shift to cleaner energy sources, affecting the OSH sector by introducing new workplace risks.	Carbon neutral, Sustainable energy	5
Data Security	The proliferation of digital data collection amplifies the need for robust cybersecurity measures, while promoting data connectivity for improved health and safety.	Big data, Encryption, Privacy rights	16
Knowledge Generation	Skepticism towards government information sources mandates effective communication strategies to combat misinformation.	International competition, Research priorities	10
Social Credit	Algorithms determining trustworthiness based on social standing can have repercussions at both the individual and organizational levels.	Corporate Social Responsibility, Trust systems	Varied
Virtual Workplace	Workplaces are no longer confined to physical locations but are redefined by the nature of tasks.	Telework, Workplace evolution	5
Work Arrangements	Flexible work arrangements are becoming commonplace, reshaping hiring practices and introducing new industries, each with its challenges and opportunities.	Gig economy, Work-life transformation	8
Workforce	Demographic shifts in the U.S. and economic trends are influencing labor markets. Employers now emphasize overall employee health in addition to physical safety.	Aging workforce, Total worker health, Workforce demographics	Numerous

Future of OSH Scenarios

Table 2 presents a summarization of the four OSH future scenarios, segmented by their archetype, and accompanied by brief characteristic descriptions.

The scenarios were constructed to serve as valuable tools for prospective planning and decision-making. The driver map facilitated the distinction of each scenario. The Continuation scenario offers a straightforward trajectory for OSH's future. Conversely, the Collapse scenario, despite its dystopian tone, provides insights into potential challenges to circumvent, while the New Equilibrium scenario delineates a potential trajectory from our present state. The Transformation scenario illustrates a visionary target for OSH's future.

Key Strategic Issues

In the concluding phase of our analysis, we pinpointed pivotal strategic challenges inherent in the scenarios (as illustrated in Figure 1. Stage 4). We meticulously examined the potential ramifications of these challenges on the OSH system for the periods H1 (2021-2026), H2 (2027-2036), and H3 (2037 and onwards). A thematic evaluation was orchestrated by the foresight team leads (JS and SF), unearthing the core strategic challenges. These challenges were then corroborated by the foresight team and systematically categorized into five primary strategic focus areas, delineated in Table 3: data security, mental health, partnerships, research, and virtual work.

To understand how these strategic issues can be turned into actionable steps, we segmented our recommendations using a time-oriented approach.

DISCUSSION

The research at hand paints a comprehensive picture of four potential futures for OSH, emphasizing the pivotal trends and challenges that could potentially redirect its course. As we move ahead, it is crucial for OSH institutions not to perceive the future merely as a linear extension of the past. Instead, they should embrace

Table 2. Overview of the four OSH future scenarios

Scenario Archetype	Scenario Title	Brief Description
Continuation	Boundaries Continue to Blur	The delineations pertaining to work locations, employment modalities, work durations, the confluence of professional and personal spheres, and the interplay between humans and machines are progressively obfuscated.
Collapse	The Perfect Storm	An inability to adapt, amplified by trust deficits and resource scarcity, compels individuals and entities to become self-reliant, often to the detriment of workers' health and safety.
New Equilibrium	Remote Controlled	The pressing need for novel research on worker-centric models, remote work paradigms, and human-machine synergy predominantly shapes the allocation of OSH resources. In this technologically advanced milieu, emphasis on mental health and data security takes precedence.
Transformation	One World Health	In this futuristic setting characterized by advanced technology, mental well-being and data protection emerge as pillars of an evolved OSH framework. Research initiatives are tailored to address population-centric needs, and industries coalesce to foster a global workforce well-being paradigm.

Table 3. Strategic focus areas for the future of OSH

Strategic Focus Areas	H1 (2021-2026)	H2 (2027-2036)	H3 (2037 and beyond)
Data Security	Bolstering advanced data protection systems. Addressing concerns regarding data breaches and unauthorized surveillance.	Integration of biometrics with robust encryption methodologies. Implementation of universally accepted data protection regulations.	Seamless and secure integration of individual data identities in the global OSH framework. Maintaining data sovereignty in decentralized work environments.
Mental Health	Initiating mental health assessments for remote workers. Offering resources to combat work-from-home fatigue and burnout.	Mental health becoming a mainstream topic in OSH policies. Integration of AI tools to monitor and suggest mental health interventions.	Holistic wellbeing, encompassing both physical and mental health, becoming a foundational principle of OSH. Global partnerships to address emerging psychological challenges of a highly virtualized workforce.
Partnerships	Fostering collaboration between industries for knowledge sharing. Establishing global OSH standards through multi-stakeholder engagements.	Nurturing cross-border partnerships to address shared OSH challenges. Leveraging public-private partnerships for OSH innovation.	Seamless international cooperation and data sharing in real-time to ensure worker safety. - Development of universal OSH protocols benefiting the global workforce.
Research	Studying emerging risks in rapidly changing work environments. Quantifying the impacts of nonstandard work arrangements on health.	In-depth research on the synergies between humans and AI in the workplace. Evolution of OSH research methodologies to be more inclusive and diverse.	Anticipating challenges and opportunities of a transhuman workforce. Continuous real-time monitoring and analysis of global workforce dynamics.
Virtual Work	Addressing challenges of work-life balance in remote work settings. Ensuring ergonomic standards in home offices.	Global normalization of virtual workplaces with set universal standards. Advancing technologies to aid in the virtual collaboration of teams.	Almost complete dissolution of traditional physical workspaces. Evolving the role of humans in a largely automated virtual work ecosystem.

Table 4. Strategic options and actions

Focus Area	Near-term	Mid-term	Far-term
Data Security	Improve communication between data security and science personnel.	Nurture relationships with longstanding partners and key interest groups.	Develop new data security paradigms for OSH research.
Mental Health	Acquire human capital resources. Increase occupational mental health surveillance efforts.	Establish workgroups for mental health literature.	Integrate mental health priorities into OSH research portfolios.
Partnerships	-	Embed OSH staff into different industries.	Strengthen relationships with partners and stakeholders.
Research	Acquire human capital resources. Identify high-priority industry sectors.	Collaborate with early adopters in high-priority sectors.	Enhance systems that track traditional hazards.
Virtual Work	Modernize HR policies related to remote work.	-	-

a versatile vision, accounting for the myriad possible futures that could be crafted by systemic disruptions, ground-breaking innovations, and unforeseen variables.

CONCLUSION

Strategic foresight stands as an indispensable tool that needs to be interwoven with organizational planning. This synthesis demands an unwavering commitment from institutions and a keen focus on the horizon. While models from the corporate world offer some insights, the responsibility falls upon agencies like NIOSH to discern approaches that resonate with the unique contours of a federal environment. Here are some recommendations based on our findings:

Adaptive learning: OSH organizations should prioritize continuous learning and adaptation, making them more resilient to potential future disruptions.

Collaborative endeavors: Engage in inter-agency and cross-sectoral collaborations to benefit from diverse perspectives and resources. This could foster more holistic strategies for OSH's future.

Stakeholder engagement: Regular dialogues with stakeholders can offer valuable feedback and insights, helping tailor strategies more effectively.

Methodological mix: It might be advantageous for NIOSH to blend various methods, allowing for a broader and more adaptable foresight framework.

Scalability: Given the dynamic and ever-evolving landscape of OSH, methods adopted should be scalable, accommodating both micro and macro perspectives.

Global perspective: While the focus of this study zeroes in on the U.S., its foundational methodology can serve as a benchmark for OSH initiatives worldwide. Efforts should be made to contextualize and adapt this framework to cater to diverse geographical needs.

Signal monitoring: As the Foresight Framework for OSH suggests, vigilant and proactive monitoring for signs of change is paramount. Institutions should invest in sophisticated monitoring tools and technologies to stay ahead of the curve.

In sum, the future of OSH is not set in stone, but is malleable, shaped by the decisions we make today. By integrating a forward-looking approach, informed by a blend of methodologies and underpinned by collaboration and adaptability, OSH organizations can navigate the uncertainties of tomorrow with confidence.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethical Committe of Faculty of İstinye University (Date:16.07.2023, Decision No: 2023-07).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

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Original Article

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Anoplasty and information pollution in health on YouTube

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ABSTRACT

Aims: One of the most fundamental human rights is the right to information. The aim of our study is to investigate the accuracy, reliability and comprehensibility of the videos made on YouTube about anal stenosis. However, users often do not question this information's accuracy, adequacy, and efficiency. Anal stenosis is a disease that we frequently encounter for iatrogenic reasons, especially after post hemorrhoidectomy. When many publications are reviewed, anal stenosis can be seen in 1.2%-10% of patients undergoing hemorrhoidectomy.

Methods: Our study primarily and mainly YouTube videos about anoplasty published in English were preferred. However, when sufficient videos could not be reached scientifically, other videos were translated into English and included in the study. As of March 1, 2021, "anoplasty" was typed into the youtube search engine, and Thirty-eight videos of the most relevant videos on this subject were examined.JAMA,DISCERN,GQS was used for assessment in this study.

Result: The averages of the JAMA, DISCERN, and GQS fitness parameters used in the study were found to be 2.55 (1-4), 36.58 (18-59), and 2.84 (1-5), respectively. Of the 38 videos evaluated, 7 got 5 points according to GQS, and 8 got 4 points according to JAMA. According to DISCERN, none of them got full points. It could get a maximum of 59 points. It was also a single video. A statistically significant relationship was found among these parameters (GQS, JAMA, DISCERN) ($p<.05$). There was no significant relationship between view rate, like rate, and VP index. No statistically significant relationship was found in comparing these parameters with the individual GQS, JAMA, DISCERN scores. ($p > .05$)

Conclusion: We believe that this study will contribute to those who will share about health on YouTube within the framework of more accurate and scientific rules; therefore, it will raise awareness. Primarily this is necessary and essential for videos made in the name of health.

Keywords: Anal stenosis, health, YouTube, surgery, information pollution

INTRODUCTION

One of the most fundamental human rights is the right to information. Today, people generally use the internet to access this information. Technological products; For example, smartphones, tablets, computers are intermediary elements in accessing the internet. However, users often do not question this information's accuracy, adequacy, and efficiency. The importance of social media emerges here.[1] The significance of videos on social media, especially in information sharing, has come to the fore with YouTube, Facebook, and Twitter. In social media, YouTube is an application that has more than 1 billion users and is the most referenced as a source of information. For this reason, video content is critical.[2]

In a study, it has been revealed that about half of the data searched on the internet is about health. People often search for doctors' diagnoses, treatments, and approaches through the internet.[3,4] However, informative research and presentations made with YouTube are incomplete and insufficient as a source of accurate information. In these sources, information pollution is more prominent. In addition, this information is not presented so that the other party can understand. 1.9 billion people apply for health every month to this data. However, studies have shown that the ingredient quality of these videos is also inadequate. People need more accurate information.[5-9]

This study investigated how anal stenosis is explained on YouTube.

Anal stenosis is a disease that we frequently encounter for iatrogenic reasons, especially after post hemorrhoidectomy. When many publications are reviewed, anal stenosis can be seen in 1.2%-10% of patients undergoing hemorrhoidectomy. This disease, which occurs with stenosis in the anal canal and difficulty in defecation, can also occur after inflammatory bowel diseases, anal fissures, radiotherapy, venereal diseases, chronic laxative addiction, and tuberculosis. It can also

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be seen congenitally in newborn children.[10,11] Anoplasty is one of the most preferred treatment methods in surgery in such patients.

The aim of our study is to investigate the accuracy, reliability and comprehensibility of the videos made on YouTube about anal stenosis and, also the adequacy and of its treatment and approaches.

METHODS

Because animals and humans were not included in this study, the study was not confirm by the ethics committee. All procedures were carried out in accordance with the ethical rules and the principles.

Our study primarily and mainly YouTube videos about anoplasty published in English were preferred. However, when sufficient videos could not be reached scientifically, other videos were translated into English and included in the study. As of March 1, 2021, "anoplasty" was typed into the youtube search engine, and Thirty-eight videos of the most relevant videos on this subject were examined. We cannot reach any other relevant videos on YouTube. Sponsored and advertising videos were excluded from this study. The videos deemed suitable for the study were reviewed and evaluated by an anatomist and two general surgeons. Thirty-eight videos were included in the study by examining whether they contain animation, the amount of views, the amount of likes, the amount of dislikes, sources, contents, and lengths. Videos were categorized according to their source. Surgical techniques were applied, and patient information was classified separately. Quality and conformity assessments were made by calculating the evaluated videos' Journal of American Medical Association (JAMA), DISCERN, and Global Quality scores (GQS). The amount of likes and views was multiplied to reach the video power index(vpindex). Considering these results, video popularity was evaluated.

A four-part JAMA score was used to measure the reliability and accuracy of the published video information. In this scoring, a score between one and zero is given for each section (Authority, Bibliography, Copyright, Relevance). Thus, a total value between 0 and 4 is obtained with JAMA scoring (Table 1).

Table 1. JAMA Score

JAMA scoring system rating sections	No	Yes
Authorship authors and contributors,their affiliations, and relevant credentials should be provided	0	1
Attribution references and sources for all content should be listed clearly,and all relevant copyright information should be noted	0	1
Disclosure website "ownership" should be prominently and fully disclosed,as should any sponsorship	0	1
Advertising, underwriting, commercial funding arrangements or support,or potential conflicts of Interest	0	1
Currency dates when content was posted and updated should be indicated	0	1

The DISCERN score was used for the reliability of the videos watched and the accuracy and suitability of the treatment options. This scoring consists of 16 questions. The first eight questions measure the evaluation of the reliability of the videos, the following six questions about the features of the treatment alternatives, and the 15th question about the general quality. every question is scored between 1 and 5. 16-26 points are very inadequate, 27-38 points are insufficient, 39-50 points are moderate, 51-62 points are good, and 63-75 points are excellent (Table 2).

Table 2. DISCERN Score

Section 1—Is the publication reliable?	Section 2—How good is the quality of information?
1.Are the aims clear?	9. Does it describe how each treatment works?
2.Does it achieve its aims?	10. Does it describe the benefits of each treatment?
3. Is it relevant?	11. Does it describe the risks of each treatment?
4. Is it clear what sources of information were used to compile the publication?	12. Does it describe what would happen if no treatment is used?
5. Is it clear what sources of informaiton used in the publication?	13. Does it describe how the treatment choices affect overall quality of life?
6. Is it balanced and unbiased?	14. Is it clear that there may be more than one possible treatment choice?
7. Does it provide details of additional sources of support and information?	15. Does it provide support for shared decision-making?
8. Does it refer to areas of uncertainty?	Section 3—Overall rating of the publication? 16. Based on the answers to all of the above questions, rate the overall quality of the publication as a source of information about treatment choices

We also evaluated the usefulness of patients, accessibility to information, general information flow, and adequacy level of information with the Global Quality Scoring system. In this classification, scoring is done between 1 and 5. The lowest quality videos are evaluated with 1 point and the highest with 5 points (Table 3).

Table 3. Global quality score

Score	Global score description
1	Poor quality, poor flow of the site, most information missing, not at all useful for patients
2	Generally poor quality and poor flow, some information listed but many important topics missing of very limited use to patients
3	Moderate quality, suboptimal flow, some important information is adequately discussed but others poorly discussed, somewhat useful for patients
4	Good quality and generally good flow, most of the relevant information is listed, but some topics not covered, useful for patients
5	Excellent quality and excellent flow, very useful for patients

In this study, it was evaluated whether there is a statistical relationship among vpindex, likes, dislikes, viewing rates, the amount of days to upload to the internet, as well as whether there is JAMA, DISCERN, GQS, whether there is animation content, content type and whether there is a source of uploading to the internet.

Like rates and viewing, rates give information about how people who research information on youtube like, dislike, and watch.

A video's engagement rate is calculated based on the amount of likes, dislikes, and comments it receives based on the amount of video views.

Because animals and humans were not included in this study, the study was not confirm by the ethics committee.

Statistical Analysis

Frequency and percentage analysis were used for categorical variables in the data, and mean, and standard deviation were given for descriptive statistics and numerical variables. Kolmogorov-Smirnov and Shapiro-Wilk tests were used for normal distribution tests in GQS, DISCERN, and JAMA scores. Pearson correlation analysis technique was used to evaluate the relationships between variables (GQS, JAMA, DISCERN). The level of significance in the calculations was accepted as $p < 0.05$. Analyzes were made with SPSS 24.0 software

RESULT

Thirty-eight videos about anal stenosis were reviewed in our study. There were not enough youtube videos related to this field. The average video length (Minimum-Maximum) values were 415 (18-2404) seconds. The average amount of watching videos was 38729 (2741-970175). At the same time, the amount of likes, dislikes, uploads, and video power indexes(vpindex) of these videos was also evaluated. Their averages are 140 (0-3700), 22 (0-642), 1078 (8-3429), and 64 (0-1900), respectively. Like rate and view rates were 90 (64-100) and 72 (0-2230), respectively (Table 4). It was also evaluated whether the videos included in the study were academic or not. 15.8% (6) were academic and 84.2% (32) were non-academic. These videos were also about 100% surgical technique and approach in terms of content. The averages of the JAMA, DISCERN, and GQS fitness parameters used in the study were found to be 2.55 (1-4), 36.58 (18-59), and 2.84 (1-5), respectively. Of the 38 videos evaluated, 7 got 5 points according to GQS, and 8 got 4 points according to JAMA. According to DISCERN, none of them got full points. It could get a maximum of 59 points. It was also a single video (Table 5).

Table 4. General features of videos

Features	Minimum	Maximum	Mean
Length	18	2404	415.29
Number of views	2.741	970175.000	38728.98839
Number of like	0	3700	140.05
Dislikes	0	642	22.50
Number of days of uploading	8.0	3429.0	1078.500
Like rate	64.00	100.00	90.2110
View rate	.00	2230.29	72.3246
Video Power index	.00	1900.52	63.8092

Table 5. Correlations

		GQS	DISCERN	JAMA	View ratio	Like ratio	v pik
GQS	Pearson correlation	1	.819**	.795**	.265	-.047	.265
DISCERN	Pearson correlation	.819**	1	.863**	.206	-.183	.204
JAMA	Pearson correlation	.795**	.863**	1	.243	-.301	.242

*p<.01

A statistically significant relationship was found among these parameters (GQS, JAMA, DISCERN) ($p<.05$). There was no significant relationship between view rate, like rate, and vpindex. These values were 72, 90, 64, respectively. There was no statistically significant relationship between these parameters and the individual GQS, JAMA, and DISCERN scores ($p>.05$).

DISCUSSION

Our study aims to evaluate the suitability, quality, and adequacy of YouTube videos in the approach to anal stenosis, which has not been investigated before and is frequently observed in the community after hemorrhoid surgeries. Thirty-eight videos about anal stenosis were included in this study. As it is known, YouTube has been sharing videos as a social media source since 2005. However, concerns about the adequacy of this source of information persist among physicians.[12] The fact that the internet is the first choice for health-related applications has directed the researchers to YouTube and encouraged them to research this subject. Scientists have written many publications about YouTube. Afterward, publications were started to review the articles on this subject.[13,14] In this study, 6 (15.89%) videos were created by academic sources, and independent physicians created 32 (84.2%) videos. However, the videos were not in a way that people could understand the diseases and solutions, but rather in a way that kept the surgeries in the foreground. It focused on how surgical approaches were performed rather than treatment options. While discussing treatment options with patients, this situation may create prejudice and harm the patients.[15]

In the statistical analysis, the like rate ratio was high. View rate was lower than like rate rates, vpindex was moderate. This result may be since those watching YouTube videos are not scientific professionals. In addition, health-related YouTube videos may be of interest to non-professionals, which can affect data. Most independent physicians may have uploaded these videos for advertising purposes. From this point of view, although everyone can access the videos, the quality and appropriateness of the videos should only be assessed by professional scientists.

DISCERN score was evaluated as poor in the videos included in the study. It was measured as intermediate in other scorings. 7 of the 38 videos included in the study according to GQS and eight according to JAMA received total points, and this amount was 0 in DISCERN. Although there was a statistical relationship among all three scorings, the insufficient amount of videos included in the study on YouTube may have caused the GQS and JAMA to be intermediate because DISCERN scoring is more sensitive than others. According to the DISCERN score, the amount of moderate and good videos was 16 and 3, respectively. Of these videos, six were academic, and 13 were personal doctor videos. Others were rated as inadequate and very inadequate. This situation may be because the videos were shot for marketing purposes rather than informative, and they were made of poor quality and unethical. The information in these videos emphasized that the treatment consisted of only one therapeutic option for the disease and that this approach was also successful. It did not provide other options for the patients or the researchers with information about the disease. It was not explained that this anal stenosis could be due to functional or anatomical reasons and treatment options. Information was lacking that the changes in anatomy could be caused by the deterioration of the elastic structure in the anoderm or by functional changes from the hypertonic sphincter.[16] People who researched the disease were informed about a single disease and treatment. The severity of stenosis and the importance of the surgeon's experience and information about many surgical corrective techniques are the subjects emphasized in the literature. However, this information was not presented to people who researched on the internet on YouTube.[17]

CONCLUSION

Thirty-eight videos about anoplasty that we took in this study showed that most of the videos uploaded to YouTube were published to advertise people or show their skills. Rather than informing people, these videos make presentations of one-option therapy. These presentations are also inadequate, incomplete, and unethical sharing for anoplasty. Although like rate, view rate, and vpindex rates are considered in the evaluation, the results here may not form the correct opinion about the videos. Scientific scoring (DISCERN, GQS, JAMA) and professional scientists are needed to evaluate YouTube videos more accurately. Primarily this is necessary for videos made in the name of health. We believe that this study will contribute to those who will share health videos on YouTube within the framework of more accurate and scientific rules; therefore, it will raise awareness

ETHICAL DECLARATIONS

Ethics Committee Approval: Because animals and humans were not included in this study, the study was not confirm by the ethics committee.

Informed Consent: Because animals and humans were not included in this study, informed consent not need.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

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Colonoscopy indications and findings in older adults

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ABSTRACT

Aims: The share of older population is increasing globally. Colonoscopy is a frequently used diagnostic/therapeutic procedure, no study to our knowledge comprehensively examines the indications and findings of colonoscopy in geriatric population. We aimed to reveal these in older adults.

Methods: Colonoscopy procedures performed in older adults (≥65 years), which covered a 5-year period (2017-2022), were analyzed retrospectively. Indications and findings of colonoscopies were assessed. The relationship between the indications and the associated findings was also evaluated on an indication basis.

Results: In the study, 2370 colonoscopy procedures were examined. 27.8% were performed in very old (≥75 years) patients. Colonoscopy was completed in 84.3%. Colon cleansing was not optimal in approximately one-fourth. The frequency of completion of colonoscopies and optimal cleaning were similar in the very old. Iron deficiency anemia (IDA) or fecal occult blood test (FOBT) positivity and screening colonoscopy were the common indications. Regarding indications, IDA-FOBT positivity and bleeding were more frequent, screening colonoscopy, IBD and polyp control were less frequent in the very old group. Colonoscopy was reported as normal in 42.4% of the patients, while polyps (28.3%) and diverticula (17.5%) were the common findings. Among findings tumor, diverticula and solitary rectal ulcer were higher in the very old. IDA -FOBT positivity, bleeding, and colonoscopy performed due to findings of other imaging modalities were related to diagnosis of a tumor.

Conclusion: In this study, we presented the indications and results of colonoscopy in a large number of older patients. The main indications for colonoscopy can be listed as IDA-FOBT positivity, screening colonoscopy and control of previous polyp-tumor. Near one of two colonoscopies were found to be normal, polyps and diverticula were the major pathologies in the rest. It should be emphasized that IDA -FOBT positivity, bleeding, and findings of other imaging modalities were related to tumor in colonoscopy.

Keywords: Colonoscopy, elderly, geriatric, colorectal carcinoma

INTRODUCTION

The share of the elderly population is increasing both in Turkiye and in the world.[1] There is an increase in the number of chronic diseases, malignancies, multiple drug or anticoagulant-antiaggregant use, constipation and other geriatric syndromes with aging.[2] The need for colonoscopy may arise due to aging, side effects of drugs used, or physiological or pathological changes in the gastrointestinal (GI) system associated with diseases occurring in the older population.[3] On the other hand, colonoscopy also has a very important place in the early diagnosis of colorectal carcinoma.[4]

Among the indications for colonoscopy, colorectal carcinoma screening, clinical signs and symptoms ranging from constipation to bleeding, and some laboratory findings such as iron deficiency anemia (IDA), fecal occult blood test. (FOBT) positivity can be listed.[5] Other causes of colonoscopy include endoluminal therapeutic approaches to pathologies like stenosis or angiodysplasia. Advanced age poses a risk for colorectal carcinoma, such that only 10% of diagnosed patients are younger than 50 years of age, and the diagnosis of tumors in the older population is 3 times higher than in the 50-64 age group.[6] Therefore, physicians via colonoscopy also aim to investigate whether there is underlying colorectal carcinoma in older patients.

Although colonoscopy is a frequently used diagnostic/therapeutic procedure, to the best of our knowledge, there are no studies that comprehensively evaluate the indications and findings of colonoscopy in older adults. In this study, we aimed to reveal the indications and findings of colonoscopy in older adults and to assess their associations.

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METHODS

The study was carried out with the permission of İstanbul University- Cerrahpaşa Clinical Researches Ethics Committee (Date: 06.07.2023, Decision No: 727524). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Group

In this study, we evaluated colonoscopy procedures performed in older adults (≥65 years) at a tertiary referral center's gastroenterology clinic. The endoscopy registry, which covered a 5-year period (2017-2022), was analyzed retrospectively. Both inpatient and outpatient groups were included in the study. Patients whose demographic data, colonoscopy indications, or findings could not be accessed were excluded from the study. Adults aged more than 75 years were evaluated as a subgroup (very old adults). Various studies have defined old (60-65) and very old (75-80-85) differently. The life expectancy at birth in Turkey is reported as 77 years at latest reports, and we defined very old adults as aged more than 75 years as Au AM et al.[7,8]

Data

Indications and findings of colonoscopies were evaluated in groups. In patients who underwent multiple colonoscopies with the same indication, the first procedure was included into study as a single procedure, other colonoscopies were excluded. The relationship between the indications and the associated findings was also evaluated. The analysis was performed on an indication basis by comparing the findings of colonoscopies performed with the selected indication to the findings of colonoscopies without that particular indication.

Statistical Analysis

Distribution analyzes of continuous data were assessed with the Kolmogorov-Smirnov test. Data with parametric, non-parametric, and categorical characteristics were expressed as mean ± standard deviation (SD), median (interquartile range (IQR)), and frequency, respectively. The Mann-Whitney U test was used to compare non-parametric data. The Chi-square test was used to evaluate the relationship between categorical data. A p-value < 0.05 was accepted as the limit for statistical significance. Statistical analysis was performed using SPSS 29.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The data of a total of 2370 old patients were evaluated. 27.8% of the patients were in the very old group (n: 659; age >= 75). Nearly half (48.3%) of the patients were male, and the median age was calculated as 70 (IQR: 8) for whole group, as 78 (IQR: 5, max: 97) for very old group. The frequency of female gender was higher in the very old group (55.2%-50.3% p:0.031).

While colonoscopy was completed in 84.3% of the procedures, the cecum could not be reached in 15.7%. Colon cleansing was not optimal in approximately one-fourth (25.2%) of the procedures. Inadequate cleaning was reported in 79% of patients in incomplete colonoscopies; Other causes of subtotal procedure were technical reasons, presence of a mass lesion or luminal stenosis, and bleeding. There were no differences in the very old group in terms of the frequency of completed colonoscopies and optimal cleaning (p:0.195; p:0.382).

Colonoscopy indications are summarized in **Table 1**. Iron deficiency anemia (IDA) or fecal occult blood test (FOBT) positivity are the most common indications, while screening colonoscopy was the second most common one.

Table 1. Colonoscopy indications in older population

IDA-Positive FOBT	36%	Findings of other imaging modalities	3.9%
Screening	17.4%	Chronic diarrhea	3.2%
Previous colon polyp	9.8%	Constipation	3%
Bleeding	8.2%	Malignancy (?) workup	1.2%
Previous colon tumor	7.2%	Other	2.9%
UC-CD control	7.1%		

IDA: Iron deficiency anemia; FOBT: Fecal occult blood test; UC: Ulcerative colitis; CD: Chron's disease

The very old group was further evaluated in terms of the indications. IDA-FOBT positivity was significantly more frequent in the very old group (40.1%- 34.4% p:0.010). Bleeding was also a more common indication for the very old group (11.8%-6.8% p:0:01). Screening colonoscopy, inflammatory bowel disease (UC-CD) and polyp control were seen less frequently in the very old among indications (14.7-18.5%, p:0.031; 4.6-8.1%, p:0.003; 7-10.9%, p: 0.042). Constipation, control of a previous colon tumor, chronic diarrhea, colonoscopy due to other imaging findings and malignancy workup indications were found to have similar frequencies in the very old group. When the indications were evaluated in terms of their differences between the sexes, chronic diarrhea and IDA-FOBT positivity were significantly more common in women (p:0.009, p:0.001); control of a previous colon tumor or polyp were more common in men (p:0.007, p<0.001). There were 68 patients aged ≥85 years old, IDA or FOBT positivity (n:26, 39.7%) and bleeding (n:16, 23.5%) were the main indications of colonoscopy in these patients. Screening colonoscopy was performed on 5 (%7.4) patients of this age group. The oldest patient had bleeding as an indication of colonoscopy.

Procedures performed with the indication of inflammatory bowel disease (IBD) or chronic diarrhea had a higher completion rate (p:0.003, p:0.046), while colonoscopies performed for hemorrhage and due to other imaging findings had a lower rate (p<0.001, p:0.005). Again, the frequency of insufficient cleaning was lower in the colonoscopies performed with the indication of IBD and control of polyp (p<0.001, p:0.041).

Table 2 shows the colonoscopy findings in older patients. Colonoscopy was reported as normal in 42.4% of the patients, while polyps (28.3%) and diverticula (17.5%) were the most common findings. When the findings were compared in terms of gender, the frequency of normal colonoscopy was found to be higher in females (p<0.001). Polyps (33.9-23% p<0.001), ulcerative colitis (3.7-2.1% p:0.024) and angiodysplasia were significantly more common in males (4.5-2.5% p:0.008). Although the tumor frequency was numerically higher in older male patients, the difference was not statistically significant (4.8-4.2% p:0.451). When the very old group was further evaluated in terms of colonoscopy findings, the frequency of normal colonoscopy and Crohn's disease were found to be significantly less (37.3-44.3% p:0.002; 1.1-2.5% p:0.028). The frequency of polyps did not differ in the very old group (26.4 -29%, p:0.21). Tumors, diverticula and solitary rectal ulcers were seen more frequently in the very old group (6.8-3.6%, p<0.001; 26.4-14%, p<0.001; 1.1-0.3, p:0.025 respectively). Patients aged ≥ 85 had normal colonoscopy in 26%, had polyps in 26%, diverticula in %33.8 and tumor in 14.7% (n:10). Screening colonoscopies of these were reported as normal for 2 patients, to have diverticula for 2 patients and 1 patient was diagnosed with tumor.

Table 2. Colonoscopy findings of older population

Normal	42.4%	Ulcerative colitis	2.9%
Polyp(s)	28.3%	Crohn's disease	2.1%
Diverticula	17.5%	Other inflammatory pathology	1.2%
Tumor	4.5%	Solitary rectal ulcer	0.6%
Angiodysplasia	3.5%	Ischemic colitis	0.4%
Pseudo polyp	0.9%	Other	1.9%

The relationship in-between the indications and the findings were also assessed (Figure). IDA-FOBT positivity were found to be associated with tumor and angiodysplasia (p:0.043, p:0.039 respectively). For screening indication, the frequency of normal colonoscopy was significantly higher (53% p<0.001).

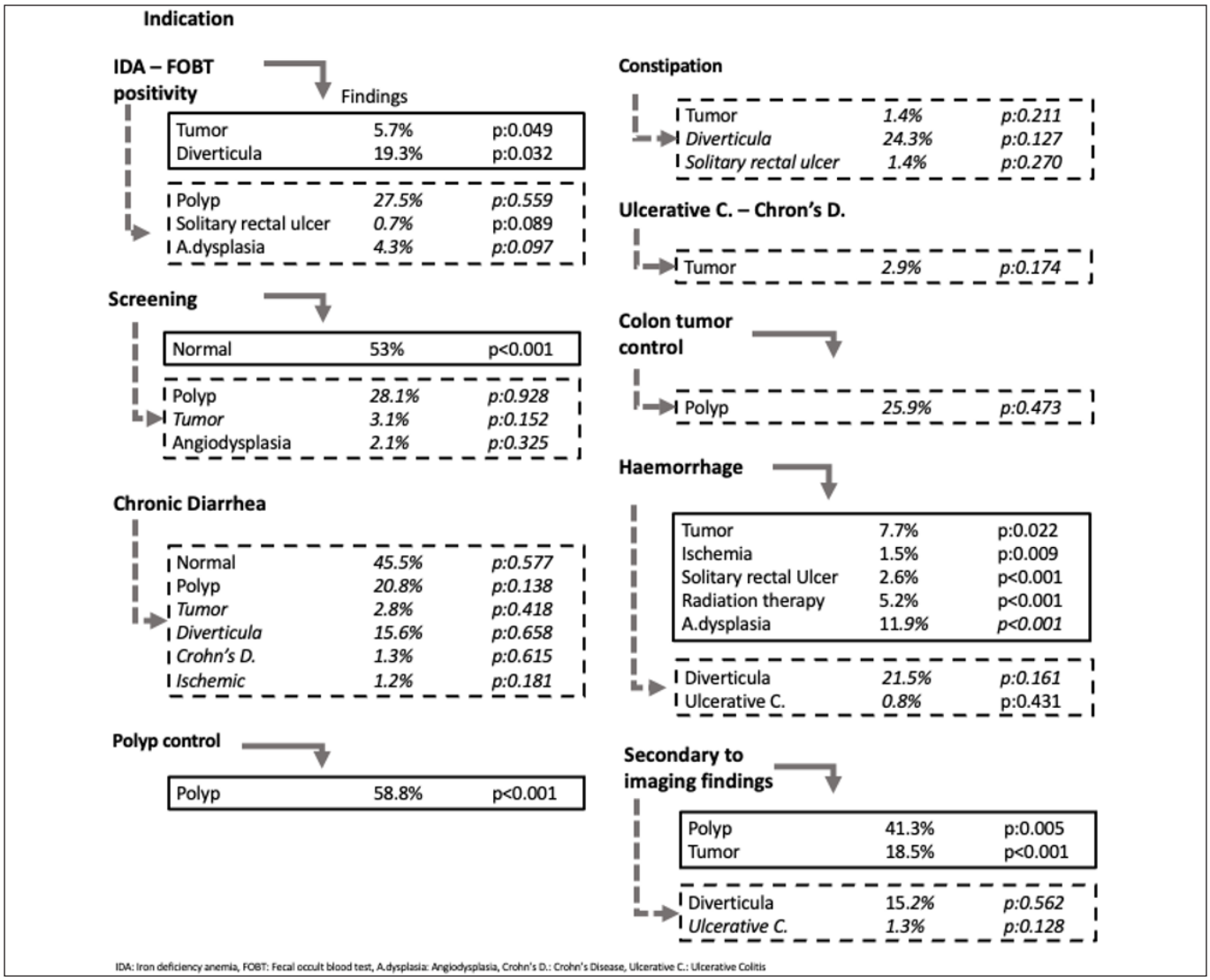

Figure. Relation between selected indications and findings.
Dotted lines enclose statistically insignificant relations, continuous lines enclose statistically significant relations, percentages refer to the frequency of given finding in the relevant indication.

Although diverticula frequency was found numerically higher in colonoscopies performed for constipation, the difference was not significant (24.3-17.3 p:0.127). While the frequencies of UC (p:0.125) or CD (0.624) were not significantly different in colonoscopies performed for chronic diarrhea, other inflammatory pathologies were found significantly frequent (7.8-1% p<0.001). Colonoscopies performed for signs of GI hemorrhage showed higher frequencies of tumor (7.7-42%, p:0.022), ischemic colitis (1.3-0.1% p:0.009), solitary rectal ulcer (2.6-0.3% p:0.002), radiation colitis (5.2 -0.4%, p<0.001) and angiodysplasia (11.9-2.8%, p<0.001). The frequency of polyp detection in the control colonoscopy of a patient with history of polyps was significantly higher (58.8-4.9 %, p<0.001), but there was no difference in terms of detecting tumor (3-4.6% p:0.254). The frequency of normal colonoscopy decreased when performed due to findings in different imaging methods (30.4%, p:0.018), while the frequency of polyps (41.3-27.7, p:0.005) and tumors (18.5-3.9%, p<0.001) increased significantly in these.

DISCUSSION

In our study, we evaluated colonoscopies performed in the older patient group in a tertiary referral center. It can be expected that the prolongation in expected life, and the increase in access to health services will cause an increase in the number of colonoscopies in the older population. Our study is valuable in terms of evaluating colonoscopy indications and findings holistically in a very high number of old patients. This is the first study, to our knowledge, that comprehensively review the indications and findings of colonoscopy in older patients.

In our patient group, colonoscopy was completed in approximately 85% of the patients. Although the rate of completion of colonoscopy varies according to the selected patient population and technical approaches in the literature, it is reported as 60-99%.[9] Being older (>80) was reported to be associated with lower completion rate10, we could not show this difference in the very old group in our study. This may be due to the fact that all procedures were performed under sedation, or it may be related to center related factors.[11] In addition to luminal causes such as mass lesions and luminal stenosis, insufficient cleaning was the leading cause of incomplete colonoscopy, which is parallel to the literature.[9,12] However, the very old group did not differ in terms of insufficient cleansing frequency. The high rate of achieving complete colonoscopy in the indications of IBD and chronic diarrhea may be due to the goal of evaluating the terminal ileum in this patient group. This suggests that in the older population, endoscopists do not force total colonoscopy in some patients considering indications. On the other hand, the higher rate of adequate cleansing in polyp control and IBD indications may be due to the repetitive colonoscopies in the history of these patients, that increased the compliance of them to bowel cleansing procedure. This probably also influenced the completion rate of colonoscopies in the indication of IBD.

Colonoscopy indications may differ in several studies depending on the study center and patient population characteristics.[13-15] In our study, the main three indications were IDA-FOBT positivity, screening colonoscopy, previous polyp-tumor history. These indications cover approximately 70% of our study group. The fact that our study was performed in a tertiary referral center probably increases the number of colonoscopies performed due to IBD or findings of different imaging studies. On the other hand, there may be relatively fewer patients who were scheduled for colonoscopy due to bleeding, for the same reason. In parallel with the increase in the frequency of additional pathologies in the very old patient group, the rate of screening colonoscopy was lower as expected. Despite screening is not recommended at the age of 85 and afterwards, there were few patients in our study that colonoscopy was performed with this indication. Unfortunately, we do not have any data regarding frailty status and performances of these patients, but it could be commented that physicians and endoscopists seems to take into account this indication if the patient is fit enough even aged ≥85 years old. The frequency of chronic diarrhea in the general population is reported to be 3-7%,[16] and although it is reported to be more common in the older patient group, it is also reported that seeking medical attention is also proportionally less.[17] It is seen as a colonoscopy indication at a similar rate in our study, in addition, this indication was found to be significantly more common in female gender, which is also supported by the literature.[18] On the other hand, considering that colon tumor is seen more in younger age males, it can be stated that the tumor and polyp control indication would be more frequent in this gender as in our study.[19]

In our study, it was observed that some kind of pathology was revealed in colonoscopy in one of two patients. The two most common pathologies were polyps and diverticula. The higher frequency of normal colonoscopy in women in the older population may be due to the predominance of relatively common pathologies such as polyps in men. Also, indications like chronic diarrhea of which majority had normal colonoscopy, and probably is related to functional diarrhea, was more frequent in older women. The tumor incidence was 4.5% in the whole group, and it was found to be significantly higher in the very old patient group. While the frequency of normal colonoscopy decreased in the very old group, pathologies such as diverticula and solitary rectal ulcer increased

in addition to the frequency of tumor. Especially the second pathology is related to the weakening of the supporting tissue in the ano-rectal region with age, and the deterioration of the synergy in defecation.[20,21]

When the relationship between indications and findings was evaluated, it was seen that IDA-FOBT positivity, GI bleeding and colonoscopy performed due to findings in different imaging modalities were associated with tumor. Other pathologies related to the indication of GI bleeding can be listed as angiodysplasia, solitary rectal ulcer and ischemic colitis. All three pathologies have the potential to be seen more frequently in the older age group and have been reported as a cause of bleeding.[22] Also post radiation therapy mucosal changes like telangiectasias-mucosal frailty is an important finding of colonoscopies performed due to hemorrhage in older patients as cumulative incidence of this increases with age. The higher frequency of finding recurrent polyps-in more than one of two procedures-suggests that surveillance colonoscopy is important in older adults. Not knowing the details of findings of the prior colonoscopy and the interval between procedures prevents us to interpret if this is due to skipped lesions or novel polyps. However, this sometimes is the case in the clinical setting and the higher frequency should be kept in mind in geriatric practice. In addition to detection of tumor, polyps and diverticula were the other common findings in colonoscopy performed due to imaging findings. Especially positron emission tomography combined cross-sectional studies can reveal colon polyps and even have the potential to differentiate the malign ones.[23] It can be assumed that this will lead to more frequent detection of these pathologies in older adults by colonoscopy, especially with the increased use of various imaging modalities.[24]

Study Limitations

Our study has some limitations. These can be listed as the retrospective design, not including pathology findings, and data from a single tertiary referral center. In addition, not knowing the comorbidities, medications, frailty and functionality of the patients prevented us from evaluating the relationship of our findings with such geriatric syndromes. However, we think that our study contributes to the literature as evaluating the indications and findings of colonoscopy holistically in a very high number of patients in the older population, and to our knowledge this is the first comprehensive study in this manner.

CONCLUSION

Eighty-five percent of colonoscopies can be completed in the older patient group, and both this rate and the frequency of insufficient cleansing seem to be similar in the very old patient group. The main indications for colonoscopy it the older population can be listed as IDA-FOBT positivity, screening colonoscopy and control of previous polyp-tumor. In these patients, near one of two colonoscopies was found to be normal, while polyps and diverticula were the major pathologies. It should be emphasized that among the indications related to tumor detection, besides IDA -FOBT positivity and gastrointestinal bleeding, colonoscopies performed due to findings of other imaging modalities can be listed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul University-Cerrahpaşa Clinical Researches Ethics Committee (Date: 06.07.2023, Decision No: 727524).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

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The diagnostic weight of hemogram parameters in diagnosis, severity, and disease duration of childhood atopic dermatitis: a thorough evidence-focused study

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ABSTRACT

Aims: We aimed to assess the association of hemogram parameters with atopic dermatitis (AD), severity of AD, and disease duration.

Methods: We included the hemogram parameters of patients under follow-up in our pediatric allergy outpatient clinic and healthy group. The blood samples were drawn when they had no complaints or after at least 30 days of infection or a drug-free period. We built H1 and H0 (null) hypotheses, subjected data to Bayesian statistics, and assessed which hemogram parameters have potential and which shall not be used, with presenting evidence levels. We split the transactions into two groups (<49 and ≥49 months old) as there is a lymphocyte predominancy before four years of age and built another model with all individuals.

Results: We included 197 AD-diagnosed patients and 150 controls in the study. Eosinophil was the significant confounder for AD, and White Blood Cell Count, Absolute Neutrophil Count, Platelet Count, and Red Cell Distribution Width (RDW)/Platelet Ratio were independent of AD. Eosinophil/Lymphocyte Ratio (ELR) was correlated with SCORAD index (anecdotal evidence) under four years old, ELR and total IgE in older four years old, and ELR and Eosinophil/Neutrophil Ratio in all age groups. None of the hemogram parameters were correlated with disease duration in our under-4-year-old patient group. However, there was anecdotal evidence for RDW correlation with disease duration in the older four years group. Age, Neutrophil/Lymphocyte Ratio, and Platelet/Lymphocyte Ratio had a strong association with disease duration.

Conclusion: We presented which hemogram parameter could be used and should not be used in children for AD diagnosis and AD follow-up. Multicenter studies are needed for the final conclusion.

Keywords: Atopic dermatitis, hemogram, parameters, children

INTRODUCTION

Atopic dermatitis (AD) is a chronic and recurrent skin condition commonly linked to a combination of genetic susceptibility, immune system response, and environmental factors.[1,2] While studies have shown that it can affect all age groups, it has been emphasized that it is more common in childhood.[3] One of the scales used to assess the severity of the disease is the Scoring Atopic Dermatitis (SCORAD) index. According to this scale, patients with a score below 25 have a mild, those between 25 and 50 have a moderate, and those above 50 have a severe form of the disease.[4]

While the barrier dysfunction in the skin and abnormal immune response resulting in local inflammation play a significant role in AD development, recent studies have emphasized the importance of systemic inflammation.[5-7] Previous studies emphasized that various cells and cytokines play a role in AD pathogenesis.[8,9] Also, some studies draw attention to the relationship between the severity of the disease and various substances such as serum thymus and activation-regulated chemokines and serum interleukin (IL)- 10, IL-17, and IL-23 levels.[9,10] Neutrophils, lymphocytes, and platelets are prominent parameters involved in inflammation and can be easily measured through hemogram tests. Biomarkers created from complete blood count values not only form the basis for allergy research but also underpin many studies in various other disciplines.[11-13] Studies conducted in pediatric patients with AD have also drawn attention to the relationship between serum total IgE, eosinophil, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and eosinophil/lymphocyte ratio (ELR) levels and AD.[14-16] It has been demonstrated that neutrophilic inflammation is linked to

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eosinophilic inflammation in patients with AD.[15] In this study involving 91 AD patients, the authors determined that there was a relationship between the severity of AD and the neutrophil count, where the lymphocyte count had a negative correlation with the disease severity.[15] This study aimed to assess which complete blood count parameters are significant and which are independent factors on diagnosis, disease severity, and disease duration in pediatric patients with AD.

METHODS

The study was carried out with the permission of Dr. Lutfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 29.03.2023, Decision No: 2023/514/246/23). All procedures in the study were performed in accordance with ethical rules and the principles of the Declaration of Helsinki.

We conducted this case-control study retrospectively between December 2022 and March 2023, including a total of 196 patients who were followed-up with AD in the pediatric allergy clinic and 150 healthy controls, without any chronic or allergic diseases who presented to the pediatric clinic for routine follow-up without active complaints or infections. We recorded the patients' clinical assessments, SCORAD index data, disease duration, serum total IgE and complete blood count parameters (White Blood Cell Count (WBC), Mean Corpuscular Volume (MCV), Absolute Neutrophil Count (NC), Absolute Lymphocyte Count (LC), Absolute Eosinophil Count (EC), percentage of eosinophils (E%), Red Cell Distribution Width (RDW %), Absolute Platelet Count (PC), Platelet Distribution Width (PDW), Mean Platelet Volume (MPV), NLR, PLR, ELR, Eosinophil/Neutrophil Ratio (ENR), Platelet/Neutrophil Ratio (PNR), Red Cell Distribution Width/Platelet Ratio (RDW/P)) from hospital records. The patient group was diagnosed with AD by a pediatric allergy specialist based on the Hanifin and Rajka criteria. The clinical severity of AD was scored using the SCORAD index. Based on this index, AD was categorized as mild (0-24.9), moderate (25-50), and severe (>50).[17] Because lymphocyte dominance is present in children under the age of four, patients were divided into two groups: Those under four years old (<49 months) and those four years and older (≥49 months). Patients with concomitant chronic inflammatory skin infections during their application, those with systemic infection symptoms receiving antibiotic treatment, those with anemia or receiving treatment due to anemia, and those receiving topical or systemic glucocorticoid therapy and multivitamin supplements within the last month were excluded from the study. In our country, iron and vitamin D prophylaxis is given to children under 1. Considering the possible effects of these drugs on hemogram parameters, we kept the control group large and paid attention to randomization. The parameters WBC, MCV, NC, LC, EC, E%, RDW, PC, PDW, and MPV were recorded from the individuals' complete blood count results. The Neutrophil/Lymphocyte Ratio (NLR) was obtained by dividing NC by LC; the PLR by dividing PC by LC; the ELR by dividing EC by LC; the ENR by dividing EC by NC; the PNR by dividing PC by NC; and the RDW/P by dividing RDW by PC. The measurements of hemogram parameters were performed using the Coulter Hmx Hematology Analysis Device. Serum total IgE was measured by nephelometric method with Siemens Healthcare Diagnostics Products, Marburg, Germany.

Statistical Analysis

Data is interpreted as mean+/-sd, median (Interquartile range), and n(%) regarding the distribution and data type. We used the Kolmogorov-Smirnov test, skewness, kurtosis, and Q-Q plot to conclude normal distribution.

We used Bayesian Kendall's tau and Bayesian Pearson tests to calculate H1 (difference) and H0 (null) hypotheses and interpreted BF_{10} evidence as anecdotal (BF_{10}>1), moderate (BF_{10}>3), strong (BF_{10}>10), very strong (BF_{10}>30) and extreme (BF_{10}>100) for H1 hypothesis. We interpreted BF_{10} evidence as anecdotal (BF_{10}<0.9), moderate (BF_{10}<0.3), and strong (BF_{10}<0.1) evidence for the H0 hypothesis. The stretched beta prior width was assumed 1 for bayesian correlation calculations. We transformed the data with logarithms, BOXCOX transformation, square root, or exponential.

We used a generalized linear model (GLM) for multivariate calculations to assess confounding factors among potential factors with the "backward elimination" method and interpreted the results with a graphic and an estimated marginal means table. P<0.05 were considered for statistical significance.

RESULTS

We included 197 AD-diagnosed patients (median age 28.0 months (11.0-59.0) and 150 control (median age 37 (16.8-68.5)) in the study. The patient and control groups, according to the age of individuals, are provided in Table 1. The mean diagnosis age was 8 months (1-40), and the follow up time 8 months (5-18). The mean SCORAD score was 27.2±11.1 in < 4 years and 26.6±11.9 in ≥ 4 years age group. The two groups were comparable regarding age (p>0.05, Mann-Whitney U test). Female ratios were 50.8% and 50.6% in the patient and control groups, respectively (p>0.05, chi-square test). We split the transactions into two groups (<49 and ≥49 months old) as there is a lymphocyte predominancy under four years.

Table 1 . The patient and the control groups regarding the individuals' age

	< 49 months	≥ 49 months	Total
Patient	129	68	197
Control	100	50	150

We aimed to present evidence levels with Bayesian statistical calculations in this study. We hypothesized that complete blood count parameters had a correlation between two independent variables (H1), and the null hypothesis (H0) indicated no correlations between the variables. All the transactions focused on assessing the evidence level for both the H1 (correlation) and H0 (null) hypotheses.

Correlation Hypotheses of Hemogram Parameters with Atopic Dermatitis

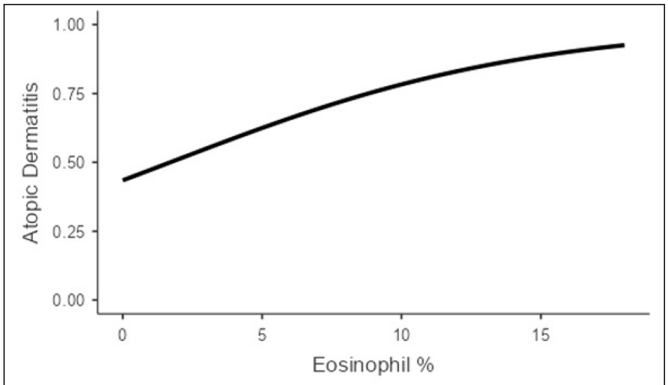
<4 years: H1 hypothesis: There was strong evidence (BF_{10}>10) that E% had correlation with AD, moderate (BF_{10}>3) evidence for EC and ENR, and anecdotal (BF_{10}>1) evidence for ELR. H0 (null) hypothesis: There was strong evidence that WBC, NC, PC, and RDW/P were independent from AD (BF_{10}<0.1), moderate evidence for LC, MPV, NLR, PLR, and PNR (BF_{10}<0.3), and anecdotal evidence for MCV, RDW, and PDW (BF<0.9) (Table 2).

As we subjected the correlated four factors (E%, ENR, EC, and ELR) as covariates in a multivariate model (GLM), likelihood ratio tests resulted in X^2:0.6 X^2:0.3, X^2:0.4, and X^2:0.3, respectively (Loglikelihood ratio test). After eliminating insignificant factors, the E% (Loglikelihood ratio X^2:8.1, p=0.005) remained the most significant confounder (GLM, R^2:0.03). Each 1% increase in E% increased AD odds by 1.17 (95%CI:1.05-1.32). The graphic and the estimated marginal means are presented in Figure 1.

Table 2. Bayesian statistics results of correlation hypotheses of hemogram parameters with atopic dermatitis

	<4 years				>4 years				All patients			
	C	AD	τ	BF_{10}	C	AD	τ	BF_{10}	C	AD	τ	BF_{10}
Age (months)	18 (10-28)	16 (9-27)	-0.043	0.138 N,M	71.5 (60.5-88.8)	67.5 (57.8-91.3)	-0.037	0.143 N,M	28 (13.3-60)	28 (11.0-59.0)	-0.014	0.076 N,*
WBC (*1000/µL)	9.7 (7.8-11.2)	9.5 (7.7-11.7)	0.020	0.096 N,*	8.5 (6.9-10.0)	8.75 (7.2-11.5)	0.087	0.315 N,M	9.3 (7.4-11.0)	9.1 (7.6-11.7)	0.044	0.147 N,M
MCV (fl)	77.3 (74.2-80.8)	78.4 (75.1-80.9)	0.077	0.383 N,A	80.5 (78.2-82.2)	80.4 (78.0-82.9)	0.036	0.142 N,M	78.4 (75.1-81.5)	79.0 (76.6-82.0)	0.061	0.299 N,M
NC (*1000/µL)	2.7 (1.8-4.3)	2.7 (2.1-3.6)	-0.018	0.094 N,*	3.7 (2.8-5.7)	4.2 (2.8-5.5)	0.014	0.123 N,M	3.1 (2.0-4.6)	2.9 (2.2-4.2)	-0.012	0.075 N,*
LC (*1000/µL)	5.3 (4.1-6.4)	5.37 (4.1-7.1)	0.058	0.203 N,M	3.3 (2.5-3.9)	3.4 (2.6-4.1)	0.052	0.169 N,M	4.4 (3.1-5.7)	4.5 (3.3-6.3)	0.040	0.133 N,M
EC (*100/µL)	2.3 (1.4-3.7)	2.8 (1.9-4.7)	0.131	6.640 M	200 (100-323)	245 (158-570)	0.134	1.204 A	210 (120-365)	270 (170-530)	0.134	68.5 **
RDW (%)	13.9 (13.2-14.8)	13.5 (12.9-14.7)	-0.084	0.509 N,A	13.1 (12.6-13.8)	13.3 (12.9-13.7)	0.020	0.127 N,M	13.7 (13.0-14.6)	13.4 (12.9-14.4)	-0.063	0.328 N,M
PC (*1000/ml)	354 (296-427)	348 (306-420)	-0.011	0.089 N,*	330 (280-413)	353 (314-409)	0.064	0.201 N,M	349 (292-422)	348 (308-418)	0.013	0.075 N,*
PDW (%)	10.4 (9.7-11.6)	10.6 (9.7-12.5)	0.082	0.477 N,A	10.4 (9.3-12.0)	10.7 (9.8-11.4)	0.043	0.152 N,M	10.4 (9.5-11.7)	10.7 (9.8-12.0)	0.069	0.431 N,A
MPV (fl)	9.8 (9.5-10.3)	9.8 (9.3-10.8)	0.030	0.108 N,M	9.6 (9.1-10.6)	9.8 (9.3-10.2)	0.050	0.166 N,M	9.8 (9.3-10.3)	9.8 (9.3-10.6)	0.032	0.105 N,M
NLR (*100)	52.9 (33.7-82.7)	49.5 (32.6-76.7)	-0.051	0.167 N,M	109 (85.5-201)	112 (90-179)	-0.015	0.124 N,M	73.6 (42.9-112)	68.5 (38.0-113)	-0.028	0.095 N,*
PLR (*100/1000)	7.5 (5.5-9.5)	7.1 (4.9-9.1)	-0.072	0.323 N,M	10.2 (8.6-14.1)	10.9 (8.5-13.3)	0.030	0.135 N,M	8.2 (6.2-10.5)	8.2 (5.9-10.7)	-0.025	0.089 N,*
ELR (*100)	4.6 (2.8-6.9)	5.3 (3.4-9.1)	0.117	2.781 A	5.5 (3.5-10.7)	7.5 (4.1-17.5)	0.104	0.483 N,A	4.8 (2.9-8.2)	5.7 (3.8-11.1)	0.108	6.371 M
ENR (*100)	7.8 (3.9-15.2)	10.5 (6.0-20.6)	0.120	3.180 M	4.9 (3.0-9.3)	6.7 (3.5-14.2)	0.115	0.648 N,A	6.7 (3.3-13.8)	9.4 (4.8-17.5)	0.118	14.5 *
PNR (*100/1000)	12.7 (8.4-18.7)	13.1 (9.2-17.3)	0.028	0.105 N,M	8.5 (6.2-13.2)	8.7 (6.4-11.4)	0.015	0.124 N,M	11.3 (7.5-17.5)	11.8 (8.1-16.4)	0.019	0.081 N,*
RDW/P (*100)	3.9 (3.3-4.9)	4.0 (3.2-4.8)	-0.014	0.091 N,*	4.0 (3.2-5.0)	3.8 (3.2-4.4)	-0.088	0.325 N,M	3.9 (3.3-5.0)	3.9 (3.2-4.5)	-0.039	0.126 N,M
E% (*100)	2.5 (1.5-3.9)	2.94 (2.0-4.8)	0.138	10.6 *	2.3 (1.4-4.0)	2.7 (1.5-6.7)	0.097	0.403 N,A	2.4 (1.4-3.9)	2.9 (1.9-5.3)	0.127	34.3 *

AD: Atopic dermatitis group, C:Control group. WBC: White Blood Cell Count, MCV: Mean Corpuscular Volume, NC: Neutrophil Count, LC: Lymphocyte Count, EC: Eosinophil Count, RDW: Red Cell Distribution Width (%), PC:Platelet Count*1000, PDW: Platelet Distribution Width (%), MPV: Mean Platelet Volume (fl), NLR: Neutrophil/Lymphocyte Ratio*100, PLR: Platelet/Lymphocyte Ratio (*100), ELR: Eosinophil/Lymphocyte Ratio (*100), ENR: Eosinophil/Neutrophil Ratio (*100), PNR: Platelet/Neutrophil Ratio (*100), RDW/P: Red Cell Distribution Width (%)/Platelet Ratio (*100), E%: Eosinophil Count / White Blood Cell Count(*100).τ: Bayesian Kendall's Rank Correlation Coefficient. The correlation and Bayesian results are rounded for a better presentation. A: Anecdotal evidence for alternative or null hypothesis, M: Moderate evidence for alternative or null hypothesis, *:Strong evidence for alternative hypothesis, **: Very strong evidence for alternative hypothesis, ***: Extreme evidence for alternative hypothesis, N*: Strong evidence for null hypothesis

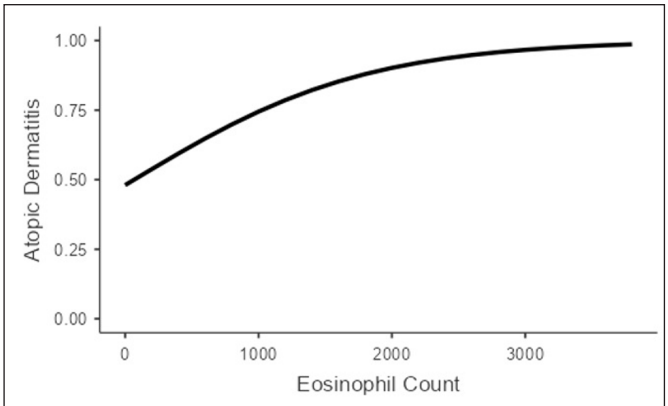


Eosinophil Count / WBC Count (*100)	Mean Atopic Dermatitis Probability (95%CI)
1.7	50.0% (42.1-57.8)
2.7	53.8% (47.0-60.5)
4.4	60.1% (52.8-66.9)

Figure 1. The association between eosinophil count / WBC count and atopic dermatitis probability and the estimated marginal means with 95% confidence intervals (95%CI)

>4 years: H1 hypothesis: There was anecdotal evidence (BF_{10}>1) that EC had correlation with AD. H0 (null) hypothesis: There was moderate evidence that WBC, MCV, NC, LC, EC, RDW, PC, MPV, NLR, PLR, PNR, and RDW/P were independent from AD (BF_{10}<0.3), and anecdotal evidence for ELR, ENR, and E% (BF<0.9) (Table 2).

As we subjected EC as a covariate in a multivariate model (GLM), the loglikelihood ratio test resulted in X^2:4.4 (p=0.035, GLM, R^2:0.03). Each 100 unit increase in EC increased AD odds by 1.12 (95%CI:1.01-1.29). The graphic and the estimated marginal means are presented in Figure 2.

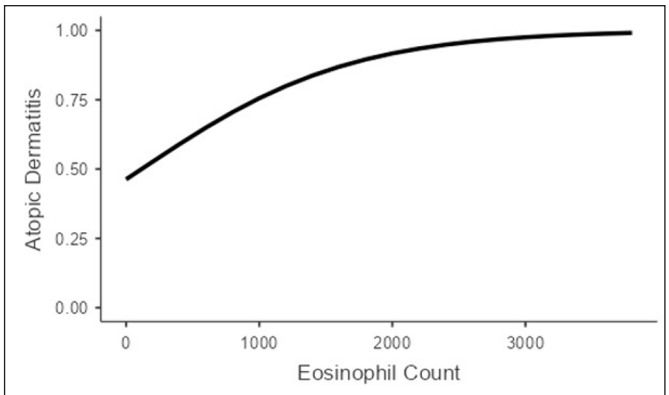


Eosinophil Count	Mean Atopic Dermatitis Probability (95%CI)
1.3	51.8 (41.0-62.4)
2.3	54.6 (45.1-63.9)
4.6	60.9 (50.7-70.3)

Figure 2. The association between eosinophil count and atopic dermatitis probability and the estimated marginal means with 95% confidence intervals (95%CI) in >4 years old group

All age groups: H1 hypothesis: There was strong evidence (BF_{10}>10) that EC, ENR, and E% had correlation with AD had correlation with AD, and moderate evidence (BF_{10}>3) for ELR. H0 (null) hypothesis: There was strong evidence that NC, PC, NLR, PLR, and PNR were independent from AD (BF_{10} 0.1), moderate evidence for WBC, MCV, LC, RDW, MPV, and RDW/P (BF_{10}<0.3), and anecdotal evidence for PDW (BF<0.9) (Table 2).

As we subjected the correlated four factors (E%, EC, ENR, and ELR) as covariates in a multivariate model (GLM), likelihood ratio tests resulted as X^2:0.0, X^2:0.4, X^2:0.1, and X^2:0.2, respectively (Loglikelihood ratio test). After eliminating insignificant factors, EC (Loglikelihood ratio X^2:12.3, p<0.001) remained the most significant confounder (GLM, R^2:0.03). Each 100 unit increase in EC increased AD odds by 1.14 (95%CI: 1.05-1.24). The graphic and the estimated marginal means are presented in Figure 3.



Eosinophil Count	Mean Atopic Dermatitis Probability (95%CI)
1.5	51.1% (44.8-57.3)
2.5	54.3% (48.7-59.7)
4.5	60.3% (54.4-66.0)

Figure 3. The association between eosinophil count and atopic dermatitis probability and the estimated marginal means with 95% confidence intervals (95%CI) in all age groups

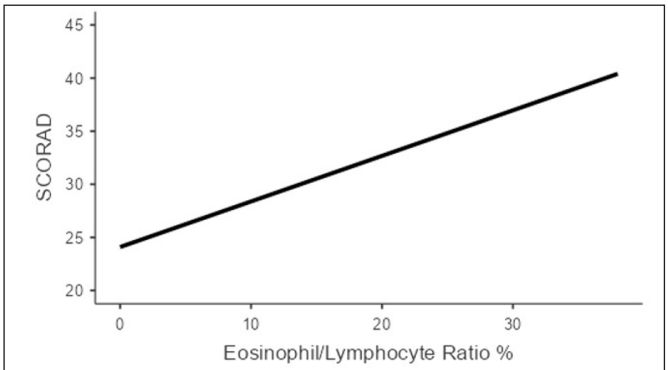
Correlation hypotheses of hemogram parameters with SCORAD index and disease duration: We subjected hemogram parameters to correlation calculations with SCORAD index and disease duration. We hypothesized H1 hypothesis (correlation) and the null (H0) hypothesis (not correlated, independence).

<4 years, SCORAD index: H1 hypothesis: There was anecdotal evidence (BF_{10}>1) that ELR had correlation with SCORAD index. H0 (null) hypothesis: There was moderate evidence (BF_{10}<0.3) that age, WBC, MCV, NC, LC, RDW, PC, PDW, MPV, NLR, ENR, PNR, RDW/P, and IgE (BF_{10}<0.3) were independent from SCORAD index, and anecdotal evidence (BF_{10}<0.9) for disease duration, EC, PLR, and E% (Table 3). Each 1% increase in ELR increased SCORAD index by 0.4 (95%CI:0.3-0.6) points in the multivariate model (loglikelihood ratio test: X^2:27.5, GLM, R^2:0.05). The graphic and the estimated marginal means are presented in Figure 4.

Table 3. Bayesian statistics results of correlation hypotheses of hemogram parameters with SCORAD index and disease duration

	<4 Years Old				>4 Years Old				All			
	SCORAD index		Disease duration		SCORAD index		Disease duration		SCORAD index		Disease duration	
	r	BF_{10}	r	BF_{10}	r	BF_{10}	r	BF_{10}	r	BF_{10}	r	BF_{10}
Disease duration	-0.157	0.52 N,A	—		-0.164	0.36 N,A	—		-0.137	0.56 N,A	—	
Age (months)	-0.073	0.15 N,M	0.427	33009 ***	0.017	0.15 N,M	-0.017	0.15 N,M	-0.060	0.13 N,M	0.455	$4.87x10^6$ ***
WBC (*1000/µL)	-0.005	0.11 N,M	-0.118	0.26 N,M	0.030	0.16 N,M	-0.099	0.21 N,M	0.004	0.09 N*	-0.130	0.47 N,A
MCV (fl)	0.047	0.13 N, M	-0.029	0.12 N, M	0.188	0.48 N,A	0.030	0.16 N,M	0.082	0.17 N,M	0.075	0.15 N,M
NC (*1000/µL)	0.053	0.13 N,M	0.079	0.16 N,M	-0.051	0.17 N,M	-0.064	0.17 N,M	0.005	0.09 N*	0.139	0.59 N,M
LC (*1000/µL)	-0.096	0.20 N,M	-0.159	0.55 N,A	-0.187	0.47 N,A	-0.198	0.55 N,A	-0.102	0.25 N,M	-0.316	2219 ***
EC (*100/µL)	0.151	0.47 N,A	-0.102	0.21 N,M	0.353	10.8 *	-0.089	0.20 N,M	0.230	17.1 *	-0.089	0.19 N,M
RDW (%)	0.010	0.11 N,M	-0.065	0.14 N,M	0.010	0.15 N,M	-0.246	1.12 A	0.012	0.09 N*	-0.157	1.01
PC (*1000/ml)	0.114	0.25 N,M	-0.072	0.15 N,M	-0.101	0.21 N,M	-0.013	0.15 N,M	0.046	0.11 N,M	-0.053	0.12 N,M
PDW (%)	-0.072	0.15 N,M	-0.116	0.26 N,M	-0.019	0.15 N,M	0.068	0.18 N,M	-0.052	0.12 N,M	-0.086	0.18 N,M
MPV (fl)	-0.092	0.19 N,M	-0.161	0.56 N,A	0.020	0.15 N,M	0.017	0.15 N,M	-0.055	0.12 N,M	-0.127	0.43 N,A
NLR (*100)	0.095	0.20 N,M	0.155	0.50 N,A	0.082	0.19 N,M	0.057	0.17 N,M	0.067	0.14 N,M	0.292	477 ***
PLR (*100/1000)	0.149	0.45 N,A	0.103	0.21 N,M	0.152	0.32 N,M	0.193	0.51 N,A	0.121	0.37 N,A	0.278	206 ***
ELR (*100)	0.195	1.24 A	-0.020	0.11 N,M	0.393	32.5 **	-0.037	0.16 N,M	0.250	45.1**	0.041	0.10 N,M
ENR (*100)	0.113	0.25 N,M	-0.133	0.34 N,A	0.337	7.26 M	-0.057	0.17 N,M	0.196	4.0 M	-0.151	0.84 N,A
PNR (*100/1000)	0.027	0.12 N,M	-0.115	0.25 N,M	0.007	0.15 N,M	0.057	0.17 N,M	0.017	0.09 N*	-0.152	0.85 N,A
RDW/P (*100/1000)	-0.116	0.26 N,M	0.033	0.12 N,M	0.104	0.22 N,M	-0.042	0.16 N,M	-0.042	0.11 N,M	-0.010	0.09 N*
E% (*100)	0.167	0.65 N,A	-0.065	0.14 N,M	0.351	10.4 *	-0.059	0.17 N,M	0.241	28.8 *	-0.045	0.11 N,M
IgE (IU/ml)	-0.039	0.12 N, M	0.040	0.12 N,M	0.442	160 ***	-0.049	0.16 N,M	0.097	0.22 N,M	0.162	1.15 A

WBC: White Blood Cell Count, MCV: Mean Corpuscular Volume, NC: Neutrophil Count, LC: Lymphocyte Count, EC: Eosinophil Count, RDW: Red Cell Distribution Width (%), PC:Platelet Count*1000, PDW: Platelet Distribution Width (%), MPV: Mean Platelet Volume (fl), NLR: Neutrophil/Lymphocyte Ratio*100, PLR: Platelet/Lymphocyte Ratio (*100), ELR: Eosinophil/Lymphocyte Ratio (*100), ENR: Eosinophil/Neutrophil Ratio (*100), PNR: Platelet/Neutrophil Ratio (*100), RDW/P: Red Cell Distribution Width (%)/ Platelet Ratio (*100), E%:Eosinophil Count / White Blood Cell Count(*100), IgE:Total Immunoglobulin E. r: Bayesian Pearson's correlation coefficient. A: Anecdotal evidence. M: moderate evidence. *: strong evidence NA: Not applicable (could not be transformed into normal-distributed data with arithmetic calculations). All calculations were performed after transforming into normal distributed data with LN (Logarithm Natural), square-root, or Box Cox calculations in order to use with Bayesian Pearson test. The correlation and Bayesian results are rounded for a better presentation. A: Anecdotal evidence for alternative or null hypothesis, M: Moderate evidence for alternative or null hypothesis, *:Strong evidence for alternative hypothesis, **: Very strong evidence for alternative hypothesis, ***: Extreme evidence for alternative hypothesis, N*: Strong evidence for null hypothesis



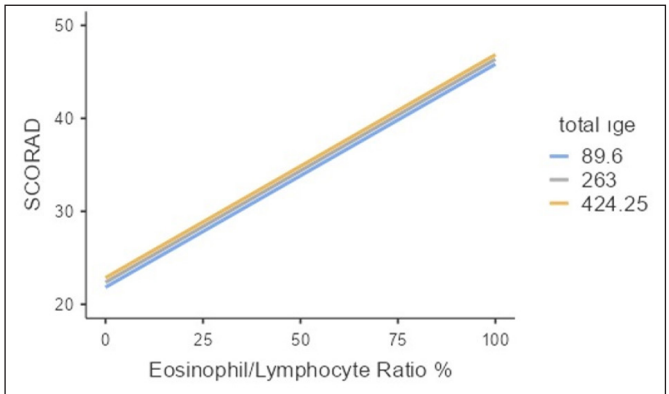
Eosinophil/Lymphocyte Ratio %	Mean SCORAD Index (95%CI)
3.4	25.5 (24.5-26.6)
5.4	26.4 (25.5-27.3)
9.1	28.0 (27.0-29.0)

Figure 4 . The association between eosinophil/ lymphocyte ratio and SCORAD index and the estimated marginal means with 95% confidence intervals (95%CI)

<4 years, disease duration: H1 hypothesis: None for disease duration. H0 (null) hypothesis: There was moderate evidence that WBC, MCV, NC, EC, RDW, PC, PDW, PLR, ELR, PNR, RDW/P, E%, and IgE (BF_{10}<0.3) were independent from disease duration, and anecdotal evidence for LC, MPV, NLR, and ENR (BF<0.9) (Table 3).

>4 years, SCORAD index: H1 hypothesis: There was extreme evidence (BF_{10}>100) that IgE had correlation with SCORAD index, strong for EC, ELR, and E% (BF_{10}>10) and moderate (BF_{10}>3) evidence for ENR. H0 (null) hypothesis: There was moderate evidence that age, WBC, NC, RDW, PC, PDW, MPV, NLR, PLR, PNR, and RDW/P (BF_{10}<0.3) were independent from SCORAD index, and anecdotal evidence for disease duration, MCV, and LC (BF<0.9) (Table 3).

As we subjected EC, ELR, IgE, and E% as covariates in a multivariate model (GLM), likelihood ratio tests resulted in X^2:0.8, X^2:15.0, X^2:7.7, X^2:0.5, respectively (Loglikelihood ratio test). After eliminating insignificant factors with the backward elimination method, ELR (X^2:38.7)and IgE (X^2:8.9) remained as significant confounders (GLM, R^2:0.247). The graphic and the estimated marginal means are presented in Figure 5.



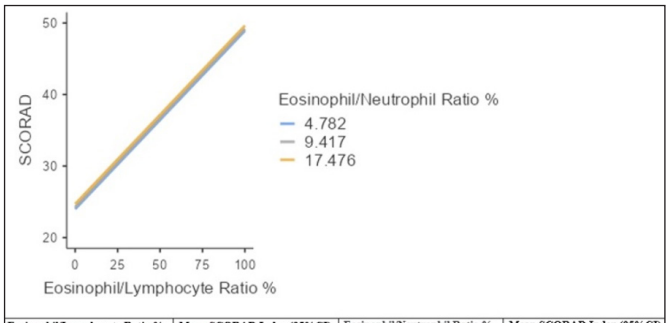
Eosinophil /Lymphocyte Ratio	Mean SCORAD index (95%CI)	Total IgE	Mean SCORAD index (95%CI)
0.041	24.1 (22.4-25.7)	89.6	25.4 (23.9-26.8)
0.075	24.9 (23.6-26.2)	263	25.9 (24.6-27.2)
0.175	27.3 (26.0-28.6)	424.3	26.4 (25.2-27.6)

Figure 5 . The association between eosinophil/ lymphocyte ratio, IgE and SCORAD index and the estimated marginal means with 95% confidence intervals (95%CI)

>4 years, disease duration: H1 hypothesis: There was anecdotal evidence (BF_{10}>1) that RDW resulted in anecdotal evidence for association with Disease duration (BF_{10}<0.9). H0 (null) hypothesis: There was moderate evidence that age, WBC, MCV, NC, EC, PC, PDW, MPV, NLR, ELR, ENR, PNR, RDW/P, E% and IgE (BF_{10}<0.3) were independent from disease duration, and anecdotal evidence for LC and PLR (BF_{10}<0.9) (Table 3).

All age groups, SCORAD index: H1 hypothesis: There was very strong evidence (BF>30) that ELR had correlation with SCORAD index, strong (BF>10) for EC and E%, and moderate (BF_{10}>3) for ENR. H0 (null) hypothesis: There was strong (BF_{10}<0.1) that evidence that WBC, NC, RDW, and PNR were independent from SCORAD index, moderate (BF_{10}<0.3) for age, MCV, LC, PC, PDW, MPV, NLR, RDW/P, and IgE, and aencdotal evidence for disease duration and PLR (BF<0.9) (Table 3).

As we subjected EC, ELR, E%, and ENR as covariates in a multivariate model (GLM), likelihood ratio tests resulted in X^2:0.3, X^2:12.1, X^2:0.6, and X^2:1.9, respectively (Loglikelihood ratio test). After eliminating insignificant factors with the backward elimination method, ELR (X^2:40.8) and ENR (X^2:3.2) remained as significant confounders (GLM, R^2:0.1). The graphic and the estimated marginal means are presented in Figure 6.



Eosinophil/Lymphocyte Ratio %	Mean SCORAD Index (95%CI)	Eosinophil/Neutrophil Ratio %	Mean SCORAD Index (95%CI)
3.8	25.5 (24.6-26.4)	4.78	26.4 (25.5-27.4)
5.7	26.0 (25.2-26.7)	9.42	26.7 (25.9-27.5)
11.1	27.3 (26.6-28.0)	17.48	27.1 (26.4-27.9)

Figure 6. The association between eosinophil/ lymphocyte ratio, eosinophil/neutrophil ratio and SCORAD index and the estimated marginal means with 95% confidence intervals (95%CI)

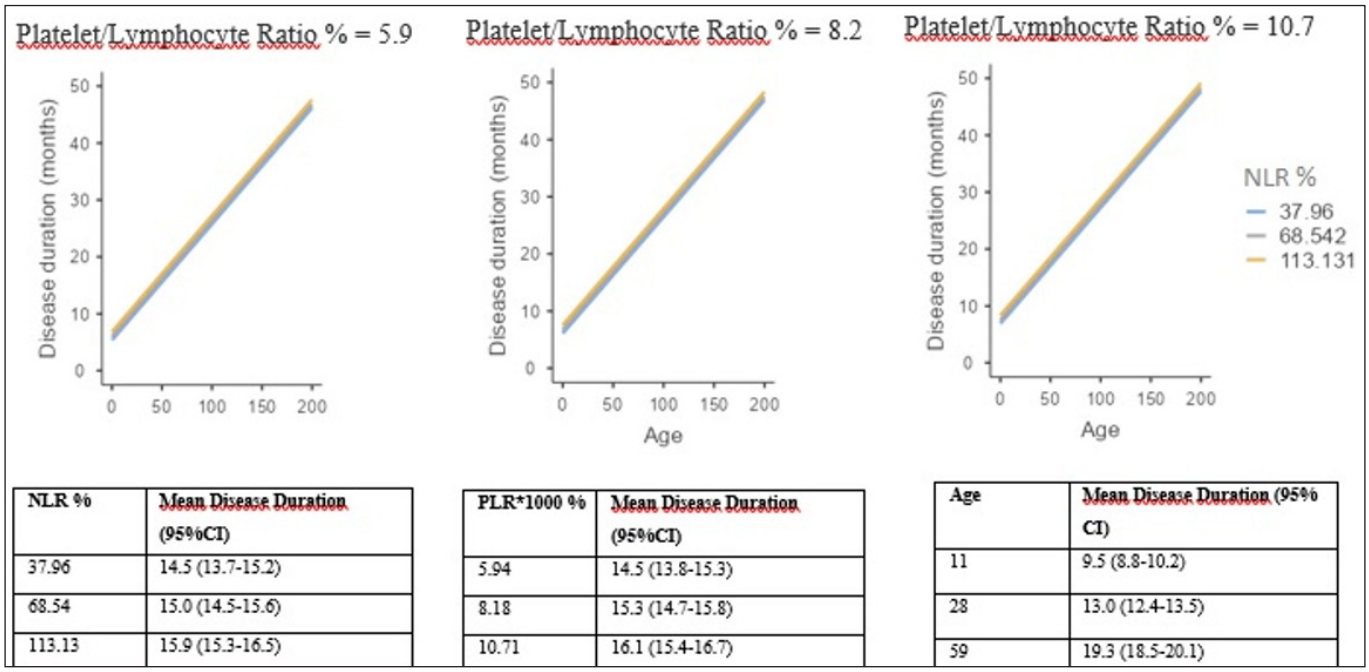
All age groups, disease duration: H1 hypothesis: There was extreme evidence (BF_{10}>100) that age, LC, NLR, and PLR had correlation with disease duration. H0 (null) hypothesis: There was moderate evidence that (BF_{10}<0.3) MCV, NC, EC, PC, PDW, ELR, and E% were independent from disease duration and anecdotal evidence (BF_{10}<0.9) for WBC, MPV, ENR, PNR, and IgE. Also, RDW gave no evidence (BF_{10}:1.01)

As we subjected age, LC, NLR, and PLR as covariates in a multivariate model (GLM), likelihood ratio tests resulted in X^2:301.7, X^2:0.3, X^2:10.4, and X^2:6.5, respectively (Loglikelihood ratio test). After eliminating insignificant factors with the backward elimination method, age (X^2:306.9), NLR (X^2:11.8) and PLR ((X^2:11.8)) remained as significant confounders (GLM, R^2:0.257). Each 1 month increase in age increased SCORAD index by 0.2 points (95%CI:0.18-0.23), 1% unit increase in NLR increased by 0.02 points (0.01-0.03), and 1% unit increase in PLR increased by 0.3 points (0.1-0.5). The graphic and the estimated marginal means are presented in Figure 7.

DISCUSSION

In the under-4-years group, there was strong evidence for E% correlation with AD, moderate evidence for EC and ENR, and anecdotal evidence for ELR, which were affected by eosinophils. In the multivariate analysis, E% was the significant confounder in our study.

In our study group, WBC, NC, PC, and RDW/P values were independent of AD disease. Similar to this result, a study reported that they did not find a correlation with AD regarding WBC, MCV, or RDW values; however, they reported increased MPV and decreased PDW in the AD group.[18] Another study (aged 14.03±13.17 months patient group) did not find significant differences regarding MPV, NLR, or



NLR %	Mean Disease Duration (95%CI)
37.96	14.5 (13.7-15.2)
68.54	15.0 (14.5-15.6)
113.13	15.9 (15.3-16.5)

PLR*1000 %	Mean Disease Duration (95%CI)
5.94	14.5 (13.8-15.3)
8.18	15.3 (14.7-15.8)
10.71	16.1 (15.4-16.7)

Age	Mean Disease Duration (95% CI)
11	9.5 (8.8-10.2)
28	13.0 (12.4-13.5)
59	19.3 (18.5-20.1)

Figure 7. The association between NLR (neutrophil/ lymphocyte ratio), PLR (platelet/ lymphocyte ratio) age and disease duration and the estimated marginal means with 95% confidence intervals (95%CI)

PLR, but they reported decreased PDW in the AD group,[19] and increased E% and decreased PDW were the significant confounder factors.[19] In another study (6.4+/-3.5 months), MPV and PLT were lower in the AD group, where WBC, NC, LC, EC, NLR, PLR, ELR, and RDW were not statistically different.[20]

In the older-4 years group, EC remained the only factor to differentiate AD from the control group with anecdotal evidence, and other parameters had moderate and anecdotal evidence for the independence hypothesis in our study group. In the all-age group, there was strong evidence for EC, ENR, and E% correlation with AD and moderate evidence for ELR, and in the multivariate analysis, the significant confounder was EC. Another considering finding was that NC, PC, NLR, PLR, and PNR were independent of AD, and MCV, RDW, MPV, and RDW/P were likely to be independent of AD (moderate evidence) in our study.

A study (patient group aged between 1 month and 18 years) reported that ELR could be a significant factor in AD diagnosis, similar to our results; however, they also reported higher NLR in the AD group.[21] However, another study (aged 5.6+/-2.8 years) reported no significant difference between the two groups regarding NLR.[22] Another study (60.0±46.5 months-aged patient group) reported increased NLR and PLR in AD but no difference regarding MPV.[6] Also, a study (7.3±3.5 years-aged patient group) reported increased NLR, PLR, EC, WBC, NC, and LC in the AD group, where they did not find any significant difference regarding RDW, MPV, and RPR.[23] Another study (2.8+/-2.8 years-aged patient group) reported increased PC, PNR, LC, and EC and decreased NC in AD, where MPV was not significantly different between the two groups.[24] An adults and adolescents-based study reported that E% and EC were higher in the AD group.[25]

There was strong evidence that NC, PC, NLR, PLR, and PNR were independent of AD and moderate evidence for WBC, MCV, LC, RDW, MPV, and RDW/P in our study. We think that as hemogram parameters are affected by the age of the children and as there is a lymphocyte predominancy in the under-4-years age group,[26] we could expect a wide range of different results regarding the age distribution of the study because of LC and the other parameters that LC affects.

A study (14.0±13.2 months-aged children) reported that MPV was higher in the severe-AD group, and PDW was lower in the mild-AD group.[19] However, another study (mean age 14 months) reported that MPV, PDW, and PLT/MPV did not correlate with AD severit.[18] Another study (mean age 6.4+/-3.5 months) reported a PLT and SCORAD correlation, where age, MPV, and IgE did not significantly alter between mild, moderate, and severe AD.[20] Likewise, another study (mean age 60.01±46.45 months) reported no significant correlation between NLR, PLR, and MPV with SCORAD.[6] Another study (mean age 8.1+/-4.8 months) reported a positive correlation with EC and E%.[27] There was anecdotal evidence that ELR correlated with the SCORAD index in our study, and other hemogram parameters were independent of SCORAD with moderate and anecdotal evidence under the 4-year age group.

In the older-4 years group, there was extreme evidence that serum total IgE, EC, ELR, and E% correlated with the SCORAD index and moderate evidence for ENR. ELR and total IgE remained significant confounders among these parameters. There was moderate evidence that age and other studied parameters were independent of the SCORAD index. In all age groups, we found strong evidence for ELR, EC, and E% and moderate for ENR that these parameters correlated with the SCORAD index. In the multivariate analysis, ELR and ENR were the significant confounders in our study. A study reported a positive correlation between serum total IgE levels, WBC, and EC with the SCORAD index.[28] Another study (Mean age 5.6+/-2.8 years) reported that NLR had a positive correlation with SCORAD, but age ELR, ENR, E%, and serum total IgE levels were not statistically different between 3 groups (mild, moderate, and severe AD).[22] Another study (mean age 2.8+/-2.8 years) reported a correlation between PLT, LC, and EC with SCORAD, where MPV, NLR, PNR, and NC did not correlate.[24]

A study (60.01±46.45 months) reported a correlation between NLR and SCORAD.6 However, we could not find evidence for a hemogram parameter correlating with disease duration in our under-4-year-old patient group. RDW had anecdotal evidence for correlating with disease duration.

In all patient groups, a study did not find any statistical difference between mild, moderate, and severe AD regarding disease duration,[22] which was consistent with our results that we did not find any evidence for the SCORAD index correlation with disease duration. Age, NLR, and PLR were significant confounders regarding disease duration in our study group. We linked this situation to decreasing lymphocytes by age[26] and topical steroids, which might increase neutrophil and platelet levels indirectly affecting the ratios. Also, we should notice that increasing age means increased disease duration.

There are conflicting data regarding hemogram parameters in the diagnosis and follow-up of AD; therefore, we aimed to present our results focusing on the evidence level. In addition, to our knowledge, since there is no data in the literature on which hemogram parameters are independent of AD diagnosis and follow-up, this study has been examining this hypothesis, and we think it will make significant contributions to the literature on this subject. One of the main limitations of our study is the inability to assess factors that could affect disease severity, such as comorbid conditions that can accompany atopic dermatitis.

CONCLUSION

Clinicians should consider that age is an independent factor for LC, which will affect hemogram parameters in AD diagnosis and severity indexes. The E% was the most significant parameter for AD diagnosis in the under-4 years age group, and EC in older-4 years and all age groups. NC, PC, NLR, PLR, and PNR were independent of AD in all age groups.

ELR had an anecdotal correlation with the SCORAD index in the under-4-year-old group. ELR and total IgE were significant confounders for SCORAD index correlation in the old group, whereas ELR and ENR were significant confounders in all age groups.

Disease duration correlated with age, NLR, and PLR, which are related to follow-up time and lymphocyte predominancy under four years old.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dr. Lutfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 29.03.2023, Decision No: 2023/514/246/23).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Determination of the frequency of food allergen sensitivity in children with atopic dermatitis

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ABSTRACT

Aims: We aimed to evaluate the frequency of food allergen sensitivity in children with atopic dermatitis (AD).

Methods: The study is a descriptive study in a retrospective design. Children aged 0-18 years with AD were included in the study. The sociodemographic characteristics, laboratory parameters and the frequency of food allergen sensitivity were evaluated. Allergen sensitization was defined as a positive allergen-specific IgE or skin prick test.

Results: The data of 295 patients with AD were evaluated. Food allergen sensitivity was detected in 34.2% (n=101) of them. Of the patients 21.4% (n=63) had a single food allergen sensitivity, whereas 12.9% (n=38) had multiple food allergen sensitivity. Egg was the most common food allergen (n=78, 26.4%). Patients with single food allergen sensitivity and multiple food allergen sensitivity were both significantly younger than those without food allergen sensitivity ($p<0.001$ for both). Total IgE values of AD patients with multiple food allergen sensitivity were significantly higher than those with single allergen sensitivity and those without food allergen sensitivity ($p=0.002$ and $p=0.003$, respectively).

Conclusion: A significant relationship was found between age, total IgE values and the presence of food allergen sensitivity in atopic dermatitis patients. Factors that may be associated with the development of food allergen sensitivity should be considered in the treatment and management of the disease in children with AD.

Keywords: Atopic dermatitis, children, allergy, food allergen sensitivity

INTRODUCTION

Atopic dermatitis (AD) is one of the most commonly seen skin diseases among children.[1] Atopic dermatitis is a chronic, recurrent and highly itchy dermatitis.[2] The prevalence of AD is increasing all over the world.[3,4] Atopic dermatitis usually develops in early childhood and is usually associated with elevated IgE values, eosinophils, and other allergic diseases.[5]

In the pathogenesis of AD, genetic factors, immune dysregulation, disruption of the skin's barrier function, environmental factors, and nutrients play important roles.1 The pathophysiological mechanisms of allergic diseases are similar to each other.[6] Atopic march; is the clinical definition in which AD that develops at an early age is accompanied by other allergic diseases such as food allergies, asthma and allergic rhinitis in older ages.[7]

Food allergy occurs as a result of immunological reactions against food proteins. Allergies to milk, eggs, soy, shellfish, and nuts are the most commonly observed types of food allergies.[8] The frequency of food allergies is increasing, and it is more commonly seen in children than adults.[9] In a meta-analysis study, the point prevalence of food allergy determined with specific IgE sensitivity was reported as 16.6% (95% CI 12.3-20.8). In the same study, the prevalence of food allergy determined with the skin prick test was reported as 5.7% (95% CI 3.9-7.4).[10]

There are studies that demonstrate a causal relationship between atopic dermatitis and the development of food allergies.[11] Food allergen-specific IgE positivity is observed in approximately half of patients with AD. Positive symptoms are observed in approximately one-third of patients with severe AD during the oral food test.[12] Similarly, type 2 inflammation is observed in patients with AD and those with food allergies.[13] In addition, with the deterioration of the barrier function of the skin in AD patients, the development of food sensitivity can be observed by absorbing the allergen nutrients by the

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skin and reaching the lower layers of the skin.[13,14] Some food allergy cases are accompanied by an impaired skin barrier even if AD is not present.[15]

It is important to evaluate possible allergy-related conditions in patients with AD and to predict the emergence of other allergic phenotypes in the future. Knowing the frequency of food allergy in patients with AD will help to better plan the prioritized approach and treatments in the management of the disease. In this context, we aimed to evaluate the frequency of food allergen sensitivity in children with atopic dermatitis in our study.

METHODS

The study was carried out with the permission of Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date:04.07.2023, Decision No: 240). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study is a descriptive study in a retrospective design. Children with AD who applied to our pediatric allergy and immunology outpatient clinic between May 2022 and May 2023 were included in the study. Since the study was retrospective in design, data from all patients diagnosed with atopic dermatitis in the hospital database within a 1-year period were analyzed for the study. Patients with a diagnosis of a skin disease other than AD were excluded from the study.

Measures

Children's sociodemographic characteristics (age, gender), laboratory parameters (eosinophils, total IgE values), food allergen sensitizations were examined.

For the food allergen-specific IgE measurements, ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) was used. Specific IgE values, equal to or greater than 0.35 kU/L, were considered as positive. Skin prick test was performed to the patients who had negative results for allergen specific IgE. Epidermal skin prick tests were performed with the use of allergen extracts (ALK-Abello, Madrid, Spain) along with a positive control (10 mg/dl of histamine phosphate) and a negative control (0.9% sterile saline). Horizontal and vertical measurements were performed for the indurations. Indurations were considered positive, if the average diameter at least 3 mm greater than the negative control.

Allergen sensitization was defined as a positive allergen-specific IgE or skin prick test. The food allergen sensitization was confirmed with clinical history (including dietary history, maternal dietary history for breastfed infants) and physical examination of patients, and food elimination and food provocation tests.

Statistical Analysis

SPSS (Statistical Package for Social Sciences for Windows 25.0 program was used for the analysis and the recording of data. Descriptive data was presented with median values, interquartile range, numbers (n) and percentages (%). For the comprasion of continuous variables that non-normally distributed; Kruskal Wallis test was used for more than two groups and Mann Whitney U test was used for two groups. The statistical significance level was set at $p<0.05$.

RESULTS

In the study, data from 295 pediatric patients diagnosed with atopic dermatitis (AD) were evaluated. Among these patients, 52.9% (n=156) were male, and 47.1% (n=139) were female. The median age was 3 years (1-7). Eosinophil and total IgE values of the patients were examined. The median values of absolute eosinophils and eosinophils (%) were 360.0 103/µL (210.0-600.0) and 4.2% (2.6-6.9), respectively. The median total IgE value was 88.0 IU/ml (22.0-304.0) (Table 1).

Table 1. Eosinophil and total IgE values of atopic dermatitis patients

	Median (IQR)
Eosinophil (10^3/ul)	360.0 (210.0-600.0)
Eosinophil (%)	4.2 (2.6-6.9)
Total IgE (IU/ml)	88.0 (22.0-304.0)

IQR:Interquartile range

The sensitization to food allergens in AD patients was evaluated. Egg allergy was the most common allergen among the patients (n=78, 26.4%). The frequencies of sensitization to cow's milk, peanut and hazelnut allergens were 12.2% (n=36), 9.5% (n=28) and 4.1% (n=12), respectively. Three patients had walnut and two patients had pistachio allergen sensitization (Table 2).

Table 2. Distribution of food allergen sensitization in atopic dermatitis patients

Allergen sensitization	n	%
Egg	78	26.4
Cow's milk	36	12.2
Peanut	28	9.5
Hazelnut	12	4.1
Walnut	3	1.0
Pistachios	2	0.7

The frequency of single and multiple food allergen sensitization in AD patients was also evaluated in the study. Food allergen sensitization was detected in 34.2% (n=101) of the patients. Of the patients 21.4% (n=63) had a single food allergen sensitization. Of the patients 12.9% (n=38) had multiple allergen to sensitization (Table 3).

Both egg and cow's milk allergen sensitization was seen in 6.1% (n=18), egg and nuts allergen sensitization was seen in 2.0% (n=6), and egg, cow's milk and nuts allergen sensitization was seen in 4.8% (n=14) of patients with multiple allergen sensitization (Figure).

Table 3. Frequency of single and multiple food allergen sensitization in atopic dermatitis patients.

Allergen sensitization	N	%
No	194	65.8
Yes	101	34.2
Single allergen sensitization	63	21.4
Multiple allergen sensitization	38	12.9

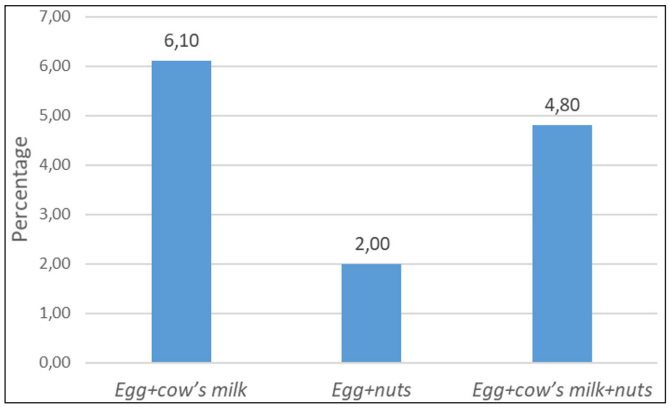

Figure. Frequency of multiple food allergen sensitization.

A significant relationship was found between age, total IgE values and the presence of food allergen sensitization in AD patients. Patients with single food allergen sensitization and multiple food allergen sensitization were both significantly younger than those without food allergen sensitization (p<0.001 for both). There was no significant difference between the median age values of those with single food allergen sensitization and multiple food allergen sensitization (p=0.878). Total IgE values of AD patients with multiple food allergen sensitization were significantly higher than those with single allergen sensitization and those without food allergen sensitization (p=0.002 and p=0.003, respectively). There was no significant difference in total IgE values between those without food allergen sensitization and those with single food allergen sensitization (p=0.606). There was no significant relationship between eosinophil values and the presence of food allergen sensitization (p>0.05) (Table 4).

DISCUSSION

Atopic dermatitis is one of the most common skin diseases in children. Food allergies are also common, especially in early childhood. Foods are triggers in approximately 20-30% of patients with moderate to severe AD.[17] In this context, we evaluated the frequency of food allergen sensitization in children with AD.

There is increasing evidence in the literature that AD predisposes to food allergy.[18,19] It is recommended that food allergen-specific skin tests or specific IgEs be performed in all children under 5 years of age, especially those with moderate to severe AD who do not respond to topical treatment.[18] In our study, 34.2% (n=101) of the children had food allergen sensitization. The frequency of food allergen sensitization was found to be mostly against eggs (26.4%), cow's milk (12.2%), and peanuts (9.5%). In a study in the literature, the frequency of food allergy in children with AD was reported as 27%. In the same study, allergies to eggs (21%), peanuts (15%) and milk (8%) were the most common, similar to our study.[20] In a study conducted in our country, the frequency of food allergen sensitization in children with AD was reported as 59%. In the same study, the most common allergens were egg white (39%), egg yolk (31%), cow's milk (13%) and wheat flour (5%).[21] The fact that the frequency of food allergen sensitization was found to be lower in our study than in the other study in our country may be due to the fact that clinical severity scores of AD patients were not performed in our study. In addition, according to studies, food allergen sensitization was reported more frequently in patients with more severe AD than in mild AD patients. The difference between study results may also be related to the clinical severity of AD patients.[21,22] In a study conducted in our country in 2012, the frequency of food allergen sensitization in children with asthma and rhinitis was observed to be 5.8%. When compared with the results of our study (34.2%), it can be considered that over the years, there has been an increase in food allergen sensitivity in children. There is a need for community-based prospective studies in this field.

Table 4. The relationship between single and multiple food allergen sensitization and age, eosinophil and total IgE in atopic dermatitis patients

	No sensitization (n=194)	Single allergen sensitization (n=63)	Multiple allergen sensitization (n=38)	P value*
	Median (IQR)	Median (IQR)	Median (IQR)	
Age (years)	5.0 (2.0-8.0)	2.0 (1.0-4.0)	2.0 (1.0-3.0)	<0.001
Eosinophil (10^3/ul)	350.0 (210.0-540.0)	400.0 (180.0-730.0)	415.0 (220.0-620.0)	0.371
Eosinophil (%)	4.1 (2.6-6.7)	4.7 (2.5-7.8)	4.5 (2.5-7.0)	0.515
Total IgE (IU/ml)	82.0 (19.0-301.0)	52.0 (20.0-211.0)	201.0 (88.0-400.0)	0.005

IQR:Interquartile range, *Kruskal Wallis test

In our study, 21.4% of the patients had single food allergen sensitization, and 12.9% had multiple allergen sensitization. The majority of those with multiple allergen sensitization exhibited a combination of egg and milk allergen sensitization. In a study conducted in our country, 38% of children with AD had an allergy to a single food, whereas multiple allergen sensitization was found in 21% of AD patients.[21] Although the frequency of single and multiple food allergen sensitization was found to be higher than in our patients, the ratio of the frequency of single and multiple food allergen sensitization to each other is similar to that in our study.

In our study, the ages of both patients with single and multiple food allergen sensitization were significantly lower than those without food allergy. There was no difference in age between those with multiple food allergen sensitization and those with a single food allergen sensitization. In a study, children with AD with food allergen sensitization were mostly in the younger age group, although statistical significance was not observed.[21] Similarly, in a different study, the risk of developing food allergy was reported to be higher in AD patients under the age of 2 years.[23] Since the development of food allergen sensitization is seen at younger ages in AD patients, especially younger age groups should be followed up for the development of allergy in clinical follow-up.

In our study, total IgE values of AD patients with multiple food allergen sensitization were significantly higher than those with single allergen positivity and those without food allergen sensitization. Since IgE plays a role both in the pathogenesis of AD and in the pathogenesis of food allergy,[5,24,25] it is expected that total IgE levels are higher in AD patients with food allergen sensitization, and this elevation is more pronounced in those with multiple food allergen sensitization. In the light of our study results; there is a need for multicenter studies to evaluate some clinical factors such as the clinical severity of AD and the duration of the disease, and to clarify other factors that may be associated with the development of food allergen sensitization in AD patients.

Limitations and Strengths

The fact that our study was conducted in a single center creates a limitation in terms of the generalizability of the results. In addition, the lack of clinical severity scores of AD patients may have caused to find a lower rate of food allergen sensitization in AD patients compared to the literature. This is another limitation of our study. In addition, the evaluation of the frequency of food allergen sensitization in children with AD, the presence of multiple food allergen sensitization and the factors associated with the presence of food allergen sensitization contributes to the literature with a broad perspective. This is the strength of the study.

CONCLUSION

In the study we conducted in children with AD, approximately one out of every three children (34.2%) had food allergen sensitivity. The frequency of multiple food allergen sensitivity was 12.9%. The frequency of food allergen sensitivity was found to be mostly against eggs (26.4%), cow's milk (12.2%), and peanuts (9.5%). A significant correlation was found between age, total IgE values and the presence of food allergen sensitivity in AD patients. Children with food allergen sensitivity had significantly lower age and higher total IgE values. Factors that may be associated with the development of food allergen sensitivity should be considered in the treatment and management of the disease in children with AD. Thus, preventive measures can be taken more quickly and practically in children who are more prone to the development of food allergies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date:04.07.2023, Decision No: 240).

Informed Consent: Because the study was conducted retrospectively, no written informed consent form was obtained from parents and the patients.

Referee Evaluation Process: Externally peer reviewed.

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Original Article

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The evaluation of tear production and dry eye symptoms in patients with osteoporosis

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ABSTARCT

Aims: Osteoporosis is a systemic skeletal disorder characterized by decreased bone mass, compromised bone density and strength. Dry eye is a common disease of the ocular surface characterized by tear film instability with ocular discomfort, pain, and visual disturbances. Both conditions share risk factors, including age, gender, and hormonal factors. In this study, our aim is to assess the tear production and dry eye symptoms in patients with osteoporosis and compare their results a control group without osteoporosis.

Methods: In this cross-sectional study, we evaluated 32 osteoporosis patients and 30 age-matched controls without osteoporosis. Tear production was assessed using Schirmer test and the symptoms of dry eye using Ocular Surface Disease Index (OSDI) questionnaire. The results of both groups were compared.

Results: The mean age of the osteoporosis group was 61.4±4.9 years, and the mean age of the control group was 57.7±6.4 years (p:0.224). The Schirmer test results were 12.3±7.4 mm for the osteoporosis group and 23.1±13.7 mm for the control group. The Schirmer test results were significantly lower in the osteoporosis group (p:0.009). The mean OSDI scores for the osteoporosis group was 30.4±23.1 while it was 20.6±14.6 for the control group. The difference was not statistically significant (p:0.329).

Conclusion: This study reveals a potential connection between osteoporosis and dry eye. Patients with osteoporosis have lower tear production compared to control group without osteoporosis. Further research is necessary to understand this relationship and its implications.

Keywords: Osteoporosis, dry eye, Schirmer test, ocular surface disease index

INTRODUCTION

Osteoporosis is a systemic skeletal disorder characterized by decreased bone mass, compromised bone density and strength.[1,2] A bone mineral density (BMD) equal or lower than 2.5 standard deviations from the values observed in healthy, young adults is accepted as osteoporosis.[3] It impacts a substantial portion of the population, affecting individuals of varying genders, ethnic backgrounds, and is expected to rise in prevalence with the aging population.[4] It is more prevalent among women than men.[4] The clinical importance of osteoporosis primarily lies in the fragility fractures which occur as a consequence of this condition. There is a significant elevation in the risk of fractures in areas such as the proximal femur, distal radius, and vertebra.[3,5] These can cause significant morbidity, mortality and cost which makes this condition an important public health problem.

Dry eye is a common disease of the ocular surface characterized by tear film instability and often accompanied by symptoms such as ocular discomfort, pain, and visual disturbances.[1] The prevalence of dry eye disease (DED) is higher among women compared to men, and it tends to increase with advancing age.[6,7] It is accepted as a multifactorial disease with various factors contributing to its pathophysiology including ocular inflammation, environmental factors, systemic comorbidities, topical and systemic medications and lifestyle.[8,9]

These two diseases exhibit similar risk factors and epidemiological patterns. Both conditions are more prevalent in females and in patients with older age.[1] Both diseases share common underlying mechanisms including hormonal imbalances and inflammation. Osteoporosis is reported as a risk factor for dry eye development.[8] It is also frequently associated with Sjögren Syndrome, an important cause of severe dry eye with impaired tear production.[10] These data

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suggest the existence of a connection between the two diseases. Despite the possibility of a connection, there is a limited number of studies exploring the relationship between osteoporosis and dry eye. Most of these studies are population-based studies using medical records or studies using questionnaires without using tear function tests. Visual disturbances are correlated with an increased susceptibility to falls.[11] If there is a connection, by treating dry eye, it can be possible to prevent dry eye-related vision problems in osteoporotic patients which may reduce the likelihood of falls.

In this study, our aim is to assess the tear production and dry eye symptoms in patients with osteoporosis and compare their results a control group without osteoporosis.

METHODS

The study was carried out with the permission of Niğde Ömer Halisdemir University Non-interventional Clinical Research Ethics Committee (Date: 14.08.2023, Decision No: 2023/68).All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted in Niğde Ömer Halisdemir University Bor Physical Therapy and Rehabilitation Training and Research Hospital. Information regarding the procedures was provided to both the patients and the control group, and their informed consent was obtained through both written and verbal means.

The cross-sectional study involved 32 individuals diagnosed with osteoporosis and included a control group comprising 30 participants. The assessment of osteoporosis patients took place at the outpatient clinics of the department of physical medicine and rehabilitation. Osteoporosis patients aged 45 years and older were included in the study, and the diagnosis of osteoporosis was established through bone mineral density (BMD) measurements conducted using dual-energy X-ray absorptiometry (DXA). A BMD T-score of -2.5 or lower measured from hip or spine is accepted as osteoporosis. The control group encompassed 30 patients without osteoporosis who visited the outpatient clinics for musculoskeletal pain. Comprehensive systemic and ocular histories were collected, which included information about systemic illnesses, previous ocular surgeries, and ocular diseases. Individuals with pre-existing conditions such as Sjögren's syndrome, rheumatoid arthritis, corneal pathologies, or a history of corneal surgery were excluded from both study groups. Both patients and controls underwent the Schirmer test (ST) without anesthesia, along with the completion of the Ocular Surface Disease Index (OSDI) questionnaire. During the Schirmer test, a standard ST filter strip (Bio Schirmer®, Bio-Tech Vision Care, Ahmedabad, Gujarat, India) was gently placed into the lateral inferior fornix, positioned at the intersection of the middle and lateral thirds of the lower eyelid. Patients were instructed to maintain their eyes open and blink naturally. Following a five-minute interval, the filter strip was carefully removed, and the wetting of the measurement strip was documented. The results of both eyes of the patients were included in the study. The OSDI questionnaire is a is a 12-item questionnaire commonly employed in dry eye studies, providing an assessment of symptom frequency, identification of environmental triggers, and an evaluation of vision-related quality of life.[12,13] The Turkish adaptation of the OSDI questionnaire has demonstrated its validity and reliability as an effective tool for assessing ocular symptoms in dry eye. It is recommended as a practical tool in the diagnosis of dry eye for routine clinical practice and for clinical research.[14]

Statistical Analysis Statistical analysis was conducted using SPSS version 20.0 (IBM Corporation, Armonk, NY). Quantitative data were presented in the format of means±standard deviations, while qualitative data were expressed as percentages (%). The independent-samples t-test was employed to compare groups regarding age, ST values and OSDI scores. In these analyses, statistical significance was defined as p-values less than 0.05.

RESULTS

A total of 32 participants were enrolled in this study group consisting of 32 females (100%). A control group including 30 female participants constituted the control group. The mean age of the study group was 61.4±4.9 years, and the mean age of the control group was 57.7±6.4 years. There was no significant difference between the groups in terms of age (p:0.224). The Schirmer test results were 12.3±7.4 mm for the osteoporosis group and 23.1±13.7 mm for the control group. The Schirmer test results were significantly lower in the osteoporosis group (p:0.009). The mean OSDI scores for the osteoporosis group was 30.4±23.1 while it was 20.6±14.6 for the control group. The difference was not statistically significant (p:0.329).

DISCUSSION

In this cross-sectional study we found that osteoporosis patients have lower Schirmer test results compared to control group without osteoporosis. This result indicates that patients with osteoporosis have lower tear production and supports the previous studies indicating osteoporosis as a risk factor for dry eye. Although the OSDI scores are lower in the osteoporosis group the difference between the groups was not significant. While the mean value of Schirmer test remained above the commonly utilized cutoff value of 10 mm, it's noteworthy that these patients do not manifest ocular symptoms, and

their measurements are lower than those observed in the control group. Collectively, within our study group, osteoporosis patients exhibit reduced tear production and demonstrate lower symptom severity, potentially suggesting the presence of a mild form of dry eye.

Several studies have hinted at the potential connection between osteoporosis and dry eye.[8] However, most of these studies have relied on medical records or questionnaires, without utilization of tear function tests to investigate this relationship. In the existing literature, we did not come across studies that specifically investigated dry eye in osteoporosis patients using dry eye tests and subsequently compared them with a control group without osteoporosis. In a retrospective cohort study in Taiwan utilizing data from the Health Insurance Database, Jeng et al.[1] suggested that osteoporosis represents a risk factor for the subsequent onset of dry eye syndrome. While the findings of this study are consistent with our findings, a direct comparison cannot be made due to the absence of dry eye test results in that study. Another study has also identified osteoporosis as a common comorbidity in patients with Sjögren's syndrome, a condition known to be a significant cause of severe dry eye.[10] Collectively, these findings suggest a relationship between dry eye and osteoporosis.

The effect of sex hormones was suggested as a factor in the development of both osteoporosis and dry eye. Symptoms of the dry eye are frequent among postmenopausal women, and there are sex hormone receptors on the ocular surface.[15] These findings have supported the hypothesis that sex hormones could have influence on tear production.[16,17] Although we did not investigate the levels of sex hormones in the current study, we expected similar sex hormone profiles in both groups since there were only age matched female patients in the study and control groups in this study. Our results suggest factors other than sex hormones are affecting tear production in patients with osteoporosis.

Vitamin D may be another important factor in the pathogenesis of both diseases. Calcium and vitamin D are crucial for the preservation of bone health, and there appears to be a positive correlation between vitamin D deficiency and the occurrence of osteoporosis.[18] It is reported that deficiency in vitamin D could be a risk factor for the development of dry eye syndrome and deficiency in vitamin D could impair tear production.[19] Tear production measured by Schirmer test was also found to be decreased in patients with low serum 25(OH) D levels which is the active metabolite of Vitamin D.[20] Our results showing lower tear production in patients with osteoporosis support these findings. Vitamin D may play a significant role in the coexistence of these two diseases.

In individuals with osteoporosis, falls can result in subsequent disabilities and mortality, and visual impairment plays a significant role in these incidents.[1,11] Our study underscores the elevated risk of developing dry eye syndrome among osteoporosis patients. It's crucial to note that dry eye can lead to visual disturbances, potentially increasing the likelihood of falls. Raising awareness of this relationship is important to decrease the risk of falls among individuals with osteoporosis.

Limitations

There are some limitations of the current study. The study did not investigate the levels of sex hormones or vitamin D, which are potential factors in the development of both osteoporosis and dry eye. Including such measurements could provide deeper insights into the mechanisms involved. The study primarily focused on female patients, and the results may not be directly applicable to males with osteoporosis. We used the Schirmer test and the OSDI questionnaire to assess dry eye syndrome. While these tests provide valuable insights, we recognize that a more comprehensive evaluation of tear function could enhance our understanding of the relationship between osteoporosis and dry eye.

CONCLUSION

Our study reveals a potential connection between osteoporosis and dry eye, with female patients with osteoporosis showing lower tear production compared to a control group. Although symptom severity was not significantly different, this suggests a mild or asymptomatic form of dry eye in osteoporosis patients. The shared risk factors, including age and gender, hint at common underlying mechanisms. Vitamin D deficiency may also play an important role. Further investigation is necessary to provide a more comprehensive understanding of the relationship between these two conditions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Niğde Ömer Halisdemir University Non-interventional Clinical Research Ethics Committee (Date: 14.08.2023, Decision No: 2023/68).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Investigation of dermatological manifestations in maintenance hemodialysis patients

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ABSTRACT

Aims: Skin findings are common in patients with both chronic kidney disease and undergoing hemodialysis. These findings are observed as nonspecific and specific dermatological manifestations. Our study aimed to describe the characteristics of dermatologic findings of patients with end-stage renal disease undergoing maintenance hemodialysis treatment and to investigate the relationship between these findings and the demographic and clinical features of those patients.

Methods: Patients who were admitted to a private hemodialysis clinic in August 2023 were prospectively analyzed. Age, gender, type of vascular access, hemodialysis duration, etiology of end-stage renal disease, duration and frequency of hemodialysis sessions, dermatological findings, and the most recent complete blood count, parathyroid hormone, calcium, phosphorus, urea, and creatinine levels were examined and the findings were documented. Calcium x phosphorus levels were calculated. Statistical significance was accepted as $p<0.05$.

Results: A total of 43 patients with chronic kidney disease undergoing maintenance hemodialysis were included in the study. 23 (53.5%) of the patients were female and 20 (46.5%) were male. The ages of the patients ranged from 28 to 86 years (mean age: 62.79±12.63). Xerosis was the most common dermatological finding with a rate of 90.7%. Hyperpigmentation was found in 46.5%, pruritus in 41.9%, nail disorders (subungual hyperkeratosis, absent lunula, koilonychia, half and half nail, onychorrhexis) in 37.2%, pallor in 30.2% and ecchymosis in 14%. In addition, 55.8% of the patients had mucosal changes (mucosal pallor, xerostomia, oral candidiasis, black hairy tongue, burning mouth), and 27.9% had hair findings (lusterless hair, sparse hair, telogen effluvium). Pruritus was more frequent in patients with higher predialysis urea levels (173.27±49.75 mg/dl vs. 137.04±38.19 mg/dl), ($p<0.011$). Xerosis and hair findings were more common in women (100% vs. 80%, 92% vs. 0%), ($p<0.039$, $p<0.001$). Hyperpigmentation was found more frequently in patients with long-term hemodialysis duration (median: 6.50 years vs. 2.00 years), ($p<0.003$).

Conclusion: Dermatologic findings are frequently observed in patients under maintenance hemodialysis treatment and may have a negative impact on quality of life. Therefore, dermatologic evaluation should be considered an essential part of treatment in patients under maintenance hemodialysis.

Keywords: Skin findings, chronic kidney disease, hemodialysis

INTRODUCTION

Chronic kidney disease (CKD) is seen in 8.5-9.8% of prevalence worldwide and is defined as structural kidney damage or functional impairment lasting longer than 3 months.[1] Especially in end-stage renal disease (ESRD), at least one dermatological finding can be observed in 50-100% of patients.[2] Moreover, these dermatological problems adversely affect the quality of life in those patients.[2-5] Dermatological findings related to CKD may be observed both during the progression of CKD and during hemodialysis (HD). The most common nonspecific dermatological findings include itching, dryness, hyperpigmentation, nail and hair disorders, mucosal changes, pallor, ecchymosis, and uremic frost, whereas specific dermatological conditions include acquired perforating diseases, calciphylaxis, calcinosis cutis, bullous disease and nephrogenic systemic fibrosis.[2,3,6] Since the dermatologic aspect of HD is a neglected topic, in this study, we aimed to contribute to the current literature by evaluating dermatological findings in patients with ESRD under maintenance hemodialysis and investigating the relationship between dermatologic manifestations and clinical and demographic characteristics of the patients.

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METHODS

The study was carried out with the permission of Medicana International Ankara Hospital Ethics Committee (Date: 14.07.2023, Decision No: 16). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This single-center prospective cross-sectional study was conducted at a private dialysis center in Ankara in August 2023. A total of 43 patients aged ≥18 years with ESRD undergoing maintenance hemodialysis were intended to participate in the study. Written informed consent forms were obtained from the patients. Demographic characteristics, including age, gender, primary etiology and duration of CKD, as well as the duration and frequency of HD, types of access for HD, and dermatological findings, were also recorded from the registries of the dialysis center. Patients with primary dermatological diseases, those under topical treatment, and individuals with cirrhosis were excluded. Xerosis and pruritus were classified as local if they were present on the extremities or in one region and generalized if they did not fit the criteria for local involvement. Pigmentation disorders were classified as palmoplantar, diffuse, mucosal, and photosensitive areas. Nail findings (absent lunula, half and half nail, koilonyhcia, onychorrexis, Mees lines, subungual hyperkeratosis), hair findings (lusterless hair, sparse hair, telogen effluvium), and mucosal findings (mucosal pallor, xerostomia, oral candidiasis, black hairy tongue, burning mouth, macroglossia, taste changes, gingival bleeding) were screened and when more than one finding was detected for each patient, all findings were recorded.

Statistical Analysis

SPSS Version 22.0 for Windows (Statistical Package for the Social Sciences) was used for analyses of data. The normality of the numeric variables was tested by using Kolmogorov-Smirnow and skewness and kurtosis tests. Parametric and nonparametric variables were presented as mean ± standard deviation and median (minimum and maximum), respectively. Categorical variables were presented as percentages. Independent Samples T-test was used in comparisons of parametric variables. Pearson's chi-squared test and Fisher's exact test were used for comparison of categorical variables. Statistical significance was accepted as $p<0.05$.

RESULTS

A total of 43 patients were evaluated. Of these patients, 23 (53.5%) were female, and 20 (46.5%) were male. The ages of the patients ranged from 28 to 86 years (mean age: 62.79±12.63). The median HD duration was 3 (0.5-15) years. Twenty-nine patients (67.4%) received HD treatment via a functioning arteriovenous fistula, while 14 patients (32.6%) had a central venous catheter. Thirty-three patients (76.7%) underwent HD sessions three times a week, and ten patients (23.3%) received treatment twice a week. The most common comorbidities in this cohort were hypertension (HT) and diabetes mellitus (DM). Demographic and clinical characteristics of the patients are provided in Table 1.

Table 1. Demographic and clinical characteristics of the patients

	n (%) (Total n=43)
Gender	
Female	23 (53.5)
Male	20 (46.5)
Age (year)	
Mean±Sd (min-max)	62.79±12.63 (28-86)
Hemodialysis duration (year)	
Median (min-max)	3 (0.5-15)
Hemodialysis frequency	
Two times/week	10 (23.3)
Three times/week	33 (76.7)
Hemodialysis access	
Central venous catheter	14 (32.6)
Arteriovenous fistula	29 (67.4)
Co-morbidities	
None	8 (18.6)
HT	14 (32.6)
DM	6 (14)
HT+DM	13 (30.1)
HT+Thyroid disease	2 (4.7)
Primary etiology of ESRD	
Unknown	4 (9.3)
HT	12 (27.9)
DM	6 (14)
HT+DM	8 (18.6)
HT+DM+CHF	2 (4.7)
DM+Hereditary hemorrhagic telangiectasia	1 (2.3)
Nephrotic syndrome	4 (9.3)
Polycystic kidney disease	2 (4.7)
Drug	3 (7)

HT:hypertension, DM:diabetes mellitus, CHF:chronic heart failure, ESRD: end stage renal disease

Laboratory findings were analyzed in terms of leukocyte, hemoglobin, platelet, calcium, phosphorus, Ca x P, parathyroid hormone, urea and creatinine levels at the time of admission and the mean levels were determined. Ca x P levels of the patients are mostly lower than 55 (86%, n=37) for this reason advanced statistical analysis was not performed (Table 2).

Table 2. Laboratory findings in the patients

	Mean±Sd
WBC (cell/mcL)	7457.07±2197.44
Hemoglobin (g/dl)	10.77±2.00
Platelets (cell/ml)	212000±72588
Calcium (mg/dl)	8.09±1.01
Phosphor (mg/dl)	5.20±1.46
CaxP (mg^2/dl^2)	41.89±21.26
Parathyroid hormone (pg/ml)	367.95±225.20
Urea (mg/dl)	152.57±46.63
Creatinine (mg/dl)	8.20±2.81

All patients had at least one skin or mucosa finding (100%, n=43). Xerosis was the most common finding with a rate of 90.7% (n=39). Hyperpigmentation was found in 46.5% (n=20), pruritus in 41.9% (n=18), nail disorders in 37.2% (n=16), pallor in 30.2% (n=13) and ecchymosis in 14% (n=6). In addition, 55.8% (n=24) of the patients had mucosal changes, 27.9% (n=12) had hair findings, and 20.9% (n=9) had nail or mucosal fungal infection. None of the patients had uremic frost, keratosis pilaris, or issues at the insertion site, and no ESRD-specific dermatosis was observed except calcinosis cutis (n=1).

Xerosis and pruritus were most commonly localized in the extremities. Hyperpigmentation was observed in photo-exposed areas (face, upper extremities). Ecchymosis was mostly observed in the forearms and dorsum of the hands. The most common nail findings were the absence of lunula and subungual hyperkeratosis (14%, n=6). Among the mucosal findings, mucosal pallor (32.6%, n=14) was predominant and lusterless hair was the most common hair finding (**Table 3**), (**Figure**).

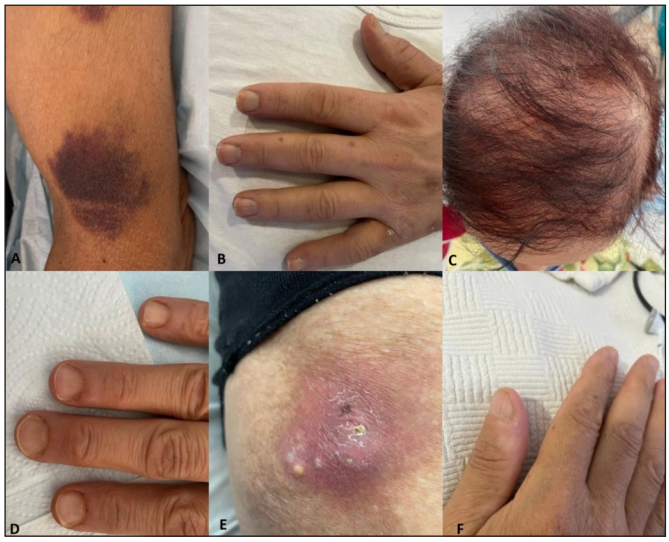

Figure. A: Ecchymosis, B: Half&half nail, C: Hair loss, D: Koilonychia, E: Calcinosis cutis, F: Absent lunula

Table 3. Dermatologic findings in the patients

	n (%) (total n=43)
Xerosis	
No	4 (9.3)
Yes	39 (90.7)
Localized	28 (65.1)
Generalized	11 (25.6)
Pruritus	
No	25 (58.1)
Yes	18 (41.9)
Localized	10 (23.3)
Generalized	8 (18.6)
Pallor	
No	30 (69.8)
Yes	13 (30.2)
Hyperpigmentation	
No	23 (53.5)
Yes	20 (46.5)
Ecchymosis	
No	37 (86)
Yes	6 (14)
Nail findings*	
No	27 (62.8)
Yes	16 (37.2)
Absent lunula	6 (14)
Subungual hyperkeratosis	6 (14)
Koilonychia	3 (7)
Half and half nail	2 (4.7)
Onychorrhexis	2 (4.7)
Mucosal findings*	
No	19 (44.2)
Yes	24 (55.8)
Pallor of mucosa	14 (32.6)
Xerostomia	10 (23.3)
Oral candidiasis	6 (14)
Black hairy tongue	6 (14)
Burning mouth	1 (2.3)
Hair findings*	
No	31 (72.1)
Yes	12 (27.9)
Lusterless hair	9 (20.9)
Telogen effluvium	4 (9.3)
Sparse hair	2 (4.7)
Calcinosis cutis	
No	42 (97.7)
Yes	1 (2.3)
Infections	
No	30 (69.8)
Yes	13 (30.2)

*Patients have more than one finding.

There was a statistically significant relationship between xerosis and hair findings and gender. Xerosis and hair findings were more common in women (100% vs. 80%, 92% vs. 0%), (p<0.039, p<0.001). The mean age in patients with nail finding-free (65.56±13.87 years) was higher compared to patients with nail findings (58.13±8.77 years, p<0.037). The patients with mucosal findings (mean age: 66.38±11.44 years) were older than patients with non-mucosal findings (mean age: 58.13±8.77 years, p<0.038).

Hyperpigmentation was found more frequently in patients with long-term hemodialysis and the difference was statistically significant (median: 6.50 years vs. 2.00 years, p<0.003).

The mean urea level was higher in patients with pruritus (173.27±49.75 mg/dl vs. 137.04±38.19 mg/dl), (p<0.011), whereas urea level was lower in patients with xerosis compared to patients without xerosis (147.47±44.82 mg/dl vs. 201.00±38.49 mg/dl), (p<0.027). Phosphorus, and creatinine levels were lower in patients with xerosis compared to those without xerosis (5.10±1.49 mg/dl vs. 6.24±0.74 mg/dl), (8.04±2.91 mg/dl vs. 9.72±0.74 mg/dl), (p<0.041, p<0.013, respectively). The mean hemoglobin level and the mean creatinine level were lower in patients with ecchymosis (9.61±0.65 g/dl vs. 10.95±2.06 g/dl), (5.96±1.88 mg/dl vs. 8.58±2.79 mg/dl), (p<0.005, p<0.034, respectively) (Table 4).

DISCUSSION

In the current study, skin and mucosal findings were evaluated in patients with ESRD patients undergoing HD and it was observed that all patients had at least one skin or mucosa finding. The most common finding was xerosis with 90.7%. Xerosis was most commonly localized and seen on the extremities, whereas in more severe cases, it was observed all over the body. In other studies, xerosis was reported with rates ranging from 54.8% to 96%.[7-12] In a meta-analysis of studies conducted in patients with ESRD in Iran, results ranging from 7.3 to 78.3% were reported.[13] Conducting the studies in different seasons and environmental factors may explain these differences. In other studies reported from Turkey, the prevalence of xerosis was found to be 87% and 98%, similar to our study.[14,15] It has been suggested that dryness is due to a defect in the structure of the stratum corneum or a functional abnormality in the eccrine sweat glands. However, it has been reported in other studies that there is no correlation between dry skin and water content of the stratum corneum[16] and changes in vitamin A metabolism, excessive diuretic use and chemical irritations are among the factors blamed for xerosis.[11,16] In our study, xerosis was found more frequently in women and urea, creatinine and phosphorus levels were lower in patients compared to those without xerosis.

Pruritus is another finding that affects the quality of life negatively. Pruritus was found with a rate of 41.9% in our study; localized and generalized pruritus rates were found to be close to each other. Pruritus is observed at a higher rate in patients on dialysis among patients.16 It has been reported to be observed more frequently in HD and to occur at a higher rate, especially as the duration of HD increases.[4] In other studies, rates ranging between 19.3-58.3% have been reported.[7-15] Inadequate dialysis, hyperparathyroidism, calcium and phosphorus dysregulation, xerosis, elevated magnesium and aluminum levels, anemia, male gender, hypervitaminosis-A, increased beta-2 microglobulin levels, HLA-B35, congestive heart failure and neurological disease, sensitivity to dialysis components, mast cell proliferation, and low vitamin D levels are among the factors accused in the etiology of pruritus.[2,9] In our study, pruritus was found more frequently in patients with high urea levels. However, no relation was found between parathyroid hormone, calcium, phosphorus levels and creatinine levels and

Table 4. The relationship between demographic and laboratory characteristics of patients and dermatological findings

p value	Xerosis	Pruritus	Pallor	Hyper pigmentation	Ecchymosis	Nail findings	Mucosal findings	Hair findings
Gender [a,b]	**0.039*[a]**	0.40	0.98	0.10	0.19	0.32	0.47	**<0.001***
Age [c]	0.27	0.96	0.62	0.25	0.076	**0.037***	**0.038***	0.090
HD duration [c]	0.49	0.68	0.063	**0.003***	0.88	0.85	0.24	0.10
HD frequency [b]	>0.99	0.48	0.14	0.73	0.61	>0.99	0.73	0.24
HD access [a,b]	0.29	0.57	0.077	0.32	0.077	0.89	0.90	0.72
Calcium [c]	0.10	0.38	0.71	0.50	0.56	0.51	0.49	0.84
Phosphor [c]	**0.041***	0.29	0.75	0.68	0.74	0.95	0.37	0.16
WBC [c]	0.23	0.94	0.50	0.42	0.24	0.12	0.65	0.41
Hemoglobin [c]	0.10	0.28	0.058	0.59	**0.005***	0.74	0.75	0.79
Platelets [c]	0.43	0.87	0.54	0.81	0.45	0.55	0.27	0.24
Parathyroid hormone [c]	0.66	0.090	0.72	0.14	0.11	0.61	0.72	0.20
Urea [c]	**0.027***	**0.011***	0.67	0.16	0.30	0.74	0.68	0.47
Creatinine [c]	**0.013***	0.37	0.87	0.20	**0.034***	0.10	0.13	0.75
Xerosis [a]		0.628						

*If p value<0.05 the result is indicated in bold, HD: hemodialysis, a: Chi-squared test, b: Fisher's exact test, c: Samples t-test

pruritus. No correlation was found between dryness and pruritus. Although studies are reporting that parathyroid hormone elevation causes pruritus, the lack of correlation between parathyroid hormone, calcium, phosphorus and uremic pruritus in other studies suggests that other factors may play a role in the etiology of uremic pruritus.[9,11,17]

Pallor was found with a rate of 30.2% in our study. In other studies, rates between 3.9-60% have been reported in HD patients.[7-10,14] Pallor is generally associated with anemia and accumulation of some fat-soluble pigments and hemosiderin in the skin.6 In our study, no significant correlation was found between hemoglobin level and pallor.

Hyperpigmentation was observed in 46.5% of the patients and was localized in photosensitive areas. In previous studies, the frequency of hyperpigmentation was found between 9.2-62%.[7-11,14] The diffuse hyperpigmentation observed in the photo-exposed areas is due to increased melanin in the basal layer and this is due to poor dialyzed of β-Melanocyte stimulating hormone (β-MSH). Increased pigmentation is observed more frequently as the duration of HD increases.[16] In our study, the increase in pigmentation with long-term HD and CKD was consistent with this literature.

Ecchymosis was localized especially on the forearms and was observed more frequently in patients with low hemoglobin and creatinine values among laboratory findings. It has been reported that increased skin fragility, heparin use and high urea levels may alter platelet aggregation.[11,18] In studies, rates ranging between 9% and 60% have been reported.[10,11,18]

When nail findings were analyzed in the current study, the most common findings were the absence of lunula and subungual hyperkeratosis. Patients with nail findings were younger, but no difference was found in laboratory tests. Many nail findings may occur due to both CKD and HD. The most common nail abnormalities are half-and-half nails and the absence of lunula. Although half and half nail has been reported most frequently in studies, the most frequently reported nail abnormality in studies conducted in our country has been the absence of lunula.[14,19] The absence of a lunula is one of the most common findings in our study and may be observed in conditions other than presence of CKD. It has been found in 7.7-58.7% of patients in studies.[14,19] Some metabolic changes together with anemia are thought to be involved in its pathogenesis.15 Although half and half nail is not a specific finding in CKD, it is observed in approximately 40% of patients on HD and it is thought to develop due to increased melanocyte-stimulating hormone.[9] It has also been reported that this nail sign disappears after renal transplantation.[3] Its frequency has been reported to be 15.7-51% in different studies.[4,7,9,10,14,19] In our study, in patients with subungual hyperkeratosis this finding was compatible with fungal infection.

Mucosal findings are also frequently observed in patients on maintenance hemodialysis. In our study, mucosal pallor and dry mouth were observed most frequently. While mucosal findings were associated with anemia in one study, this relationship was not shown in our study.[11] Differently, patients with mucosal findings consisted of older patients. In a study examining oral mucosal findings, mucosal findings were found with a rate of 48%; the most common findings were dry mouth, taste disturbance and burning mouth.[20] Malnutrition, anemia, impaired salivary gland function and sensitivity to oral pathogens may play a role in the formation of these findings.[20] This situation also leads to candida infection and the development of black hairy tongue. In our study, black hairy tongue and candida stomatitis were found in patients. The frequency of candida in saliva was also found to be higher in patients on HD.[21] While macroglossia has been reported at different rates in patients with CKD, this finding was not observed in any patient in our study.[9]

Hair findings were observed only in female patients and this difference was statistically significant. Lusterless hair was the most common hair finding in maintenance hemodialysis patients. Lusterless hair is a finding frequently shown in other studies.[9-11] This finding has been tried to be explained with anemia, decreased sebum secretion and elevated parathyroid hormone.[11] In our study, there was no laboratory finding associated with lusterless hair.

The most common infections were onychomycosis (14%) and oral candida infection (14%). One patient (2.3%) had scabies. It is thought that impairment in the cellular immune system and a decrease in the number of T lymphocytes in patients with CKD facilitate the development of infection.[9]

In our study, calcinosis cutis, one of the specific dermatoses, was found in only one patient. The patient's gender was female, the lesions were located near the knee, elbow and hip joints and parathyroid hormone and calcium levels were markedly elevated. Calcinosis cutis is a benign nodular calcification caused by the accumulation of insoluble calcium deposits in the skin and subcutaneous tissue. It appears as hard papules, nodules and plaques and can be excreted through the epidermis. It is most commonly seen in periarticular areas and fingertips. Its severity is related to calcium and phosphorus levels.[6] Although other specific dermatoses including calciphylaxis, acquired perforating dermatoses, bullous disease and nephrogenic systemic fibrosis have been reported in studies, they were not found in our study.

Study Limitations

The study's sample size is relatively small, which may limit the generalizability of the findings to a larger population. The study is conducted at a single center, which may limit the diversity of patient demographics and experiences,

potentially leading to selection bias. The study lacks a control group, which would be essential for comparing the observed findings with a group of individuals not undergoing HD. The study identifies associations between certain variables and findings but does not establish causative relationships, making it difficult to draw definitive conclusions about the etiology of these findings.

CONCLUSION

Various skin, nail, hair and mucous membrane findings are observed in patients with CKD due to both renal disease and HD. At least one of these findings can be seen in patients and negatively affect quality of life. Regular follow-up of the patients is important for the detection, prevention and treatment of these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medicana International Ankara Hospital Ethics Committee (Date: 14.07.2023, Decision No: 16).

Informed Consent: Written informed consent form was obtained from the patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The effect of 18F-FDG PET/CT findings on prognosis in patients with diffuse large B cell lymphoma

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ABSTRACT

Aims: 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT), plays an important role in both staging at the time of diagnosis and follow-up of treatment response in lymphoma. Our aim was to investigate the effect of different quantitative metabolic parameters, which are not used in routine practice, on treatment response and overall survival (OS) in patients with diffuse large B-cell lymphoma.

Methods: A total of 26 patients were included in our retrospective cohort study. Deauville 5-point scale (5-PS), and cut-off values for changes in maximum standardized uptake value (SUVmax), peak SUV (SUVpeak), metabolic tumor volume (MTV) (2.5-%41- PERCIST -aort) and total lesion glycolysis index (TLG) (2.5-%41- PERCIST-aort) effect of metabolic parameters on treatment response and OS was investigated.

Results: Metabolic parameters did not predict treatment response, while TLGPERCIST (p=0.034), TLGAORT (p=0.040), MTV41 (p=0.040) and TLG41 (p=0.034) parameters were statistically significant for OS. Median OS (months) was statistically significant in TLGPERCIST groups (p=0.047). While the median OS (months) in the TLGPERCIST <4411.90 group was inaccessible, the median OS in the ≥4411.90 group was 32.00 (95%CI: 0.00-87.43) months. Median OS (months) was statistically significant in MTV41 groups (p=0.047). While median OS (months) was inaccessible in the MTV41<376.10 group, median OS in the ≥376.10 group was 32.00 (95%CI: 0.00-87.43) months.

Conclusion: The MTV41 and TLGPERCIST appear to be the best parameter to predict OS in patients diagnosed with DLBCL by 18F-FDG PET/CT.

Keywords: Diffuse large cell lymphoma, metabolic tumor volume, overall survival, PET response, total lesion glycolysis

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma and is an aggressive malignancy with heterogeneous disease morphology, biology, clinic and treatment response.[1-2] Clinical risk scores are used for prognosis.[3-5] The generally preferred treatment is rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) and a recent study showed a 2-year progression-free survival (PFS) of 75% and overall survival (OS) of 85%.[6] Positron emission tomography/computed tomography with 18F-fluorodesoxyglucose (18F-FDG PET/CT) is a favourable imaging modality for pre-treatment staging.[7] In addition, 18F-FDG PET/CT showed a high predictive value for both PFS and OS at end-of-treatment evaluation.[8] Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are the most commonly used volumetric parameters that best reflect metabolic tumor burden. In some studies, MTV and TLG have been shown to be significantly associated with clinical parameters such as OS and PFS in DLBCL patients, and tumors with high metabolic volume have been shown to have more progression or disease-related mortality.[9-12] Although volumetric parameters have prognostic significance in DLBCL patients, there is no standardized method for their calculation. Our aim was to investigate the prognostic predictive effect of different parameters in 18F-FDG PET/CT, such as clinical risk scores at diagnosis.

METHODS

Study Design

A retrospective, analytic study was performed following approval from University of Health Sciences Hamidiye Faculty of Medicine Ethics Committee (Date: 01.09.2023, Decision No: 2023/16-12). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Study Population

The data of patients with diffuse large B-cell lymphoma admitted to the adult hematology outpatient clinic between 2020 and 2022 were retrospectively analysed. Twenty-six patients who had 18F-FDG PET/CT before and after treatment were included in our study. Clinical symptoms and findings at the time of diagnosis, complete blood and biochemical parameters, tissue pathology data, and 18F-FDG PET/CT findings at the time of diagnosis and at the end of treatment were analysed retrospectively. International prognostic score (IPI), which has a predictive value in terms of OS and relapse-free survival in aggressive non-Hodgkin lymphoma, was calculated.13 Age >60 years, serum lactate dehydrogenase (LDH) concentration greater than normal, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, clinical stage III or IV and >1 extranodal disease site were scored. It was classified as low risk IPI score of zero or one, low-intermediate risk IPI score of two, high-intermediate risk IPI score of three, high risk IPI score of four or five.

Study Techniques: Radiotracer, Imaging and Processing Protocol

Patients with DLBCL were referred to the Nuclear Medicine Department for 18F-FDG PET/CT scanning before treatment. Patients were advised to fast for at least 6 hours before the scan. Patients with blood glucose levels less than 200 mg/dl were included in the study. Patients were injected intravenously with 40 MBq 18F-FDG per kilogram. After radioisotope injection, the patients were kept in a room for 55-60 minutes to rest. Meanwhile, iodinated contrast medium was administered orally. Patients were asked to empty their bladder to reduce the physiological activity of the bladder before the scan. PET/CT scanning was performed on a Siemens Biograph Horizon device. The PET/CT scan was obtained in the cranio-caudal direction, covering the region from the top of the head to the proximal third of the thigh.

Parameters Used

- **Threshold 2.5:** Contains tumor tissue with SUV greater than 2.5 in the drawn area of interest.
- **Threshold 41%:** The plotted area of interest contains tumor tissue with metabolic activity higher than 41% of the SUVmax of the lesion.
- **PERCIST threshold:** This value was calculated by adding 2 standard deviations to the mean SUV value of a 3 cm diameter sphere centered on the eighth segment of the right liver lobe.
- **Threshold value aorta:** This value was calculated by adding 2 standard deviations to the mean SUV value of a cylinder 2 cm long in the vertical plan and 1 cm in diameter in the axial plan in the thoracic section of the descending aorta.
- **MTV2.5:** Tumor volume with metabolic activity greater than 2.5 was automatically calculated by the programme (in cm^3).
- **TLG2.5:** The MTV was automatically calculated by the programme by multiplying 2.5 by the mean SUV measured within the lesion.
- **MTV41:** Tumor volume with metabolic activity greater than 41% of the SUVmax of the lesion was automatically calculated by the programme (in cm^3).
- **TLG41:** MTV was automatically calculated by the programme by multiplying 41% by the mean SUV measured within the lesion.
- **MTVPERCIST:** The tumor volume with metabolic activity higher than the PERCIST threshold was automatically calculated by the programme (in cm^3).
- **TLGPERCIST:** MTV was calculated automatically by the programme by multiplying the PERCIST threshold and the mean SUV of the lesion.
- **MTVAORT:** The tumor volume with metabolic activity higher than the aortic threshold was automatically calculated by the programme (in cm^3).
- **TLGAORT:** MTVAORT calculated by aortic threshold was automatically calculated by the programme by multiplying the mean SUV measured within the lesion.

Statistical Analysis

Statistical analyses were performed using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as n and % for categorical variables and Median (IQR) for continuous variables. ROC curve was used to analyse the predictive value of various clinical parameters for mortality. Kaplan Meier method was used to compare survival times between various clinical parameter groups. $p<0.05$ was considered statistically significant.

RESULTS

When the international prognostic score (IPI) of 26 patients included in our study was evaluated, 4(15.3%) had an IPI score of 1, 4(15.3%) had an IPI score of 2, 6(23%) had an IPI score of 3, 11(42.3%) had an IPI score of 4, and 1(3.8%) had an IPI score of 5. ECOG performance status was ≥2 in 19 (73%) patients. The median follow-up period was 22,19±23,50 months. Sociodemographic and clinical characteristics were summarised in Table 1. Among the participants, 14 (53.8%) were in stage 4, 5 (19.2%) in stage 3, 1 (3.8%) in stage 2, and 6 (23%) in stage 1, and 3 (11.5%) had bulky disease and 10 (38.4%) had bone marrow involvement on biopsy. Among the patients, 22 (84.6%) were DLBCL of non-germinal center cell origin. Ki-67 proliferation index was ≥90 in 4 (15.3%), immunohistochemical myc expression was positive in

4(15.3%), myc expression was negative in 10 (38.4%), and myc expression was not evaluated in 12 patients. Myc expression and Ki-67 proliferation index were not correlated with metabolic parameters (p>0.05). R-CHOP chemotherapy was given to 23 (88.4%) of the participants and response was achieved in 21(80.7%) of them. Recurrence was observed in 2 (7.7%). No statistically significant difference was found between metabolic parameters and response to treatment (p>0.05) (Table 2).

Table 1. Sociodemographic and clinical characteristics data

Variables	N	%
Follow-up time (months), Mean±SD	22.19±23.50	
Age (years)		
Mean±SD	56.38±14.00	
Median (min-max)	55 (22-87)	
≤60	15	57.7
>60	11	42.3
Gender		
Female	15	57.7
Male	11	42.3
Comorbidity		
No	13	50.0
Yes	13	50.0
Relapse		
No	20	76.9
Yes	2	7.7
Response		
No	5	19.2
Yes	21	80.8
Mortality		
Lives	21	80.8
Exitus	5	19.2
Laboratory Parameters	**Mean±SD**	
WBC (10^3/µl)	7.36±3.24	
Neutrophil (10^3/µl)	5.23±2.95	
Lymphocyte (10^3/µl)	1.58±0.81	
Hemoglobine (g/dl)	11.47±2.61	
Platelet (10^3/µl)	253.19±92.35	
Creatinine (mg/dl)	0.75±0.18	
Uric acid (mg/dl)	4.86±1.72	
Calcium (mEq/L)	9.06±0.66	
Potassium (mmol/L)	4.45±0.56	
Beta2 mikroglobuline (ng/ml)	3.98±2.58	
D-dimer (µg/ml)	1.47±1.27	
INR	1.29±0.54	
aPTT (sn)	23.61±2.85	
Fibrinogen (g/L)	4.18±1.38	

Table 2. Comparison of various clinical parameters with responses to treatment

Variables	Response to treatment		p
	Yes (N=5) Median (IQR)	No (N=21) Median (IQR)	
SUVmax	20.3 (21.5)	27.1 (19.2)	0.205
SUVpeak	18.5 (18.5)	23.7 (16.1)	0.229
MTV2.5	628.0 (1926.3)	522.7 (463.8)	0.626
TLG2.5	2656.1 (9781.1)	4782.8 (10489.7)	0.313
MTV PERCIST	490.8 (804.5)	447.1 (582.1)	0.770
TLG PERCIST	2157.6 (8403.0)	3740.0 (4403.0)	0.495
MTVAORT	845.4 (2269.9)	982.8 (815.4)	0.416
TLGAORT	3498.0 (10175.2)	4312.5 (4684.1)	0.820
MTV41	256.2 (481.3)	302.0 (1062.2)	0.720
TLG41	1726.0 (5382.4)	2452.4 (3356.3)	0.770
AORT	2.1 (0.5)	1.6 (1.2)	0.329
LIVER	3.3 (1.1)	2.9 (1.2)	0.229

Mann Whitney U test, p<0.05 statistically significant

A total of 21 (80.7%) of the participants are alive. TLGPERCIST (p=0.034), TLGAORT (p=0.040), MTV41 (p=0.040) and TLG41 (p=0.034) parameters were statistically significant with mortality. In the ROC analysis designed to discriminate mortality by TLGPERCIST values, the AUC was 0.819 (95% [CI], 0.660-0.978). In case of exitus, the sensitivity and selectivity of TLGPERCIST values with a cut-off value of ≥4411.90 were 80.0% and 76.2%, respectively. In the ROC analysis designed to discriminate mortality by TLGAORT values, the AUC was 0.800 (95% [CI], 0.626-0.975). In case of exitus, the sensitivity and selectivity of TLGAORT values with a cut-off value of ≥5394.25 were 60.0% and 66.7%, respectively. In the ROC analysis designed to discriminate mortality by MTV41 values, the AUC was 0.800 (95% [CI], 0.603-0.997). In case of exitus, the sensitivity and selectivity of MTV41 values at a cut-off value of ≥376.10 were 80.0% and 76.2%, respectively. In the ROC analysis designed to discriminate TLG41 values for mortality, the AUC was 0.810 (95% [CI], 0.637-0.982). In case of exitus, the sensitivity and selectivity of TLG41 values with a cut-off value of ≥3371.20 were 60.0% and 66.7%, respectively. Summarized in Table 3.

TLGPERCIST and MTV41 were statistically significant in terms of median OS (p=0.047 for both). While median OS was inaccessible in the TLGPERCIST <4411.90 group, it was 32.00 (95%CI: 0.00-87.43) months in the ≥4411.90 group. While median OS was inaccessible in the MTV41 <376.10 group, median OS was 32.00 (95%CI: 0.00-87.43) months in the ≥376.10 group (Table 4). Figure 1A-C shows the Kaplan-Meier curves for OS.

Table 3. Analysis of predictive values of various parameter values in differentiating mortality

Variables	AUC	%95 CI	Cut-off	Sensitivity (%)	Specificity (%)	p
TLGPERCIST	0.819	0.660-0.978	≥4411.90	80.0	76.2	0.029
TLGAORT	0.800	0.626-0.975	≥5394.25	60.0	66.7	0.040
MTV41	0.800	0.603-0.997	≥376.10	80.0	76.2	0.040
TLG41	0.810	0.637-0.982	≥3371.20	60.0	66.7	0.034

AUC, Area under the curve; 95%CI, Confidence interval

Table 4. OS comparisons of patients

OS (months)	2 years %	5 years %	Median (%95 CI)	p
OS	88.5	59.0	- (-)	
TLG PERCIST				0.047
<4411.90	100.0	66.7	- (-)	
≥4411.90	66.7	44.4	32.00 (0.00-87.43)	
TLGAORT				0.379
<5394,25	93.8	62.5	- (-)	
≥5394,25	80.0	53.3	- (-)	
MTV41				0.047
<376.10	100.0	66.7	- (-)	
≥376,10	66.7	44.4	32.00 (0.00-87.43)	
TLG41				0.379
<3371,20	93.8	62.5	- (-)	
≥3371,20	80.0	53.3	- (-)	

Kaplan Meier curve, Long rank test, p<0.05 statistically significant

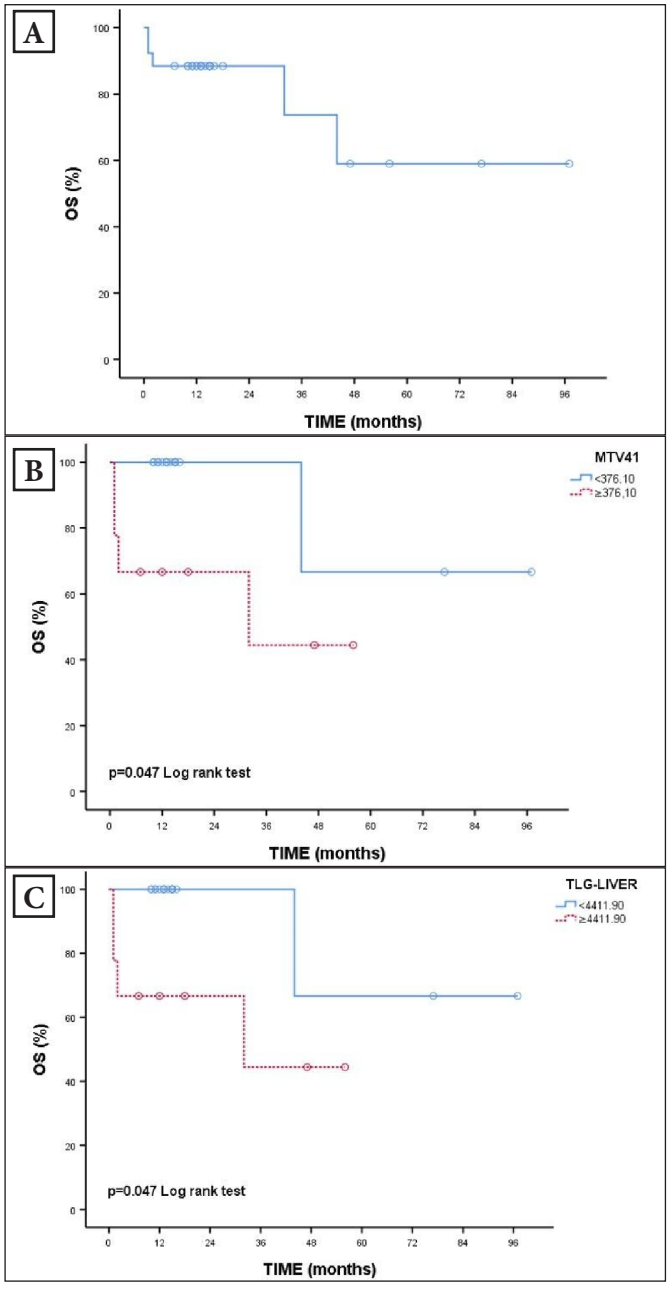

Figure 1A-C. Kaplan-Meier curves for OS.

DISCUSSION

In our study, no correlation was found between metabolic parameters and treatment response in patients with DLBCL, while TLGPERCIST and MTV41 were found to have predictive value for OS. The small number of patients, partial lack of pathological data and retrospective study are the limitations of our study. Whether these parameters are guiding in terms of both treatment response and the type of treatment remains a matter of curiosity. As a result of studies with a larger patient population, measurement of these parameters may provide additional contribution to the routine SUVmax, Deauville score.

The current approach is to define the high-risk subtype of DLBCL and to consider different treatment regimens instead of the standard regimen of R-CHOP. Genetic features, myc expression, cell origin, 18F-FDG PET/CT are used to define the subtype with poor prognosis.[14] In many lymphoma subtypes, MTV predicts the total tumor burden more accurately than the simple size of the tumor, Ann Arbor stage, or even the clinical risk score.[15,16] High pretreatment MTV results in shorter PFS and OS.[17-20] High total MTV and TLG were associated with both worse OS and incomplete response.[21] In another study, it was also defined as a marker of relapse.[15] In our study, MTV and TLG were not found to be associated with treatment response. This may be due to the small number of patients. However, higher MTV and TLG were associated with worse OS. In a study evaluating various methods to measure tumor volume, although the parameters used predicted both PFS and OS, the use of SUV2.5 was recommended because it was easier for clinicians to evaluate with the method.[22] In another study, in univariate Cox regression analysis, whole-body MTV was found to be a significant determinant of OS, but in the multivariate Cox proportional hazards model, neither MTV nor TLG was identified as predictive factors. So, to put it simply, "whole-body MTV" and "whole-body TLG" do not offer any additional prognostic information compared to what is already available through NCCN-IPI in DLBCL.[23]

In clinical practice, there are several challenges associated with the calculation of MTV in lymphomas. First and foremost, there is no consensus on which threshold value to use for the delineation of lymphoma lesions and the calculation of MTV. In our study, with the aim of reducing this limitation somewhat, we utilized four different threshold values for MTV calculation: MTV2.5, MTV41, MTVPERCIST, and MTVAORT, and endeavored to demonstrate which threshold value contributed more effectively. Secondly, measuring MTV using existing software programs can be time-consuming. To surpass this limitation, the development of automated software programs can facilitate easier measurements and save time. Thirdly, the contribution of MTV calculations in DLBCL to prognostic information beyond what is determined by

commonly used clinical risk scores is a subject of debate in the field of research.

Imaging interpretation analyses with the evaluation of different metabolic volumetric parameters are improving day by day. We believe that predictive risk analyses developed by combining these parameters with pathological and clinical data will be useful in predicting treatment response, recurrence and OS.

CONCLUSION

High tumor burden is associated with poor survival. We believe that extending the pre-treatment volumetric-metabolic parameters and evaluating whether they have a predictive value not only in terms of OS but also in terms of treatment response should be evaluated with studies involving a larger patient population.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences Hamidiye Faculty of Medicine Ethics Committee (Date: 01.09.2023, Decision No: 2023/16-12)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

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Reappraisal of the role of *Helicobacter pylori* in chronic spontaneous urticaria

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ABSTRACT

Aims: Chronic spontaneous urticaria (CSU) is one of the most prevalent skin disorders. *Helicobacter pylori* (HP) infection has been linked to CSU, and HP eradication therapy has been questioned as a viable treatment option. However, studies have produced contradictory results. In addition, recent studies suggest that gastritis, rather than HP bacteria, may be responsible for CSU symptoms. Herein, we aimed to ascertain the prevalence of HP infection in CSU, explore associations between HP infection, gastritis, and CSU severity or treatment response in CSU, and investigate the impact of HP eradication therapy on the CSU course.

Methods: We retrospectively analyzed CSU patients who were investigated for HP infection. Patient characteristics, in-clinic urticaria activity scores (ic-UAS) and urticaria control test (UCT) scores, and CSU treatment responses were compared across different patient groups.

Results: The study included 325 CSU patients, of whom 57.2% were HP-positive and 60.9% had gastritis. The mean baseline ic-UAS showed no difference between HP-positive and HP-negative patients (2.55±2 vs 2.45±1.98, p>0.05) or between patients with and without gastritis (2.33±2 vs 2.51±2, p>0.05). HP-positive patients had higher rates of elevated CRP levels (45% vs 29.9%, p=0.023) and ASST positivity (54.8% vs 29.8%, p<0.001). The AH response exhibited a statistically significant increase in HP-positive patients compared to HP-negative patients (78.4% vs 61.2%, p=0.006) and in patients with gastritis compared to patients with no gastritis (76.8% vs 61.3%, p=0.013). There was no difference in response to omalizumab treatment between HP-positive and HP-negative patients (90% vs 86.5%, p=0.528) or between patients with gastritis and patients with no gastritis (91.3% vs 85.3%, p=0.404). No significant difference was observed in response rates to antihistamines or omalizumab between HP-positive patients who had not received eradication therapy and those who had received such therapy (p>0.05).

Conclusion: Over half of CSU patients have been found to be infected with HP. However, the HP bacterium itself, the eradication of HP, or gastritis have no significant effect on CSU severity or treatment response.

Keywords: Disease severity, eradication, gastritis, *Helicobacter pylori*, treatment response, urticaria

INTRODUCTION

Chronic urticaria is a dermatological condition characterized by the recurring presence of pruritic wheals and/or angioedema lasting for a duration exceeding six weeks. It has two subtypes based on the presence of a specific stimulus that causes the appearance of lesions: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU).[1] The clinical manifestations of these conditions are caused by the stimulation of cutaneous mast cells and the subsequent discharge of their mediators. While it is widely accepted that autoimmunity is the fundamental mechanism involved in mast cell activation, stress, infections, foods, and medications are implicated as modulators or exacerbators of the disease.[1-3] One of the infections that is suggested to contribute to CSU disease activity is the *Helicobacter pylori* (HP) infection.[1]

Helicobacter pylori is a gram-negative, spiral-shaped microaerophilic bacterium, and more than 50% of the population is afflicted with its infection, with strong differences between geographical areas.[4,5] It invades the gastric mucosa and triggers the release of cytotoxic substances from both the bacterium itself and the host organism, leading to the development of a pronounced inflammatory response. Approximately 80% of patients

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who are infected with HP do not exhibit symptoms, but all develop gastritis.[6] The etiopathogenetic role of HP in gastrointestinal disorders, including peptic ulcer, gastric cancer, and lymphoma, is also widely recognized.[6,7]

Additionally, there is an increasing amount of evidence supporting the hypothesis that HP infection has systemic implications, potentially contributing to the development of extragastrointestinal conditions including vascular, autoimmune, and dermatological disorders. The link between HP infection and CSU has been the subject of extensive research for over three decades. However, the findings from these studies have presented contradictory outcomes.[1,7] Multiple studies have found a positive link between the presence of HP and the development of CU, and the commencement of HP eradication therapy has been shown to be beneficial in reducing symptoms in certain patients.[8-13] On the other hand, a number of additional studies have been unable to establish a statistically significant correlation between HP infection and CSU, and the complete eradication of HP has not consistently resulted in the resolution of CSU in all individuals.[14-16] Also, a recent meta-analysis reported that CSU patients who received antibiotic therapy for the eradication of HP demonstrated a notably higher rate of CSU remission, regardless of whether HP eradication was achieved or not.[17]

In addition to infectious diseases, chronic inflammatory processes from a variety of other diseases have been identified as potential causes of CSU.[1] Some authors suggest that the development of CU may be attributed to inflammation from gastritis rather than HP bacteria, based on the high prevalence of CU in patients with peptic ulcer disease (PUD) in the absence of HP and the positive correlation between healing of gastritis and erosions and improvement in CU symptoms.[18-21]

Still, although the association between HP and urticaria is not clear on an individual level and evidence from eradication studies is limited, the International Guideline for the Management of Urticaria suggests performing diagnostic tests for HP and commencing eradication therapy if the results are positive because HP is linked to the development of cancer. According to the guideline, the recommended first-line therapy for the treatment of urticaria involves the initial administration of a standard dose of second-generation H1-antihistamine (sgAH). In cases where there is no response to this initial dose, it is advised to increase the dosage of sgAHs up to fourfold. As a second-line therapy, the guideline suggests combining antihistamines with omalizumab for patients who are resistant to antihistamines.[1]

In this study, we aimed to ascertain the prevalence of HP infection in CSU, investigate the potential associations between HP infection and/or gastritis and CSU disease severity or resistance to CSU treatment, and determine if HP eradication therapy led to a decrease in disease activity or an increase in control of CSU. We also aimed to address the discrepancies about the association between HP and CSU in the existing literature.

METHODS

The study was carried out with the permission of İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Researches Ethics Committee (Date: 19.04.2021, Decision No: 163-2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We conducted a retrospective analysis of CSU patients who were referred to UCARE (Urticaria Center of Reference and Excellence) Center of Okmeydanı Training and Research Hospital during the period from January 2013 to July 2019. CSU patients who were investigated for the presence of HP were included in the study. The patients who had CIndU without CSU and those who had a known diagnosis of gastritis without HP investigation were excluded.

Patient features such as age, gender, duration of disease, presence of angioedema, concurrent CIndU, family history of CU, emergency referrals, short-term systemic corticosteroid (CS) use, non-steroidal anti-inflammatory drug (NSAID) intolerance, atopic disorders and chronic infections (e.g. within the oral cavity, nasal sinuses, gastrointestinal tract, and urogenital system), presence of stress, presence of endoscopic diagnosis of gastritis, total IgE, anti-thyroid peroxidase antibody (anti-TPO), anti-thyroglobulin antibody (anti-TG), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) amounts, eosinophil counts, skin prick test (SPT) results and autologous serum skin test (ASST), HP stool antigen test (SAT) results, baseline in-clinic urticaria activity scores (ic-UAS), baseline and follow-up urticaria control test (UCT) scores, CU treatments, HP eradication therapies (for 14 days, regimen 1: clarithromycin, amoxicillin, and lansoprazole; or regimen 2: bismuth, metronidazole, tetracycline/doxycycline, and proton pump inhibitor), and gastritis treatments (H_2 antagonists and/or proton-pump inhibitors) were retrieved from patients' files. Patients with positive SAT results have been defined as 'HP-positive', whereas patients with negative SAT results have been defined as 'HP-negative'. All HP-positive patients and those whose files indicated an endoscopic diagnosis of gastritis were considered to have gastritis.[6]

Baseline disease severity in CSU patients was assessed using the ic-UAS, which incorporates the assessment of pruritus intensity and wheal counts.[22] The assessment quantifies the quantity of wheals and the severity of pruritus using

a four-point scale.[23] Treatment responses were evaluated with UCT, where a score of 12 or higher denoted effective management of urticaria, while a score of 11 or lower indicated inadequate control of the disease.[24,25] If UCT scores ≥12 were achieved using a treatment, this was considered a 'response to that treatment'. 'Antihistamine refractoriness' was used as a reference term for patients who do not respond to updosed/combined antihistamines. The patients used only second-generation H1-antihistamine; no H2 receptor blockers were employed.

Statistical analysis was conducted using IBM SPSS Statistics for Windows v.21.0. (IBM Corp., Armonk, NY). The frequencies and percentages were used to present categorical variables, while the mean±standard deviation or median were used to present quantitative variables. The Kolmogorov-Smirnov test was employed to assess the normality of the distribution of numeric variables. The student's t test, Mann-Whitney U test, chi-square test, and Fisher's exact test were used for independent group comparisons. The statistical significance level was considered to be $p<0.05$.

RESULTS

The Study Population

A total of 325 CSU patients were included in the study. A total of 186 patients (57.2%) tested positive for HP, while 198 patients (60.9%) were diagnosed with gastritis. The details of patient characteristics are shown in Tables 1 and 2.

Table 1. Clinical characteristics

Characteristics	N=325
HP infection, n (%)	186 (57.2)
Eradication therapy for HP, n (%) (n=323)	60 (18.6)
Gastritis, n (%)	198 (60.9)
Sex, female, n (%)	249 (76.6)
Age (y), mean±sd; min-max	41.57±13.07; 11-85
Accompanying CIndU, n (%)	42 (12.9)
Disease duration (mo), mean±sd; median; min-max	34.17±54.9; 12; 2-360
Angioedema, n (%)	178 (54.8)
Family history of CU, n (%) (n=323)	55 (17)
Emergency referral, n (%) (n=209)	157 (75.1)
Short-term systemic CS use, n (%) (n=201)	141 (70.1)
NSAID intolerance, n (%) (n=232)	22 (9.5)
Atopic disorder, n (%) (n=293)	84 (28.7)
Autoimmune thyroiditis, n (%) (n=213)	32 (15)
Stress, n (%) (n=293)	112 (38.2)
Chronic infections, n (%) (n=291)	127 (43.6)
Baseline ic-UAS score, mean±sd; min-max (n=208)	2,4±2; 0-6
Baseline UCT score, mean±sd; min-max (n=189)	7.4±4.02; 0-16
Baseline UCT score ≤12, n (%) (n=189)	164 (86.8)

CIndU: chronic inducible urticaria, CS: corticosteroid, CU: chronic urticaria, HP: *Helicobacter pylori*, NSAID: nonsteroidal anti-inflammatory drug, UAS: urticaria activity score, UCT: urticaria control test

Table 2. Laboratory characteristics

Characteristics	
CRP levels >5 mg/L, n (%) (n=217)	83 (38.2)
ESR levels >20 mm/h, n (%) (n=209)	91 (43.5)
Total IgE levels >100 IU/ml, n (%) (n=256)	202 (78.9)
Total IgE levels ≤40 IU/ml, n (%) (n=250)	47 (18.8)
Total IgE level, mean±sd; min-max (n=250)	298.81±604.4; 0-7158
Blood eosinopenia, n (%) (n=97)	21 (21.6)
Anti-TPO >34 IU/ml, n (%) (n=254)	51 (20.1)
Anti-TG >34 IU/ml, n (%) (n=192)	25 (13)
SPT positivity, n (%) (n=154)	60 (39)
ASST positivity, n (%) (n=198)	85 (42.9)

anti-TPO: anti-thyroid peroxidase antibody, anti-TG: anti-thyroglobulin antibody, ASST: autologous serum skin test, CRP: C-reactive protein, ESR: estimated sedimentation rate, SPT: skin prick test

Helicobacter pylori Infection does not Increase CSU Disease Severity

The disease activity showed no difference between HP-positive and HP-negative patients with regard to mean baseline ic-UAS (2.55±2 vs 2.45±1.98, $p>0.05$).

Helicobacter pylori Infection is Linked to Increased CRP Levels and ASST Positivity

Comparing HP-negative patients, a greater proportion of HP-positive patients exhibited elevated CRP levels (45% vs 29.9%, $p=0.023$) and ASST positivity (54.8% vs 29.8%, $p<0.001$), but other laboratory parameters did not differ ($p>0.05$) (Table 3).

Table 3. Comparison of laboratory characteristics between HP-positive and HP-negative patients

Characteristics	HP-positive n/N (%)	HP-negative n/N (%)	P value
CRP levels >5 mg/L	54/120 (45)	29/97 (29.9)	0.023
ESR levels >20 mm/h	50/114 (43.9)	41/95 (43.2)	0.919
Total IgE levels >100 IU/ml	113/138 (81.9)	89/118 (75.4)	0.207
Total IgE levels ≤40 IU/ml	21/134 (15.7)	26/116 (22.4)	0.174
Blood eosinopenia	14/52 (26.9)	7/45 (15.6)	0.175
Anti-TPO >34 IU/ml	29/143 (20.3)	22/111 (19.8)	0.928
Anti-TG >34 IU/ml	13/105 (12.4)	12/87 (13.8)	0.772
SPT positivity	35/88 (39.8)	25/66 (37.9)	0.811
ASST positivity	57/104 (54.8)	28/94 (29.8)	<0.001

anti-TPO: anti-thyroid peroxidase antibody, anti-TG: anti-thyroglobulin antibody, ASST: autologous serum skin test, CRP: C-reactive protein, ESR: estimated sedimentation rate, HP: *Helicobacter pylori*, SPT: skin prick test

No statistically significant differences were observed between HP-positive and HP-negative patients regarding age and sex distribution, disease duration, presence of angioedema, concurrent CIndU, emergency referrals, systemic CS use, NSAID intolerance, family history of CU, atopic disorders, autoimmune thyroiditis, chronic infections, and stress ($p>0.05$ for all).

Helicobacter pylori Infection is not Linked to Resistance to CSU Treatment

While there was no difference in response to omalizumab treatment between HP-positive patients who had not received eradication therapy and HP-negative patients (90% vs 86.5%, p=0.528), HP-positive patients who had not received eradication therapy exhibited a higher AH response compared to HP-negative patients (78.4% vs 61.2%, p=0.006) (Table 4).

Helicobacter pylori Eradication Therapy does not Improve CSU Treatment Responses

Helicobacter pylori eradication therapy was initiated in 60 HP-positive patients (32.2%). There was no difference in response rates to neither antihistamines nor omalizumab treatment between HP-positive patients who had not received eradication therapy and HP-positive patients who had received such therapy (p > 0.05) (Table 4). Also, the rates for chronic infections other than HP were similar between these two groups (44.4% vs 51%, p=0.438).

Gastritis is not Associated with CSU Disease Severity

No difference in mean baseline ic-UAS (2.33±2 vs 2.51±2, p=0.553) was observed between patients with and without gastritis.

Gastritis is not Associated with Resistance to CSU Treatment Regardless of *Helicobacter pylori* Infection

While there was no difference in response to omalizumab treatment between patients with gastritis and patients with no gastritis (91.3% vs 85.3%, p=0.404), overall AH response was significantly higher in patients with gastritis than in patients with no gastritis (76.8% vs 61.3%, p=0.013) (Table 5).

No difference was observed in response rates to neither antihistamines nor omalizumab treatment between patients with HP-negative gastritis and patients with no gastritis (p>0.05) (Table 5).

DISCUSSION

Helicobacter pylori is a common cause of chronic bacterial infections in humans. The reported prevalence of HP infection shows significant variation, influenced by factors including age, socioeconomic status, and geographic regions. In developed countries, the prevalence ranges from 10% to 50%, while in developing countries, it reaches as high as 80%.[4,5,26] Between 2014 and 2020, the prevalence of adult HP infection decreased from 50-55% to 43% worldwide. This decline is primarily linked to advancements in living standards, socioeconomic status, and hygiene, as well as a rise in the use of eradication therapies.[4,6,27] The prevalence of HP infection in Turkey was reported as 82.5% with the 13C-Urea Breath Test (UBT), whereas in two different studies performed in Istanbul, the prevalence of HP was determined to be 36.6% using the SAT and 41.44% using the urease test.[28-30]

The prevalence of HP infection in CSU patients also varies across different regions, ranging from 25% to 83%.[31,32] Some authors suggested a potential causal relationship between CSU and HP infection based on the high prevalence of HP in CSU.[10,33] A recent case-control study using SAT to diagnose HP infection claimed that HP-positive patients had a 6-fold higher risk of developing CSU than HP-negative patients.[34] A meta-analysis comprising 16 studies revealed a weak positive correlation between HP infection and CU.[35] However, the authors of the study indicated that the majority of the included studies used the serology method to detect HP-specific antibodies, and no association was observed when only the studies using the UBT were considered.[35] Non-invasive diagnostic methods such as the UBT and SAT allow for the identification and confirmation of an active infection with high sensitivity and specificity (95-100%). The identification of serum HP-specific IgG/IgA antibodies through serological methods cannot differentiate between a current infection and a past infection with HP; confirmation by UBT or SAT is

Table 4. Comparison of CU treatment response rates between HP-negative patients, HP-positive patients who had not received eradication therapy, and HP-positive patients who had received eradication therapy

Treatments	HP-negative n/N (%)	HP-positive eradication therapy (-) n/N (%)	HP-positive eradication therapy (+) n/N (%)	P value*	P value**
AH response	71/116 (61.2)	80/102 (78.4)	39/58 (67.2)	0.006a	0.119a
Omalizumab response	32/37 (86.5)	18/20 (90)	15/18 (83.3)	0.528b	0.448b

AH, antihistamine; HP, *Helicobacter pylori*, *Comparison between 'HP-negative' and 'HP-positive, eradication therapy negative' groups, **Comparison between 'HP-positive, eradication therapy negative' and 'HP-positive, eradication therapy positive' groups, aPearson chi-square test, bFisher exact test

Table 5. Comparison of CU treatment response rates between patients without gastritis, patients with gastritis, and HP-negative patients with gastritis

Treatments	No gastritis n/N (%)	Gastritis n/N (%)	HP-negative gastritis	P value*	P value**
AH response	65/106 (61.3)	86/112 (76.8)	6/10 (60)	0.013a	0.593b
Omalizumab response	29/34 (85.3)	21/23 (91.3)	3/3 (100)	0.404b	0.638b

AH, antihistamine; HP, *Helicobacter pylori*, *Comparison between 'No gastritis' and 'Gastritis' groups, ** Comparison between 'No gastritis' and 'HP-negative gastritis' groups, aPearson chi-square test, bFisher exact test

required.[6] Thus, the use of the serological method to determine the presence of a causal relationship between HP infection and CU may certainly lead to misleading conclusions. Besides, many studies have shown that the prevalence of HP infection among healthy individuals and CSU patients is comparable.[11,13,16,36-39] In our routine clinical practice, the SAT is used for the detection of active HP infection. This test is rapid, noninvasive, cost-effective, and reliable.[6] The prevalence of HP infection in CSU was found to be 57.2% in our study. Despite the lack of a comparison group, our results suggest that the prevalence of HP infection among CSU patients is higher than that of the population in the same region.[28,29] Our study suggests that there may be a causal relationship between HP infection and CSU; however, the lack of a control group limits the strength of this statement.

There is no difference in age, gender, the presence of angioedema, or disease duration between HP-positive and HP-negative CSU patients in the literature, as observed in our study.[9,11,15,16,37,40-43] As we also found, accompanying CIndU rates were comparable between these two groups.[11] Infection with HP has been reported to be associated with a chronic increase in circulating inflammatory markers, especially CRP, which was also higher in HP-positive patients in our study compared to HP-negative patients.[44] In previously published studies, CU disease activity was evaluated with UAS. In three of these studies, no difference between the groups regarding disease severity was observed.[9,40,41] In one study, however, HP-positive patients experienced a more severe disease, whereas in another, HP-negative patients did.[37,45] In addition, the authors reporting higher disease severity in HP-positive patients noted that gastric inflammation and bacterial colonization were also higher in these patients.[37] In our study, we evaluated CSU disease activity using baseline ic-UAS, which did not differ between HP-positive and HP-negative patients. Our research indicates that HP infection does not cause more severe disease. In addition, in our study, parameters such as emergency referrals, short-term CS use, and the presence of angioedema, which have been linked to a more severe disease, did not differ between the two groups.[46,47]

Atopic disorders, such as asthma, allergic rhinitis, and atopic dermatitis, are frequently observed as comorbid conditions in patients with CU.[20] HP-positive patients have previously been reported to have a lower rate of concomitant atopic disorders compared to HP-negative patients.[42,48] This result can be explained by the fact that the HP infection is mainly associated with low socioeconomic status and poor hygiene conditions, whereas high hygiene standards are a risk factor for the development of allergic conditions.49 However, in our study, there was no difference between the two groups regarding atopic disorders or total IgE elevation, the latter of which was found to be similar in another study.[11]

Autoimmune CSU (type 2b autoimmunity) is one of the most prevalent CSU endotypes and is characterized by circulating autoantibodies against IgE (IgG anti-IgE) and/or the α subunit of the high-affinity IgE receptor (IgG anti-FcεRI).50 Autoimmune CSU is frequently associated with other autoimmune disorders, elevated anti-TPO levels, and lower total IgE levels.[50,51] The present clinical assessment of patients exhibiting autoimmune antibodies involves the use of ASST. A positive test result supports the possibility of an autoimmune etiology, but it does not definitively establish the diagnosis.[51,52] One of the proposed pathogenetic mechanisms for the link between HP infection and CSU is the induction of autoimmune reactions, possibly as a result of an abnormal immune response to HP-specific antibodies through molecular mimicry.[21,53] Concerns regarding the role of HP infection in the formation of autoantibodies drove studies on the relationship between ASST and HP infection. While two separate analyses concluded that ASST positivity rates did not differ between HP-positive and HP-negative patients, another study found a notable increase in ASST positivity among HP-positive patients.[54-56] In our study, we also observed a higher prevalence of ASST positivity among HP-positive patients. However, there were no significant differences in the rates of autoimmune thyroiditis, thyroid autoantibody, or low total IgE between the two groups. However, the low predictive value of the ASST and the lack of predominance of autoimmune CSU features in our HP-positive patients mitigate the hypothesis of a possible role of HP infection in autoimmune CSU.[51]

Additional evidence supporting the proposed causal relationship between CSU and HP infection is presented by several studies demonstrating clinical improvement of CU in many HP-positive patients after eradication of the bacterium.[8,9,13,37,39,57] However, the evidence supporting the efficacy of HP eradication in CU patients is weak and contradictory. Other research groups reached the conclusion that eradication therapy failed to provide remission in CU.[11,14-16,31,36,38,42,58] There are many limitations that may account for the opposing outcomes observed in previous studies. The diagnostic methods for HP infection, the eradication regimens, the methods used to define complete remission, partial remission, and improvement of CU, which were mostly subjective, and the follow-up periods for patients after eradication therapy (ranging from 4 weeks to 24 weeks) varied between studies. This widespread heterogeneity of studies casts serious doubt on the efficacy of HP eradication in CU therapy. In addition, the sample size of patients included in the studies was considerably limited. A significant proportion of these studies did not employ

statistical analysis methods for comparisons.[8,9,11,15,16,31,42,57] Some of the studies did not report the outcomes of patients who did not undergo eradication therapy and did not perform comparisons.[14,33,37-39,41,45] The results of these studies are also in question because most studies did not mention the concurrent use of antihistamines and corticosteroids, which may have improved the symptoms of CU.[8,9,11,13,15,16,33,37,42,57] When all of these significant factors are taken into account, the overall evidence level for or against HP eradication as a treatment for CSU is very low. In our study, we reported comparisons of response rates to antihistamines and omalizumab between patients who received eradication therapy for HP and those who did not. There was no difference observed in CSU treatment responses between the two groups. Our study showed that eradication of HP does not have a significant impact on the course of CSU or on the treatment response.

One possible explanation for the observed correlation between eradication therapy for HP and CU remission in previous studies may be that the antibiotherapy may have effectively eliminated an undetected occult bacterial infection. This argument is supported by the observation that, while eradication therapy does not successfully eradicate HP in certain patients, it is still associated with rapid improvement in urticaria symptoms.[31] In our study, the distribution of a known chronic infection other than HP was found to be comparable among patients who received eradication therapy and those who did not. Perhaps this is the reason why a difference between the two groups could not be identified. It should also be noted that the natural course of CSU exhibiting spontaneous remission can potentially be misinterpreted and attributed to the efficacy of eradication therapy in previous studies.

In the literature, very few studies exist that assess the effect of HP bacteria itself on the CU course or on CU treatment, with conflicting results. In one small-sample study, the patients with untreated HP infection had a higher remission rate than HP-negative patients, whereas another one reported no difference between the two groups.[15,42] On the other hand, a recent meta-analysis stated that the HP-negative patients exhibited significantly more remission of CSU symptoms than the patients with untreated HP infection.[17] Also, HP positivity was found to be higher in AH-refractory patients than in AH-responsive patients in an earlier study.[59] However, in our study, the antihistamine response in HP-positive CSU patients was higher than that in HP-negative CSU patients. Also, there was no difference in the omalizumab response between the two groups in our study. In line with our finding, HP-positivity did not differ between omalizumab responders and non-responders in another study.[60] Based on our findings, we suggest that HP infection is not associated with CSU remission or resistance to CSU treatment.

Chronic inflammatory conditions, such as gastritis and PUD, have been linked to the development of CSU.[1,18,20,61] The rate of patients who developed CU was observed to be higher in PUD-positive patients compared to PUD-negative patients in HP-negative patients.[19] Patients with healed gastric ulcers had a higher rate of CU improvement than patients with unhealed ulcers, regardless of HP infection.[18] Therefore, recent studies suggest that CU may be caused by gastritis-related inflammation rather than by HP bacteria. However, in our study, mean baseline ic-UAS did not differ between patients with and without gastritis. And, the overall antihistamine response in CSU patients with gastritis was higher than that in those without gastritis. Additionally, there was no difference in response rates to neither antihistamines nor omalizumab between CSU patients with HP-negative gastritis and CSU patients without gastritis. Our findings indicated that gastritis is not associated with disease severity and is not associated with resistance to CSU treatment, regardless of HP infection.

This study was subject to various limitations. This was a retrospective study, and recall bias cannot be excluded. There was no healthy control population from which the HP prevalence could be determined. Most patient files lacked information on eradication regimens, and those that did contained different HP eradication regimens. There was also no information regarding the confirmation of the success of the eradication therapy. On the other hand, our study's strengths were the use of SAT to detect active HP infection, the assessment of CSU disease activity using ic-UAS, the assessment of treatment response using UCT, and the knowledge of comorbid chronic infections.

CONCLUSION

CSU patients have a higher HP infection rate than the general population. This observation prompts further investigation into the potential association between HP infection and the development of CSU. However, HP infection does not play a role in the development of a more severe disease. Neither the HP bacterium itself nor the eradication of HP have any significant effect on the course or treatment response of CSU. Moreover, no association existed between gastritis and disease severity or resistance to CSU treatment, regardless of HP infection. Nevertheless, in spite of the absence of a correlation between HP infection and CSU course, it is best to initiate eradication therapy for HP-positive patients as recommended by the International Guideline for the Management of Urticaria to provide complete healthcare for CSU patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Researches Ethics Committee (Date: 19.04.2021, Decision No: 163-2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Does nutrition knowledge level affect food group preferences and obesity in individuals aged 19 years and older?

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ABSTRACT

Aims: This study was conducted to determine the relationship between nutrition knowledge level, food group preferences, and obesity in individuals who applied to family health centers.

Methods: This study is a cross-sectional study and was conducted with individuals aged 19 years and over. The nutrition knowledge level of the individuals was determined with the nutrition knowledge test, anthropometric measurements were taken, and nutrition status was evaluated with a food frequency questionnaire and 24 hour-recall food consumption records. The data obtained from the study were analyzed with the SPSS 21.0

Results: Of the 1797 individuals who participated in the study, 70.5% were female, 22.0% were single, and 22.8% were university graduates. The mean nutrition knowledge score (NKS) was higher in singles (43.39±13.93) ($p=0.001$), university graduates (46.05±13.69) ($p<0.001$), and those who had previous knowledge about nutrition (42.95±13.83) ($p<0.001$). A significant difference was found between the mean NKS and body mass index (BMI) classification ($p<0.05$). Accordingly, it was observed that the nutrition knowledge scores of overweight and obese individuals were lower than those of normal-weight and underweight individuals. A negative correlation was found between NKS and body weight, BMI, waist circumference, and waist-to-height ratio ($p<0.001$). It was determined that the amount of meat-egg-legume group foods, butter, and olive oil consumed daily increased with the increase in NKS, while the amount of bread and cereal group foods (bread, rice, pasta, bagel, etc.) and margarine consumption decreased ($p<0.05$). In addition, food group preferences also differed according to the NKS level.

Conclusion: Since it has been determined that BMI is associated with a nutrition knowledge score, it is necessary to increase the level of knowledge about nutrition in order to prevent obesity and obesity-related diseases and consequently to increase well-being. Therefore, it is thought that it would be useful to organize awareness-raising education on adequate and balanced nutrition periodically in Family Health Centers.

Keywords: Eating habits, food consumption, nutrition, nutrition knowledge, overweight

INTRODUCTION

The estimates for global levels of overweight and obesity (BMI ≥25kg/m²), suggest that over 4 billion people may be affected by 2035, compared with over 2.6 billion in 2020.[1] With the rapid change in lifestyles such as nutrition in developed and developing societies, the prevalence of obesity is increasing rapidly and is seen as a public health problem.[2] The prevalence of obesity is increasing in Türkiye (Turkey), as it is around the world, with 36.6% of adults being overweight and 34.1% having obesity, according to the National Nutrition Survey 2019 report.[3]

According to reports, obesity is a multifactorial disorder that is brought on by both unchangeable factors such as gender, ethnic background, age, and familial characteristics as well as changeable ones like physical activity level, eating habits, and nutrition knowledge. It is important to have sufficient nutrition knowledge in order to develop healthy eating behaviors and make them a habit.[4]

Prevention of obesity and nutrition-related chronic diseases (such as obesity, Type 2 diabetes, heart diseases, and some kinds of cancers), which are frequently seen in the society and impair the quality of life, improvement and development of lifestyle and environmental conditions, and ensuring sustainable food security are possible by raising awareness and education of individuals on nutrition and health issues.[5] Individuals make choices about their dietary patterns in line with the nutrition knowledge they have.[6] Inadequate nutrition knowledge is one of the prominent problems in Türkiye (Turkey) and the low level of nutrition knowledge of the society throughout the country leads to incorrect food selection, incorrect preparation, cooking, storage methods, and causes an increase in the dimensions of nutrition problems.[7]

Countries carry out national programs and action plans to combat obesity, which is a global public health problem. One of the important activities of these programs is to increase the nutrition knowledge level of individuals and society by

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organizing nutrition education.[8] However, governments need to take into account the factors affecting food choices when formulating healthy living policies. Factors affecting the modern diet, such as food composition, taste, availability, affordability, marketing, the modern environment, contemporary food culture, and gene-environment interaction have been reported to cause impulsive food selection behavior that governs instantaneous choices to consume low- or high-energy foods.[9]

No study was found in the literature to determine the nutrition status and nutrition knowledge levels of individuals applying to Family Health Centers (FHCs) in Kırıkkale. This study was conducted to determine the relationship between nutrition knowledge level, food group preferences, and obesity in individuals who applied to FHCs in Kırıkkale.

METHODS

The study was carried out with the permission of Kırıkkale University Social and Humanities Researches Ethics Committee (Date: 20.07.2016, Decision No: 3). An informed consent form from all patients was obtained for the procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study is a cross-sectional study and was conducted with individuals aged 19 years and over who applied to FHCs in Kırıkkale city center between July and August 2016, as determined according to the study scheduling. Family health centers are centers that provide primary health care services and are the first health institutions to which individuals of all ages from all segments of the society apply for their health problems (except in cases requiring emergency intervention). In order to reach individuals with different characteristics more easily, the study was conducted with volunteer individuals who applied to 13 FHCs in the provincial center.

Male and female individuals without any physical or mental disabilities were included in the study. Exclusion criteria included using drugs (antidepressants) for conditions affecting appetite, psychiatric diseases, and/or receiving eating behavior therapy; and pregnancy or lactation. Detailed information about the study was given to the participants who met the criteria of the study and agreed to participate in the study.

Individuals were informed about the study and included in the study after their consent was obtained. A questionnaire, including questions about demographic characteristics and dietary habits, food consumption frequency, a 24-hour food consumption record, and a nutrition knowledge level test was applied to the individuals by researchers within the scope of the study.

A food frequency questionnaire (FFQ) was used to determine how often and how much food groups or foods were consumed by individuals in the last one month. The frequency of consumption was questioned in terms of days, months, or weeks. In addition to FFQ, by 24-hours recall method foods and their quantities consumed by the individuals for 1 day (24 hours) were questioned in detail and recorded. Then, the foods consumed daily by individuals were grouped according to the food groups that specified in the Turkish Dietary Guidelines. Five groups as milk and milk products group; meat-egg-legumes group; bread and cereals group; vegetables group and fruits group, and the types of fat consumed by the individuals were evaluated also taken into consideration.[5]

The nutrition knowledge test (NKT), which includes 15 questions developed by Öktem Güngör,[10] was used to measure the level of nutrition knowledge of individuals. The scores obtained by the individuals from the test were named the nutrition knowledge score (NKS), and it was accepted that the individuals were successful as the score approached 100 points. The demographic characteristics (gender, marital status, educational status, presence of disease, knowledge of healthy eating) and anthropometric measurements of the individuals participating in the study were evaluated by comparing the mean of the NKS they received from this test.

Body weight (BW), height, waist circumference (WC), and hip circumference measurements were taken according to the technique to determine the obesity of the individuals.[11] TANITA BC 545 model scale was used to measure BW and body fat percentage (BF%), a stadiometer was used for height, and a non-flexible tape measure was used for body circumference measurements. The World Health Organization (WHO) BMI classification was used to assess body weight. According to this classification, BMI ≤18.5 kg/m² is underweight, 18.5-24.9 kg/m² is normal, 25.0-29.9 kg/m² is overweight, 30.0-34.9 kg/m² is class-1 obesity, 35.0-39.9 is class-2 obesity, and ≥40 kg/m² is class-3 obesity.[12]

There has been a consensus that health risks are associated with the distribution of adipose tissue rather than the total adipose tissue in the body.[13] There are various methods that directly measure the amount of fat in the body, which is related to abdominal fat and chronic diseases. These methods include total isotope dilution detection of body water, total body potassium detection, underwater weighing, neutron activation, radiological imaging methods (Ultrasound, MRI, CT scan), the fat-soluble gas method, and the dual energy x-ray absorption method (DEXA). These methods are difficult and costly to implement.[14] Therefore, in this study, anthropometric measurements, which are easy to apply, low-cost and reliable 14 were used for evaluating the risk of abdominal

obesity and chronic diseases according to different anthropometric parameters. One of these parameters is WC. A waist circumference of ≥80 cm for women and ≥94 cm for men is considered a "risk" for chronic diseases; a WC of ≥88 cm for women and ≥102 cm for men is considered a "high risk" for chronic diseases.[12,15] Another parameter is the waist-to-hip ratio (WHR) . A ratio of ≥0.85 for women and ≥0.90 for men indicates the risk of abdominal obesity and obesity-related chronic diseases.[12] Since WC and WHR measurements do not take into account the height of individuals, they may give the same risk ratio to individuals with different heights.16 Therefore, in this study, abdominal obesity was also evaluated according to the waist-to-height ratio.[17] A waist-to-height ratio >0.5 was accepted as abdominal obesity.[16,18]

Statistical Analysis

The data obtained from the study were analyzed with the SPSS 21.0 (Statistical Package for Social Science) statistical program. Statistical analyses were evaluated based on the questions answered in the questionnaire, available food consumption record data and anthropometric measurements. First of all, the distribution and skewness of the data were determined by normality tests, and the data were expressed as mean ( ) and standard error (Sx) values. In the comparison of the differences between two independent groups, parametric (t-test) or nonparametric (Mann-Whitney U test) hypothesis tests appropriate for quantitative data were used; The Pearson chi-square test was used for qualitative data. Bonferroni correction was applied as a Post-Hoc test to find out which group or groups caused the difference between the BMI groups. Non-parametric Spearman rank correlation analysis was used to determine the relationship between numerical variables. Statistical significance was determined by p<0.05.

RESULTS

Of the 1797 individuals who participated in the study, 70.5% were female, 29.5% were male, 70.9% were married, 29.5% were high school graduates, and 22.8% were university graduates. 45.1% of the individuals had a diagnosed disease. In the study, some general characteristics that are thought to affect the mean NKS were analyzed. The mean nutrition knowledge score (NKS) of the women participating in the study was 41.75±13.59, while that of the men was 40.32±12.89. In the study, it was observed that the mean NKS of single women was higher than that of non-single women (p<0.05). In addition, a significant difference was found between the mean NKS and educational status and the status of receiving information about adequate and balanced nutrition (p<0.05) (Table 1).

Table 1. Nutrition knowledge score (NKS) means according to general characteristics of individuals

General characteristics	n	%	NKS X±SD	p
Gender				0.056[a]
Woman	1267	70.5	41.75±13.59	
Man	530	29.5	40.32±12.89	
Marital status				0.001[b]
Married	1274	70.9	40.96±13.23	
Single	396	22.0	43.39±13.93	
Divorced/Widow	12	7.1	38.78±12.82	
Education status				<0.001[b]
Illiterate	93	5.2	38.26±13.18	
Literate	27	1.5	41.53±10.71	
Primary school	528	29.4	39.24±12.75	
Secondary school	209	11.6	38.04±12.71	
High-school	531	29.5	41.59±13.26	
University	409	22.8	46.05±13.69	
Presence of diagnosed disease				0.897[a]
Yes	811	45.1	40.73±13.37	
No	986	54.9	41.85± 13.42	
Having knowledge about healthy nutrition				<0.001[a]
Yes	1067	59.4	42.95± 13.83	
No	729	40.6	38.89±12.40	

a: Student t test (independent samples t test), b: One way ANOVA

In the study, the mean NKS of individuals was evaluated according to their anthropometric measurements in order to evaluate the effect of anthropometric measurements on the nutrition knowledge level. Accordingly, to this, a statistically significant difference was detected between the NKS average and BMI classification groups (p<0.05) (Table 2). A Bonferroni correction was made to determine which groups had a difference between the BMI classification and the mean NKS. Accordingly, a difference was observed between individuals of normal weight and those with class-1 obesity. Individuals with obesity-1 class have lower NKS than those with normal weight. At the same time, WC values, which are a risk factor for abdominal fat and chronic diseases, were higher in those with low nutrition knowledge (p<0.05).

Table 2. Mean nutrition knowledge score (NKS) according to anthropometric measurements of individuals

	n	%	NKS X±SD	p
BMI (kg/m²)				0.003b
Underweight	54	3.1	45.18±13.12	
Normal	469	27.3	42.71±13.64	
Overweight	573	33.4	41.55±13.43	
Obesity 1.class	402	23.4	39.81±13.67	
Obesity 2.class	152	8.8	40.26±12.59	
Obesity 3.class	68	4.0	38.82±12.07	
WC (cm)				0.03a
Risk +	1219	67.8	40.93 ±13.55	
Risk -	481	26.8	42.50±13.20	
WHR				0.621a
Risk +	916	54.6	41.14±13.71	
Risk -	762	45.4	41.69±13.18	
Waist-to-height ratio				0.69a
Risk +	1256	74.9	40.73±13.28	
Risk -	422	25.1	43.23±13.48	

a: Student t test (independent samples t test) b: One way ANOVA
BMI: Body Mass Index; WC: Waist circumference; WHR: waist-to-hip ratio; Risk: Chronic diseases risk

Since the mean NKS score a differed according to anthropometric measurement values in the study, an appropriate correlation test was performed to support the findings. A low but significant (p<0.001) negative correlation was found between NKS and BW, BMI, WC, and waist-to-height ratio (Table 3).

Table 3. The relationship between nutrition knowledge scores (NKS) and anthropometric measurements of individuals

Anthropometric measurements	NKS r (p)
BW (kg)	-0.08 (0.00)*
BMI (kg/m²)	-0.10 (0.00)*
WC (cm)	-0.09 (0.00)*
WHR	-0.04 (0.05)
Waist-to-height ratio	-0.10 (0.00)*
BF (%)	*0.00 (0.85)

*Spearman rank correlation, BW: Body weight; BMI: Body Mass Index; WC:Waist circumference; WHR: waist-to-hip ratio; BF: Body fat

It is thought that nutrition knowledge level also affects the daily food groups and amounts consumed. For this reason, in the study, the relationship between food groups and the amount of fat taken with NKS was examined, and an appropriate correlation test was applied. While the portion amount of meat-egg-legume group foods and the amount of olive oil consumed daily increased with the increase in NKS, the consumption of bread and cereal group foods (bread, rice, pasta, bagels, etc.) decreased (Table 4). This result shows that the level of nutrition knowledge has an effect on people's daily food preferences and quantities.

Table 4. The relationship between individuals' nutrition knowledge score and their consumption of 5 food groups and fats

Food groups and fat/oil types	NKS r(p)
Food groups	
Milk group	-0.02 (0.28)
Meat-egg-legumes group	0.11 (0.00)*
Bread and cereal group	-0.05 (0.04)*
Vegetable group	-0.02 (0.39)
Fruit group	0.01 (0.72)
Fat/Oil types	
Olive oil (g)	0.09 (0.00)*
Sunflower oil (g)	-0.02 (0.30)
Butter (g)	0.05 (0.03)*
Margarine (g)	-0.07 (0.00)*

*Spearman rank correlation

DISCUSSION

The study aims to investigate if there is a relationship between individuals' level of nutrition knowledge, their dietary preferences in terms of food groups and their obesity. Inadequate nutrition knowledge; it can be a significant barrier to maintaining healthy behaviors and a healthy body weight.[19] At the same time, nutrition knowledge can have effects beyond the individual level.[20] Therefore, it is important to determine the level of nutrition knowledge and to reveal the relationship between obesity and food group preferences. In this study conducted for this purpose, a negative relationship was found between individuals' NKS and body weight, BMI, WC, waist-to-height ratio (p<0.05). Individuals' food group preferences also differed depending on their NKS level.

In this study, the level of nutrition knowledge was found to be higher in single individuals, university graduates, and those who had previously received information on adequate and balanced nutrition. Although the study by Rose et al. stated that nutrition knowledge level was not related to gender.[21] there are studies reporting that women's nutrition knowledge level is higher than men.[22,23] In this study, although not statistically significant, it was observed that women's NKS was higher than men's. The fact that food shopping and cooking is usually done by women in the family also has an impact on women's knowledge about nutrition.[23]

In different studies, it has been emphasized that education level affects nutrition knowledge.[22,24,25] Individuals with higher levels of education tend to have better nutrition knowledge compared to those with lower levels of education. In a systematic review by Barbosa et al.[22] in which 25 articles were analyzed, it was shown that there was a positive correlation between education level and NKS, and it was stated that education is a basic tool for obtaining information about nutrition. In this study, the fact that the mean NKS was also higher in individuals with higher education levels and who had previously received education on adequate and balanced nutrition.

In a study, BW, BMI, BF%, WC, and hip circumference were found to be lower in women who received nutrition education, and it was emphasized that nutrition education may have an effect on healthy food selection and body composition components.[26] In another study, no significant correlation was found between the BMI, WC, BF%, and WHR values of female and male university students and their nutrition knowledge level and food preferences.[27] This situation suggested that nutrition knowledge could not be transformed into behavior. In this study, it was observed that the BMI of overweight and obese individuals was lower than that of normal and underweight individuals, and the difference between BMI and BMI groups was statistically significant. This finding led to the conclusion that individuals with nutrition knowledge eat more consciously and are more successful in body weight management. On the other hand, it was thought that the presence of underweight individuals among the individuals with nutrition knowledge may be related to aesthetic concerns and the perception of being thin as being healthy in the media. The difference between the NKS of those with and without chronic disease risk according to the parameters of WHR and waist-to-height was not found to be statistically

significant. This result suggested that individuals should increase their nutrition knowledge and raise awareness about transforming their knowledge into behavior in order to prevent not only obesity but also abdominal obesity, which is a risk factor for chronic diseases.

The relationship between nutrition knowledge level and obesity-related anthropometric measurements has been examined by various researchers.[28-30] In some studies examining the relationship between nutrition knowledge and BMI, no significant relationship was found.[21,30] On the other hand, a study by Valmórbida et al.[29] reported a negative relationship between nutrition knowledge level and BMI, WC, and waist-to-height ratio In this study, a low but significant negative correlation was found between NKS and BW, BMI, WC, and waist-to-height ratio. These contradictory results indicate that more comprehensive and specific studies investigating the relationship between nutrition knowledge and anthropometric measurements are needed.

Nutrition is an important factor in the treatment and prevention of many diseases as well as health protection. It is extremely important to determine the level of nutrition knowledge and to understand its relationship with food consumption.[31] In this study, the portion amount of meat-egg-legume group foods (red meat, white meat, etc.) and the amount of olive oil consumed per day increased with increasing NKS, while the consumption of bread and cereal group foods (bread, rice, pasta, bagels, etc.) and margarine consumption decreased. For adequate and balanced nutrition, foods in the five food groups should be consumed in the recommended amounts every day. Meat-egg-legume group foods are important as a source of protein. Olive oil is one of the most important components of the Mediterranean diet and is recommended for a healthy diet.[5] It is thought that these foods are consciously preferred as the NKS increases, and the consumption of bread and cereals, and margarine is also consciously limited. Butter is a type of fat that should be limited due to its saturated fat content.[5] However, in this study, it was observed that individuals with higher NKS than others preferred butter as a solid fat. The use of butter is common in Turkish cuisine and it is thought that butter is preferred to margarine in terms of traditional and cultural values. There are contradictions in the results of studies examining the relationship between NKS and food consumption. Similar to the present study, some studies have found a positive relationship between NKS and consumption of meat group foods and olive oil, while a negative relationship was found between NKS and carbohydrate intake.[32,33] However, studies have also reported that there is no relationship between NKS and food consumption or that various different results have been obtained.[31,34] In a study, it was also reported that nutrition knowledge does not translate into correct dietary behavior and that nutrition knowledge level alone is not effective on dietary behavior.[35] In addition to many individual factors such as taste, food preference, food costs, cultural and religious beliefs, it has been stated that the differences in study groups also affect this result.[31]

Study Limitations

In this study, the food group choices of individuals were examined, but the determinants of food choice, such as the characteristics of the foods they choose, familial, cultural, and social factors were not questioned. In addition, the disproportion between the numbers of male and female participants, the disproportion between BMI groups, the selection of participants from a single region, and the recording of food consumption for a single day can also be considered as limitations of the study.

CONCLUSION

In this study, it was observed that the nutrition knowledge scores of overweight and obese individuals were lower than those of normal weight and underweight individuals, and the difference between those with normal weight and those with 1st-degree obesity was found to be significant. In the study, it was determined that the mean nutrition knowledge score of individuals was low. Individuals' NKS also showed a negative relationship with anthropometric measurements associated with obesity. As NKS increased, consumption of meat-egg-legume group foods and olive oil increased, while consumption of bread and cereal group foods and margarine decreased. However, since this study's result based on an observation and correlation analysis, cause-effect relationships should not be conclusively inferred. Further research and analysis may be required. In future studies, the effects of factors related to food group choices should also be investigated.

Since BMI is associated with education level, consumption of daily food groups, and anthropometric measurements, the level of knowledge about adequate and balanced nutrition should be increased to prevent obesity and chronic diseases and to improve quality of life. For this purpose, it is thought that it will be useful to organize periodic and effective nutrition education by dietitians to be assigned to family health centers where the individuals can easily reach them.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Social and Humanities Researches Ethics Committee (Date: 20.07.2016, Decision No: 3).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer reviewed.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Retrospective assessment of pediatric patients with tube thoracostomy inserted in a tertiary pediatric intensive care unit

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ABSTRACT

Aims: The aim of this study was to examine the indications for tube thoracostomy (TT) procedures in pediatric intensive care units and to analyze the role of chest X-rays in the subsequent monitoring and management of patients.

Methods: A retrospective evaluation of 31 pediatric patients aged 1 month to 18 years who had been admitted between January 2023 to July 2023 at Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, were performed. Children who underwent TT were included. Demographic data, clinical variables, and outcome data were analyzed

Results: The median age was 50 (4-214) months, and the gender distribution of the patients was almost equal. The median duration of a PICU stay was 10 (4-100) days. Pneumothorax (PTX) was diagnosed in 45,1%, pleural effusion in 38,7%, and hemothorax in 16,1% of patients. Six (19,4%) patients experienced complications related to chest tubes. Invasive mechanical ventilation (IMV) was required in 19 patients (61,3%), and the median duration of IMV was 9 (3-93) days. A total of 23 patients (74,2%) required non-invasive mechanical ventilation (NIMV) support during their stay in PICU. There was no statistically significant difference between indications of TT and length of stay, NIMV and IMV requirement, duration of TT, complications, and mortality.

Conclusion: TT is a life-saving interventional procedure in emergencies. The absence of proper execution of this technique may result in considerable morbidity and fatality. Hence, all clinicians must possess a comprehensive understanding of the tube thoracostomy operation.

Keywords: Pediatrics, pleural effusion, pneumothorax, trauma, thoracostomy

INTRODUCTION

Pediatric intensive care units (PICUs) are designated facilities that are dedicated to the management and treatment of challenging clinical scenarios. These facilities offer treatments to critically ill children who suffer from multiple organ system involvement, requiring careful coordination of their treatment. One of the therapeutic options involves the placement of a tube thoracostomy in the pleural space. Tube thoracostomy (TT) is indicated in various pathological conditions, including pneumothorax, hemothorax, empyema, pleural effusion, and chylothorax.[1] Furthermore, the necessity for TT may arise in children undergoing treatments such as anesthesia and chemotherapy, as well as following lung and heart surgeries, due to drainage requirements.[2]

Chest X-rays (CXR) play a crucial role in the management of TT. The American College of Radiology (ACR) has put up a recommendation advocating for the daily use of radiographs in critically ill patients.[3] Nevertheless, the management and utilization of TT vary significantly heterogeneity across different healthcare organizations.[4]

The objective of this study was to examine the indications for tube thoracostomy procedures in pediatric intensive care units and to analyze the role of chest X-rays in the subsequent monitoring and management of patients.

METHODS

The study was carried out with the permission of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Researches Ethics Committee (Date: 17.02.2023, Decision No: 2023/07). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki, and all study-related anonymized data are available upon reasonable request. We obtained informed consent from all parents before hospitalization and during all procedures.

A retrospective evaluation of 31 pediatric patients who underwent tube thoracostomy was performed (between 0 and 18 years of age) at Sancaktepe Şehit Prof Dr İlhan Varank

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Training and Research Hospital PICU from January 2023 to July 2023. Healthcare provision for children aged from 1 month to 18 years is provided in our PICU, which is equipped with 12 beds, 12 ventilators, 5 Prismaflex™ hemofiltration machines (Baxter, USA), and 9 isolation rooms. A total of 525 patients were hospitalized and followed up during the study period. The study excluded patients who were admitted to the PICU more than 24 hours following the insertion of a thoracostomy tube or died prior to TT removal. Tube thoracotomies were placed by the pediatric surgeon. To maintain consistency, only the last TT removal event was reviewed. Therefore, TT removals in a given patient were not reviewed for removal details while another TT remained intact. In the study, patients who underwent the simultaneous removal of two TTs were included as a single count.

Following TT removal, a post-removal CXR was obtained. The timing was variable; therefore, CXR following removal between 2 h and up to 12 h following TT removal was considered as a post-removal CXR.

A detailed form was used to collect data on the patient's age, gender, comorbid disease, reasons for admission, length of stay in PICU, requirement for invasive mechanical ventilation (IMV) and noninvasive ventilation (NIV), TT indications and duration, complications, and mortality. For the calculation of the Pediatric Risk of Mortality III (PRISM III) Score, data from 16 variables regarding temperature, systolic blood pressure, heart rate, partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), GCS, pupillary reaction, prothrombin time (PT) and activated partial thromboplastin time (APTT), serum creatinine, serum urea nitrogen, serum potassium, blood glucose, and serum bicarbonate levels, white blood cell and platelet counts were recorded within 24 hours of PICU admission.

Statistical Analysis

SPSS statistical software 20.0 for Windows (Armonk, New York: IBM Corp.) was used for statistical analyses. Numbers, frequencies [%], ratios, medians, and standard deviation values were used in the descriptive statistics of the data. The distribution of variables was checked by using the Kolmogorov-Smirnov test. The $\chi 2$ test was used to compare categorical variables, and the Fischer test was used when chi-square conditions could not be met.

RESULTS

A total of 31 pediatric patients who required tube thoracostomy were included in our study. The median age was 50 (4-214) months, and the gender distribution of the patients was almost equal. The median duration of a PICU stay was 10 (4-100) days. The median PRISM score was 6 (0-29). Eight patients (25.8%) had co-morbid diseases, while respiratory tract diseases were the most common (12.9%). Respiratory diseases (64.5%) such as pneumonia and asthma attacks were among the most common causes of admission to the PICU in patients undergoing TT, followed by trauma (22.6%) (Table 1).

Table 1. Clinical characteristics of patients admitted to pediatric intensive care

Gender, n (%)	
Male	16 (51.6)
Female	15 (48.4)
Age (month), median (min-max)	50 (4-214)
PRISM III score), median (min-max)	6 (0-29)
Comorbid diseases, n (%)	
Respiratory diseases	4 (12.9)
Neurological diseases	2 (6.5)
Hematology-oncological diseases	1 (3.2)
Metabolic diseases	1 (3.2)
Etiologies of admission, n (%)	
Respiratory diseases	20 (64.5)
Trauma	7 (22.6)
Neurological diseases	2 (6.5)
Others	2 (6.5)
Length of stay, median (min-max)	10 (4-100)
Requirement of IMV, n (%)	19 (61.3)
IMV duration, median (min-max)	9 (3-93)
Requirement of NIMV, n (%)	23 (74.2)
NIMV duration, median (min-max)	4 (1-11)
NIMV modality, n (%)	
HFNC	16 (69.5)
NIMV-oronasal	5 (21.7)
NIMV-nasal	2 (8.7)
NIMV, n (%)	
Inisial	13 (56.5)
Postextubation	10 (43.5)
Mortality, n (%)	6 (19.4)

HFNC: High-flow nasal cannula, IMV: Invasive mechanical ventilation, NIMV: Noninvasive mechanical ventilation, PRISM III: Pediatric Risk of Mortality III,

Analysis of the patients' TT indications reveals that pneumothorax (PTX) accounts for roughly 45.1% of them, followed by pleural effusion (38.7%), and hemothorax (16.1%). Six (19.4%) patients experienced complications related to chest tubes (Table 2). Effective oscillation could not be achieved due to malposition in 2 patients. The thoracic tube was removed unplanned in 2 patients. In 2 patients, recurrent pneumothorax was observed after tube removal. CXR was performed in 17 patients after tube removal. Recurrent PTX was identified in one of these patients while conducting a post-removal chest X-ray, despite the absence of accompanying symptoms. In the CXR of the second patient, recurrent PTX was seen, which was taken after the occurrence of desaturation during the follow-up period. The other 13 patients who did not undergo CXR were asymptomatic.

Invasive mechanical ventilation (IMV) was required in 19 patients (61.3%), and the median duration of IMV was 9 (3-93) days. A total of 23 patients (74.2%) required non-invasive mechanical ventilation (NIMV) support during their stay in PICU. NIMV support was required after extubation in 43.5% of the patients. High-flow nasal oxygen therapy was

given in 69.5% of the patients as NIMV support, followed by NIMV-oronasal in 21.7% and NIMV-nasal in 8.7%. The median duration of NIMV was 4 (1-11) days. Of 9 patients with PTX who required NIMV support, 6 underwent HFNC and 3 underwent nasal NIMV. No increase in air leakage was observed during NIMV administration in these patients.

Table 2. Clinical characteristics of chest tubes placed in pediatric intensive care

TT indication, n (%)	
Pneumothorax	14 (45.2)
Pleural effusion	12 (38.7)
Hemothorax	5 (16.1)
Location TT , n (%)	
Right	24 (77.4)
Left	4 (12.9)
Both sides	3 (9.7)
TT duration, days, median (min-max)	5 (2-36)
Complications, n (%)	6 (19.4)
Chest X-Ray after TT removal	
Yes	17 (54.8)
No	14 (45.2)

TT: Tube thoracostomy

In univariate analyzes for indications of TT, no statistically significant difference was found in terms of PICU length of stay, NIMV and IMV requirement, duration of TT, complications, and mortality (Table 3).

DISCUSSION

Therapeutic tube thoracostomy is indicated in both pediatric and adult populations, presenting a range of clinical manifestations. The majority of the studies on the management of thoracostomy tubes and catheters have been done in adults. There is a limited number of research that has been conducted in the pediatric population. The effectiveness of therapeutic TT in pediatric patients appears to be superior to that observed in adult populations. Due to differences in anatomical and metabolic characteristics, earlier detection of respiratory failure in children causes symptoms to appear earlier compared to adults. Earlier diagnosis and treatment correlate with better outcomes.[5]

According to pediatric studies, there is a higher prevalence of thoracic trauma and the requirement for TT placement in the male gender within the childhood age group.[6,7] In our study, we found almost equal distribution between the genders. This difference in distribution was attributed to the diagnosis of the patients. Since patients other than trauma are admitted in our PICU, gender distribution may be different compared to TT studies in which only trauma patients are included.

The placement of a thoracostomy tube is a frequently performed medical intervention aimed at evacuating air (pneumothorax), fluid (effusion), pus (empyema), or blood (hemothorax) from the pleural cavity, as well as administering drugs into this region for therapeutic purposes such as pleurodesis or fibrinolysis.[8] In our study, TT was mostly used for PTX drainage, followed by pleural effusion. This can be explained by patients with high auto-positive end-expiratory pressure (PEEP) such as asthma, bronchiolitis, and subsequent trauma exposure. In addition, we found the rate of hemothorax to be 16.1%, consistent with the literature.[9,10]

Acute respiratory failure can be induced by clinical circumstances such as respiratory tract infections and severe thoracic injuries, which result in alveolar collapse and destruction.[11] Hence, for decades, the utilization of invasive mechanical ventilation accompanied by PEEP has been advocated as the sole viable method of providing respiratory support to enhance gas exchange. IMV has been performed in up to 50% of patients with chest injuries.[12] While tracheal intubation and mechanical ventilation are essential medical interventions that can save lives, they are not without potential drawbacks. These interventions have been associated with complications such as barotrauma, ventilator-associated infections, and other issues related to sedation and immobility.[13] Non-invasive mechanical ventilation (NIMV) has the potential to enhance gas exchange and potentially mitigate the need for intubation and mechanical ventilation in certain pediatric patients.[14] In cases with PTX, especially positive pressure ventilation can increase air leakage and eventually lead to hypertensive pneumothorax. However, Chiumello et al.[12] showed no significant relationship between the use of NIMV and the incidence of pneumothorax. Given that continuous positive airway pressure (CPAP) presents a reduced physiological risk of barotrauma while maintaining comparable efficacy to non-invasive mechanical ventilation (NIMV), it is recommended as the primary therapeutic approach for those suffering from severe chest trauma. In our study, no increase in air leakage was observed in patientes requiring NIMV support during the TT insertion period.

Table 3. Comparison of chest tube indications

	Pneumothorax	Pleural effusion	Hemothorax	p
Length of stay, median (min-max)	12.5 (7-100)	9 (4-17)	16 (4-64)	0.181
Requirement of IMV, n (%)	10 (52.6%)	5 (26.3%)	4 (21.1%)	0.193
IMV duration, median (min-max)	12.5 (4-93)	6 (5-7)	15 (3-32)	0.069
Requirement of NIMV, n (%)	9 (39.1%)	11 (47.8%)	3 (13%)	0.308
NIMV duration, median (min-max)	5 (1-11)	3 (1-10)	3 (1-10)	0.406
TT duration, median (min-max)	5 (2-25)	5 (3-15)	6 (3-36)	0.777
Complications, n (%)	4 (66.7%)	0 (0.0%)	2 (33.3%)	0.082
Mortality, n (%)	5 (83.3%)	1 (16.7%)	0 (0.0%)	0.071

IMV: Invasive mechanical ventilation, NIMV: Noninvasive mechanical ventilation, TT: Tube thoracostomy

The tube thoracostomy placement carries inherent risks. Numerous issues may arise throughout the application process or during the subsequent follow-up period. Although estimates of the rate of injury in children are often greater than those for adults, with some publications citing rates as high as 30%, the risks of complications are thought to be the same for both children and adults.[15-17] The most common complication of tube thoracostomy is malposition of the tube, as in our study.[18]

Since TTs are often used for the drainage of pleural fluid or the evacuation of air leaks, a new air leak or fluid can accumulate in the pleural cavity upon removal of TT. These potential side effects of chest tube removal can cause respiratory distress and require immediate attention. Generally, a post-removal CXR was obtained after TT removal to rule out any complications. However, considering the number of complications found in post-removal CXR in studies, the place of routine CXR has become controversial to reduce radiation exposure and be cost-effective, especially in pediatric patients.[4,19] In our study, recurrent PTX was seen in 2 patients, routine CXR was not performed in only 1 of them. PTX was detected in the CXR taken due to respiratory distress in the patient. Due to the insufficient number of patients, there was no statistical significance in our study in terms of routine CXR. However, multicenter and large studies are needed to establish post-removal guidelines instead of routine CXR, especially considering radiation exposure in pediatric patients.

Study Limitations

The most important limitation of our study is the small number of patients. With medical advances and the development of less invasive treatment strategies, there have been fewer TT insertions and subsequent removals in patient subgroups, making our overall numbers for analysis small.

CONCLUSION

TT is a life-saving interventional procedure in emergencies. This method, which must be implemented universally across all age groups, might arise as a result of either traumatic or non-traumatic causes. The absence of proper execution of this technique may result in considerable morbidity and fatality. Hence, all clinicians must possess a comprehensive understanding of the tube thoracostomy operation.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Sancaktepe Şehit Prof Dr İlhan Varank Training and Research Hospital Scientific Researches Ethics Committee (Date: 17.02.2023, Decision No: 2023/07).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Evaluation of color stability of bulk-fill restorative materials with different properties

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ABSTRACT

Aims: The present study aims to evaluate the color stability of bulk-fill restorative materials with different properties over different time periods when immersed in a coffee solution.

Methods: According to the selected restorative materials, the study groups were formed as follows: CNT/light (Alkasite, Cention N, Ivoclar Vivadent, light cure mode), CNT/self (Alkasite, Cention N, self cure mode) EQF (Glass hybrid restorative, Equia Forte HT, GC Corporation), AU (Single-shade bulk fill, Aura Bulk Fill, SDI), Z550 (Filtek Z550, 3M) (control group). A total of 50 samples (n=10) were prepared using standard molds (2mmx10mm). After finishing and polishing procedures, all samples were kept in distilled water at 37°C for 24 hours. The first color measurement (L*a*b) was performed with Vita Easy Shade V (VITA Zahnfabrik). Samples were added to the coffee solution. Color was measured at times simulating 7 days, 1 month, 6 months and 1 year of clinical service. Color changes (ΔE1, ΔE2, ΔE3 and ΔE4) were calculated according to the CIE L*a*b system. Normality of the data was examined by D'Agostino & Pearson omnibus normality test. One-way ANOVA analysis and Tukey test were performed. Statistical significance level was set at p 0.05 and statistical analysis software (GraphPad Prism 6.0, GraphPad Software, USA) was used for the analysis.

Results: According to ΔE1 results; clinically unacceptable color change (ΔE>3.3) values were observed in CNT/light and CNT/self groups. The color change values of EQF, Z550 and AU groups were statistically similar (p>0.05). According to ΔE2 results; an unacceptable color change (ΔE>3.3) was observed in all groups except EQF. According to ΔE3 results; an unacceptable color change (ΔE>3.3) was observed in all groups. According to ΔE4 results; an unacceptable color change (ΔE>3.3) was observed in all groups. The color change values of EQF, Z550 and AU groups were statistically similar (p>0.05). CNT/light group showed the highest color change in all time periods, followed by CNT/self group.

Conclusion: The color stability of single-shade bulk fill material and glass hybrid restorative materials is similar to the control group. The color stability of alkasite material needs to be improved.

Keywords: Alkasite, bulk fill, cention N, color stability, glass hybrid

This study was presented as an oral presentation at the "Zonguldak Bülent Ecevit University Faculty of Dentistry 1st International Congress of Dentistry" (September, 2022) with the title "Comparative Evaluation of Color Stability of Alkasit Restorative Material with Different Restorative Materials".

INTRODUCTION

The physicochemical characteristics of dental materials have undergone continuous improvements since their initial appearance in the dentistry market. Furthermore, novel products are consistently being introduced to address current problems associated with restorative materials.[1] The rapid application of restorative materials is especially important in hard-to-reach areas and with uncooperative patients. Therefore, in recent years, manufacturers have focused on simplifying techniques.[2]

Composite resin materials are among the most commonly used tooth-colored restoration materials.[2,3] In order to achieve effective light transmission and adequate polymerization, it is recommended that composite resins are applied by a layering technique with a maximum of 2 mm. However, there are disadvantages of this technique: it is time-consuming as each layer requires separate light polymerization, there is a possibility of air bubbles between layers, and there is a risk of moisture contamination.[1,3] Recently, bulk-fill composite resins have been produced which overcome these problems as it has been stated that these products can be applied up to a thickness of 4-5 mm thickness at one time.[4] Another simplification development in composite resins has been the production of singe-shade composite resins that have a "chameleon effect".[2] In this way, time is not wasted with shade selection. Today, some companies have started to produce composite resins with both bulk-fill and single-shade properties.

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Another product line that manufacturers are working on to simplify procedures is 'self-adhesive' restorative materials. Self-adhesive materials are chemically bonded to hydroxyapatite via monomers that can erode enamel and dentin, and this eliminates the need for a separate adhesive application step. These self-adhesive materials can also be applied as bulk-fill.[5-7]

Recently, a new self-adhesive bulk-fill material Cention N (Ivoclar Vivadent, Schaan, Liechtenstein) has been introduced. This material, defined as alkasite, is essentially a subgroup of composite resin. It is a tooth-colored material, but its mechanical properties have been noted as comparable to an amalgam. It can release fluoride ions and can be polymerized light-cured or self-cured.[8,9]

Another group of self-adhesive bulk-fill restorative materials produced in recent years is "glass hybrid restorative materials".[10] These materials were introduced to the market to overcome the disadvantages of conventional glass ionomer materials and resin composites without compromising their advantages. The latest version of these materials, Equia Forte HT (GC, Tokyo, Japan), manufactured in 2019, can release fluoride ions and can be used for permanent posterior restorations.[10,11]

Today, with increasing aesthetic demands, the color match and color stability of restorative materials have become important in determining the longevity of a restoration, even in the posterior region. There are, however, few studies on the color stability of the new bulk-fill restorative materials mentioned in the literature.[9,12,13]

The present study aims to evaluate the color stability of bulk-fill restorative materials with different properties over different time periods when immersed in a coffee solution.

The hypothesis formulated for this purpose is "The type of restorative material will not affect color stability".

METHODS

Only restorative materials were used in this study. It was not tested on humans or animals and no materials derived from humans or animals were used. Therefore, ethics committee approval is not required. All procedures were carried out in accordance with the ethical rules and the principles.

The present study exclusively utilized restorative material in an in vitro setting, which eliminated the need for ethical approval. All specimens and phases of the experiment were handled by the same operator. The manufacturer, classification, content, and application procedure of the materials used in the study are listed in **Table 1**. The flowchart of the experimentation method is illustrated in **Figure 1**.

Table 1. Manufacturer, classification, content, and application procedure of the materials used in the study

Group	Material	Classification	Content	Application Procedure
CNT/light CNT/self	Cention N, A2 (Ivoclar Vivadent, Liechtenstein)	Alkasite Restorative Material: Self-curing with light-curing option, Bulk fill, Self adhesive	Liquid: UDMA DCP Aromatic aliphatic-UDMA PEG-400DMA Powder: Barium aluminum silicate glass filler Ytterbium trifluoride Isofiller Calcium barium aluminum fluorosilicate glass filler Calcium fluorosilicate (alkaline) glass filler	Mix 2 drops of liquid to 2 measuring spoons of powder until smooth. Condense using a plastic filling instrument. Light cure: for 20 sec Self-cure :5 min (from the start of mixing)
EQF	Equia Forte HT, A2 & Equia Forte Coat (GC Corporation, Japan)	Glass hybrid restorative material: Bulk fill, self adhesive	Liquid: Polybasic carboxylic acid, water Powder: Fluoroaluminosilicate glass, polyacrylic acid, iron oxide Coat: Methyl methacrylate, colloidal silica, camphorquinone, urethan methacrylate, phosphoric ester monomer	Mechanically mixed for 10 sec Deposited in inside mold and closed on the surface by a mylar strip Wait for 10 min Equai Forte Coat was applied and light-cured for 20 sec
AU	Aura Bulk-fill universal shade (SDI, Australia)	Universal bulk fill composite	Diurethane dimethacrylate (3-20% wt.) Bis-EMA UDMA TEDGMA Bis-GMA Amorphous SIO Barium alumino-borosilicate glass Pre- polymerized filler (81% wt.)	Light cure for 20 sec using a high powered LED curing light
Z550	Filtek Z 550 A2, (3M ESPE, USA)	Nanohybrid resin composite	Bis-GMA UDMA TEGDMA PEGDMA Bis-EMA Silica Zirconia	Light cure for 20 sec using a high powered LED curing light

Bis-EMA: Bisphenol A ethoxylate dimethacrylate; Bis-GMA: Bisphenol A glycerolate dimethacrylate; PEGDMA: Polyethylene glycol dimethacrylate; TEGDMA: Triethylene glycol dimethacrylate; UDMA: Urethane-dimethacrylate

Specimen Preparation

G*power software (version 3.1.9.4) was used to determine the sample size. The minimum number of specimen required for each group was determined to be 9, with 95% confidence (1-α) and a f=0.655 effect size. Considering the possible specimen loss, the study was planned with 10 specimens for each group.

The study groups were formed as follows:

- CNT/self: Alkasite restorative material cured / self-cure mode (Cention N)
- CNT/light: Alkasite restorative material cured / light-cure mode (Cention N)
- EQF: Glass hybrid restorative material (Equia Forte HT)
- AU: Single-shade bulk-fill composite resin (Aura Bulk Fill)
- Z550: Control group, nanohybrid composite resin (Filtek Z550)

A total of 50 samples (n=10) were prepared and placed in standard (2 mm × 10 mm) disk-shaped metal molds. A mylar strip was placed to cover the surface of the sample and then a glass slide was added to create pressure. This allowed excess material to be forced out of the slide. The groups to be cured as self-cure (CNT/self and EQF) were left to set as specified in the manufacturer's instructions. The light polymerized specimens were cured using an LED lamp (SmartLite Focus, Dentsply, USA) for 20 sec from a distance of 1 mm (1000 mW/cm²). After the glass slide was removed, additional polymerization was performed for 10 seconds from the top surface of the samples. Then, the top surfaces of all specimens were polished with course (10 sec), medium (10 sec), fine (10 sec), and super fine (10 sec) aluminum oxide impregnated discs (OptiDisc, Kerr Corporation, USA) respectively, with a micromotor of 10,000 rpm set and with linear movements under dry conditions.[14] A new disk was used for each specimen. A surface sealant (Equia Coat, GC, Japan) was applied to the EQF group according to the manufacturer's instructions and polymerized with the same LED lamp. The specimens were kept in distilled water at 37°C for 24 h to allow the polymerization to complete.

Staining of the Specimens

To prepare the coffee solution, a soluble granulated coffee was chosen. It was prepared using 2 g of coffee per 200 ml of boiling water and allowed to stand until the solution temperature reached 37°C. 1.5 mm Eppendorf tubes were used to hold the specimens separately in the solution and these tubes, in which the solution and specimen were placed, were kept at 37°C to replicate oral conditions. The specimens were kept in the coffee solution for a total of 12 days representing 1 year clinically.[15] The solutions in the tubes were changed daily.

Color Measurement

Color measurement was performed at 5 time points: T0 (initial), T1 (336min), T2(24h), T3 (144h), T4 (12 days). (Figure 1). The color measurement at T0 was taken before the staining procedures. At time points T1, T2, T3, and T4, the stained specimens were removed from each Eppendorf tube and washed with distilled water for 10 sec, and then dried with paper for 10 sec. Color measurement was then performed immediately and this procedure was repeated for each specimen individually. Color measurement was performed on a gray card with a contact-type spectrophotometer (VITA EasyShade V, VITA Zahnfabrik, Germany) using the CIE L*a*b* system. The 3-point measurement mode was selected, and the instrument was re-calibrated after each measurement. The averages of the obtained L*, a*, and b* values were recorded. The total color difference (ΔE) for each specimen was calculated using the following equation:

$$[(\Delta L)2+(\Delta a)2+(\Delta b)2]½$$
$$\Delta L=L2^*-L1^*$$
$$\Delta a=a2^*-a1^*$$
$$\Delta b=b2^*-b1^*$$

'The colour changes between T1 and T0, T2 and T0, T3 and T0, and T4 and T0 were named ΔE1, ΔE2, ΔE3, and ΔE4 respectively.

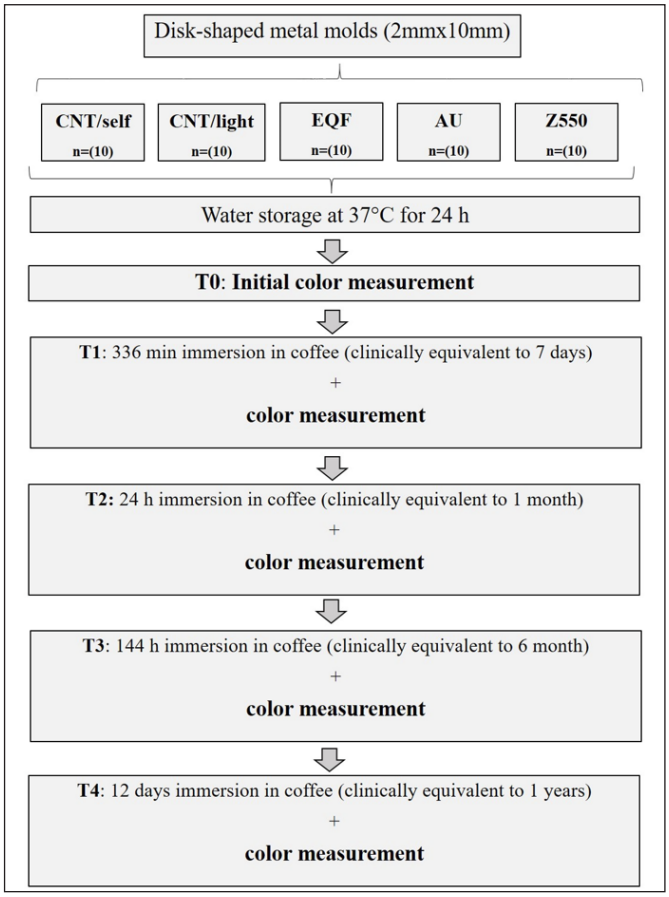

Figure 1. The flowchart of the experimentation method.

Statistical Analysis

The normality of the data was examined with the D'Agostino & Pearson omnibus normality test. After it was determined that the data were suitable for normal distribution, the One-way ANOVA analysis and Tukey test were performed. The statistical significance level was accepted as $p<0.05$ and a piece of statistical analysis software (GraphPad Prism 6.0, GraphPad Software, La Jolla, CA, USA) was used for analysis.

RESULTS

The ΔE1, ΔE2, ΔE3, and ΔE4 color change values, together with their statistical similarities and differences are summarized in Table 2.

Table 2. Color change values of groups according to different time periods

Group	ΔE1 Mean±SD	ΔE2 Mean±SD	ΔE3 Mean±SD	ΔE4 Mean±SD
CNT/light	12.2±1.496[a]	15.53±1.768[a]	25.03±3.278[a]	40.79±4.671[a]
CNT/self	8.635±1.09[b]	13.64±1.947[b]	19.05±1.435[b]	30.82±3.077[b]
EQF	2.006±0.366[c]	3.22±0.6878[c]	4.891±0.492[c]	16.24±2.455[c]
Z550	2.703±0.5753[c]	4.86±0.7523[cd]	6.477±0.936[cd]	18.23±1.98[c]
AU	3.07±0.6107[c]	4.974±0.859[d]	8.173±0.833[d]	19.26±1.78[c]

Superscript lowercase letters compare the means in each column. There is no statistically significant difference between means shown with the same superscript letter ($p>0.05$).

When the results of ΔE1 were evaluated (Figure 2):

CNT/light (12.2±1.496) group showed significantly higher color change than the other groups. Clinically unacceptable color change (ΔE>3.3) values were observed in CNT/light and CNT/self (8.635±1.09) groups. The color change values of EQF (2.006±0.366), Z550 (2.703±0.5753) and AU (3.07±0.6107) groups were statistically similar ($p>0.05$).

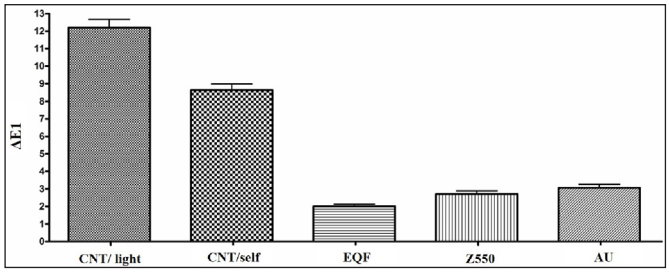

Figure 2. ΔE1: Mean color change values according to groups between T1-T0.

When ΔE2 results were evaluated (Figure 3):

Although the color change values of groups EQF (3.22±0.6878) and Z550 (4.86±0.7523) were statistically similar, an unacceptable color change (ΔE>3.3) was observed in all groups except EQF. CNT/light (15.53±1.768) showed significantly higher color change than all other groups ($p<0.05$).

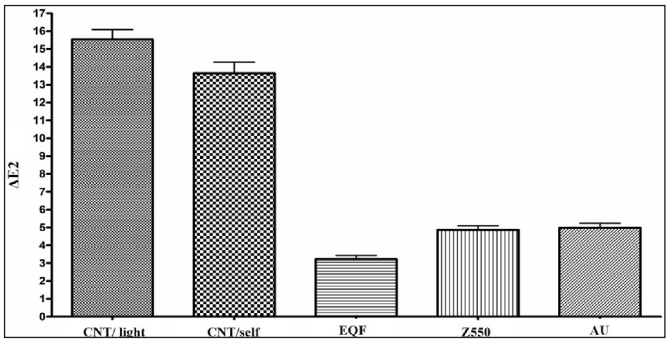

Figure 3. ΔE2: Mean color change values according to groups between T2-T0.

When ΔE3 results were evaluated (Figure 4):

An unacceptable color change (ΔE>3.3) was observed in all groups. CNT/light (25.03±3.278) showed significantly higher color change than all other groups. The color change value of EQF (4.891±0.492) was significantly lower than CNT/light, CNT/self (19.05±1.435), AU (8.173±0.833) and similar to Z550 (6.477±0.936).

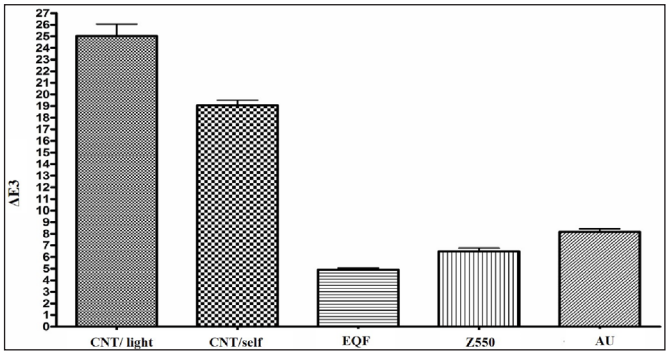

Figure 4. ΔE3: Mean color change values according to groups between T3-T0.

When ΔE4 results were evaluated (Figure 5):

An unacceptable color change (ΔE>3.3) was observed in all groups. Group CNT/light (40.79±4.671) showed significantly higher color change than all other groups ($p<0.05$). Group CNT/self (30.82±3.077) showed higher color change than groups EQF (16.24±2.455), Z550 (18.23±1.98) and AU (19.26±1.78) ($p<0.05$). The color change values of EQF, Z550 and AU groups were statistically similar ($p>0.05$).

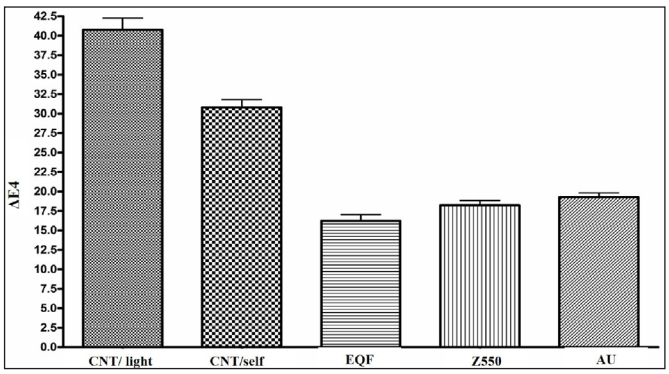

Figure 5. ΔE4: Mean color change values according to groups between T4-T0.

DISCUSSION

In the present study, the color stability of current, bulk-fill restorative materials with different properties was investigated by comparing them with a commonly used nanohybrid composite resin. In the color analysis of all time periods, both light-cure and self-cure modes of the alkasite restorative material showed significantly higher color change than the other groups. Therefore, the hypothesis "The type of restorative material will not affect color stability " was rejected.

Restorative materials are constantly exposed to food and beverages. In the literature, the most commonly used solutions to evaluate the color stability of composite resins are coffee, tea, red wine, and cola.[16] There is no definite application procedure regarding the temperature of the coloring solutions, the residence time of the materials in the solutions, and the frequency of changing the solutions. However, there are studies in the literature in which the coloring solution was used at different temperatures, such as 37°C, room temperature, or at the recommended consumption temperature. The most preferred method is to use the solution at 37°C to simulate the oral environment as used in the present study.[16]

In studies investigating the color stability of restorative materials, immersion times in coloring solutions also varies. It has been stated that a cup of coffee is consumed in about 15 min. and the average daily coffee consumption per person is 3.2 cups, and in many studies, soaking in coloring solutions was made based on this average value.[15,17] When composite resin materials are in contact with liquids, most of the water absorption by the organic matrix occurs in the first 4 days and the highest absorption occurs during the first week. Color pigments in colorant solutions can enter the resin matrix through water. Since the colorant solution also has a tendency to follow water absorption, most coloration occurs in the first week.[18] The most commonly evaluated immersion time in studies is clinically 7 days.[16] In the present study, immersion times corresponding to 7 days, 1 month, 6 months, and 1 year were selected to detect early and relatively later color changes.

Similar to the present study, the clinically acceptable threshold value $\Delta E \leq 3.3$ has been accepted in many studies when color change is calculated with the CIE L*a*b* system.[9,16]

The alkasite restorative material groups (CNT/light and CNT/self) showed clinically unacceptable color change at all color analysis times. In addition, the CNT/light group showed significantly more discoloration than the CNT/self-group at all time points. The authors have found only two studies in the literature comparing the color stability of different curing modes of alkasite restorative material.[12,19]

In one of these studies, specimens were immersed in cherry juice, iced tea, and distilled water. For cherry juice and iced tea, the self-cured Cention N group showed less coloration than the light-cured group. The groups kept in distilled water showed similar color changes. In addition, a different color change calculation system, the CIEDE 2000 system, was used in the aforementioned study.[12] Despite the methodological differences, we can conclude that the mentioned study does not support the present study.

In the other study on the subject, the specimens were kept in distilled water without using coloring solution. After 28 days of immersed in distilled water, the light-cure Cention group showed higher color change than the self-cure Cention group.[19] Discoloration of restorative materials in distilled water without a staining solution may be due to changes in the interface between unreacted monomers, fillers and resin matrix, oxidation of the resin matrix and is defined as intrinsic discoloration.[20] Although the aforementioned study[19] provides some information, it cannot be compared to the present study because the present study does not have a methodology where only intrinsic coloration can be evaluated.

In a study investigating the surface roughness and flexural strength values of light-cured and self-cured modes of Cention N, the self-cure mode of Cention N was found to be superior and the authors stated that this was probably due to the slow and prolonged curing of self-cured Cention N.[8] This may explain the higher coloration of the CNT/light group in the present study.

In a study examining the color stability of Cention N and a glass hybrid restorative material (Equia forte, GC, Japan), the color analysis of specimens immersed in a coffee solution at different time periods showed that the color stability of the glass hybrid restorative material was superior to Cention N.[21] Although the aforementioned study used a previous version of the glass hybrid restorative material than that used in the present study, the results of the two studies support each other.

In another study using coffee immersion and thermal aging, Cention N (self-curing) showed lower color stability than nanohybrid composite resin, but higher color stability than glass hybrid restorative material.[9] These results are partially different from the present study. However, the glass hybrid restorative material used in the aforementioned study is a previous version of the one used in the present study.

The lack of additional methods such as brushing simulation and thermal aging are limitations of this study. More extensive studies on the color stability of simplified bulk-fill restorative materials should be conducted.

The authors also believe that one of the reasons for the conflicting results in the literature regarding the color stability of Cention N material is that the material is in powder-liquid form and is mixed by hand. Testing the newly available capsule form may yield more consistent results.

CONCLUSION

The conclusions reached within the limitations are as follows:

The color stability of glass hybrid restorative material and single-shade bulk-fill composite resin materials is similar to that of conventional nanohybrid composite resin. The color stability of the alkasite restorative material needs to be improved. Alkasite restorative material changes color more when light-cured than when self-cured.

ETHICAL DECLARATIONS

Ethics Committee Approval: Only restorative materials were used in this study. It was not tested on humans or animals and no materials derived from humans or animals were used. Therefore, ethics committee approval is not required.

Informed Consent: Only restorative materials were used in this study. Therefore, informed consent is not required.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Pediatric forearm fractures: evaluating implant removal timing and complications with exposed titanium-elastic nail tips

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ABSTRACT

Aims: The current study investigates complication rates, timing of implant removal, and correlations between removal timing and complications/refractures in pediatric forearm fracture patients who had exposed titanium-elastic nail (TEN) tips.

Methods: This retrospective single-center study analyzed pediatric forearm fractures in patients who underwent TEN with exposed tips. Inclusion criteria covered cases between August 2018 and January 2022, focusing on children with both-bone forearm fractures and unsuccessful conservative treatment. Data included demographics, fracture details, reduction type, implant removal timing, complications, and refracture rates.

Results: Between August 2018 and August 2022, the study involved 65 children (54 boys, 11 girls), aged 4 to 15 years. Implant removal occurred at 4 to 11 weeks, on average at 7.17±1.52 weeks. Fracture location was distal 1/3 (9.2%), middle 1/3 (78.5%), proximal 1/3 (12.3%). The predominant causes of fractures were falls (89.2%). Fracture types consisted of open fractures (6.2%) and closed fractures (93.8%). Reduction methods included mini-open reduction (9.2%) and closed reduction (90.8%). Implant removal occurred at or before 6 weeks for 43.1% of cases, while it exceeded 6 weeks for 56.9% of cases. Complications were noted in 21.5% of cases, encompassing delayed union (14.3%), hypertrophic granuloma (7.1%), infection (21.4%), skin irritation (42.9%), and refracture (14.3%). Clinical outcomes were classified as excellent in 83.1% of cases and good in 16.9% of cases. No statistically significant differences were observed in complications (p=0.351) or clinical outcomes (p=0.441) based on implant removal timing.

Conclusion: Contrary to belief, exposing nail tips, not burying them, is safe, cost-effective, and leads to minimal complications with positive clinical outcomes. Implant removal timing did not significantly impact clinical outcomes or complications. TENs used in forearm fractures can be removed before 6 weeks when adequate union is observed.

Keywords: Pediatric forearm fractures, titanium elastic nail, exposed tips, implant removal

INTRODUCTION

Forearm fractures are frequently observed in the paediatric population, ranking high in terms of prevalence.[1-3] While the treatment for most of these fractures involves reduction and casting, unstable fractures frequently necessitate fixation in order to ensure proper alignment during the course of recovery.[4,5] The prevalence of surgical procedures has grown in recent years.[6] Titanium-elastic intramedullary nails (TENs) have been employed in clinical practice since the beginning of the 1980s. Superior outcomes have been documented with TENs in comparison to open reduction internal fixation (ORIF) due to its inherent benefits, including reduced soft tissue trauma and shorter surgical duration.[7,8] Fixation of forearm fractures in individuals with immature skeletons has mostly shifted towards the use of TENs.[6,9,10]

There is significant variation between institutions and physicians in their adherents regarding the removal of these implants, and a consensus has not been reached regarding the optimal timing for removal.[11-15] While proponents of leaving exposed tips argue for their removal within an average timeframe of 6 weeks, advocates of burying subcutaneous tips recommend elective removal within an average timeframe of 6 months.[16,17] Exposing the tips of the implants during a surgical procedure offers the advantage of facilitating a simplified and effective operative process as well as reducing the extent of anaesthesia required.[17] Supporters of early implant removal argue that keeping the exposed tips of implants may offer the advantage of enabling implant removal to be performed in an office setting, thereby eliminating the necessity for a subsequent

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surgical procedure and exposure to anaesthesia. This approach could potentially result in a secondary benefit of decreased financial burden.18 The migration of implants in TENs with buried tips can present challenges due to the complexities associated with monitoring, which are influenced by external variables. Previous research in the field of literature has demonstrated that the clinical and radiological outcomes of burying or exposing the tips of TENs were found to be similar in cases of forearm fractures in paediatric patients.[19] Nevertheless, the existing body of literature on the complications associated with the removal of TEN nails is limited in terms of studies that specifically investigate the timing of removal. Early removal of TEN carries a significant risk of refracture. The primary aim of the current study was to investigate the complication rates in paediatric patients who underwent TEN with exposed tips for forearm fractures. The secondary aim of the present study was to investigate the relationship between the timing of TEN removal and the occurrence of complications and refracture.

METHODS

The current study was carried out with the permission of the Fırat University Non-interventional Researches Ethics Committee (Date: 10.08.2023, Decision No: 2023/11-16). All procedures were carried out in accordance with the ethical rules and principles of the Declaration of Helsinki.

The present investigation included a retrospective analysis of a database from a single centre, focusing on forearm fractures in children who underwent TEN with an exposed tip. The consecutive patients who underwent TEN with an exposed tip at our hospital between August 2018 and January 2022 were considered for inclusion in the cohort. The study enrolled children who had both-bone forearm fractures and received unsuccessful closed reduction and long-arm splint treatment, as well as those with type 1 open fractures and patients who experienced unacceptable angulation (for mid and distal shaft fractures: >15° angulation, >30° malrotation, and 100% displacement for children under 8 years old; >10° angulation, >30° malrotation, and 100% displacement for children over 8 years old; for proximal shaft fractures: >10° angulation, >30° malrotation, and 100% displacement for children under 8 years old; anatomic reduction with internal fixation recommended for children over 8 years old) during the post-reduction follow-up period.[20] After conducting a comprehensive review of hospital records, the study retrospectively analysed data including age, gender, fracture type, fracture location, cause of injury, whether the fracture was open or closed, type of reduction performed, timing of implant removal (≤ 6 weeks or >6 weeks), complications encountered, and rates of refracture development during the follow-up period. The information was gathered at the time of admission as well as at each subsequent appointment until the treatment was over. Excluded from the study were patients with fractures in close proximity to the epiphyseal plate, individuals with isolated fractures of the radius and ulna, individuals who had Monteggia or Galeazzi injuries, individuals with additional fractures in that specific extremity, individuals with multiple injuries, patients who discontinued follow-up or were unreachable, patients with type II-III open fractures, as well as those with pathological fractures.

Surgical Procedure and Follow-up

In each instance, one single nail was employed for each bone, with the use of a TEN (TST Istanbul Medical Devices) across all cases. All surgeries were conducted with the patient supine on the operating table, and either a closed or open reduction was performed via fluoroscopic assistance by the same team of five surgeons with a combined five years of expertise in orthopaedic trauma. Following appropriate preparation, the initial insertion was made into the radial metaphysis through the extensor carpi radialis brevis and extensor carpi radialis longus tendons, specifically targeting the radius lateral to the Lister tubercle. The antegrade technique was employed to treat the ulna by positioning its insertion point on the posterior side of the olecranon. The potential risk of developing olecranon epiphyseal injury was explained to the family and informed consent forms were obtained. After three unsuccessful attempts at closed reduction and nail penetration to the proximal fragment, the reduction of fracture in radial fractures was achieved through a dorsal approach using a mini-Thompson incision, while for ulna shaft fractures, reduction was performed from the lateral side using a transcutaneous mini-incision. The determination of nail diameter was conducted with the aid of fluoroscopic control, ensuring that it was not less than 40% of the total width of the medullary canal.[21] To avoid harming the skin, the tips of all applied nails were curved and exposed. Following surgery, the patient was given intravenous pain medication, had their arm immobilized in a long-arm splint, and began rapid finger and elbow exercises. The long-arm splint was taken off after two weeks. All cases underwent follow-up visits at biweekly intervals starting from week 2 until the completion of 3 months. Subsequently, follow-up visits were conducted at six months as well as one year. The presence of callus in three out of four cortexes observed in the images, along with the absence of tenderness upon palpation at the location of the fracture during clinical examination,

were deemed indicators of union.[22] The patients who were deemed to have achieved union underwent the removal of their implants in an outpatient clinic setting, followed by the acquisition of control images. The durations for the removal of implants in the patients were assessed and documented as follows: ≤6 weeks or >6 weeks. The patients were monitored for a minimum of one year, regardless of the timing of implant removal. The rates of complications and refractures were documented. The pain and supination/pronation range of motion of patients were measured using a scale proposed by Price CT et al.[23] and Daruwalla et al.[24] The clinical assessment of Price CT, as used by Daruwalla, is based on daily activity and loss of range of motion. It involves categorising range of motion into 10 degrees, 11-30 degrees and 31-90 degrees. The clinical results were evaluated using the Price and Flynn criteria.[25]

Statistical Analysis

The IBM SPSS Statistics 22 (IBM SPSS, Turkey) programme was used for statistical analyses while evaluating the findings obtained in the study. The conformity of the parameters to the normal distribution was evaluated by the Shapiro-Wilks test. In addition to descriptive statistical methods (mean, standard deviation, and frequency), Fisher's exact test and continuity (Yates) correction were used to compare qualitative data. Significance was evaluated at $p<0.05$ level.

RESULTS

The study was conducted between August 2018 and August 2022 with a total of 65 children, 54 (83.1%) boys and 11 (16.9%) girls, aged between 6 and 15 years. The mean age of the children was 10.34±2.44 years (Table 1). All 65 eligible patients were assessed and none of them were unreachable.

Table 1. Distribution of demographics

	Min-Max	Mean±SD
Age	6-15	10.34±2.44
Gender	**n**	**%**
Male	54	83.1
Female	11	16.9

The timing of implant removal ranged between 4 and 11 weeks, with a mean of 7.17±1.52 and a median of 7 weeks. The duration of follow-up ranged between 12 and 16 months, with a mean of 13.51±1.21 and a median of 13 months (Table 2).

The location of the fracture was observed to be distal 1/3 in 9.2% of the children, middle 1/3 in 78.5% of the children, and proximal 1/3 in 12.3% of the children. The primary cause of injury was attributed to falls in 89.2% of cases, while direct strikes accounted for 4.6% and traffic accidents accounted for 6.2%. The open fracture type accounted for 6.2% of cases, while the closed fracture type accounted for 93.8% of cases. The mini-open reduction type was observed in 9.2% of cases, while the closed reduction type was observed in 90.8% of cases (Table 2).

Table 2. Distribution of the operating parameters

	Min-Max	Mean±SD (Median)
Timing of implant removal (weeks)	4-11	7.17±1.52 (7)
Duration of follow-up (months)	12-16	13.51±1.21 (13)
	n	%
Fracture location		
Distal 1/3	6	9.2
Middle 1/3	51	78.5
Proximal 1/3	8	12.3
Cause of injury		
Fall	58	89.2
Direct Strike	3	4.6
Traffic accident	4	6.2
Fracture Type		
Open	4	6.2
Closed	61	93.8
Reduction type		
Mini-Open	6	9.2
Closed	59	90.8
Timing of implant removal (weeks) group		
≤6	28	43.1
>6	37	56.9
Complications		
None	51	78.5
Delayed union	2	3.1
Hypertrophic granüloma	1	1.5
Infection	3	4.6
Refracture	2	3.1
Skin irritation	6	9.2
Complications Group		
No	51	78.5
Yes	14	21.5
Complications (n=14)		
Delayed union	2	14.3
Hypertrophic granüloma	1	7.1
Infection	3	21.4
Skin irritation	6	42.9
Refracture	2	14.3
Clinical outcomes		
Good	11	16.9
Excellent	54	83.1

In 43.1% of the cases, the duration for implant removal in children was 6 weeks or less, whereas in 56.9% of the cases, it exceeded 6 weeks. A total of 78.5% of individuals experienced no complications, while 21.5% encountered complications. The observed complications included delayed union in 14.3% of cases, hypertrophic granuloma

in 7.1% of cases, infection in 21.4% of cases, skin irritation in 42.9% of cases, and refracture in 14.3% of cases (Figures 1 and 2). The clinical outcomes were deemed good in 16.9% of cases and excellent in 83.1% of cases (Table 2).

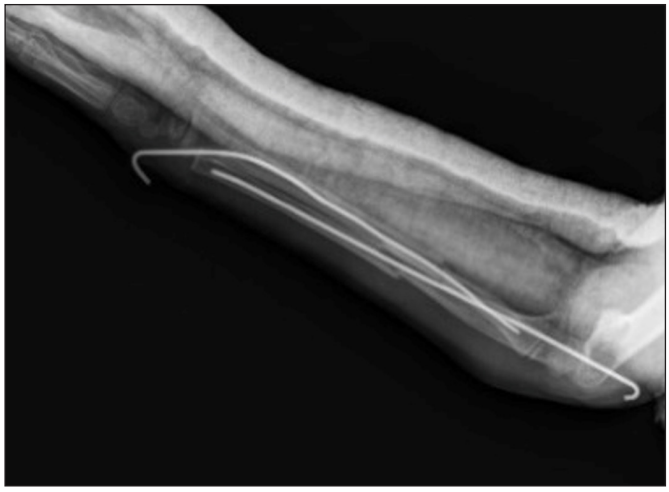

Figure 1. Initial postoperative radiograph of an 8-year-old male patient.

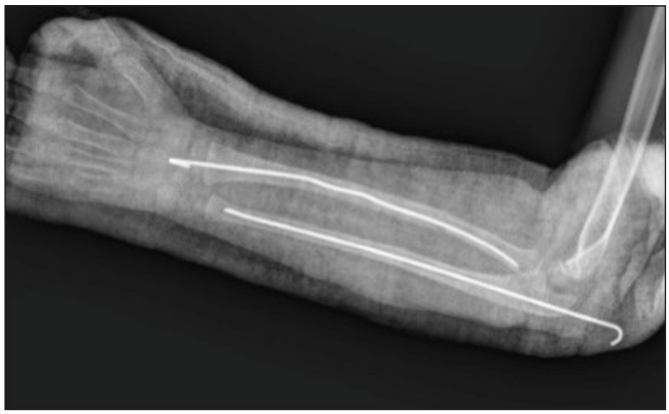

Figure 2. The radiograph obtained at approximately six weeks after the surgical procedure and just before to the extraction of the elastic nail.

Upon comparing the complication rates based on the timing of implant removal, no statistically significant difference was observed between the groups (p=0.351, p>0.05) (Table 3).

Table 3. Evaluation of the presence of complications and clinical outcomes between implant removal time groups

	Timing of implant removal (weeks) group		p
	≤6 n (%)	>6 n (%)	
Complications Group			10.351
No	24 (85.7)	27 (73)	
Yes	4 (14.3)	10 (27)	
Complications			20.175
Delayed union	0 (0)	2 (20)	
Hypertrophic granuloma	0 (0)	1 (10)	
Infection	0 (0)	3 (30)	
Skin irritation	3 (75)	3 (30)	
Refracture	1 (25)	1 (10)	

1Continuity (Yates) Correction, 2Fisher's Exact Test

No statistically significant difference was found between the groups when comparing the clinical results based on the time of implant removal (p=0.441, p>0.05) (Table 4).

Table 4. Evaluation of clinical outcomes between implant removal time groups

Clinical outcomes	Timing of implant removal (weeks) group		p
	≤6 n (%)	>6 n (%)	
Good Excellent	4 (14.3) 24 (85.7)	7 (18.9) 30 (81.1)	0.441

Fisher's Exact Test

DISCUSSION

The primary outcome of the current study revealed a lack of association between the time of implant removal and the incidence of complications and refractures in paediatric individuals who underwent TEN with exposed tips for forearm fractures. An additional significant discovery of the research is its strong emphasis on the low occurrence of complications and the excellent clinical results associated with the use of TENs with exposed tips. These findings support the idea that exposing IM implants during the surgical treatment of paediatric forearm fractures is a feasible option.

According to a study conducted by Dinçer et al.[19] in 2019, the clinical and radiological outcomes of both-bone forearm fractures in children were found to be comparable when the tips of TENs were either buried subcutaneously or left exposed. Consistent with the aforementioned study, existing literature indicates that there are no significant disadvantages associated with leaving the tips of the elastic nails exposed.[17,26] The patients received a single administration of general anaesthesia solely for the purpose of reduction procedures. Implant removal can be efficiently conducted in an outpatient clinic setting without the requirement for anaesthesia. Moreover, drawing on the data obtained in the current study, we would like to highlight the high level of compliance shown by patients who had TENs with exposed tips in terms of adhering to follow-up appointments. This noteworthy characteristic has potential advantages for ensuring effective patient monitoring and continuity of care.

The research conducted by Kelly et al.[17] reported a complication rate of 17.2% among a sample of 128 patients who had the implant tips exposed. The findings from this study match closely with the current study, which also observed a complication rate of 21.5%. Dinçer et al.[19] found that among 74 patients with exposed implant tips, 26 (35%) experienced at least one complication, with skin irritation being the most

prevalent. The complication rates observed in the current study are comparatively lower than those reported by Dinçer et al.[19] However, it is noteworthy that both studies identified skin irritation as the most commonly observed complication.

The occurrence of nonunion and delayed union in paediatric forearm fractures is rare. The literature has shown a prevalence of nonunion in the range of 0.3% to 1% as a result of open reduction as well as other contributing factors.[27,28] Adolescents may have difficulties with delayed union after TEN, particularly after open fractures or open reduction of ulnar fractures.[19] No instances of nonunion were detected in any of the patients included in the current study. Delayed union was observed in two patients who underwent TEN with an exposed tip. Both patients underwent open reduction of their forearm bones, with union times of 11 weeks and 10 weeks, respectively.

The migration of implants in TENs with buried tips might present an obstacle due to the complexities associated with follow-up, which can be influenced by patient and external factors. With exposed TENs, a second surgery is not necessary. In one instance within the current study, a hypertrophic granuloma was debrided subsequent to the extraction of the elastic nail. The wound successfully healed without necessitating suturing. It is well known that tendons (particularly the extensor pollicis longus) and the superficial sensory branch of the radial nerve may be irritated or damaged by buried tip TEN implantation. The absence of any detected tendon or nerve injury in our patient cohort serves to further support the safety of using TENs with an exposed tip. Infections of the bone and soft tissues are another major concern for orthopaedic surgeons. Similar to the literature, in three instances, accounting for 4.6% of the cases, pintract infections occurred in patients with exposed tips. Kelly et al.[17] identified an infection incidence of 2.7% in patients with exposed TENs, whereas another investigation evaluating distal humeral fractures revealed a prevalence of 3%.[22] The infections were successfully cured within a period of one week with the administration of adequate antibiotherapy. There was no occurrence of a deep infection among any of the patients.

The duration of the extraction of intramedullary devices is a matter of concern due to the potential risk of refracture. The literature reports a refracture rate of approximately 5-10% in patients who are managed conservatively.[29,30] In contrast, cases treated with TEN have shown a rare occurrence of refracture, with a rate of 0.5%.[31,32] The current study found refracture in two individuals, accounting for 3.1% of the sample (**Figures 3** and **4**). Dinçer et al.[19] reported a surprising finding of refracture in 2.1% of exposed implants and 3.1% of buried cases following removal. Lascombes et al.[16] hypothesised that implants should be buried under the skin for 6-12 months to provide biomechanical support and reduce the risk of refracture. However, this hypothesis contradicts both the present study and the study conducted by Dinçer et al.[19] In a study conducted by Qairul et al.[33] involving 100 paediatric patients with forearm fractures, it was found that the fractures typically healed within a period of 3-6 weeks. The preservation of the periosteum during TEN applications, along with the slight movement of the fracture, contributes to the promotion of callus formation, thereby positively impacting the process of fracture healing.[34] In the current study, the likelihood of refracture following the removal of implants within 6 weeks was comparable to the likelihood of refracture following the removal of implants after 6 weeks. This similarity may be attributed to the achievement of adequate bone union before the 6-week mark. The current study did not find any statistically significant association between the timing of implant removal and the incidence of any other complications ($p>0.05$). Considering the complication rates associated with both methods, it may be reasonable to remove TENs before 6 weeks, taking into consideration the level of union.

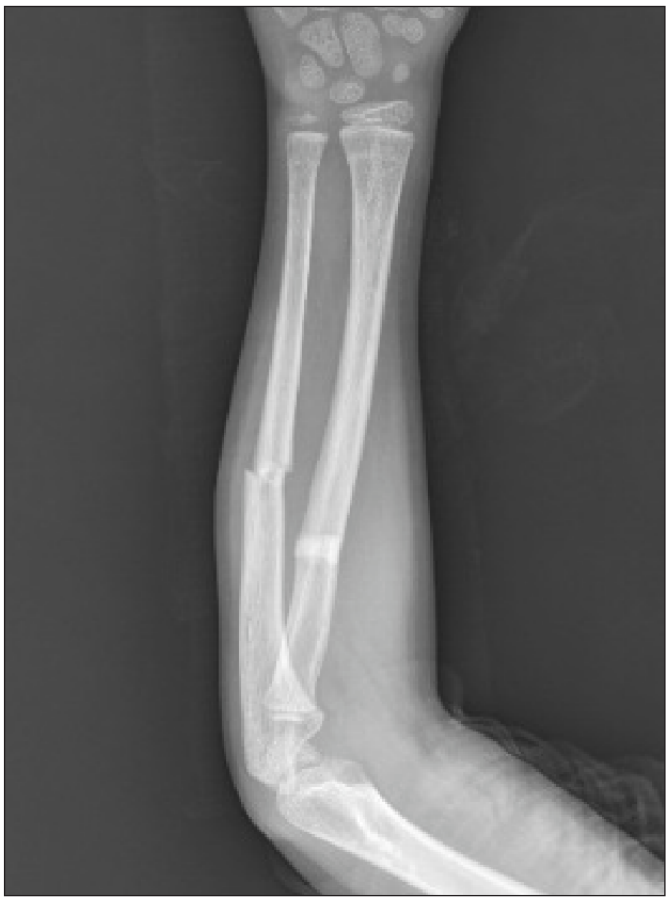

Figure 3: The child experienced a fall approximately 8 months after the removal of the implant, resulting in a diagnosis of refracture

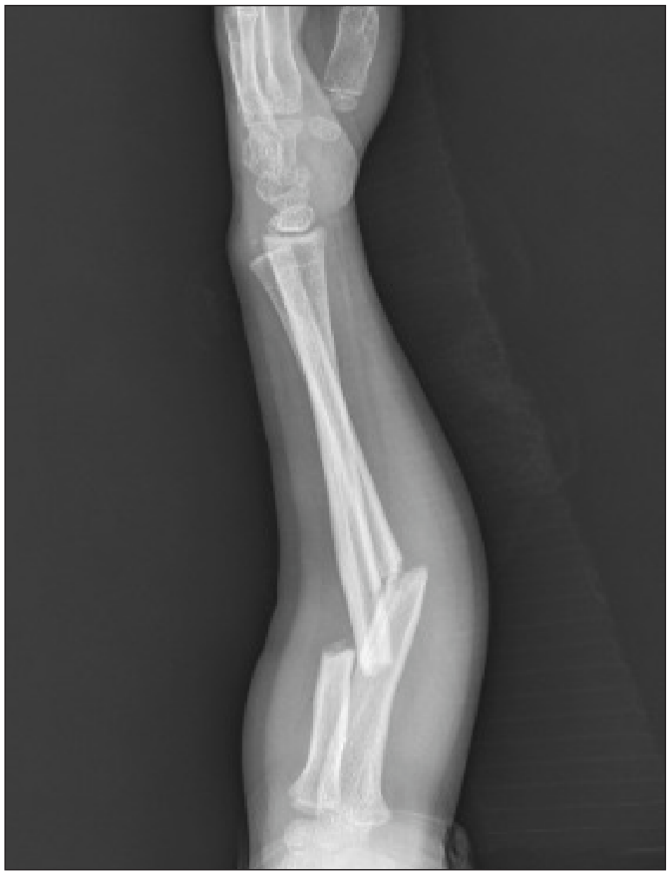

Figure 4: Lateral radiograph of the patient with refracture. The patient rejected the offer of surgery and discharged themselves from the hospital.

An additional significant finding of the current study was that the clinical outcomes were excellent in 83.1% of cases and good in 16.9% of cases, regardless of the timing of implant removal. The union was achieved in all patients, and the removal of implants was performed in a cost-effective manner within the outpatient clinic setting.

Limitations and Strengths

The present investigation is subject to several limitations. The research is limited to a single tertiary institution within our nation, making it a retrospective study with inevitable drawbacks. The limited patient population and low occurrence of complications restricted the possibility of conducting a statistical analysis on some data. The potential influence of patients' social and educational backgrounds on complication rates and subsequent study findings should be considered. An additional limitation is the absence of age-specific analysis for the complication rates of the patients included in the study. A primary factor contributing to this is the insufficient sample size, which rendered the statistical findings insignificant. One notable strength of the research is its comprehensive assessment of clinical outcomes and complications, suggesting that the use of TENs for the management of forearm fractures in paediatric patients with exposed tips is a viable and efficacious therapeutic approach. Another notable aspect of the current study is its attempt to partially address the existing controversy within the literature about the optimal timing for implant removal.

CONCLUSION

Contrary to popular belief, the technique of allowing the nail tip to be exposed is a secure treatment choice that serves as an alternative to subcutaneously burying the tips. The rates of complications are minimal, clinical outcomes are highly favourable, and the process of removing the implant is both cost-effective and straightforward. Our observations indicate that the timing of implant removal did not have a significant impact on clinical outcomes and rates of complications. TENs used in forearm fractures can be removed before 6 weeks when adequate union is observed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The current study was carried out with the permission of the Fırat University Non-interventional Researches Ethics Committee (Date: 10.08.2023, Decision No: 2023/11-16).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Comparison of the effects of manual therapy and scapular stabilization exercises on pain, functional status, and quality of life in subacromial impingement syndrome

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ABSTRACT

Aims: This study aimed to determine the effects of manual therapy and scapular stabilization exercises combined with conventional physiotherapy on pain, functional status, and quality of life, and whether they are superior in individuals with subacromial impingement.

Methods: 30 patients between the ages of 25-65 who were diagnosed with subacromial impingement syndrome were included in the study. Individuals were randomized 1:1 to "conventional physiotherapy+scapular stabilization" and "conventional physiotherapy+manual therapy" groups. Individuals' age, gender, medication use, and presence of chronic disease were recorded. The presence of pain was measured by the Visual Analogue Scale, shoulder range of motion was measured by a goniometer, quality of life was measured by Short Form-12 Quality of Life Survey, and functional status was evaluated with the Questionnaire Quick Disability of the Arm, Shoulder, and Hand Problems. The conventional physiotherapy program applied to both groups included electrotherapy, passive and active assisted range of motion exercises, and rotator cuff strengthening exercises. Both groups received a total of 12 sessions of physiotherapy, 3 days per week, for 4 weeks.

Results: 19 females and 11 males, participated in the study. There were no statistically significant differences between the groups at baseline assessment for pain at rest, activity, and night (p=0,37; 0,39; 0,17, respectively), range of motion of shoulder flexion, abduction, internal rotation, and, external rotation (p=0,5; 0,1; 0,91; 0,9, respectively), Questionnaire Quick Disability of the Arm, Shoulder, and Hand Problems score (p: 0,09) and Short Form-12 Quality of Life Survey scores physical and mental component (p=0,23; 0,98, respectively). After treatment, both groups observed positive improvements in pain at rest, activity, and night (p=0,001), range of motion of shoulder flexion, abduction, internal rotation, and, external rotation (p=0,001), Questionnaire Quick Disability of the Arm, Shoulder, and Hand Problems score (p=0,001) and Short Form-12 Quality of Life Survey scores physical and mental component (Group1; p=0,001; 0,001, Group 2; p=0,001; 0,005, respectively). There was no statistically significant advantage among the treatment methods except for shoulder abduction and internal rotation range of motion parameters (p=0,04; 0,009, respectively).

Conclusion: When applied with traditional physiotherapy, both treatment methods provided significant improvements in pain, functional condition, quality of life, and joint motion clarity compared to before treatment. However, the methods applied are not superior to each other. It is important to choose the appropriate technique for the patient in the treatment of subacromial impingement syndrome, and it is useful to prepare personalized, combined programs. It is envisaged that researching more effective exercise methods for patients with subacromial impingement syndrome in the future will increase the usefulness of the treatment.

Keywords: Manual therapy, scapular stabilization, rehabilitation, subacromial impingement syndrome

INTRODUCTION

The shoulder complex is the most mobile joint in the human body. This range of motion is due to the incompatibility between the articular surfaces. This mismatch and increased range of motion make the shoulder joint vulnerable to injury and degeneration.[1]

Shoulder pain is the third most common reason for admission to the orthopedic clinic due to musculoskeletal system problems, and subacromial impingement syndrome is one of the pathologies that most frequently causes shoulder pain. Chronic or recurrent subacromial impingement syndrome negatively affects individuals' quality of life.[2]

Subacromial impingement syndrome is a syndrome that occurs due to reasons such as overuse, insufficient shoulder stabilization, and trauma, and if left untreated, results in movement limitation, functional limitation, and poor quality of life.[3]

While the first stage of this syndrome, which is staged in 3 degrees according to Neer, is reversible, irreversible degeneration is observed in the third stage. 4 Pain, loss of strength and proprioceptive sensation, and functional limitations are common symptoms.[5,6]

Chronic nociceptive stimuli cause cortical delay of motor output and decreased activity of the painful muscle,

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resulting in isometric and isokinetic rotator cuff muscle strength weakness, especially in shoulder abductors and external rotators.[5] Kinesthesia and decreased joint position sense in the affected shoulder are shown to be risk factors for increasing injury.[7] These symptoms cause functional disabilities and negatively affect people's daily living activities, roles, and participation in recreation.[8]

Pharmacological, surgical, and conservative treatments, reduce pain in subacromial impingement syndrome and treat mechanical problems that cause functional limitation. The main aim of the applied treatments is to increase joint range of motion and therefore shoulder mobility by reducing pain and inflammation, to restore normal scapulohumeral rhythm, and to increase quality of life by increasing participation in daily life activities.[9] Conservative treatment includes patient education and protection, modalities, manual therapy techniques, and exercise treatments for stretching, strengthening, postural control, proprioceptive, and neuromuscular control.[2,10-13] Manual therapy is an effective treatment for shoulder pain.[14,15] In addition, although studies on the effectiveness of exercise emphasize that exercise is an important treatment option, the most effective type of exercise remains unclear.[12,16,17]

This study aimed to determine the effects of manual therapy and scapular stabilization exercises combined with conventional physiotherapy on subacromial impingement syndrome, pain, functional status, and quality of life, and whether they are superior.

METHODS

The current study was carried out with the permission of İstanbul Atlas University Non-interventional Scientific Research Ethics Committee (Date: 28.04.2022, Decision No: E-22686390-050.01.04-17615). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

30 patients between the ages of 25-65 who were diagnosed with subacromial impingement syndrome by an orthopedist in Azerbaijan/ Baku were included in the study. The study was carried out in the HB Güven Clinic Physical Therapy and Rehabilitation unit. 18 The purpose and content of the study were explained to the individuals and their verbal and written consent was obtained. Thirty patients diagnosed with SIS by an orthopedist were included in the study.

Individuals were randomized 1:1 to conventional physiotherapy and scapular stabilization (n=15) and conventional therapy and manual therapy (n=15) groups. Individuals who were diagnosed with rheumatoid arthritis, frozen shoulder, cervical radiculopathy, had a previous fracture or operated shoulder joint, had steroid injections within 6 months, Neer 3 stage of SIS, which is considered to be irreversible degeneration phase, presence of additional rotator cuff injuries which requires invasive treatments, and had contraindications to exercise and modalities were excluded from the study.[19]

After recording the sociodemographic characteristics of the individuals such as age, gender, medication use, presence of chronic disease; the presence of pain at night, at rest, and during activity was measured by Visual Analogue Scale (VAS), shoulder joint range of motion was measured by goniometer, quality of life was measured by short form-12 quality of life survey (SF-12), and functional status was evaluated with the questionnaire quick disability of the arm, shoulder and hand problems (Q-DASH).

Visual Analog Scale was evaluated with a horizontal line of 0-100 mm in size and recorded by measuring with a ruler on the left side after the patient marked. High scores are associated with higher pain.[20] Painless and voluntary flexion, abduction, and internal and external rotation movements of the shoulder were evaluated with goniometric measurement. To perform goniometric measurements of shoulder movements, it is imperative to ensure the patient's comfort. The goniometer was meticulously set, and anatomical landmarks were precisely identified. Adjacent body parts were stabilized to isolate shoulder movement. Subsequently, the goniometer is carefully aligned along the axis of the shoulder joint. The patient is then directed to execute the specific shoulder movement, during which the degree of motion is recorded. With the data obtained by this measurement, the data attached to the person's mobility and function can be revealed objectively.[21] In the quality of life evaluation, which was evaluated by SF-12, a higher score between 0 and 100 is associated with a better quality of life.[22,23] Physical function and symptoms were evaluated with Q-DASH, and higher scores were considered to indicate difficulty in performing activity or more severe symptoms.[24,25]

The conventional treatment program was created by compiling studies in the literature examining electrotherapeutic methods for the treatment of subacromial impingement syndrome.[12] As conventional therapy, 20 minutes of TENS, 5 minutes of Ultrasound, and 20 minutes of high voltage intermittent galvanic current have been applied as therapeutic electrotherapy.[10,11,26] In addition to passive and active assistive joint range of motion exercises, in line with the literature, Wand exercises, Codman pendulum exercises, and rotator cuff strengthening exercises were applied.[17] This program was applied to 3 sessions a week for 4 weeks, a total of 12 sessions.[27,28] While the exercises remained the same, exercise duration, intensity, and frequency were modified within the framework of an individualized program according to the progress, treatment compliance, and tolerance of the patient.[29,30]

In addition to the conventional therapy, wall push-up, shoulder wall roll (the elbow is in full extension and the shoulder in 90 degrees flexion, without dropping the ball on the wall, clockwise movement of the shoulder), lawnmower pull, which requires retraction and external rotation of the shoulder during trunk rotation, scapular depression, which is performed by pushing a bed, and transfer of body weight from the unaffected shoulder to the affected shoulder and vice versa exercises has given to the scapular exercises group (group 1).[31-33]

In addition to conventional therapy, scapular mobilization including passive adduction, abduction, elevation, depression, and rotation of the scapula, upper trapezius myofascial release with light pressure for 20 seconds, and posterior and inferior mobilization of the glenohumeral joint was applied to the manual therapy group (Group 2).[34-36]

Statistical Analysis

SPSS v26 (IBM SPSS Statistics Inc., USA) program was used for statistical analysis. The given normal distribution analysis was performed using the Shapiro-Wilk test. Qualitative variables were analyzed with the chi-square test ($\chi 2$). In normally distributed numerical data, the Paired Sample T-test was used for intra-group comparisons, and the Independent Samples T-test was used for inter-group comparisons. Wilcoxon test for within-group comparisons of non-normally distributed or ordinal data, Mann Whitney U test was used for intergroup comparisons. The statistical significance level was accepted as $p<0.05$ for all analyses.

RESULTS

Of the individuals participating in the study, 19 (group 1=9, group 2=10) were female, and 11 (group 1=6, group 2=5) were male. There was no significant difference between the groups in terms of age, gender, height, weight, body mass index, chronic disease existence, and medication use (p=0,86; 0,7; 0,6; 0,45; 0,41; 0,92; 1, respectively).

In the pretreatment assessment, there was no statistically significant difference between groups in terms of the range of motion at rest, activity, and night pain (respectively, p=0.37; 0.39; 0.17), shoulder flexion, abduction, internal rotation, and external rotation (respectively, p=0.5; 0.1; 0,91; 0,9), Q-DASH scores (p=0.09), SF-12 physical component and mental component (respectively, p=0.23; 0.98) (Table 1).

Table 1. Pre-treatment evaluation parameters of Groups 1 and 2

	Group I (n=15)	Group 2 (n=15)	p value
Pain			
VAS rest (mm)	34.07±17.40	28.87±12.06	0.372
VAS activity (mm)	70.67±11.44	72.60±12.77	0.394
VAS night (mm)	71.20±16.38	65.53±18.21	0.171
Range of Motion			
Shoulder flexion (°)	108.06±10.73	110.86±10.51	0.506
Shoulder abduction (°)	89.40±10.97	94.23±10.73	0.105
Shoulder internal rotation (°)	50.13±6.55	50.20±7.01	0.917
Q-DASH			
Shoulder external rotation (°)	60.93±8.19	60.60±7.50	0.901
Q-dash score	68.86±11.44	60.75±15.89	0.097
SF-12			
SF12 - Physical component	28.85±4.16	32.53±6.67	0.237
SF12 - Mental component	41.81±5.61	40.41±12.87	0.983

The results are given as x ± sd. VAS: Visual Analogue Scale; mm: millimeter; °: degree; Q-Dash: Quick DASH (Quick Questionnaire for Arm, Shoulder and Hand Problems); SF12: Short Form-12 Quality of Life Survey

After treatment, patients in both groups had better rest, activity, and night pain (p=0.001), shoulder flexion, abduction, internal rotation and external rotation joint range of motion (p=0.001), Q-DASH scores (p=0.001), SF-12 physical component and mental component (Group 1, p=0.001; 0.001; Group 2, p=0.001; 0.005, respectively) parameters showed a statistically significant difference (Table 2).

Table 2. Comparison of pre-and post-treatment evaluation parameters of Groups 1 and 2

	Group I (n=15)			Group 2 (n=15)		
	Pre-Treatment	Post-Treatment	p-value	Pre-Treatment	Post-Treatment	p-value
Pain						
VAS rest (mm)	34.07±17.40	28.53±14.46	0.001	28.87±12.06	23.13±10.94	0.001
VAS activity (mm)	70.67±11.44	41.33±12.57	0.001	72.60±12.77	37.07±11.59	0.001
VAS night (mm)	71.20±16.38	28.53±14.46	0.001	65.53±18.21	23.13±10.94	0.001
Range of Motion						
Shoulder flexion (°)	108.06±10.73	134.53±13.63	0.001	110.86±10.51	136.40±14.35	0.001
Shoulder abduction (°)	89.40±10.97	109.86±12.02	0.001	94.23±10.73	110.66±10.91	0.001
Shoulder internal rotation (°)	50.13±6.55	63.13±7.50	0.001	50.20±7.01	59.93±6.61	0.001
Shoulder external rotation (°)	60.93±8.19	73.46±7.63	0.001	60.60±7.50	72.40±7.31	0.001
Q-DASH						
Q-dash score	68.86±11.44	41.04±10.60	0.001	60.75±15.89	32.25±11.37	0.001
SF-12						
SF12 - physical component	28.85±4.16	41.38±5.20	0.001	32.53±6.67	42.61±6.44	0.001
SF12 - mental component	41.81±5.61	51.92±4.33	0.001	40.41±12.87	50.94±7.17	0.005

The results are given as x ± sd. VAS: Visual Analogue Scale; mm: millimeter; °: degree; Q-Dash: Quick DASH (Quick Questionnaire for Arm, Shoulder and Hand Problems); SF12: Short Form-12 Quality of Life Survey.

According to the post-treatment intergroup analysis, there were no significant changes in resting, activity, and night pain scores (p=0.93; 0.36; 0.93, respectively), and shoulder flexion and shoulder external rotation joint range of motion values (p=0.66; 0.6, respectively), Q-DASH scores (p=0.8), physical component and mental component parameters of SF-12 scoring (p=0.22; 0.69, respectively). No significant difference was found between the groups (Table 3).

Table 3. Comparison of parameters between groups

	Group I (n=15)	Group 2 (n=15)	p value
Pain			
VAS rest (mm)	-42.66±13.35	-42.40±12.48	0.934
VAS activity (mm)	-28.86±15.06	-24.33±8.82	0.361
VAS night (mm)	-42.66±13.35	-42.40±12.48	0.934
Range of Motion			
Shoulder flexion (°)	26.46±6.95	25.53±5.09	0.662
Shoulder abduction (°)	20.46±6.93	15.93±4.11	0.043
Shoulder internal rotation (°)	13.00±3.56	9.73±2.49	0.009
Shoulder external rotation (°)	12.53±3.81	11.80±1.97	0.6
Q-DASH			
Q-Dash score	-27.82±6.20	-28.50±9.92	0.803
SF-12			
SF12 - physical component	12.53±5.44	10.08±5.98	0.221
SF12 - mental component	10.11±5.29	10.53±11.75	0.694

The results are given as x ± sd. Δ: Delta (difference); VAS: Visual Analogue Scale; mm: millimeter; °: degree; Q-Dash: Quick DASH (Quick Questionnaire for Arm, Shoulder and Hand Problems); SF12: Short Form-12 Quality of Life Survey

Post-treatment shoulder abduction and shoulder internal rotation difference values were significantly higher in group 1 compared to group 2 (p=0.04; 0.009, respectively) (Table 3).

Since the parameter that most causes patients' functional limitations is pain during activity, the actual power of the study is 0.97, and the effect size is 2.5193590, with a 0.05 error rate and 0.95 power, according to the post-power analysis calculated by taking into account the pain parameter at the activity level of the patients.

DISCUSSION

Our study aims to determine the effectiveness of manual therapy and scapular stabilization exercise program and their superiority over each other in patients diagnosed with subacromial impingement syndrome. In the research process, it was aimed to add manual therapy and scapular stabilization exercise programs to conventional physiotherapy practices in patients diagnosed with subacromial impingement syndrome and to compare the results. According to the results of our study, although scapular stabilization exercises and manual therapy applied in addition to conventional physiotherapy have positive effects on pain, function, and quality of life, these applications do not have superiority over each other.

There are different levels of evidence in the literature regarding the usefulness of exercise and electrotherapy agents used in the treatment of shoulder injuries.[37] In their study, Gunay Ucurum et al.[27] compared three different electrotherapy agents (TENS, US, interferential current) given in addition to exercise in the treatment of SIS. It has been shown that all three agents have positive effects on pain, function, and quality of life, but they are not superior to each other.[27] Our study was designed in accordance with the literature with the conventional physiotherapy program it contains. In addition, the data we obtained supports the existing literature.

Pain and limitation of movement, which are the most common symptoms in SIS, often occur during overhead activities and weight bearing. Reducing pain, which also affects functional activity performance, should be the primary goal of treatment.[38] Ginn et al.[39] reported a reduction in shoulder pain with the long-term exercise, mobilization, and modalities they applied to the patients, and they reported a decrease in shoulder pain with the treatment they used. Similarly, Bergman et al.[40] in a study on shoulder pain, showed that both conventional physiotherapy and manual therapy helped a significant reduction in pain levels. Lombardi et al.[41] on the other hand, applied exercise therapy to patients with SIS and reported statistically significant decreases in VAS scores used to assess pain. It was thought that the joint mobilization applied in our study led to an increase in joint range of motion and functionality by activating joint mechanoreceptors and reducing pain.

Surenkok's[42] study reported that scapular mobilization provided significant improvements in shoulder range of motion, scapula upward rotation, and pain. In the study of Turgut et al.[43] the effects of scapular stabilization exercises on scapular kinematics were emphasized and the importance of reducing pain was emphasized. In light of these data, the effectiveness of the scapular mobilization technique and scapular stabilization exercises was compared in our study. Similar results were obtained within the group, but no difference was found between the groups.

Camargo et al.[28] compared manual therapy and exercise training in addition to manual therapy in people with SIS and showed that pain, mechanical sensitivity, and DASH scores improved similarly at the end of the intervention period in both groups. In our study, scapular stabilization and kinematic improvement were thought to be the reason for the increase in functionality and decrease in pain, which was similar and not superior to each other in both groups.

In their systematic review and meta-analysis study, Steuri et al.[44] reviewed 200 studies comparing treatment

strategies in patients diagnosed with SIS. Exercise has been reported to be more effective than doing nothing, and specific exercise has been reported to be more effective than nonspecific exercise for pain and function. For pain, manual therapy was superior to doing nothing or a placebo, while exercise combined with manual therapy was found to be superior to exercise alone.[44] In our study, we observed that scapular stabilization exercises in addition to conventional physiotherapy - which can be defined as specific exercise - and manual therapy in addition to conventional physiotherapy do not have any superiority over each other in terms of pain and function. We think that future studies may contribute to the determination of an effective protocol in the treatment of SIS by adding conventional physiotherapy + scapular stabilization exercise + manual therapy group.

In our study, only shoulder abduction and shoulder internal rotation range of motion values improved more in the scapular stabilization group than in the manual therapy group. However, there was no statistically significant difference between the groups in other parameters, except for the difference in values of shoulder abduction and shoulder internal rotation joint range of motion after treatment. Although the cause of this statistically significant difference, which is detected only in shoulder abduction and shoulder internal rotation, is unclear, it is foreseen that the positive effects of the personalized exercise program on kineziophobia have this condition. To reveal the cause of this difference, detailed randomized controlled studies are required.

To our best knowledge, no study has been found in the literature comparing the effectiveness of manual therapy and scapular stabilization exercise, applied in addition to conventional physiotherapy, on pain, function, ROM, and quality of life in the treatment of SIS. Although our study has strengths, it also has some limitations. The small sample size in our study and the lack of long-term follow-up on the effectiveness of the treatment are the main limitations of the study. In addition, considering the differences in the tissue healing process with age, it is thought that the wide age range of the patients included in the study may affect the results of the study. On the other hand, not having a control group containing only conventional physiotherapy may be among our limitations.

CONCLUSION

The results obtained from the study, in line with the literature, showed that scapular stabilization exercises and manual therapy applied in addition to conventional physiotherapy in patients diagnosed with SIS provided a significant improvement in pain, functional status, quality of life, and joint range of motion compared to the pre-treatment assessment. The additional methods, which were applied as an addition to conventional therapy, were not superior to each other. Results in accordance with the ICF framework were obtained. In this regard, it is important to choose the appropriate technique for the patient, such as patient compliance, joint mobility status, etc., in planning the physiotherapy program for SIS and it would be beneficial to prepare an individualized, combined (exercise, manual therapy, and electrotherapy) program. It is envisaged that researching more effective exercise methods for patients with SIS in the future will increase the usefulness of the treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The current study was carried out with the permission of İstanbul Atlas University Non-interventional Scientific Research Ethics Committee (Date: 28.04.2022, Decision No: E-22686390-050.01.04-17615).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Comparison of preoperative MRI and surgical findings in perianal fistulas and factors affecting recurrence

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ABSTRACT

Aims: Anal fistula occurs most commonly when the anal glands become obstructed and infected in the intersphincteric plane. Although it has a high recurrence rates, its treatment is surgical. Magnetic resonance imaging (MRI) is the gold standard for accurate preoperative evaluation of the patient and detection of the relationship to the muscle groups that provide continence. The aim of this study was to evaluate the compatibility of MRI with surgery and to determine the parameters effective on recurrence.

Methods: Primary perianal fistulas with MRI between 2016 and 2023 were retrospectively evaluated. Patient demographics were documented. Fistula classifications according to MRI findings, abscess locations, internal and external opening regions on MRI were compared with surgical findings. The surgical procedures performed were documented. Univariate and multivariate evaluations of recurrence performed by Cox regression analysis. Disease-free survival data were analyzed.

Results: A total of 180 cases with a mean age of 43.75±12.57 years were included in the study. At the end of MRI, there were 69 (38.3%) cases with an fistula external orifice > 3 cm. The largest group in Parks classification were intersphincteric patients with 127 (66.7%), 52 (28.9%) of the patients were in the complex group. The level of agreement between surgery and MRI internal opening was 13.4% and statistically significant (Kappa coefficient of agreement 0.134; p<0.01). Total recurrence was observed in 33(18.3%) patients. Recurrence was statistically significant in patients with external orifice >3 cm, transsphincteric, complex and patients requiring loose seton in surgery (p=0.001, p=0.001, p=0.001, p=0.001, p=0.007; p<0.01 respectively).

Conclusion: In our study, we found that the recurrence rate was higher in patients with an external orifice of more than 3 cm, transsphincteric, 3-4th degree complex fistulas, and patients with loose setons.

Keywords: Anal fistula, magnetic resonance imaging, recurrence, classification

INTRODUCTION

Perianal fistula is an abnormal condition that develops between the anal canal and the perineal skin or in the perianal region.[1] Anal fistula results from infected anal glands, most commonly secondary to perianal abscesses.[2] Although the overall incidence is not high, it causes serious morbidity in young and middle-aged men.[3] Anal fistula is a vexing problem due to their its high recurrence rate and serious postoperative complications. Patients with perianal fistulas may be completely asymptomatic or present with local pain and discharge.[4] In general, anal fistulas do not heal spontaneously and require surgical management. The primary aims of surgery are to control the local infection, eliminate the fistula and achieve of anal continence.[5] The classification of the fistula, the degree of involvement of the surrounding pelvic structures, secondary tracts and abscesses are factors that affect the success of surgical treatment. Therefore, physical examination alone is not as successful as imaging methods in detecting these features of the fistula and recurrences are usually due to missed or inadequately treated infectious components. Therefore, accurate and comprehensive preoperative evaluation of perianal fistulas is an important diagnostic strategy that can increase the success rate of surgery.[6]

Magnetic resonance imaging (MRI) is the most accurate and widely accepted gold standard imaging modality for defining the anatomy of the anal canal and perianal fistulas.[7]

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The use of MRI for the preoperative evaluation of perianal lesions can help to accurately identify potential risk factors and assist in the selection of the best surgical approach to minimize recurrence. Recurrences are common and difficult to manage after anal fistula surgery and can lead to significant morbidity, multiple surgeries, increased local fibrosis and increased risk of continence problems. This has a negative impact on patient's quality of life.

The aim of this study was to evaluate the compatibility of MRI with surgery in perianal fistula and its characterization and to determine the parameters that may be effective in recurrence.

METHODS

The study was carried out with the permission of Göztepe Prof. Dr. Süleyman Yalçın City Hospital Ethics Committee (Date: 23.08.2023, Decision No: 2023/0546). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was conducted at a single center. Surgically treated patients with perianal fistula beetween 2016 and 2023 in the department of General Surgery were investigated retrospectively. Patients between 18-77 years of age with a perianal fistula and preop MRI were included. We obtained an informed consent form from all patients for procedure.

Exclusion criteria were as follows: patients with other perianal diseases, fistula due to inflammatory disease, recurrent cases, secondary operations with seton exchange and patients who did not attend regular follow-up visits. All surgical procedures were performed by a surgeon with at least 10 years of proctologic experience. All MRI results were evaluated by a radiologist with 5 years of experience in abdominal radiology in perianal diseases. Demographic data and operative notes were documented from the hospital data system. Parks and Standard Practice Taske Force (SPTF) classification, St. James classification, presence of abscess, internal orifice status and level, secondary tract, and external orifice information were obtained from MRI imaging. Fistulas were classified as high and low type according to the position of the internal opening. Parks classification was performed according to intersphincteric, transsphincteric, suprasphincteric and extrasphincteric types. In SPTF classification, fistulas were defined as simple and complex fistulas.

In the postoperative period, patients with clinical discharge examination findings after the 3rd month were considered as recurrent fistulas. The internal and external opening areas were determined according to the clock dial and the agreement between MRI and surgical findings was compared. Disease-free survival was analyzed.

Statistical Analyses

NCSS (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA) was used for statistical analyses while evaluating the findings obtained in the study. While evaluating the study data, quantitative variables were shown with mean, standard deviation, median, min and max values, and qualitative variables were shown with descriptive statistical methods such as frequency and percentage. Shapiro Wilks test and Box Plot graphs were used to evaluate the conformity of the data to normal distribution. Kappa concordance test was used to compare qualitative data. Kaplan Meier test was used for disease-free survival analysis. Cox regression analysis was used to determine the risk factors affecting recurrence. Results were evaluated at 95% confidence interval and significance was evaluated at $p<0.05$ level. Sensitivity: The ability of the test to identify patients among real patients. Specificity: The ability of the test to identify intact patients among the real intact patients. Positive predictive value: A measure of the conditional probability that the subject is actually sick when the test gives a positive (sick) result. Negative Predictive Value: The probability that the subject is actually healthy when the test gives a negative (healthy) result.

RESULTS

A total of 180 patients were included in the study, of whom 77.2% (n=139) were male and 22.8% (n=41) were female. The age of the patients ranged between 18 and 77 years, with a mean age of 43.75±12.57 years (Table 1).

Table 1. Distribution of descriptive characteristics

		n (%)
Gender	Male Female	139 (77.2) 41 (22.8)
Age	Mean±SS Median (Min-Max)	43.75±12.57 43 (18-77)

The external orifice was below 3 cm in 61.7% (n=111) and above 3 cm in 38.3% (n=69) of the cases. When the St. James' grades of the cases were analyzed according to MRI; 57.2% (n=103) were grade 1, 12.2% (n=22) were grade 2, 21.1% (n=38) were grade 3, 8.9% (n=16) were grade 4, 0.6% (n=1) were grade 5. When analyzing the Parks' classifications, 66.7% (n=120) of the cases were intersphincteric, 32.2% (n=58) were transsphincteric and 1.1% (n=2) were suprasphincteric. In the SPTF classification, 71.1% (n=128) were simple, while 28.9%

(n=52) were complex. The MRI findings of the fistula orifice level, secondary tracts, abscesses and their locations, and the findings of the fistula external orifice regions according to the clock quadrant are given in the table. (Table 2)

When the surgical methods applied were analyzed; 26.1% (n=47) loose seton, 23.9% (n=43) cutting seton, 21.1% (n=38) fistulotomy, 22.8% (n=41) fistulectomy, 2,2% (n=4) were LIFT, 10% (n=18) laser, 5.6% (n=10) drainage, and 0.6% (n=1) anocutaneous advancement flap. Drainage procedure was additionally performed in 5 fistulotomy, 3 loose seton, 1 cutting seton and 1 fistulectomy cases in cases with abscess. Considering the patients who underwent more than one surgical procedure in the same case; fistulectomy and loose seton were performed in 6 cases, fistulotomy and loose seton in 3 cases, and fistulectomy and cutting seton in 3 cases.

Recurrence was observed in 18.3% of the cases (n=33). The duration of recurrence varied from 5 to 72 months; the mean duration was 21.06±19.82 months.

According to the result of surgical orifice, 92.8% (n=167) of the cases were positive, whereas according to the MRI result, 99.4% (n=179) of the cases were positive. While 13 cases with negative surgical internal opening results, only 0.6% (n=1) of these cases were negative and 6.7% (n=12) were positive by MRI. While 167 cases with positive surgical internal orifice results were detected, 92.8% (n=167) of these cases were positive by MRI. The agreement between surgical and MRI internal orifice results was 13.4% and was found to be statistically significant (Kappa coefficient of agreement: 0.134; p<0.01). Accordingly, the sensitivity of the test was 100%, specificity was 7.69%, positive predictive value was 93.3%, negative predictive value was 100%, and accuracy was 93.33%. (Table 3)

Table 3. Evaluation of the compatibility of internal opening sites in MRI and surgery

	Surgery-site of internal opening			p
	Absent	Present	Total	
	n (%)	n (%)	n (%)	
MRI- site of internal opening				0.001** Kappa=0.134
No	1 (0.6)	0 (0)	1 (0.6)	
Yes	12 (6.7)	167 (92.8)	179 (99.4)	
Total	13 (7.2)	167 (92.8)	180 (100)	
Sensitivity	100.0			
Specificity	7.69			
Positive predictive value	93.30			
Negative predictive value	100.0			
Accuracy	93.33			

**p<0,01

Table 2. Distribution of characteristics of the cases

	n (%)
External opening	
<3 cm	111 (61.7)
>3 cm	69 (38.3)
MRI St. James's grade	
Grade 1	103 (57.2)
Grade 2	22 (12.2)
Grade 3	38 (21.1)
Grade 4	16 (8.9)
Grade 5	1 (0.6)
MRI Park's classification	
Intersphincteric	120 (66.7)
Transsphincteric	58 (32.2)
Suprasphincteric	2 (1.1)
MRI SPTF classification	
Simple	128 (71.1)
Complex	52 (28.9)
MRI opening level	
Low site	174 (97.2)
High site	5 (2.8)
MRI secondary tract	
No	156 (86.7)
Yes	24 (13.3)
MRI internal opening	
No	1 (0.6)
Yes	179 (99.4)
Surgery external opening	
No	13 (7.2)
Yes	167 (92.8)
MRI site of internal openings	
6-8 o'clock	104 (57.2)
3-5 o'clock	27 (15.0)
12-2 o'clock	31 (17.2)
9-11 o'clock	18 (10.0)
Abcess	
No	158 (87.8)
Yes	22 (12.2)
Abcess site	
Intersphincteric	14 (63.6)
Perianal region	7 (31.8)
Supralevator	1 (4.5)
External opening site-MRI	
6-8 o'clock	110 (61.1)
3-5 o'clock	38 (21.1)
12-2 o'clock	18 (10)
9-11 o'clock	14 (7.8)
External opening site at surgery	
6-8 o'clock	105 (58.3)
3-5 o'clock	37 (20.6)
12-2 o'clock	17 (9.4)
9-11 o'clock	13 (7.2)
Multiple	8 (4.4)
•Surgical method	
Loose seton	47 (26.1)
Cutting seton	43 (23.9)
Fistulotomy	38 (21.1)
Fistulectomy	41 (22.8)
LIFT	4 (2.2)
Laser	18 (10.0)
Drainage	10 (5.6)
Advacement flap	1 (0.6)
Recurrence	
No	147 (81.7)
Yes	33 (18.3)
Recurrence time (months) (n=33)	
Mean±Ss	21.06±19.82
Median (Min-Max)	12 (5-72)

•More than one surgical method was applied. LIFT: ligation of the intersphincteric fistula tract. SPTF:Standard Practice Taske Force

There were 105 cases with surgical external sinus opening in the 6-8 region, and 61% (n=105) of the cases were found in this region by MRI. There were 37 cases with surgical external sinus orifice in the 3-5 region, while only 20.3% (n=35) of the cases were detected in the 3-5 region by MRI. There were 17 cases with surgical external opening in the 12-2 region, and 9.9% (n=17) of the cases were found in this region by MRI. There were 13 cases with surgical external opening in the 9-11 region, while only 7% (n=12) of the cases were found in the 9-11 region by MRI. The agreement between surgical and MRI external orifice results was 96.9% and statistically significant (Kappa coefficient of agreement: 0.969; p<0.01). Accordingly, the sensitivity of the test was 100%, specificity 62.80%, positive predictive value 95.20%, negative predictive value 100% and accuracy 98.30%. (Table 4) There was a statistically significant difference between internal and external orifice on MRI in cases with an external orifice above 3 cm (p=0.001; p<0.01). The ratio of patients with an external opening zone of 6-8 on MRI to internal opening zones of 6-8 and 9-11 on MRI was higher than the ratio of patients with an internal opening zone of 3-5 and 12-2 on MRI. (Table 5)

Univariable and multivariable Cox proportional hazards regression analyses were performed to determine the factors affecting recurrence. In univariable evaluations, the effects of external orifice, St. James' grade, Park's classification and, SPTF classification on MRI, loose seton surgical method on recurrence were found to be statistically significant (p=0.001, p=0.001, p=0.001, p=0.001, p=0.001, p=0.001; p=0.007; p<0.01, respectively). The level of dehiscence on MRI, surgical internal orifice, internal opening zone on MRI, and surgical methods of cutting seton, fistulotomy, and fistulectomy did not differ significantly according to recurrence (p>0.05).

Variables that were found to have significant or near significant (p<0.200) effects in the univariable evaluation were included in the multivariable evaluation. As a result of the evaluation performed using the Enter method, it was observed that Park's classification on MRI and SPTF classification on MRI were significantly included in the model. When intersphincteric was taken as the reference value in Park's classification on MRI, transsphincteric was found to increase the recurrence rate 5.568 times [HR (95% CI)= 5.598 (1.613-19.219), p=0.007]. When low localization was taken as the reference value in SPTF classification on MRI, high localization was found to increase the recurrence rate by a factor of 3.240 times [HR (95% CI)= 3.240 (1.094-1.117), p=0.044]. (Table 6) In a total of 180 operations, 147 patients (81.7%) survived disease-free, while 33 recurrences were observed. The mean disease-free survival was 79.483±2.417 (95% CI: 74.746 - 84.220) months (Figure).

Table 4. Evaluation of the compatibility of external opening sites in MRI and surgery

	Surgery-site of external opening					p
	6-8 n (%)	3-5 n (%)	12-2 n (%)	9-11 n (%)	Total n (%)	
MRI- site of external opening						0.001** Kappa=0.969
6-8	105 (61.0)	2 (1.2)	0 (0)	1 (0.6)	108 (62.8)	
3-5	0 (0)	35 (20.3)	0 (0)	0 (0)	35 (20.3)	
12-2	0 (0)	0 (0)	17 (9.9)	0 (0)	17 (9.9)	
9-11	0 (0)	0 (0)	0 (0)	12 (7.0)	12 (7.0)	
Total	105 (61.0)	37 (21.5)	17 (9.9)	13 (7.6)	172 (100.0)	
Sensitivity	100.0					
Specificity	62.80					
Positive predictive value	95.20					
Negative predictive value	100.0					
Accuracy	98.30					

**p<0,01

Table 5. Comparison of ınternal and external opening sites on MRI in cases with external opening >3 cm (N=69)

	MRI-site of internal openings				p
	6-8	3-5	12-2	9-11	
MRI-site of external openings					0.001**
6-8	19 (59.4)	2 (22.2)	5 (27.8)	7 (70.0)	
3-5	7 (21.9)	6 (66.7)	6 (33.3)	0 (0)	
12-2	0 (0)	0 (0)	6 (33.3)	0 (0)	
9-11	6 (18.8)	1 (11.1)	1 (5.6)	3 (30.0)	

Fisher Freeman Halton Test, **p<0,01

Table 6. Univariate and multivariate assessments of risk factors on recurrence

DF	Nux		Univariable		Multivariable	
	No	Yes	HR (95% CI)	p	HR (95% CI)	p
External opening						
<3 cm	100 (90.1)	11 (9.9)	Reference			
>3 cm	47 (68.1)	22 (31.9)	3.745 (1.813-7.737)	0.001**	0.967 (0.354-2.642)	0.948
MRI St. James's grade						
Grade 1	96 (93.2)	7 (6.8)	Reference	0.001**		0.060
Grade 2	20 (90.9)	2 (9.1)	1.298 (0.270-6.251)	0.745	1.930 (0.395-9.438)	0.417
Grade 3	25 (65.8)	13 (34.2)	6.644 (2.633-16.766)	0.001**	5.906 (0.002-1.783)	0.900
Grade 4	6 (35.3)	11 (64.7)	16.917 (6.479-44.175)	0.001**	2.218 (0.005-6.718)	0.888
MRI Park's classification						
Intersphincteric	111 (92.5)	9 (7.5)	Reference			
Transsphincteric	35 (60.3)	23 (39.7)	7.202 (3.308-15.678)	0.001**	5.568 (1.613-19.219)	0.007**
MRI SPTF classification						
Simple	115 (89.8)	13 (10.2)	Reference			
Complex	32 (61.5)	20 (38.5)	4.840 (2.396-9.774)	0.001**	3.240 (1.094-1.117)	0.044*
MRI opening level						
Low site	142 (81.6)	32 (18.4)	Reference			
High site	4 (80)	1 (20.0)	0.848 (0.116-6.216)	0.871		
Surgery internal opening						
No	11 (84.6)	2 (15.4)	Reference			
Yes	136 (81.4)	31 (18.6)	1.305 (0.312-5.456)	0.716		
MRI internal opening						
6-8 o'clock	82 (78.8)	22 (21.2)	1.938 (0.456-8.240)	0.371		
3-5 o'clock	22 (81.5)	5 (18.5)	1.710 (0.332-8.812)	0.522		
12-2 o'clock	27 (87.1)	4 (12.9)	1.175 0.215-6.417)	0.852		
9-11 o'clock	16 (88.9)	2 (11.1)	Reference	0.687		
Surgical procedures						
Loose Seton						
No	115 (86.5)	18 (13.5)	Reference			
Yes	32 (68.1)	15 (31.9)	2.560 (1.289-5.088)	0.007**	1.200 (0.543-2.625)	0.652
Cutting seton						
No	110 (80.3)	27 (19.7)	1.375 (0.567-3.334)	0.480		
Yes	37 (86.0)	6 (14.0)	Reference			
Fistulotomy						
No	113 (79.6)	29 (20.4)	2.185 (0.768-6.222)	0.143		
Yes	34 (89.5)	4 (10.5)	Reference			
Fistulectomy						
No	112 (80.6)	27 (19.4)	1.530 (0.631-3.710)	0.347		
Yes	35 (85.4)	6 (14.6)	Reference			

*p<0,05 , **p<0,01

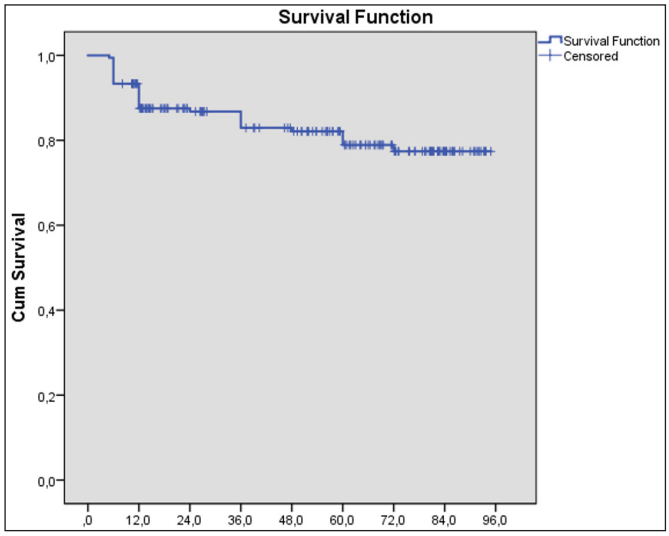

Figure. Disease free survival graph in all cases

DISCUSSION

Most cases of perianal fistula are considered idiopathic and the most common theory of pathogenesis is the cryptoglandular hypothesis. Perianal fistula mainly affects young and middle-aged men. Our study included 139 males and 41 females with a median age of 42 (18-77) and 45 (25-74) years, respectively. These results are consistent with the literature.[8]

In the surgical management of anal fistulas, it is very important to control infection, and identify secondary tracts and define the relationship of the tracts to the sphincteric musculature.[9-11] We may not have information about these features by physical examination alone, and MRI is the gold standard for recognizing these features.[12] It has been shown that surgeons' awareness of MRI

results before perianal fistula surgery can decrease the recurrence rate.[13] While most patients have a single tract, multiple tracts can be detected in some patients. In our study, 156 and 24 patients had single and multiple tracts, respectively. The classification of perianal fistulas according to MRI results is very important in terms of the chances of successful treatment. In the Park classification, the course of the fistula tract is divided into 4 groups as intersphincteric, transsphincteric, suprasphincteric, and extrasphincteric according to its relationship with the internal and external anal sphincters. In our study, the intersphincteric group was found in 120 (66.7%) cases and the transsphincteric group was found in 58 (22%) cases in accordance with the literature.[6] Evaluating the fistula channel, secondary tracts and associated abscesses with the findings obtained from MRI, the St. James classification is classified into 5 degrees.[14] In our study, grade 1 constituted the largest group with 103 (57.2%) cases. According to SPTF classification, there were 128 (71.1%) simple and 52 (28.9%) complex cases. Fluid collection in the perianal region or enlargement of the fistula diameter more than 10 mm is considered as abscess. We detected abscess in 22 (12.2%) cases in our series.

In order to use the appropriate surgical option, the course of the pathway between the fistulas should be well known and defined.[15,16] The agreement between the results of surgical opening of the fistula external opening according to the clock quadrant was found to be significant at 96.9%. Accordingly, the sensitivity of the test was 100%, specificity 62.8%, PPV 95.2%, FPV 100% and accuracy 98.3%. In a study that evaluated MRI findings of internal opening and surgical findings, sensitivity and specificity were 85.4% and 80%, respectively.[17] In our study, we found agreement of 13.4%, sensitivity 100%, specificity 7.69%, PPV 93.3%, FPV 100% and accuracy 93.3% in evaluating internal orifice compliance.

A serious rate of recurrence occurs after anal fistula surgery. According to a meta-analysis, the recurrence rate was reported between 10%-57%.[18] In our series, the recurrence rate was 18.3%. It is important that the disease with such a wide range of recurrence rates can be quite complex and that no single surgical method is the most effective. In addition to partial sphincter-sparing procedures such as fistulotomy, fistulectomy and cutting seton, many sphincter-sparing methods such as loose seton, advancement flap, ligation of the intersphinctheric fistula tract (LIFT), fibrin glue, fistula plag (FP), Fistulo-tract Laser Closure (FiLaC), video assisted anal fistula treatment (VAAFT) have been used and the search is still continuing. Depending on the type of fistula, sphincter-sparing may be chosen for those with a high probability of recurrence, while more aggressive techniques with more precise results may be chosen for those with a low probability of recurrence. In a study, inadequate preoperative diagnosis and incomplete incision of the internal orifice were found to be important in recurrence.[19] In Cox regression analyses performed for factors affecting recurrence in our series, higher recurrence rates were found in fistulas with an external opening of more than 3 cm, transsphincteric, grade 3-4 and complex fistulas. In a meta-analysis, the overall recurrence rate was found to be 20%. Previous anal surgery, high-transsphincteric fistulas, inability to detect the internal orifice, horseshoe fistulas, multiple fistula tracts and operations using seton were found to have higher recurrence rates.[20] In our study, recurrence was significantly higher in patients who underwent loose seton operation ($p=0.007$; $p<0.01$).

Limitations of our study; the study was retrospective and recurrence cases and patients with previous surgery were not included. Postoperative management differences of patients and the number of all operations were not close to each other to evaluate recurrence.

CONCLUSION

Magnetic resonance imaging has become a prerequisite for a successful surgical procedure due to its sensitivity and accuracy for all types of perianal fistulas. In addition to showing the internal and external orifice of fistulas, it is also a modality that can be used for classification. Our study evaluated the internal and external orifice of fistulas on MRI findings compared with surgical exploration findings and found statistical agreement. Advanced surgical procedures for anal fistula, a complex and recurrent disease, are constantly being investigated. In our study, we found a higher recurrence rate in patients with external orifice >3 cm, transsphincteric, grade 3-4 complex fistulas and loose seton use. Pragmatic large cohort studies are needed to understand the relationships and spesific factors between certain factors and recurrence using objective data synthesis methods. Our study strengthens clinical awareness by identifying patients at high risk of recurrence and managing them accordingly.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Göztepe Prof. Dr. Süleyman Yalçın City Hospital Ethics Committee (Date:23.08.2023, Decision No: 2023/0546).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

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Original Article

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Utilizing the MRI findings to diagnose acute appendicitis in pregnant women

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ABSTRACT

Aims: To assess the performance of magnetic resonance ımaging (MRI) scale for the diagnosis of acute appendicitis in pregnant women and to determine the added diagnostic value of MRI imaging.

Methods: In this retrospective study, the data of patients who presented to our hospital emergency department between January 2018 and December 2021, had clinical and laboratory findings consistent with acute appendicitis, and were diagnosed with radiological imaging, were extracted from the hospital automation system and used for statistical analysis. Ultrasound (US) was used as the first-line diagnostic method for pregnant patients, and magnetic resonance imaging (MRI) was used as the second-line diagnostic method. The success of US and MRI examinations in diagnosing acute appendicitis was evaluated. In MRI examinations, the mean values of appendix diameter and wall thickness parameters were examined, and the sensitivity, specificity, positive predictive value, and negative predictive value of periappendiceal fat tissue intensity increase, T2A lumen hyperintensity, and periappendiceal fluid parameters were evaluated. Additionally, the frequency of acute appendicitis according to trimesters was examined. SPSS v20.0 (IBM SPSS Statistics for Windows, Version 20.0; Armonk, NY, USA) package program was used for the analysis.

Results: When the medical records of 200 patients diagnosed with appandicitis were retrospectively examined, it was determined that there were 13 pregnant cases diagnosed with MRI during this period. Sensitivity, specificity, positive predictive value, and negative predictive value were evaluated for parameters including intraluminal T2A hyperintensity, wall thickness, periappendiceal fluid accumulation, and periappendiceal fatty tissue intensity increase. İntraluminal T2A hyperintensity and also periappendiceal fatty tissue intensity increase parameter sensitivity was 100%, however the wall thickness parameter had a sensitivity of 60% and the periappendiceal fluid accumulation parameter had a sensitivity of 80%. the periappendiceal fatty tissue intensity increase parameter had a a specificity of 33.3%, which is the lowest ratio among the other parameters. there was also no significant difference in the frequency of acute appendicitis according to trimesters

Conclusion: MRI examination has a high success rate and can be used as the primary diagnostic method for pregnant appandicitis cases. In terms of parameter evaluation, the highest positive predictive value (90.9%) is found by the parameter of intraluminal T2 hyperintensity, and the parameter of periappendiceal fluid collection is found to be in the second place. The success of T2A lumen hyperintensity and periappendiceal fat tissue intensity increase parameters, especially in excluding negative cases, was found to be quite high.

Keywords: Magnetic resonance imaging, acute, appendicitis, ultrasonography, pregnant women

INTRODUCTION

Acute appendicitis is one of the most common surgical diseases among pregnant women.[1,2] Early diagnosis of acute appendicitis in pregnant patients is crucial due to its potential to reduce both fetal and maternal mortality and morbidity. Therefore, timely visualization of the inflamed appendix on a good and appropriate imaging examination is crucial for accurate diagnosis of acute appendicitis in pregnancy to improve the maternal and fetal outcomes.[3]

Computerized tomography (CT) is very accurate for diagnosis of acute appendicitis.[4,5] Nonetheless, CT is deemed inappropriate for pregnant women and fetuses because of its ionizing radiation.[5,6]

Although ultrasound (US) examination is the first recommended diagnostic test in pregnant patients, it becomes challenging, especially in the second and third trimesters, due to the increased size of the uterus leading to a change in the position of the appendix. In the literature, it has been reported that the rate of failure to visualize the appendix with US in pregnant patients can reach up to 97% in the second and third trimesters.[7]

Magnetic resonance imaging (MRI) has been increasingly used as a second-line diagnostic method in recent years. The sensitivities and specifities of MRI on acute appendicitis have been reported to range above 90%.[3]

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METHODS

The study was carried out with the permission of Sakarya University Faculty of Medicine Non-interventional Ethics Committee (Date: 02.04.2022, Decision No: 123). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study investigates the success of US and MRI examinations in diagnosing acute appendicitis in pregnant patients. A retrospective study was conducted at our hospital between January 2018 and December 2021. The initial number of appendicitis cases was 200; however, thirteen pregnant patients with clinical, laboratory, and examination findings compatible with acute appendicitis, regardless of age, were included in the study.

All pregnant patients underwent ultrasound (US) examination as the first-line diagnostic method. Regardless of whether a appendicitis diagnosis was suspected by ultrasound, magnetic resonance imaging (MRI) was requested as the second-line diagnostic method for all pregnant patients by the surgeons to confirm the diagnosis. Patients without a histopathological diagnosis and those with inadequate quality US and MRI images were excluded from the study.

All non-contrast-enhanced MRI examinations were performed with a 1.5-Tesla scanner with anterior array body coil. Patient's trimasters were also noted during imaging . For pregnant patients who underwent MRI examination, the mean values of appendix diameter and wall thickness, as well as the sensitivity, specificity, positive predictive value, and negative predictive value of parameters such as T2A lumen hyperintensity, increased intensity of periappendiceal fat tissue, and the presence of periappendiceal fluid, were evaluated. . Axial and coronal T2-weighted sequences were obtained for visualizing the appendix. However, diffusion-weighted sequences were not included in our examinations. Contrast agents were not administered to the patients due to their pregnancy. These MRI acquisitions were retrospectively reviewed by experienced radiologists who were blinded to final diagnosis.

Statistical Analysis

Descriptive statistics were presented as number (n) and percentage (%) for categorical variables, and as mean ± standard deviation and median [1st quartile-3rd quartile] for numerical variables. Pathology results were considered the gold standard diagnostic test. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for other tests that could be used for diagnosis. Chi-square tests were used to examine the relationship between two different categorical variables in independent groups. In 2x2 tables, Fisher's exact test was used if the smallest expected value was <5, Yates' corrected chi-square test was used if it was ≥5 and ≤25, and Pearson's chi-square test was used if it was >25. Pearson's chi-square test was used for tables in the RxC format. When examining the frequency of a categorical variable at two different times within the same group (dependent groups), the Mc Nemar test (2x2 chi-square test for dependent samples) was used if the variable had two groups, and the marginal homogenity test (2xC) was used if the variable had three or more groups. When examining the difference in numerical variables between two dependent groups, the t-test was used if the data followed a normal distribution, and the Wilcoxon t-test was used if there was no normal distribution. Normal distribution was evaluated using the Shapiro-Wilk test. A statistical significance level of $p<0.05$ was considered. SPSS v20.0 (IBM SPSS Statistics for Windows, Version 20.0; Armonk, NY, USA) software package was used for the analyses.

RESULTS

In our study, firstly we investigated the success of ultrasound and mri examination in diagnosing acute appendicitis in the pregnant patient group. Ultrasound examination was used as the first-line diagnostic method in our study, and among the 13 patients with clinical and laboratory findings compatible with acute appendicitis, the appendix could be visualized by ultrasound examination in only 3 of them, with all parameters being evaluated. Only 2 patients were diagnosed with acute appendicitis through ultrasound examination, and in 1 patient whose pathology result was compatible with acute appendicitis, the appendix was evaluated as normal by ultrasound examination.

Clinical and laboratory findings were consistent with acute appendicitis, and the diagnosis of acute appendicitis was confirmed through imaging methods in 13 pregnant patients, evaluated according to trimesters. In the first trimester, acute appendicitis was diagnosed in 4 individuals, with 75% (3 individuals) having pathological results consistent with acute appendicitis and 25% (1 individual) not consistent with acute appendicitis. In the second trimester, 100% (2 individuals) had pathology results consistent with acute appendicitis, and in the third trimester, 71.4% (5 individuals) had pathological results consistent with acute appendicitis, while 28.6% (2 individuals) did not. There was no significant difference in the frequency of acute appendicitis between trimesters ($p>0.001$)

Thirteen pregnant patients underwent MRI examination. According to the radiological diagnosis, the mean appendix diameter value for the 13 patients who underwent MRI examination was 9.23 mm with a standard deviation of 2.38. The median (minimum-maximum) values were calculated as 8.0 (8.00-9.50) (**Table 1**).

Table 1. Average appendix diameter value in pregnant patients on MRI

	Mean ± Standard Deviation	Median [1st Quartile - 3rd Quartile]	Number
MRI-diameter	9.23±2.38	8 [8.00- 9.50]	13

The pregnant patients, suspected by clinical underwent MRI examination regardless of whether an appendicitis diagnosis was made by ultrasound to confirm the diagnosis by the surgeon's request. Sensitivity, specificity, positive predictive value, and negative predictive value were evaluated for parameters including intraluminal T2A hyperintensity, wall thickness, periappendiceal fluid accumulation, and periappendiceal fatty tissue intensity increase. The sensitivity of the intraluminal T2A hyperintensity parameter was 100%, its specificity was 66.7%, and its positive and negative predictive values were 90.9% and 100%, respectively. The wall thickness parameter had a sensitivity of 60%, a specificity of 66.7%, a positive predictive value of 66.7%, and a negative predictive value of 25%. The periappendiceal fatty tissue intensity increase parameter had a sensitivity of 100%, a specificity of 33.3%, and positive and negative predictive values of 83.3% and 33.3%, respectively. The periappendiceal fluid accumulation parameter had a sensitivity of 80%, a specificity of 67.7%, and positive and negative predictive values of 88.9% and 50%, respectively (Table 2) (Table 3) (Table 4) (Table 5) (Table 6).

Table 2. Appendiceal wall thickness values in patients undergoing MRI examination based on radiological diagnosis

	Mean± Standard Deviation	Median [1st Quartile - 3rd Quartile]	Number
MRI- Wall Thicknesss	1.69 ± 0. 63	2 [1.00- 2.00]	13

Table 3. MRI- evaluation of the relationship between T2A lumen hyperintensity and pathology

MRI- T2A Lumen Hyperintensity	Pathology n(%)		p value
	Positive	Negative	
Positive	10 (90.9%)	1 (9.1%)	0.038
Negative	0 (0.0%)	2 (100%)	
Fisher's Exact Test			

Table 4. MRI- periappendiceal fluid accumulation and its relationship with pathology evaluation

Periappendiceal Fluid	Pathology n(%)		p value
	Positive	Negative	
Positive	8 (88.9%)	1 (11.1%)	0.203
Negative	2 (50.0%)	2 (50.0%)	
Fisher's Exact Test			

Table 5. MRI- evaluation of the relationship between wall thickness parameter and pathology

MRI- Wall Thickness	Pathology n(%)		p value
	Positive	Negative	
Positive	6 (75%)	2 (25%)	
Negative	4(80%)	1(20%)	
Fisher's Exact Test			

Table 6. MRI- evaluation of the relationship between periappendiceal fat tissue intensity increase parameter and pathology

MRI- Periappendiceal Fat Tissue Intensity Increase	Patoloji n (%)		p value
	Positive	Negative	
Positive	10 (83.3%)	2 (16.7%)	
Negative	10 (76.9%)	3 (23.1%)	
Fisher's Exact Test			

DISCUSSION

Clinical symptoms are nonspecific on pregnant appandicitis cases, also physical examination at later stage of pregnancy can be misleading because typical presentation of appendicitis at Mcburney point is usually not elicited as a result of displaced cecum by an enlarged gravid uterus.[8] As a result, in our study, similar to the literature, it was concluded that the success of ultrasound examination in diagnosing acute appendicitis and visualizing pathological appendices is quite low to MRI examinations for pregnant cases.

Contrast-enhanced CT is an accurate and rapid tool but is inappropriate for radiosensitive pregnant women.[9] Ultrasound which is free from radiation hazard is almost as good as CT but the downside of it is operator dependent and can be afected by body habitus.[10,11]

MRI examination has become an accepted trend to replace CT for appendicitis among pregnant women.[12-15] Although there is no consensus on which sequences should be used for visualizing the appendix in MRI examinations in the current literatüre, the most common technical and sequence parameters used for visualizing the appendix in MRI include axial and coronal T2 HASTE, axial STIR, and coronal SPACE sequences. In our study, axial and coronal T2-weighted sequences were obtained for the purpose of visualizing the appendix. Regarding the imaging parameters, the following criteria were considered compatible with acute appendicitis: appendix diameter of 6 mm or greater, wall thickness measurement of 2 mm or greater, intraluminal T2-weighted hyperintensity, increased intensity in surrounding fatty tissue, and the presence of periappendiceal fluid (Figure 1, 2, 3). According to our study, both intraluminal T2 hyperintensity and periappendicieal fatty tissue intensity's sensitivity value is quite high as 100% for appendicitis cases. The most specific sign for appendicitis is periappendicieal fluid accumulation, wall thickness and intraluminal T2 hypersensitivity parameters, respectively. The periappendiceal fatty tissue intensity increase parameter is the least specific parameter for the diagnoses. The highest positive predictive value (90.9%) is found by the parameter of intraluminal T2 hyperintensity, and the parameter of periappendiceal fluid collection is found to be in the second place. Although negative predictive value is quite high (100%) for intraluminal T2 hyperintensity parameter, is the lowest for wall thickness parameter as 25%.

Some studies have also included diffusion-weighted series.[16-18] Our study was retrospective, and difussion weighted images were not recorded in our routine examninations, hence they could not be evaluated. The absence of diffusion-weighted sequences in the MRI examinations of the patients limits this study. Prospective studies can be conducted in the future to evaluate the contribution of diffusion-weighted sequences in diagnosing acute appendicitis in pregnant patients who present to the emergency department with symptoms suggestive of acute appendicitis.

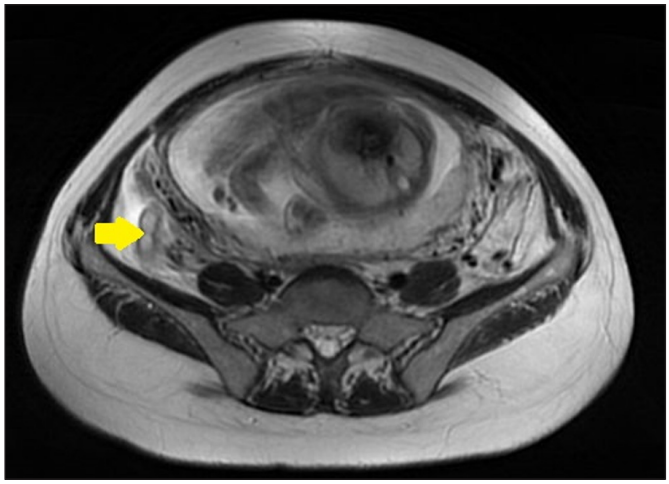

Figure 4.1. MRI Imaging Including Axial T2A Lower Abdominal Sections.
In the MRI imaging containing axial T2A lower abdominal sections; an increase in appendix diameter and wall thickness, as well as intraluminal minimal fluid-related luminal T2A hyperintensity (arrow)

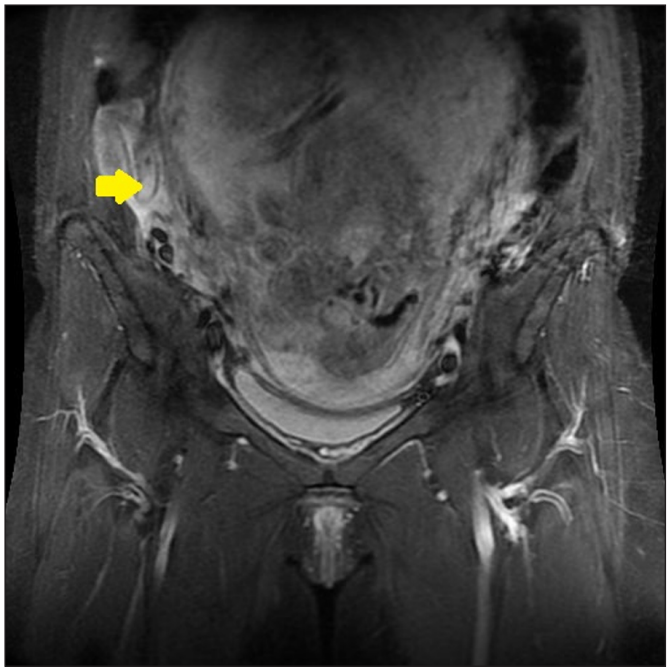

Figure 4.2. Coronal T2A Section Images of the Patient Diagnosed with Acute Appendicitis.
Coronal T2A MRI imaging of the pregnant patient diagnosed with acute appendicitis through histopathological examination; minimal increase in appendix wall thickness, intraluminal fluid-related luminal T2A hyperintensity(arrow), and minimal free fluid around the cecum.

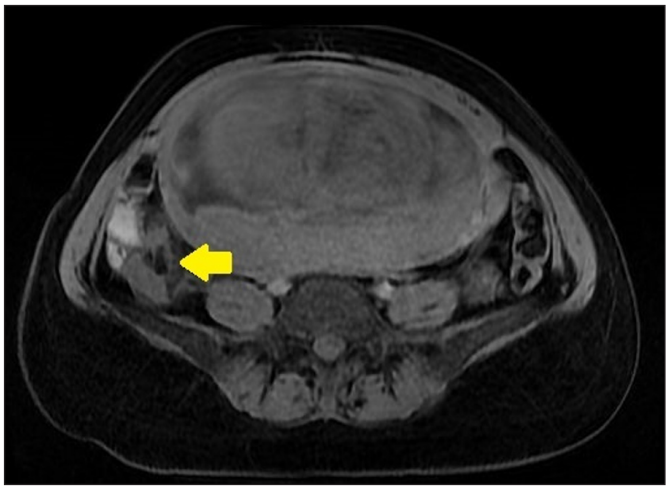

Figure 4.3. Fat-Suppressed T1A MRI Examination of the Patient Diagnosed with Acute Appendicitis.
In the MRI imaging containing axial fat-suppressed T1-weighted lower abdominal sections of the pregnant patient diagnosed with acute appendicitis through histopathological examination; there is an intensity increase, particularly in the periappendiceal fatty tissue, secondary to inflammation using the fat suppression technique

Among the 13 pregnant patients who underwent appendectomy in our study, the histopathological results were evaluated, and it was concluded that MRI examination was a highly accurate diagnostic tool for diagnosing acute appendicitis. Furthermore, it was found that MRI examination was significantly superior to ultrasound examination in diagnosing acute appendicitis, and it could be used as a first-line diagnostic method instead of ultrasound examination.

However, it should be noted that the accessibility and cost of MRI examination and the longer duration of the procedure compared to other diagnostic methods are limiting factors for the widespread use of MRI in diagnosing acute appendicitis. In recent years, many studies have been conducted on the contribution of MRI to the diagnosis of acute appendicitis in pregnant patient groups. These studies have examined the effectiveness of MRI use, its superiority over ultrasound and CT examinations, and its use in patients who cannot be diagnosed with ultrasound. Looking at sample reviews, a study by Sung Uk Cho and colleagues systematically presents the diagnostic accuracy of magnetic resonance imaging in the diagnosis of acute appendicitis in pregnant patients. This study demonstrated that MRI is generally highly accurate in diagnosing acute appendicitis in pregnant patients. Therefore, it was suggested that MRI could be used as the first-line imaging method in cases of suspected appendicitis in pregnant patients.[19] In a meta-analysis study conducted by Mania Kave and colleagues, MRI examination was found to be a reliable method for diagnosing acute appendicitis 1. In our study, similar to the literature, it was concluded that MRI is a highly successful method for diagnosing acute appendicitis in pregnant patients.

There are several limitations to this study. Firstly, the number of patients included in the study is limited. Future studies with larger patient cohorts may increase the reliability of our findings and contribute more to the literature. MRI examination has shown high accuracy in diagnosing acute appendicitis in our study of pregnant patient population. However, the success of ultrasound examination in diagnosis and imaging of pregnant appendicitis cases is quite low. Therefore, MRI examination can be used as the primary imaging method for diagnosing acute appendicitis in pregnant patients. Nevertheless, the use of MRI examination is limited due to its cost, limited accessibility, and, most importantly, the long duration of the scan. Regarding the duration, there is currently no consensus on which sequences should be taken when diagnosing acute appendicitis, as different studies have shown variations. Thus, there is no clear consensus on the duration. Prospective studies to shorten the duration during MRI examinations and to determine the necessary sequences for diagnosing acute appendicitis can be conducted in future studies.

Acute appendicitis was observed in pregnant patients in all trimesters, with the highest frequency in the second trimaster.[20] In our study, contrary to the literatüre there was no significant difference in the frequency of acute appendicitis among trimesters in pregnant patients.

CONCLUSION

In summary, MRI examination showed a high success rate in diagnosing acute pregnant appendicitis. In terms of parameter evaluation, the success of T2A lumen hyperintensity and periappendiceal fat tissue intensity increase parameters, especially in excluding negative cases, was found to be quite high. Our findings may provide valuable insights into determining the accuracy and reliability of diagnosing acute appendicitis in pregnant patients. This study may assist in better understanding how imaging methods can be utilized to increase the accuracy of diagnosing acute appendicitis in pregnant patients and reduce unnecessary surgical interventions. Future research is needed to validate and expand upon our findings in this field.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Sakarya University Faculty of Medicine Non-interventional Ethics Committee (Date: 02.04.2022, Decision No: 123).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

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Original Article

HEALTH SCIENCES
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Evaluation of one-point fixation surgery with computer-aided root mean square deviation in zygomaticomaxillary complex fractures

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ABSTRACT

Aims: Our paper aimed to present the results of the one-point fixation method in zygomaticomaxillary fractures by computer-aided mirror image superimposition with root mean square (RMS) deviation.

Methods: One-point fixation performed zygomaticomaxillary complex fracture patients (n=18) by one surgeon were included in our study. Virtual 3D data of preoperative and postoperative CT-scan images was obtained by Slicer software. Sagittal plan mirror image superpositioning were used to obtain RMS data by Slicer. Mirror image superimposition of the undamaged side to the broken side in preoperative CT-scan imaging was referred as group B or broken group. Superposition of the repaired side's postoperative imaging to the preoperative broken side was measured as group R or repair group in order to examine zygomatic bone's postoperative spatial location. Superpositioned mirror 3D images of the non-traumatic side onto post-fixation 3D in postoperative data was measured as group M or mirror group. RMS deviation values of the groups obtained by Slicer were statistically compared.

Results: Shapiro-Wilk test of groups were demonstrated normal distribution of the data for each group with no difference ($p>0.05$). In order to compare between groups, paired t-test covariance analysis were shown statistically similar data distrubition between experimental groups ($p>0.05$).

Conclusion: Considering the nature of maxillofacial surgery, which disapproves even millimetric errors, we believe that the mean square root deviation will become standard as it allows three-dimensional evaluation and precise mathematical measurements. Besides, in accordance with the recent literature, this study might pay the way for future studies that would increase the usage of the one-point fixation method conducted on larger case series, as this method prevents lower eyelid complications without a visible scar.

Keywords: Maxillofacial surgery, facial fractures, 3D imaging, 3D segmentation, root mean square, RMS

INTRODUCTION

The zygomatic bone defines the outer width and lateral projection of the face. This projection is called in the literature mid-lateral projection or malar eminence. However, the location and projection of the zygomatic bone cause widespread fracture incidence.[1] In addition to providing malar projection, the zygoma body originates in mimic musculature such as zygomatic muscles. Therefore, 3D reduction and fixation of zygomatic bone is mandatory for both aesthetic and functional outcomes in facial expression.[2] Today, reduction and rigid fixation is the golden standard for maxillofacial surgery. In zygomatic bone fracture repair many studies suggested three or two-point fixation methods.[3] Nevertheless, some studies reported that the one-point fixation method assures adequate rigidity without lower eyelid-related complications. This single-point repair method has become popular over time, as it requires a single incision intraorally which results in no visible scar.[1]

With its three-dimensional complex structure and joints of the bone, zygoma fractures may require three-dimensional measurement methods instead of reduction parameters such as distance measurements.[4] In addition, the contribution of zygomatic bone to the orbital cavity and maxillary sinus makes volume assessment compulsory in zygomatic trauma cases. Today, the widespread use of computed tomography in the diagnosis and treatment of facial fractures has allowed virtual three-dimensional postoperative evaluation. With computer-

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aided programs, not only distance measurements but also spatial positional changes and volumetric differences can be determined in millimeters.[5] Root mean square (RMS) or quadratic mean is a measurement mathematical standardization value that is unique to 3D imaging methods to obtain point-to-point or surface-to-surface data for every millimeter.[6,7] Our study aimed to determine the postoperative precise position of the zygoma with open-source computer-aided three-dimensional spatial and volumetric measurements and to investigate the effectiveness of the single-point fixation method with RMS in zygoma fractures.

METHODS

This retrospective study was carried out with the permission of Hatay Mustafa Kemal University Clinical Researches Ethics Committee (Date: 17.02.2022, Decision No: 2022/02-36). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data Collection

Twenty-eight patients who underwent one-point fixation due to zygoma fracture between 2018 and 2021 were included in the study. Patients whose CT-scan imaging resolutions were low (more than two millimeters) were excluded from the study since because exact measurements could not be made due to plaque or screw artifacts (n=18). High-resolution Maxillofacial CT DICOM data obtained before and after the surgery was processed in Slicer 4.10.0 open-source software program to obtain a virtual 3D image of the skeleton (Figure 1). The preoperative and postoperative topographic structure of the facial skeleton was revealed by marking the sella turcica, porion, nasion, and basion points that are not included in the fracture area (Figure 2). These marking points were referred to determination of sagittal plans. Sagittal plans were used for comparison of the same sides as superposition. Sagittal plans also were used for comparison of the mirror sides as superimposition. Point-to-point data for every millimeter on the surfaces were revealed by Slicer as RMS. To compare spatial positional changes and volumetric differences in millimeters. RMS deviations were measured.

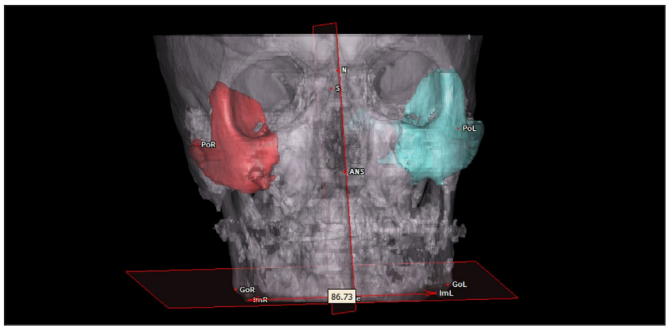

Figure 2. Topographic marking and determining the axles from virtual 3D.

3D Evaluation and Measurement

Mirror image superimposition of the undamaged side to the broken side in preoperative CT-scan imaging was obtained by the software and RMS deviations was measured (group B or broken group). RMS deviation values are calculated for this group to assess the extent of deviation from the intact (mirror) side. To compare

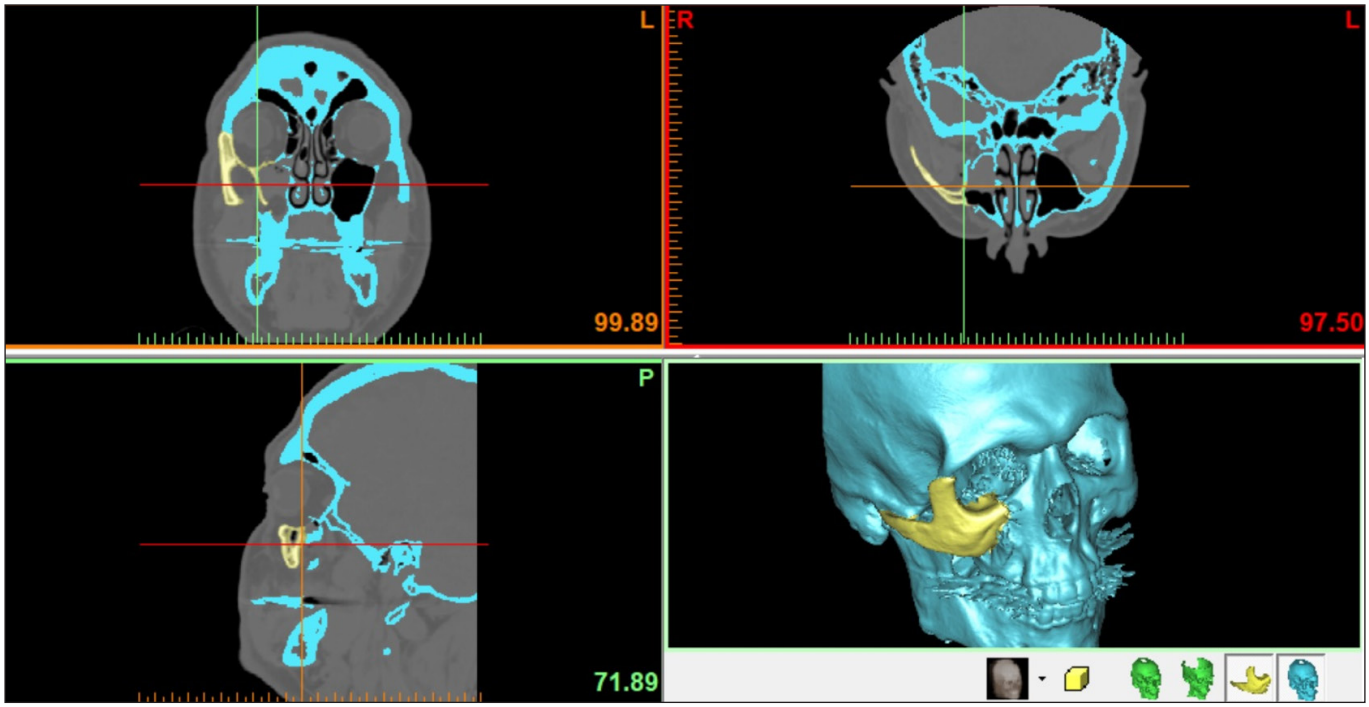

Figure 1. Virtual 3D data obtained with maxillofacial CT DICOM data.

zygomatic bone spatial location after repair, the superposition of the repaired side's postoperative data to the preoperative data broken side was obtained by the software and RMS deviation was measured (group R or repair group which represents the postoperative condition following single-point fixation surgery). RMS deviation values are calculated in this group to assess the postoperative spatial position of the zygomatic bone relative to the fractured side. In postoperative CT-scan, superimpositioned mirror 3D images of the non-traumatic side onto post-fixation 3D imaging, point-to-point RMS deviation values are calculated for this group, likely for the purpose of comparing and evaluating the symmetry of the repaired zygomatic bone, in comparison to Groups B and R by open-source software (group M or mirror group) and RMS values were statistically measured (Figure 3).

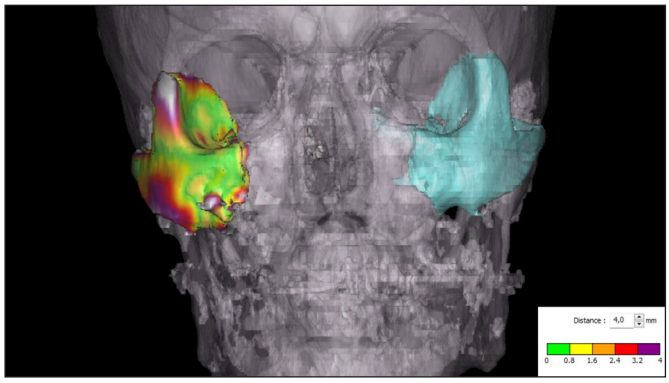

Figure 3. Superpositioning and determining RMS deviation (right lower corner: RMS deviation scale with colors).

Statistical Analysis

The data obtained by Slicer software was statistically evaluated with G*Power (latest ver. 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk Test since the number of samples was less than thirty. In addition, Skewness and Kurtosis values were calculated. Since normally distributed data were collected in a single dependent group, the Paired t-test was used for covariance analysis. p>0.05, there was no statistically significant difference between the data, and the distribution of the data was similar.

RESULTS

In order to evaluate data distrubitions of each group Shapiro-Wilk Test was used. In the broken group which represents the preoperative condition of the fractured side, p=0.457 was found by the Shapiro-Wilk Test. Skewness and Kurtosis values were calculated as 0.581 and -0.275, respectively. It was observed that the distribution was normal in the broken group.

In the repair group which includes the comparison of pre and postoperative change of single-point fixation surgery due to ZMC fractures, p=0.642 was found by the Shapiro-Wilk Test. Skewness and Kurtosis values were calculated as 0.359 and -0.896, respectively. It was observed that the distribution was normal in the repair group.

In the mirror group which represents the postoperative condition of the zygomatic bone on the non-fractured (mirror) side, p=0.877 was found by the Shapiro-Wilk Test. Skewness and Kurtosis values were calculated as 0.315 and 0.405, respectively. It was observed that the distribution was normal in the mirror group.

Since the data were normally distributed and collected in a single dependent group, as a post-hoc test paired samples t-test was used. It was observed that there was no significant difference and similar data distribution were revealed between the groups (p=0.096) within the analysis of covariance with paired samples t-test (Table).

Table. Paired samples t-test results

Paired t-test	N	Mean	SD	SEM
Group B	15	5.2973	2.46578	0.63666
Group R	15	5.5993	2.70028	0.69721
paired samples		0.30200	0.65502	0.16912
			t=1.786	p=0.096

DISCUSSION

Zygomatic Bone provides height, width, and projection for the lateral side of the facial skeleton.[1] Due to its complex location on the mid-face, zygomatic bone fractures are the second most common facial fractures following the nasal bone.[2,3] Therefore, since it allows 3D evaluation, the gold standard in the diagnosis is a maxillofacial CT scan (Figure 4).[4]

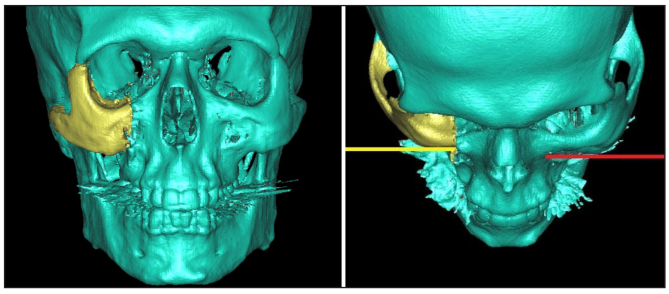

Figure 4. 3D evaluation and diagnosis of ZMC fracture with CT scan (a: isolating and marking the zygomatic bone, b: visualizing the rate of collapse).

Considering both aesthetic and functional outcomes, zygomatic bone repair is extremely complex and related to the surgeon's experience.[2] The most common treatment method for Zygomaticomaxillary Complex (ZMC) fractures is an open reduction with internal fixation. In the literature, many studies recommended three-point

fixation as a golden standard, and subsequently, the two-point fixation method was suggested by some of the authors.[3] One-point fixation was revealed to reduce complication rate and to avoid lower lid incisions and possible ophthalmic complications and revision surgeries, one-point fixation was recommended recently.[8-10] Meanwhile, other advantages of one-point fixation could be counted as no visible scar, easy-to-apply, shorter anesthesia duration, and less necessity of assistance.[2] In our study, ophthalmologic complications that may develop due to lower eyelid incisions were not observed in patients regarding the one-point fixation method. In addition, step deformity in the lower orbital rim was not observed in the patients. The results of our study are compatible with the literature in terms of the advantages such as the absence of ophthalmological complications, which are mentioned above, regarding the single point fixation method.

Linear or volume-based measurement methods used in maxillofacial surgery in the past, provide insufficient accuracy and remain old-fashioned.[11-13] On the other hand, one of the main concerns in maxillofacial surgery is the impossibility of pre-traumatic radiological evaluation.[14,15] Today, it's possible to perform three-dimensional evaluations with 3D imaging and spatial positioning or superimposition with advanced software technologies (Figure 5).[16-18] This development has paved the way for the use of advanced mathematical measurements with high consistency and the level of evidence in maxillofacial surgery.[5,19] RMS deviation ensures a 3D imaging-based point-to-point standardized evaluation method.[6,20,21]

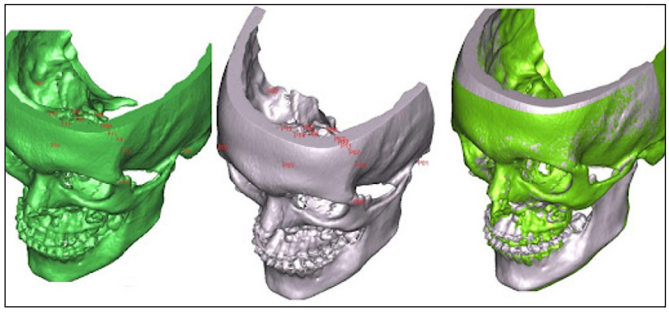

Figure 5. Superpositioning to evaluate results (left: before, middle: after repair, right: superposition of a and b).

In our study, within the scope of our investigation, the pivotal rationale behind segregating the subjects into three distinct cohorts is to methodically assess and juxtapose the postoperative positioning of the zygomatic bone among patients who have undergone single-point fixation surgery. Broken group is allocated to serve as a benchmark, denoting the preoperative zygomatic configuration. Repair group, on the other hand, signifies the postoperative state on the side affected by the fracture, while mirror group encapsulates the analysis of zygomatic symmetry or correspondence with the non-fractured side in comparison to broken and repair groups. Our work was found that the RMS deviation values before and after the repair performed with the single-point-fixation method were correlated with the RMS deviation values of the mirror image of the fractured side and the healthy side (Figure 6). This finding can be evaluated as paving the way for the use of the mirror image of the healthy side and the RMS value in the evaluation of the repair.

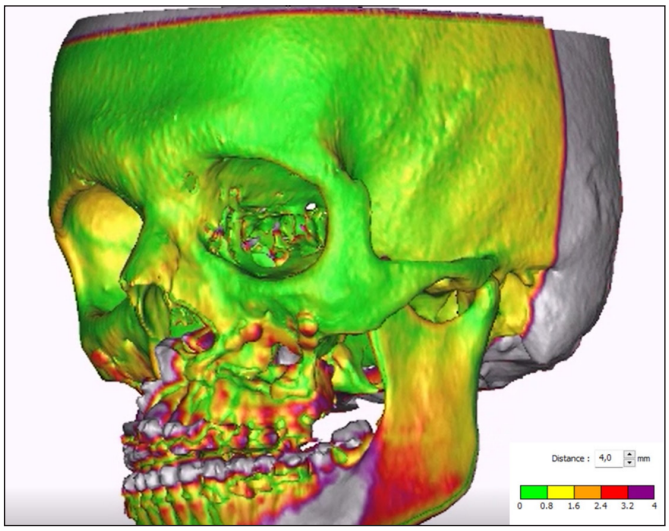

Figure 6. RMS deviation analysis after repair (right lower corner: RMS deviation scale).

A successful surgical repair is expected to show symmetry with the unbroken side. In our study, the distribution of RMS values was found to be expected and similar when the single point fixation repaired side and the mirror image of the healthy side were compared. This could be shown as evidence of the symmetry of the repaired zygomatic bone with the mirror image of the intact side.

Limitations

The constraint in our investigation may be attributed to a restricted sample size, which is a recognized limitation. Furthermore, it is important to note that our study did not entail a comparative analysis of single-point, two-point, and three-point fixation methods over an extended duration. As a result, lower lid complications stemming from the other two surgical techniques were incorporated as supplementary data, drawing upon recent scholarly sources.

CONCLUSION

In maxillofacial surgery, even submillimetric error margins are known to have negative effects on surgical evaluation and planning. We believe that the mean square root value may become the standard evaluation method in maxillofacial surgery since it allows three-dimensional evaluation and precise mathematical measurement. Thus, with the root mean square, further clinical trials would be able to use artificial intelligence to evaluate maxillofacial surgery results.

Recent surgical practice puts the one-point fixation method forward as a scarless, fast, and easy-to-apply method that eliminates the ophthalmological-based lower eyelid complications that cause the most headaches for the surgeon after zygomatic bone fracture repair.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hatay Mustafa Kemal University Clinical Researches Ethics Committee (Date: 17.02.2022, Decision No: 2022/02-36).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
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Serum-soluble receptor for advanced glycation end-products values might have diagnostic and prognostic significances in ulcerative colitis

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ABSTRACT

Aims: There is evidence of anti-inflammatory qualities associated with a soluble receptor for advanced glycation end products (sRAGE). We aimed to evaluate whether serum sRAGE levels of patients with inflammatory bowel diseases (IBDs) could serve as a biomarker by utilizing several clinical and laboratory models of disease activity for these individuals.

Methods: This case-control study included 77 ulcerative colitis (UC) patients (51 males and 26 females), 49 Crohn's disease (CD) patients (33 males and 16 females) and 54 healthy controls (38 males and 16 females). In UC, the UC Mayo Clinical Scoring system (MCS) was used for the clinical and endoscopic features. The histological activity index (HAI) of UC patients was determined by Truelove and Richards method. The Crohn's disease activity index (CDAI) was utilized for CD patients.

Results: In comparison to the control group, the median sRAGE concentrations in UC patients were significantly lower. [911.17 ng/L (322.91-1682.19 vs 1420.96 ng/L (816.68-2320.08), respectively, p=0.008)]. The patients with CD did not significantly differ from the other groups. The MCS and HAI values of UC patients negatively correlated to the serum sRAGE values (rho=-0,610, p<0.001 vs rho=-0,742 respectively, p<0.001). CD patients in remission had higher sRAGE values than patients having active disease [1720.42 ng/L (1005.68-2414.41) vs. 923.36 ng/L (601.61-1361.22 respectively, p=0.002]. CD patients under treatment had higher sRAGE values than patients without any treatment [1361.22 ng/L (821.26-1944.2) vs. 879.38 ng/L (601.61-1239.41) respectively, p=0.033]

Conclusion: Serum sRAGE might be an auxiliary biomarker for the clinical and laboratory traits of UC.

Keywords: Ulcerative colitis, receptor, advanced glycation end-products

INTRODUCTION

The term "receptor for advanced glycation endproducts" (RAGE) was initially utilized to describe a receptor for advanced glycation endproducts (AGE), and to date several other ligands including S100/calgranulins, calprotectins and advanced oxidation protein end products (AOPPs) have been identified.[1] RAGE is a cell-surface member of the immunoglobulin superfamily and ligands binding the extracellular domain of RAGE lead to nuclear factor kappa B (NFκB) activation via intracellular signaling.[2] Pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α) are released and active matrix metallopeptidase-9, which cleaves membrane-bound RAGE, and soluble RAGE (sRAGE) is released into circulation.[3]

In circulation, sRAGE has been reported to play a protective anti-inflammatory role by acting as a decoy receptor. sRAGE binds to membrane-bound RAGE ligands and prevents them interacting with cell membranes. It antagonizes the pathological effects mediated by RAGE.[4] In addition to several diseases including diabetes, cancer and rheumatic diseases, sRAGE and its ligands were implicated in inflammatory bowel diseases (IBDs).[3-9] Another innate immune system pattern-recognition receptor that is crucial to the development of chronic inflammatory diseases like IBDs is RAGE.[10,11] Previous studies about sRAGE in IBDs revealed debatable results and limited data exist about the role of sRAGE.[7-12] RAGE pathway has also been declared as a therapeutic target for IBDs.[13-16]

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The role of sRAGE with different disease activity models in IBDs has yet to be elucidated. In accordance with this, our goal was to determine whether serum sRAGE levels of IBD patients could serve as a biomarker by using the different clinical and endoscopic disease activity assessment models with the histological activity in UC patients according to Truelove Richards method.[17]

METHODS

The study was carried out with the permission of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Researches Ethics Committee (Date: 17.11.2021, Decision No: 235-211084517). The study protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee. Written informed consent was obtained from all participants.

Subjects

The study included 77 patients with ulcerative colitis (UC), 49 patients with Crohn's disease (CD) and 44 healthy controls, admitted to the gastroenterology department of our institute between December 2021 and November 2022.

Participants with any clinical conditions that could change the serum sRAGE level such as sepsis, uncontrolled diabetes and hypertension, hyperlipidemia, any malignancies, severe organ failure (heart failure, chronic renal disease, chronic obstructive lung disease, coronary artery disease) autoimmune and/or chronic inflammatory diseases, and those who had contra-indications for colonoscopy were excluded from the study. The healthy control group included participants whose colonoscopy results were normal. The disease duration, medications for IBDs, co-morbidities, and medications in all groups were recorded. Biochemical tests were performed just before the colonoscopy procedure.

Assessment of the Clinical and Endoscopic Activities

The Mayo Clinical score (MCS) was applied for the patients with UC and was scored between 0-12.[18]

Scores of ≤2 were classified as clinical remission whereas scores of >2 indicated an activation. The Crohn's disease activity index (CDAI) was used to assess the disease activity in the patients with CD.[19]

The disease extent of the patients with IBDs was defined in agreement with the Montreal classification.[20] In UC, proctitis and left-sided colitis were recorded as localized disease, whereas extensive localization and pancolitis were recorded as extensive disease. The Mayo endoscopic activity scoring (MES) index was used for the endoscopic activation of UC; normal mucosa and mild disease were recorded as endoscopic remission, whereas moderate and severe disease were recorded as active disease.[18]

Measurement of Serum sRAGE

After centrifugation of the venous blood samples at 5000×g for 10 minutes at 30°C, the supernatant serum was stored at (–) 80°C until analysis. The human RAGE Enzyme-Linked Immunosorbent Assay (ELISA) Bioassay Technology Laboratory Kit (Cat. No. E0031Hu, Lot:20221011) was used (Intra-Assay: CV<8 %, Inter-Assay:CV<10 %) with a microplate reader (Biotech Epoch 2 Microplate ELISA Reader, USA).

Histopathologic Evaluation in UC

The same pathologist who was blind to the participants evaluated the formalin-fixed paraffin-embedded H&E-stained colonic biopsies of the UC patients and performed grading through a scale similar to that developed by Truelove and Richards method. Active inflammation, chronic inflammation and crypt distortion were the components of the scale. The histopathologic activity index (HAI) was defined as the sum of the scores of these components.[17]

Statistical Analysis

Statistical analyses were conducted utilizing SPSS 15.0. Descriptive statistics were provided as proportions for categorical variables and as medians with inter-quartile ranges for continuous variables. Comparisons for continuous variables were carried out using the Mann-Whitney U test and the Kruskal-Wallis test, while the chi-square test was used for categorical variables. Spearman's correlation analysis was employed to investigate for associations between the parameters. Receiver Operating Characteristics (ROC) analysis was conducted by free-online tool 21. The confidence level for statistical significance was set at 0.95 ($p<0.05$).

RESULTS

In total, 77 UC patients (51 males and 26 females), 49 CD patients (33 males and 16 females) and 54 healthy controls (38 males and 16 females) participated in the study. Demographic, clinical and laboratory characteristics of the participants are presented in Table 1. The groups were similar with respect to age and gender.

The median sRAGE concentrations were significantly lower in UC patients compared to the control group (911.17 ng/L vs 1420.96 ng/L, p=0.008). sRAGE concentrations were not statistically significant between the patients with CD and healthy controls, UC and CD groups (Table 1).

Table 1. Demographic, clinical and laboratory characteristics of the study population

	UC Patients n=77	CD Patients n=49	Control Group n=54	p
Gender, n (%)				
Female	26 (33.8)	16 (32.7)	16 (33.3)	0.992
Male	51 (66.2)	33 (67.3)	38 (66.6)	
Age (years), median (IQR)	37 (25.50-51.5)	37 (25.5-48)	37 (29-48.25)	0.942
CRP (mg/L), median (IQR)	12.09 (3.36-40.50)	11.48 (2.68-31.62)	2.73 (0.88-4.77)	<0.0011
ESR (mm/h), median (IQR)	35 (13-70)	30 (13.5-50)	9 (3-17.25)	<0.0012
Leucocyte ($\times10^3$/µl), median (IQR)	8.01 (6.48-10.58)	8.59 (7.01-11.23)	7.70 (6.33-9.10)	0.122
Neutrophils ($\times10^3$/µl), median (IQR)	5.08 (3.80-6.97)	6.18 (4.53-8.69)	4.64 (3.76-5.96)	0.0063
Serum sRAGE (ng/L), median (IQR)	911.17 (322.91-1682.19)	1182.32 (759.1-1848.93)	1420.96 (816.68-2320.08)	0.0104
Disease duration (years), median (IQR)	2 (0.5-6)	1.5 (0-4.5)		
Location of UC , n (%)				
Remission	4 (5.2)			
Limited disease	43 (55.8)			
Extensive colitis	30 (39)			
Location of CD , n (%)				
Remission	1 (2)			
Ileal	32 (8.2)			
Colonic	4 (65.3)			
Ileocolonic	12 (24.5)			
Mayo Endoscopic Score of UC, n (%)				
Remission (0)	5 (6.5)			
Mild (1)	25 (32.5)			
Moderate (2)	29 (37.7)			
Severe (3)	18 (23.4)			
Treatments, n (%)				
No treatment	26 (33.8)	18 (36.7)		
Only Mesalamine	31 (40.2)	3 (6.1)		
Only Azathioprine	1 (1.2)	2 (4)		
Only BA	2 (2.5)	2 (4)		
Mesalamine± steroids ± azathioprine ±BA	17 (22)	24 (48.9)		
Mayo Clinical Score of UC, median (IQR)				
Remission (score ≤ 2), n (%)	16 (20.8)			
Activation (score>2), n (%)	61 (79.2)			
Histological Acitivity Index in UC, median (IQR)	6 (3-7)			
Crohn's Diaease Acitivity Index				
Remission (score <150), n (%)	20 (40.8)			
Activation (score≥150), n (%)	29 (59.2)			

Abbreviations: CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IQR: Inter quartile range; sRAGE: soluble receptor for advanced glycation end products, UC: Ulcerative colitis; CD: Crohn's disease; IBD: Inflammatory bowel disease, BA:Biological agents
Footnotes: 1Tukey HSD: Significant difference in comparison of UC vs controls, UC vs CD (p=<0.001, p<0.001); 2Tukey HSD: Significant difference in comparison of UC vs controls, CD vs controls (p<0.001, p<0.001); 3Tukey HSD: Significant difference in comparison of CD vs controls (p=0.004); 4Tukey HSD: Significant difference in comparison of UC vs controls (p=0.008).

Serum sRAGE concentrations were higher in UC patients in remission compared to patients with clinically active disease (2168,27 ng/L vs. 761,51 ng/L respectively, p<0.001) (Table 2). There was no statistically significant difference with respect to treatment status in UC patients. UC patients with limited disease and those who were in remission also had higher sRAGE values (Table 2). The MCS and HAI values of UC patients negatively correlated to the serum sRAGE values (rho=-0,6, p<0.001 vs rho=-0,742 respectively, p<0.001). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leucocyte, and neutrophil values were inversely correlated to serum sRAGE values (Table 3).

CD patients who were in remission had higher serum sRAGE values than the patients having clinically active disease (1720.42 ng/L vs. 923.36 ng/L respectively, p=0.002). CD patients who were under treatment had higher serum sRAGE values than the patients without any treatment (1361.22 ng/L vs. 879.38 ng/L respectively, p=0.033) (Table 2). The CDAI, CRP and ESR values inversely correlated to serum sRAGE concentrations (Table 3).

Table 2. Serum sRAGE values in clinical and endoscopic features of the patients with IBDs

	n	%	sRAGE (ng/L)			p
			Median	IQR		
Ulcerative Colitis						
Treatment						
No treatment	26	33.80	1142.59	632.8	1908.19	0.097
Under treatment	51	66.20	862.93	245.35	1518.43	
Mayo clinical scoring						
Remission (score ≤ 2)	16	20.80	2168.27	1174.34	4158	<0.0013
Activation (score >2)	61	79.20	761.51	245.35	1185.07	
Disease extension						
Remission	4	5.20	4857.63	3968	5360.37	<0.0013
Limited	43	55.80	1115.02	626.78	1825.34	
Extensive	30	39.00	492.62	151.57	938.2	
Mayo endoscopic activity						
Remission	30	39.00	1466.27	911.17	5156.34	<0.0013
Activation	47	61.00	755.82	177.56	2260.8	
Crohn's disease						
Treatment						
No treatment	18	36.70	879.38	601.61	1239.41	0.0331
Under treatment	31	63.30	1361.22	821.26	1944.2	
Crohn's disease activity index						
Remission (score<150)	20	40.80	1720.42	1005.68	2414.41	0.0022
Activation (score≥150)	29	59.20	923.36	601.61	1361.22	
Location of CD						
Remission	1	2.00	3942.89	3942.89	3942.89	0.261
Ileal	32	65.30	1090.4	759.1	1608.63	
Colonic	4	8.20	1482.74	1073.12	1943.47	
Ileocolonic	12	24.50	1181.36	631.68	1711.01	

Abbreviations: sRAGE: soluble receptor for advanced glycation end products; IQR: Inter quartile range; UC: Ulcerative colitis; CD: Crohn's disease; IBDs: Inflammatory bowel diseases. Footnotes: 1Statistically significant at the confidence level of 0.95; 2Statistically significant at the confidence level of 0.99; 3Statistically significant at the confidence level lower than 0.999

Table 3. Correlations between the serum sRAGE values and the clinical, laboratory variables of the patients with IBDs

Serum sRAGE (ng/L)	rho	p
Ulcerative Colitis		
CRP (mg/L)	-0.715	<0.0013
ESR (mm/h)	-0.486	<0.0013
Leucocyte (×10³/µl)	-0.371	0.0012
Neutrophil (×10³/µl)	-0,409	<0.0013
Mayo clinical scoring	-0.610	<0.0013
Histological activity index	-0.742	<0.0013
Crohn Disease, (n=49)		
CRP (mg/L)	-0.552	<0.0013
ESR (mm/h)	-0.425	0.0021
Leucocyte (×10³/µl)	-0.188	0.197
Neutrophil (×10³/µl)	-0.176	0.226
Crohn's disease activity index	-0.509	<0.0013

Abbreviations: sRAGE: soluble receptor for advanced glycation end products; IBDs: Inflammatory bowel diseases, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate. Footnotes: 1Statistically significant at the confidence level of 0.99; 2Statistically significant at the confidence level of 0.999; 3Statistically significant at the confidence level lower than 0.999

Receiver operating characteristics (ROC) analysis demonstrated that sRAGE levels possessed diagnostic utility in forecasting remission in patients with Crohn's disease (CD) and ulcerative colitis (UC), with area under the curve (AUC) values of 0.764 and 0.858, respectively (p<0.001 for both) (see Figure 1 and Figure 2). The determined cut-off levels for sRAGE values, predicting clinical remission in patients with CD and UC, were 1587.64 and 1012.29, respectively.

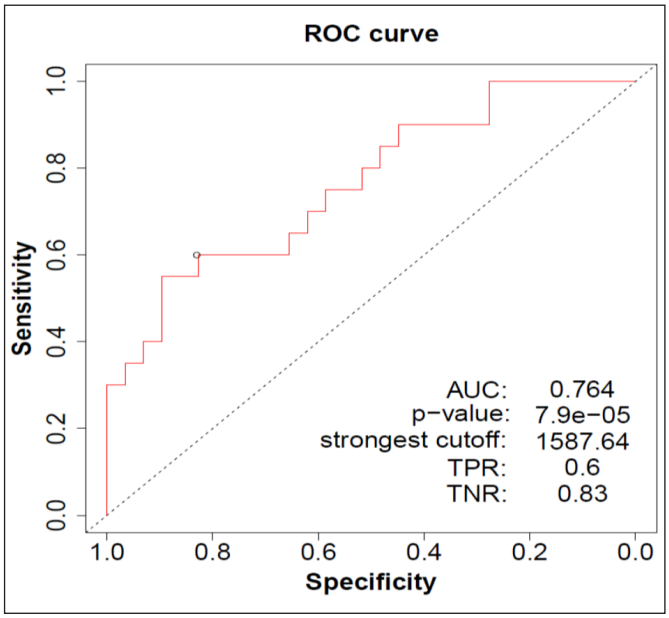

Figure 1. Diagnostic value of sRAGE levels to predict remission in patients with Crohn disease.

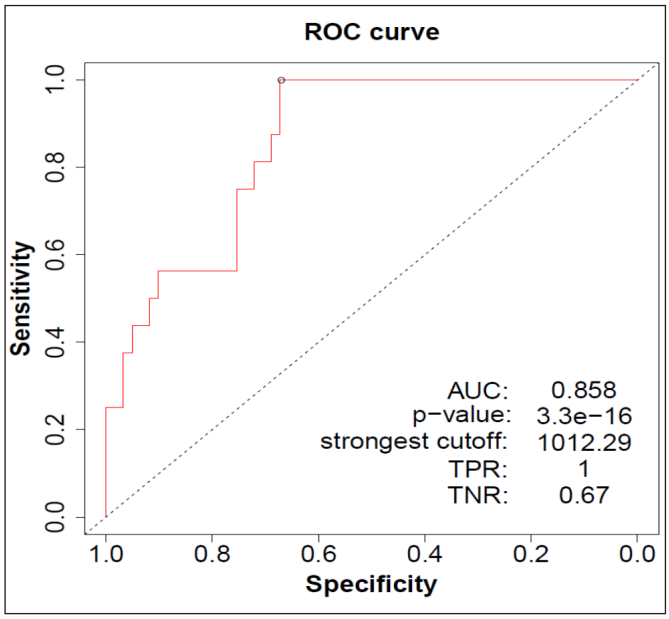

Figure 2. Diagnostic value of sRAGE levels to predict remission in ulcerative colitis patients.

DISCUSSION

Pathogenicity-related molecular pathways focusing on the diagnosis and the treatment of chronic inflammatory diseases, including IBDs, are gaining interest.[3] The patients with IBDs may undergo invasive endoscopic procedures which can cause discomfort. The clinical, endoscopic and biochemical findings can be inconsistent with each other in IBDs.[21] Searching for the ideal biomarkers correlating to all disease activity parameters, like fecal calprotectin (Fcp), is an important concern in IBDs.[22-24]

Acute inflammation is a normal protective response when host cells are repeatedly affected by injury or by microbial pathogens, and normally it is terminated silently for homeostasis. Host cells are programmed to end the noxious pro-inflammatory stimuli while the inflammatory process goes on. With this regard, some molecular pathways are defined like pro-resolving molecules and RAGE is another pathway for the control of inflammatory process.[3,25] Due to the inconsistent results according to the literature, the diagnostic and prognostic value of sRAGE in clinical settings remains controversial.[3]

Lower serum sRAGE concentrations were reported in UC patients than in the control group and the difference was statistically significant in our study. Although serum sRAGE concentrations in CD patients were lower than the control group, it was not statistically significant. Regarding the anti-inflammatory effect of sRAGE, it might be probable that the decreased sRAGE levels in patients with IBDs may increase inflammatory tendencies in addition to the other pathogenic mechanisms.

We think that lower sRAGE values in UC patients compared with the healthy controls are more likely to be due to the consuming of sRAGE with RAGE ligands because of ongoing pro-inflammatory stimuli.[8] Lower sRAGE values in the patients with IBDs than in the healthy controls were also reported in previous studies.[7,8] However, a prior study additionally identified that UC patients had greater sRAGE values than the control group (but not CD patients).[9]

Meijer et al.[7] reported lower sRAGE values in UC patients, but there was no statistically significant difference between the patients with CD and the control group. In this study, UC clinical activity was obtained by the 'Simple Clinical Colitis Activity Index' (SCCAI); the Rachmilewitz index was applied in the colonoscopy.[7,26,27]. There were inverse correlations between the serum sRAGE, endoscopic activity and the SCCAI. These results are consistent with our study in which the MCS and the MES indexes were used for UC. Despite the different methods of disease activation, these findings highlight the diagnostic and prognostic significance of lower serum sRAGE values for UC. Along with CRP, leucocyte, neutrophil and ESR values were also inversely correlated to serum sRAGE concentrations in the current study.

Meijer et al.[7] did not report statistically significant differences between the sRAGE values of CD patients and the controls. They applied the Harvey Bradshaw index (HBI) for the clinical activity of CD and mucosal scores were investigated through the 'Simple Endoscopic Score for CD'.[28,29] HBI scores correlated with the endoscopic disease activity scores in CD patients, as did CRP. In contrast, there was no correlation between sRAGE concentrations and endoscopic activity, and HBI scores.

Unlike this study, we used CDAI for the clinical activity of CD, as although HBI is a simplified scoring system of CDAI, results may be inconsistent due to the methodological differences. The CDAI scores inversely correlated to the sRAGE values. The patients in the remission phases had higher sRAGE values. As a limitation, we did not include any endoscopic activity indices for CD patients. As in the study of Meijer et al.[7] we also did not report any correlation to CD localization but we noted negative correlations between CRP, ESR and sRAGE concentrations. Larger sample-sized cohorts may reveal significant correlations in terms of the relationship between the disease extension, endoscopic activity, and the other specialties of the patients with CD and serum sRAGE values.

Ciccocioppo et al.[8] evaluated the levels of serum sRAGE, S100A12 - which is a RAGE ligand belonging to the S100 protein family - CRP and Fcp (S100A8/A9) in the IBD patients. They also consisted of patients with irritable

bowel syndrome as the control group. CDAI for CD patients and the 'Ulcerative Colitis Endoscopic Index of Severity' for UC patients were applied for the clinical activity.[26] The HAI were evaluated according to the 'Global Histologic Disease Activity Score' for CD and the 'Geboes Grading System' for UC.[8,30,31] When splitting the data amongst the groups, significantly lower levels of sRAGE were observed in UC patients than the other groups, whilst no significant difference between CD patients and controls appeared evident. These results were also consistent with our study. Serum S100A12 values were not different between the groups and Fcp was higher in patients with IBDs. An inverse correlation was found in terms of the serum levels of sRAGE with both clinical and endoscopic activity indexes either in CD or in UC. With regard to the HAI, no correlation was reported for UC, but an inverse correlation was noted between serum sRAGE values and the HAI of CD patients. There was an inverse correlation between sRAGE values and Fcp.[8]

Calprotectin is a RAGE ligand and Fcp is recognized to be a strong indicator of inflammation in IBD.[22,32] Testing Fcp is not an easy procedure and it is expensive. FCp was found to be related to both active disease and mucosal healing in evaluating the disease activity of UC but the threshold value was not accurately determined.[22,33] Thus, it could be valuable to evaluate the correlations between Fcp and serum sRAGE values. As a limitation of our study, we did not measure Fcp values in IBDs patients. Although sRAGE concentrations were not statistically significant between the patients with CD and healthy controls, UC and CD groups, we think that larger sample-sized cohorts of the patients with CD can reveal significant results. If it could be proven in future studies, as an inexpensive and easily applicable test, sRAGE might be used as a valuable marker for IBDs.

The patients with UC who were in remission according to the clinical and laboratory results, and those with limited disease in the colonoscopy had higher sRAGE values and an inverse correlation was reported between the HAI of UC and sRAGE. This was a valuable result because mucosal healing is the best therapeutic goal and an indicator for the activity of patients with IBDs.[14]

The patients with CD who were under treatment had higher sRAGE values, and inverse correlations between the disease activity of IBDs and serum-lower sRAGE values in the patients without any treatment might be ascribed to the consuming of sRAGE to prevent increased pro-inflammatory activation. It may partly be due to the disturbances in the innate immune system in IBDs because RAGE pathway is also a pattern-recognition receptor.[10,11]

Opposite results between sRAGE values and disease presentation, and laboratory features in different populations may be due to methodological differences, including the ELISA kits utilized, and also variations in the control groups. Treatment modalities might also affect the results.[7-9]

For IBDs, RAGE pathway was also declared as a therapeutic target.[13] Today, current medical treatments for IBDs focus on the inhibition of immune activation but they cannot achieve complete remission.[23] Topical delivery of sRAGE into the gut mucosa might be an adjunctive treatment modality.

The major limitation of the current study was the small number of the study population as it was a single-centered trial. Larger cohorts might reveal significant results for the diagnostic accuracy of serum sRAGE in IBDs. Comparing Fcp values with serum sRAGE concentrations could be more valuable for the assessment of diagnostic and prognostic accuracy of serum sRAGE.

CONCLUSION

Diagnostic strategies with the possibility of therapeutic interventions can be developed by identifying new, practical and objective biochemical markers in IBDs. Serum sRAGE can be a valuable biomarker for the clinical and laboratory traits of UC. Further studies are required to delineate the diagnostic and therapeutic accuracy of sRAGE in IBDs.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Researches Ethics Committee (Date: 17.11.2021, Decision No: 235-211084517).

Informed Consent: Written informed consent was obtained from all participants.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The mediating role of emotional eating in the relationship between aggression and eating attitudes

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ABSTRACT

Aims: Negative emotions and thoughts are known to be associated with eating problems. In recent years, strong relationships have been established between disordered eating attitudes and aggression, which are important in the growth of increasing eating disorders. This article examines the mediatory role of emotional eating in the relationship between aggression and disordered eating attitudes in adult individuals.

Methods: The study included 293 participants, including 70 males and 223 females, accessed through a convenience sampling method. In the study, participants completed the Demographic Information Form, the Eating Attitude Test, the Buss-Perry Aggression Scale, and the Turkish Emotional Eating Scale.

Results: Participants with disordered eating attitudes and emotional eating were found to have significantly higher average aggression scores than participants with healthy eating attitudes and without emotional eating. There has been a positive significant relationship between hostility and emotional eating and between hostility and disordered eating attitudes. The results of the structural equation model showed that among the types of aggression, only hostility and all disordered eating attitudes (preoccupation with eating, restriction, social pressure) played an instrumental role in the relationship.

Conclusion: Hostility and emotional eating behavior should be addressed in different preventive studies and intervention programs in which disordered eating attitudes seem in the fields of both mental health and health sciences.

Keywords: Aggression, emotional eating, eating attitudes

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INTRODUCTION

Character traits such as anger, hostility, and aggression are known to be related to impulsivity and cause eating problems. Aggression can be thought of as a character trait with emotional, cognitive, and behavioral components.[1] Emotional component consists of anger (that includes physiological arousal), the cognitive component consists of thoughts including hostility (negative beliefs about others' intentions), the behavioral component consists of physical aggression (physically harming others) and verbal aggression (verbally harming others) and is considered in four dimensions in total.[2] Anger acts as a bridge between hostile thoughts and physical/verbal aggression, i.e. behaviors.[1] In this context, it can be thought that hostile thoughts bring along emotions that indicate physiological arousal, such as anger, and then reveal behavior.

Although eating behavior is important for survival, it is not motivated solely by hunger and appetite. Psychological factors such as an individual's health status and body perception also affect eating attitudes.[3] It is known that disordered eating attitudes play an important role in developing eating disorders.[4] In Turkey, a study conducted with the emerging adulthood sample showed that the point prevalence of eating disorders was 1.55 % (n=27 females, 2 males).[5] Disordered eating attitudes are addressed through preoccupation with eating (bulimia/preoccupation with eating), dieting (restriction), and oral control (social pressure). In people with high preoccupation with eating, the person's mind is preoccupied with feelings and thoughts about their body and the act of eating. People with a high preoccupation with eating desire to lose weight, fear gaining weight, and think that the act of eating is a very important part of

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their lives. They also desire to have control over the act of eating. Thoughts about their bodies and exercising present themselves. Dieting is the attitude of individuals to limit their food intake, go on a diet, and avoid certain types of food intake. Oral control includes attitudes towards maintaining control over eating and the perceived pressure of others' approaches to avoid gaining weight and caring about their bodies and other people's opinions regarding eating.[6]

Macht[7] suggested that negative emotions can both increase and decrease food intake depending on their intensity: negative emotions with high arousal, such as fear or anger, can reduce food intake due to the physiological effect on metabolism, while moderate negative emotions increase food intake. Other studies in the literature have also shown that anger, hostility, and aggression are at high levels in people diagnosed with eating disorders[8-9] and that these emotions are psychopathological factors that attract attention to eating disorders.[10-16] Carmody et al.16 found that research participants with high levels of food restriction, hunger, and diet helplessness also had higher hostility scores. Stating that hostility is the antecedent of Bulimia Nervosa[17] makes it important to understand the relationship between bulimia, which is among the negative eating attitudes, and eating preoccupation with hostility.

Evidence showed that people diagnosed with eating disorders were five times more likely to accept violent acts than the healthy group.[18] Both in a study conducted with adolescent participants in a healthy population14 and in a study conducted with participants with anorexia nervosa and bulimia nervosa, who were at the borderline of health in terms of eating disorders,[1] a positive correlation was found between the tendency towards aggression and the risk of eating disorders.

Studies conducted with ecological momentary assessment in patients with eating disorders have also shown a positive relationship between binge eating episodes and negative emotions.[19-22] It has been shown that the emotions that initiate a binge eating episode are emotions that have a negative value, cause high arousal, and lead to higher avoidance behavior.[23] Berg, Crosby, Cao[24-25] revealed the role of emotions such as fear, hostility, sadness, and guilt as the precursors of the binge eating episode.

Emotional eating is defined as overeating in response to negative emotions. This type of overeating behavior can lead to excessive energy intake, affecting overall health and mental health. Although emotional eating is considered a condition seen primarily in bulimic individuals, it is also seen in individuals diagnosed with binge eating disorder, individuals who diet to lose weight or normal weight, and some obese individuals.[26] It is also known to cause consequences such as excessive food consumption, difficulty in weight control, and bulimic eating attitudes.[27]

Many studies in the literature point out the strong relationship between aggression and disordered eating attitudes.[14,18] In addition, when trying to make disordered eating attitudes healthy, it has become increasingly important to consider emotional eating as well as the effects of character traits that include negative emotions such as aggression.[26] In order to develop a specific intervention method for aggression in the treatment of eating disorders that develop with disordered eating attitudes.[14,28-30] The mechanisms between these variables should be figured out. Based on this aim, this study will examine the mediating role of emotional eating in the relationship between different types of aggression and eating attitudes.

METHODS

The study was carried out with the permission of İstanbul Arel University Ethics Committee (Date: 26.02.2020, Decision No: 2020-15). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.The informed consent form and scales used in the research were delivered to the participants via Google Forms. It took 3 months to collect data. There is no missing or lost data.

This research consists of 293 participants between the ages of 18-55, obtained through convenience sampling. Among the participants, 223 people (76.1%) were women and 70 people (23.9%) were men.

Data Collection Tools

Buss Perry aggression scale: The scale developed by Buss and Perry consists of 29 items and 4 sub-dimensions. 2 Scale sub-dimensions are physical aggression, verbal aggression, hostility, and anger.[2] The scale was adapted to Turkish and the internal consistency coefficient of the Buss Perry Aggression Scale is 0.85. From the subscales the internal consistency coefficient of physical aggression was stated as 0.78; the internal consistency coefficient of verbal aggression was stated as 0.48; the internal consistency coefficient of hostility was stated as 0.71; the internal consistency coefficient of anger was stated as 0.71.31 The scale is a 5-point Likert type (1=does not describe me at all, 5=describes me completely). Items 9 and 16 of the scale were reverse-scored.31 In the reliability analysis conducted within the scope of the research, the Cronbach Alpha coefficient of the scale was found to be 0.90 (sub-dimensions: physical aggression: 0.81, hostility: 0.79, anger: 0.80, verbal aggression: 0.63).

Turkish emotional eating scale: Turkish Emotional Eating Scale consists of 30 items. The scale is 5-point Likert (1=never, 5=almost always). Scoring 75 points or above on the scale indicates that the participants have a tendency to emotional eating. The scale consists of four sub-factors. The internal consistency coefficient of the scale is 0.95. Cronbach Alpha values for the sub-factors of the scale are 0.94 for eating under tension, 0.80 for self-control, 0.93 for eating to cope with negative emotions, and 0.64 for control in the face of stimuli.[32] In the reliability analysis conducted within the scope of the research, the Cronbach Alpha value of the scale was found to be 0.95 (sub-dimensions: eating under tension: 0.94, eating to cope with negative emotions: 0.94, eating for self control: 0.65, and self-control in the face of stimuli: 0.68).

EAT 26 eating attitude scale: EAT 26 Eating Attitude Scale examining risky eating attitudes is the short form of 40 items Eating Attitude Scale developed by Garner, Olmstad, Bohr and Garfinkel.[7] The 26-item Turkish short form of the Eating Attitude Scale was used in the study.[33] Within the scope of the reliability analysis of the original form of the scale, the internal consistency coefficient was found to be 0.84 (for sub-dimensions: dieting: 0.62, bulimia / preoccupation with eating: 0.85 and oral control: 0.76). The scale consists of A-B-C parts. Section A includes demographic information such as weight, height, lowest and highest weight. In section B, there are scale items with 26 questions, 4-point Likert type (Always=3, Very often=2, Often=1, other answers: Sometimes / Rarely / Never=0). In section C of the scale, it is checked whether there has been any deterioration in eating behavior in the last six months.[33] In this study, the reliability of the scale was found to be 0.77 (sub-dimensions of dieting: 0.76, bulimia and preoccupation with eating: 0.58 and oral control: 0.57).

Statistical Analysis

The data obtained from the research were analyzed with SPSS 22.0 and LISREL program. It was seen that the data set met normality assumptions (skewness and kurtosis values changed between -.42 and 1.16). The skewness and kurtosis values are assumed to be normal variance when they are between +1.5 and -1.5.[34] Therefore parametric tests were used in the research. In the study, the relationship between the scores obtained from all subscales was examined by correlation analysis. Then, the subscales related to aggression, which is the independent variable, and the eating attitude subscales, which are the dependent variable, were added to the model separately as latent variables to see which subscales were significant. A structural equation model was created by adding the mediator variable, emotional eating, as a single latent variable. Although it is a traditional method, structural equation modeling is considered superior to other mediation analyzes as it allows measurement errors to be taken into account at once.

To test the goodness of fit indices of the structural model, the ratio of chi square to degrees of freedom ($\chi 2$ / df), root mean square error of approximation (S-RMR), goodness of fit index (GFI), incremental fit index (IFI), root mean square error of approximation (RMSEA) and confirmatory fit index (CFI) were used. A chi-square / degree of freedom ($\chi 2$ / df) value of less than 2 is an indicator of good fit, and a value of less than 5 is acceptable. CFI, GFI, IFI values above .90 indicate a good fit. S-RMR and RMSEA values being less than .05 are indicative of good fit, while values being less than .08 are acceptable.[35,36]

RESULTS

Of the total 293 participants in the sample, 223 people (76.1%) were women and 70 people (23.9%) were men. The survey included 53 people (18.1%) in the 18-24 age range, 111 people (37.9%) in the 25-30 age range, 43 people (14.7%) in the 31-35 age range, 32 people (10.9%) in the 36-40 age range and 54 people (18.4%) over the age 40. In terms of education level, 9 (3.1%) of the participants were primary school graduates, 27 (9.2%) were high school graduates, 187 (63.8%) were university graduates, 59 (20.1%) were masters graduates and 11 (3.8%) were doctoral graduates. In terms of marital status 127 (43.3%) of the participants are married, 159 (54.3%) are single and 7 (2.4%) are living together. 34 (11.6%) of the participants stated that they had low financial status, 144 (49.1%) had medium financial status, 94 (32.1%) had upper middle status, 20 (6.8%) had high financial status and 1 had very high financial status. (0.3%).

There is a significant difference between gender according to aggression [$t(291)=-3.315$; $p<0.01$], emotional eating [$t(145.33)=3.365$; $p<0.01$], and eating attitude [$t(291)=2.613$; $p<0.01$]. Accordingly, men's aggression ($\overline{x}$ =2.74) average score was found to be significantly higher than women's aggression ($\overline{x}$=2.46) average score. Women's eating attitude ($\overline{x}$=.59) and women's emotional eating ($\overline{x}$=2.49) mean scores were found to be significantly higher than men's eating attitude ($\overline{x}$=.46) and men's emotional eating ($\overline{x}$=2.15) mean scores.

According to the Turkish emotional eating scale, a test score of 75 or above indicates emotional eating. In the study, 174 (59.4%) of the participants had emotional eating behavior. According to the EAT-26 Eating Attitudes Test, a test score of 20 points or above indicates that people may have unhealthy eating attitudes. In the study, it was found that 88 (30%) of the participants may had unhealthy eating attitudes.

Pearson product moment correlation analysis results for the variables are shown in Table. When the goodness of fit values of the structural model used to test the mediation hypothesis of the research was examined, it was seen that the model provided the necessary values for the goodness of fit indices ($x2$=39.18, df= 12, $x2$/ df= 3.2, RMSEA= .08, NFI= .93, CFI= .95, GFI= .97).

When the model is examined, it is seen that all factor loadings are between -0.04 and 0.44 as shown in Figure. Indirect effect values were calculated via LISREL. According to the tested structural equation model, the indirect effect of hostility on emotional eating, bulimia/eating preoccupation variable (β =.19, t=9.41, p<.05), dieting variable (β =.4, t=3.51, p<.05), and oral control variable (β =.4, t=2.63, p<.05) was found to be statistically significant. Accordingly, emotional eating mediates the relationship between hostility and all eating attitudes. Emotional eating explains 19% of the variance in the relationship between hostility and bulimia/ preoccupation with eating, emotional eating explains 4% of the variance in the relationship between hostility and dieting, and emotional eating explains 4% of the variance in the relationship between hostility and oral control.

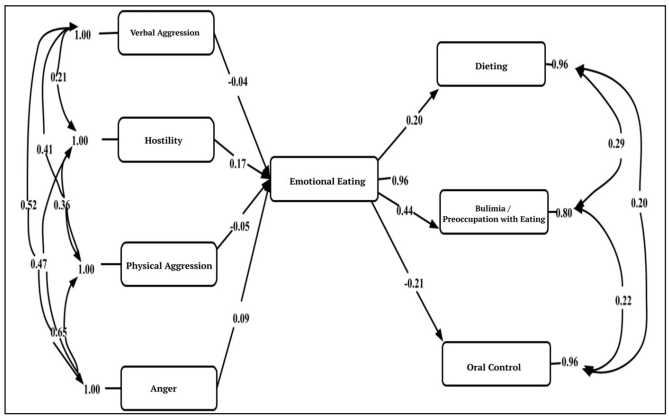

Figure. Standardized solution of structural equation model.

DISCUSSION

In this study, the mediational effect of emotional eating on the relationship between different types of aggression and eating attitudes was examined. According to the research findings, it was found that emotional eating mediated the relationship between the hostility sub-dimension of aggression, which includes the belief that other individuals' intentions are negative and they are likely to cause harm, and all eating attitudes such as bulimia/ preoccupation with eating, dieting, and oral control. According to personality profiles of patients with bulimia and obsesity, they are described as hostile and angry but unable to express these feelings directly.[37] It is suggested that hostile cognitions trigger anger, and thereby physical and verbal aggression may occur.[2] So, hostility may be the core structure within different types of aggression, and predict all distorted eating attitudes via emotional eating.

Since emotional eating inherently involves preoccupation with eating, in our study, preoccupation with eating/ bulimia has been shown to explain approximately five times more variance in disordered eating attitudes than dieting and oral control. In addition, emotional eating has been found to be important on the path to eating attitudes that include hostility and restrictive behaviors such as dieting and oral control. Carmody et al.[17] found that research participants with high levels of food restriction, hunger, and diet helplessness also had higher hostility scores and weight fluctuation. This research reveals that people turn to emotional eating in order to cope with thoughts of hostility, and this may cause distortions in their eating attitudes. However, dieting was found to be weakly associated with hostility; even general distress levels were controlled. One explanation for this weak association may be based on resricted eating after emotional eating occurs.[17] On the other hand, diet may also play an important role in the control of agression.

Table. Correlation table presenting the mean, standard deviation of observed variables, and the relationships between variables

Variables	M	SD	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. AGG	2.5	.64	1													
2. EA	0.5	.35	.12*	1												
3. EE	2.8	.83	.14*	.18**	1											
4. PA	2.0	.78	.82**	.01	.05	1										
5. VA	2.8	.76	.64**	.07	.04	.41**	1									
6. ANG	2.5	.90	.86**	.10	.11*	.65**	.51**	1								
7. HOS	2.2	.67	.69**	.32**	.18**	.35**	.31**	.47**	1							
8. BUL	0.2	.39	.17**	.57**	.43**	.08	.04	.16**	.22**	1						
9. DIE	2.4	.51	.11	.89**	.20**	.02	.08	.01	.27**	.36**	1					
10. OCO	0.5	.46	.02	.55**	-.20**	-.06	.08	-.03	.17**	.14*	.21**	1				
11. ET	2.3	1.00	.14*	.20**	.96**	.05	.04	.12*	.17**	.41**	.21**	.-17**	1			
12. ENE	2.2	1.05	.12*	.21**	.95**	.03	.06	.08	.17**	.37**	.24**	-.16**	.91**	1		
13. ESC	2.5	.70	.08	-.06	.59**	.06	.-02	.09	.05	.32**	-.03	-.33**	.45**	.43**	1	
14. EFS	2.9	.93	.11*	.12*	.65**	.03	.00	.10	.16**	.33**	-.09	-.07	.59**	.52**	.33**	1

Notes: N=293 **p< 0.01, *p< 0.05; AGG: Aggresiveness; EA: Eating Attitudes; EE: Emotional Eating; PA: Physical Aggression; VA: Verbal Aggression; ANG: Anger; HOS: Hostility; BUL: Bulimia / Preoccupation with Eating; DIE: Dieting; OCO: Oral Control; ET: Eating under Tension; ENE: Eating to Cope with Negative Emotions; ESC: Eating for Self Control; EFS: Eating in the face of stimuli

Therefore, our study model seems to capture the path in which emotional eating behavior reveal.

Research on the treatment of eating disorders has revealed that anger and hostility can hinder the psychologist or psychiatrist's guidance during the treatment process, and especially hostility can be a reason for discontinuing treatment. In addition, it has been reported that hostility, anger, and aggression in eating disorders can lead to self harming behavior and suicide.[1] It is important to consider in clinical practices the role of emotional eating, which we can think of as coping with these negative internal stimuli, in the relationship between disordered eating attitudes and thoughts related to hostility.

It is emphasized that eating disorders have increased over the years,[38] and that one of the main factors causing the increasing obesity and overweight rates in the United States is emotional eating. In Turkey, even though the point prevalence of eating disorders was 1.55%,[5] there is no evidence that shows rates of emotional eating or any fluctuation over years. Research on emotional eating and its causes may be useful in preventing obesity and planning health interventions.[39] On the other hand, in a study conducted in the Netherlands, as a result of case observations at the Lentis Mental Health Center, anger and aggression problems were considered underlying causes of eating disorders, and the psychomotor therapy method was applied in order for the clients to gain awareness of their anger and aggression problems and to cope with them. It was concluded that after therapy, improvement in eating disorders was better in the therapy group than in the control group.[40] As revealed in this research, it may be recommended that intervention methods of the psychomotor therapy method, which remove emotional eating and enable coping with these negative emotions more functionally, be added to the protocol and disseminated. It is recommended that both thoughts related to hostility, which are assumed to trigger anger[2] and characteristics of emotional eating behavior should be addressed in different preventive studies and intervention programs.

The research has several limitations. The fact that the majority of the participants were female reduces the generalizability of the research. Secondly, the data obtained based on self-report may have been affected by the social desirability of the participants. Another important limitation is body mass index values, psychiatric history, metabolic disorders, and medication use, which may accompanied by disordered eating attitudes, were not measured and controlled in the study. Finally, the fact that the data was collected during the COVID-19 pandemic period suggests that it may have been affected by the disordered eating attitudes that increased during that period.

CONCLUSION

To conclude, it is important to address hostility and emotional eating behavior when disordered eating attitudes are aimed to enhanced. Both preventive studies and intervention programs may be developed by clinical psychologists to address hostile cognitions, before emotional eating occurs and disordered eating attitudes, especially bulimia / preoccupation with eating thereafter. Future studies should be addressed with specific patient group in which disordered eating attitudes occur. Collaborative work should be done among health sicences professions to improve disorderdered eating attitudes.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Arel University Ethics Committee (Date: 26.02.2020, Decision No: 2020-15).

Informed Consent: The informed consent form were delivered to the participants via Google Forms and they responded with click-through.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Laparoscopic myomectomy is safe in patients with previous abdominal surgery

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ABSTRACT

Aims: The excision of myomas is commonly carried out in symptomatic women who choose to preserve their uterus, either using an open or minimally invasive (hysteroscopy, laparoscopy, robotic) approach. Patient selection is a critical factor in achieving a successful laparoscopic myomectomy. Prior abdominal surgery was not defined as a risk factor, however, the safest approach in these cases is still the subject of intense debate The aim of this study was to evaluate the safety of laparoscopic myomectomy in patients with previous abdominal surgery.

Methods: A retrospective cohort study was conducted on the files and operative notes of the patients who underwent laparoscopic myomectomy operation in a university-hospital based gynaecology department between January 2012 and March 2017. The patients were classified into two groups; Group 1 consisted of 34 patients who had previously undergone abdominal surgery, whereas the Group 2 comprised 118 patients who had not undergone any abdominal surgery.

Results: There were no significant difference between patients with and without a history of abdominal surgery in terms of operation time, postoperative hospital stays, blood loss, rate of operative complications, or conversion rate to open surgery.

Conclusion: A history of abdominal surgery seems to have no negative impact on the safety of a subsequent laparoscopic myomectomy.

Keywords: Laparoscopy, myomectomy, surgical outcome, minimal invasive surgery

INTRODUCTION

Uterine myomas are prevalent non-malignant neoplasms of the female reproductive system, with a lifetime incidence rate of roughly 70% to 80% prior to the onset of menopause.[1] Uterine leiomyomas are the most prevalent pelvic tumor in females and can lead to considerable morbidity, such as abnormal uterine bleeding, pelvic or abdominal pain, or subfertility.[2] The excision of myomas is commonly carried out in symptomatic women who choose to preserve their uterus, either using an open or minimally invasive (hysteroscopy, laparoscopy, robotic) approach.

In 1977, the first laparoscopic myomectomy was performed.[3,4] The laparoscopic approach to myomectomy has significant advantages like less postoperative pain, a reduced incidence of postoperative fever, and a shortened hospital stay.[5] However, this could result in prolonged time spent in the operating room. Additional possible benefits associated with the laparoscopic treatment encompass a shortened healing period, facilitating a faster resumption of occupational duties and engagement in routine daily tasks.[6]

The effectiveness of laparoscopic myomectomy refers to a surgical treatment that is minimally invasive and does not require conversion to laparotomy. This procedure aims to completely and safely remove specifically chosen myomas using surgical excision. The successful execution of laparoscopic completion of the treatment, without encountering significant difficulties, is contingent upon the adherence to more stringent selection criteria in comparison to those employed in open surgery. The laparoscopic method is considered more favourable for women with a limited number of myomas, whereas open surgery continues to be the preferred procedure for women with numerous and big myomas.

Patient selection is a critical factor in achieving a successful laparoscopic myomectomy. There are presently no widely accepted screening criteria for identifying women who are candidates for laparoscopic

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myomectomy. However, the following characteristics of a leiomyoma were linked to serious complications: >5 cm in diameter, >3 myomas removed, lie down on intraligamentous site. Prior abdominal surgery was not defined as a risk factor but one and only bowel injury occurred in a patient with previous surgery.[7] Additionally, abdominal surgery has been identified as one of the most significant risk factors for abdominal wall adhesions.[8] A history of laparotomy is no longer a contraindication to laparoscopy, but the safest approach in these cases is still the subject of intense debate.[9]

The aim of this study was to evaluate the safety of laparoscopic myomectomy in patients with previous abdominal surgery.

METHODS

The study was carried out with the permission of Ankara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 14.10.2021, Decision No: 08-230-21). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In our study, no interventional procedures were performed on the patients, and the research was conducted through file records.

Patient Selection

A retrospective cohort study was conducted on the files and operative notes of the patients who underwent laparoscopic myomectomy operation in a university-hospital based gynaecology department between January 2012 and March 2017. There were no specific criteria for inclusion in the study. In our department, laparoscopic approach is generally recommended for patients who are in premenopausal period, have 5 or less intramural/submucous fibroids and dominant fibroid size is less than 12 cm. In the presence of subserosal fibroids larger than 12 cm, laparotomic surgery is prioritized because sufficient space to allow intraabdominal manipulation of laparoscopic surgical instruments is not always provided.

During the preoperative period, each patient is evaluated with bimanual pelvic examination and 2 dimensional transabdominal or transvaginal ultrasonography. Magnetic resonance imaging (MRI) was ordered selectively in patients with ultrasonographic findings suggestive of malignancy. A laparotomic approach is recommended if the shape or borders of the fibroid are irregular, and/or if Doppler ultrasonography or MRI reveals high risk of malignancy. The entirety of the procedures was executed by gynaecologic surgeons who are certified for minimally invasive surgical procedures.

For each individual age, body mass index (BMI), parity, preoperative and postoperative haemoglobin value, diameter of the largest myoma removed from a single patient (based on preoperative imaging result), number of myomas removed, surgery duration, requirement of blood transfusion and conversion to laparotomy were recorded.

Laparoscopic Myomectomy

Each patient was evaluated with laboratory and radiological findings by the responsible anaesthesiologist 1 day before surgery. The surgical procedure was performed similarly in each patient. Surgical site prophylaxis with intravenous 2 g cefazolin (<120 kg, 3 g if >120 kg) or 900 mg clindamycin and 5 mg/kg gentamicin in case of penicillin allergy was performed 30-60 minutes before the operation. Following induction of general anaesthesia, a Foley catheter was inserted for bladder catheterisation. A simple uterine manipulator (Vcare manipulator; ConMed Corporation, Utica, NY) was placed in patients with a history of sexual intercourse. The decision of whether the abdominal access was closed (Veres needle or direct trocar) or open technique was made by the attending surgeon. In the presence of a vertical incision in the anterior abdominal wall due to previous abdominal surgeries, access to the abdomen was provided through the Palmer point. If the size of the uterus reached the level of the umbilicus, the 10 mm trocar required for the telescope was entered from the Lee-Huang point, and if the uterus was limited to the pelvis, a 10 mm trocar was entered from the umbilicus. Two 5 mm lateral trocars and one 5 mm left upper quadrant trocar were placed as accessory trocars. Haemostatic agents such as tourniquet, oxytocin or vasopressin were not used in any patient. First incision to the serosa of the uterus was done after bipolar coagulation of the incision site, with either monopolar diathermy or ultrasonic energy (Ethicon Harmonic Scalpel; Johnson&Johnson, New Brunswick,NJ). If endometrial cavity is encountered during enucleation, the cavity was first repaired with synthetic absorbable 2/0 or 3/0 sutures and then the myometrium was closed in multi-layered fashion with 1-0 polyglactin sutures or barbed sutures (V-Loc 180, Medtronic, Minneapolis, MN). Fibroids were removed from the abdomen with the help of an endobag and/or electromechanical morcellator (Rotocut G1; Karl Storz, Tuttlingen, Germany). After the abdominal cavity was washed with isotonic serum, haemostasis was checked with bipolar cautery and no antiadhesive barriers were applied. If the port site was >10 mm, the rectus sheath was repaired separately and the operation was terminated.

Postoperative Care

Hemogram control was routinely requested from all patients at the 8th postoperative hour. Mechanical prophylaxis with pressure stockings was routinely applied to each patient to reduce the possibility of deep vein thrombosis and/or pulmonary embolism. In the presence of additional risk factors, low molecular weight heparin prophylaxis at a dose appropriate for the patient's weight was added to the medical treatment plan. All low molecular weight heparin administrations were performed after hemogram control at postoperative 8th hour. The urinary catheter was withdrawn on postoperative day 1. Patients were discharged with recommendations following the return of bowel movements.

The patients were classified into two groups; Group 1 consisted of 34 patients who had previously undergone abdominal surgery, whereas the Group 2 comprised 118 patients who had not undergone any abdominal surgery. Previous abdominal surgery was described as having had any form of open or laparoscopic abdominal surgery in the past.

Statistical Analysis

Statistical analysis was performed using SPSS version 21. The conformity of the variables to normal distribution was analysed by histogram plots and Kolmogorov-Smirnov test. Mean, standard deviation and median values were used to present descriptive analyses. Student's t test or Mann-Whitney U-test was used to compare independent groups and Pearson chi-square test or Fisher's exact test was used to compare categorical variables. $P < 0.05$ was accepted as statistical significance.

RESULTS

During the study period, a total of 425 myomectomy procedures were performed. One hundred fifty-two of these women were treated with a laparoscopic myomectomy. The mean age of the whole study population was 36.6±6.43 years, the mean body mass index was 27.6±4.19 kg/m² and 101 women (66%) were nulliparous. Indications for myomectomy were abnormal uterine bleeding in 98 cases (64.5%), infertility or recurrent pregnancy loss in 36 cases (23.7%), and pelvic pain in 18 cases (11.8%). Table 1 shows the demographic characteristics of the participants. No statistical difference was observed between the groups in terms age, BMI and parity. Table 2 summarizes the number and categories of previous abdominal operations.

Table 1. Demographics of the patients

	Patients undergone L/S myomectomy (n=152)
Patient Characteristics	
Age, years, mean±SD	36.6±6.43
BMI, kg/m² , mean±SD	27.6±4.19
Nulliparity, n (%)	101 (66)
Indications, n (%) -abnormal bleeding -infertility/recurrent pregnancy loss -pelvic pain	 98 (64.5) 36 (23.7) 18 (11.8)
Dominant leiomyoma size, cm, mean SD -pre-operative scan-	6±2.9
Surgical outcomes	
Operation time, minutes, mean±SD	87.3±43.9
Hemoglobin drop, g/dl, mean±SD	1.5±0.9
Extracted myoma >10cm, n (%)	23 (15.1)
Multiple myomectomy, n (%)	44 (28.9)

Table 2. The number and categories of previous surgeries

	Patients with previous surgery (n=34)
Previous surgeries, n (%)	
Cesarean Section	9 (26.5)
Endometriosis	6 (17.6)
Laparoscopic/open	4/2
Myomectomy	6 (17.6)
Laparoscopic/open	1/5
Other Gynecologic	7 (20.6)
Other Non-gynecologic	3 (8.8)
Multiple Surgeries	3 (8.8)

The mean largest myoma diameter (according to preoperative scan) was 6±2.9 cm. In 23 cases (15.1%), a myoma >10 cm was extracted. Multiple myomectomy was performed in 44 cases (28.9%). In terms of surgical outcomes, the mean operative time was 87.3±43.9 minutes and the mean postoperative haemoglobin drop was 1.5±0.9 g/dl. In two patients (1.3%), the surgical procedure was completed with a laparotomy (one in Group 1; one in Group 2). One case was converted to open surgery due to uncontrollable bleeding, and had a dominant myoma> 15 cm with multiple myomas. Other case had a history of endometriosis surgery and conversion to laparotomy were decided due to excessive pelvic adhesions and impaired visualization. No major intraoperative complication was reported. The median duration of hospital stay after the surgery was two days (range:1-31). Histopathological examination revealed no leiomyosarcoma in any patient.

Groups were comparable in terms of myoma characteristics and intra- and post-operative outcomes (Table 3).

Table 3. Comparison of the patient and myoma characteristics and surgical outcomes between the groups

	Previous surgery (n=34)	No previous surgery (n=118)	P value
Patient demographics			
Age, years, mean±SD	36.6±5.0	36.0±6.7	0.623
BMI, kg/m², mean±SD	28.6±3.5	29.0±2.9	0.532
Parity, n (%)	0.5±0.7	0.5±0.8	0.938
Preoperative hemoglobin, g/dl, mean±SD	12.4±1.6	12.3±1.5	0.691
Surgical outcomes			
Postoperative hemoglobin, g/dl, mean±SD	11.0±1.2	10.9±1.6	0.898
Hemoglobin drop, g/dl, mean±SD	1.4±0.8	1.4±1.0	0.934
Total size, cm, mean±SD	10.5±9.6	7.8±5.9	0.039
Dominant leiomyoma size, cm, mean SD	6.0±2.5	5.8±2.8	0.752
Number of leiomyomas, cm, mean±SD	2.4±3.4	1.5±1.2	0.028
Duration of hospital stay, days, mean±SD	2.4±0.8	2.3±0.8	0.951
Operation time, minutes, mean±SD	55.9±19.7	56.9±34.9	0.870
Multiple leiomyoma, n (%)	14 (41.2)	30 (25.4)	0.074
Blood transfusion, n (%)	1 (2.9)	5 (4.2)	0.732
Conversion to laparotomy, n (%)	1 (2.9)	1 (0.8)	0.363

DISCUSSION

The current study examined the influence of previous abdominal surgery on the feasibility of performing laparoscopic myomectomy, and no negative effects were detected.

Prior abdominal surgery increases the risk of complications during initial entry to the abdominal cavity and necessitates adhesiolysis, which comes with its own set of complications in laparoscopic surgery. The incidence rate of access-related visceral injuries has been reported as 0.3-0.03%.[10-12] The likelihood of adhesions between the abdominal wall and intraabdominal organs is increased by a prior history of abdominal surgery.[13] Some surgeons avoid doing a laparoscopic operation on patients who have had prior abdominal surgery due to the risk of bowel damage during trocar insertion or impaired visualisation in the operative field due to adhesions. In our surgical procedures, we did not have any access related injury maybe liberal usage of the Palmer's point in patients with vertical incisions prevented this complication. Granata et al.[14] also found Palmer's point as a safe entrance area in their study similar to our observation in this study.

One of the most prevalent issues with laparoscopic myomectomy in the past was conversion to laparotomy. Dessolle et al.[15] reported a conversion rate of 14.8% on their study in 2001, but in the following years, the surgeon's experience increased, and in 2017, Mallick et al.[16] reported a conversion rate of 0.62%. Our conversion rate (1.3%) was slightly higher than Mallick et al.'s reported rate but similar to rates reported in other studies.[17,18] In our cohort, we finished myomectomy with open surgery in two cases, and one with extensive adhesions had a history of laparotomic endometriosis surgery. Tummers et al.[19] evaluated the effects of previous endometriosis surgery on subsequent endometriosis surgery in a recently published study. Laparotomic endometriosis surgery was found to be a risk factor for intraoperative complications in subsequent endometriosis surgery (OR 1.81, p = 0.045) rather than laparoscopic surgery. Studies involving a larger number of patients can further evaluate the impact of laparotomic endometriosis surgery on subsequent laparoscopic myomectomy.

Several researchers evaluated the feasibility of not a laparoscopic myomectomy but a total laparoscopic hysterectomy in patients with previous abdominal surgery. Although there are technical differences between the two surgical procedures, both require access to the peritoneal cavity and the removal of the uterus or myoma without damaging the adjacent organs. In the research by Seo et al.[20] the incidence of complications was comparable between the two groups (3.2 and 2.8%, respectively), and no bladder, bowel, or vascular injuries were observed. Similarly, in our study, we did not find any increased risk for blood transfusion, conversion to laparotomy, or injury to the adjacent organs in patients with previous abdominal surgery who subsequently had laparoscopic myomectomy.

Study limitations: The limited sample size of the current study, especially among patients who had previously had abdominal surgery, placed restrictions on its proficiency to do a subgroup evaluation for the identification of separate risk factors or numerous coexisting risk factors. In addition, because the retrospective nature of the study and obtaining complication rates on medical records and surgical notes, it is conceivable that recall ascertainment bias affected the results. To reduce the likelihood of a reporting bias, it is necessary to conduct additional research with complete reporting of all relevant outcomes, especially significant long-term outcomes, in large randomized controlled trials.

CONCLUSION

There were no significant difference between patients with and without a history of abdominal surgery in terms of operation time, postoperative hospital stays, blood loss, rate of operative complications, or conversion rate to open surgery. Therefore, a history of abdominal surgery seems to have no negative impact on the safety of a subsequent laparoscopic myomectomy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 14.10.2021, Decision No: 08-230-21)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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