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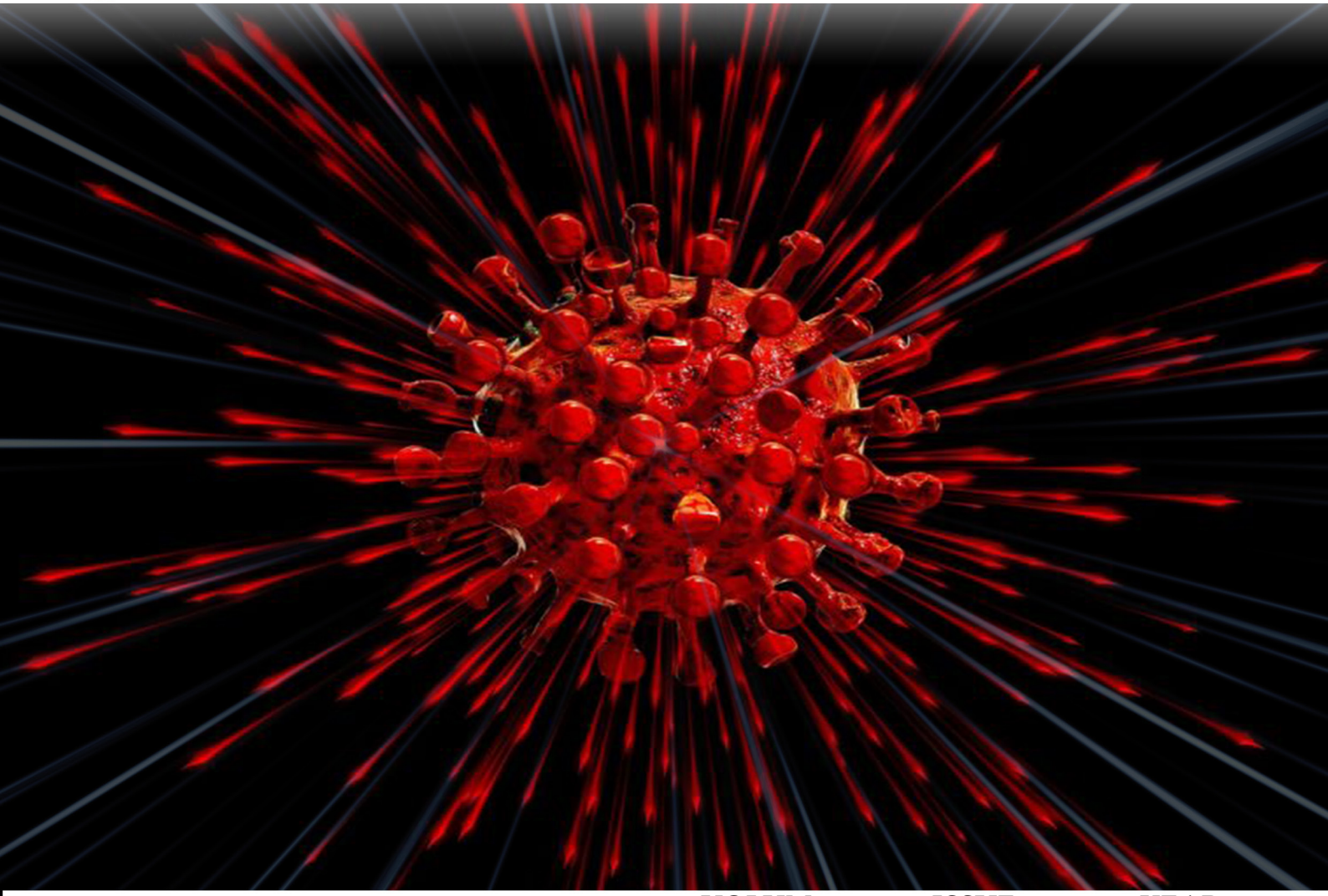

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Our dear readers,

We are proud to publish the first issue of Anatolian Current Medical Journal for 2022 with 23 articles. Day by day, we increase the scientific quality of our journal. Principally, we want to contribute to international literature at an increasing level and to increase the success bar of our journal by entering indexes such as Scopus, ESCI, PubMed and SCI-Expanded. Thanks to all the authors for their contributions to literature. with their comprehensive scientific content for publication in our Journal. I wish the new year to bring health, success and peace to all humanity and living things.

Sincerely yours

Assoc. Prof. Aydın ÇİFCİ, MD
Editor-in-Chief

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*An investigation of the diabetes health literacy level and compliance to the treatment in patients with diabetes in Turkey

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ABSTRACT

Aim: This study aims to investigate the relationship between the diabetes health literacy level and compliance to the treatment in individuals with diabetes.

Material and Method: This descriptive study was conducted in the Internal Diseases-1 and Endocrinology clinics of a hospital between January 2019 and April 2020. The target population was the patients who were hospitalized in these clinics due to Type-II diabetes between the dates when data were collected. Sampling was performed using the sampling method with a known population, and the sample was composed of 237 patients. Data were collected through the Socio-demographic Form, the Diabetes Health Literacy Scale, and the Scale for Compliance to the Treatment in Type II Diabetes Mellitus. Data analysis included Kolmogorov Smirnov test, numbers, percentages, Cronbach's Alpha, t-test, Kruskal Wallis, analysis of variance, chi-square test, and correlation test.

Result: This study found the health literacy scale total mean score as above-average (38.41±8.59), and the compliance to the treatment mean score as moderate (83.14±12.35). A negative and significant relationship was found between compliance to the treatment and diabetes health literacy scale total score and the communicative health literacy and critical health literacy mean scores ($p<0.001$). In line with the results of the study, compliance to the treatment in patients with diabetes increases as their diabetes health literacy increases.

Conclusion: It is recommended to provide individuals who have diabetes with trainings for increasing their diabetes health literacy levels to increase their compliance to the treatment.

Keywords: Chronic diseases, health literacy, diabetes mellitus, compliance, treatment

*This research was oral presented online on 7-9 January 2021 at the 2nd International 3rd National Public Health Nursing Congress.

INTRODUCTION

The World Health Organization defines health literacy (HL) as "the ability of individuals to "gain access to, understand and use health information using cognitive and social skills in ways which promote and maintain good health" (1). Health literacy affects health positively by enabling individuals to obtain knowledge about diseases, maintain self- care, and make decisions about their health. An analysis of the worldwide prevalence of health literacy shows that the number of adults who do not have a basic health literacy level is composed of 16% of the world population (2). According to the National Assessment of Adult Literacy in the USA, the health literacy level of the adult population in America was reported to be insufficient for 36% and basic for the 22% (3). Studies conducted in Turkey show that insufficient health literacy ranged from 13.1% to 55.4%, problematic health literacy ranged from 22.4% to 40.1%, sufficient health literacy ranged from 16.4% to 32.9%, and excellent health literacy ranged from 5.8% to 14.5% (4-6). A study on patients with diabetes reported that diabetes health literacy was insufficient for 1%, problematic for 12.4%, sufficient for 31.4%, and excellent for 55.2% (7).

Diabetes, with its increasing prevalence every day, is one of the chronic diseases that need to be fought off (8). The Turkish Diabetes Epidemiology (TURDEP-2) report indicates that the prevalence of diabetes increased at a proportion of 90% by increasing from 7.2% to 13.7% in 12 years (1998-2010) (9). Success in the management of chronic diseases depends on individuals' taking their own health responsibility (10). One of the primary purposes of effective individual disease management is maintaining compliance to the treatment. Compliance to the treatment

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means that the individual takes the prescribed treatment as it is recommended, at appropriate times and doses, and continues doing so in the period indicated (11). Non-compliance to the treatment is a common problem in individuals with diabetes, which prevents the efficiency of the treatment, affects the course of the disease negatively, and causes an increase in health expenditures as well as in death rates due to adding other diseases to the existing one (12). Health literacy level, one of the many factors affecting compliance to the treatment, is of more importance as it can be changed and improved (13).

The number of studies indicating the effect of health literacy level on the management of diabetes has been increasing recently (7,14). In our country, there is a limited number of studies on this issue.

MATERIAL AND METHOD

This study aims to investigate the relationship between the health literacy level and compliance to the treatment in patients with diabetes in our country.

Study Design, Setting and Ethics

This across-sectional descriptive study was conducted in the Internal Diseases and Endocrinology clinics of a hospital in Erzurum, Turkey.

This study was approved by Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Date: 29/11/2018, Decision No: 31) and institutional approval from Provincial Health Directorate were obtained for this study. Volunteerism was taken into consideration in the determination of participants, and all procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants and Setting

The target population was the patients who were hospitalized due to Type-II diabetes between the dates (January 2019-July 2019) when data were collected. Sampling was performed through the sampling method with a known population using the number of patients hospitalized in these clinics within the past one year (393 patients). The number of patients to be recruited from the clinics was identified by multiplying the sample size with the weight of strata (61 patients from the Internal Diseases clinic and 176 patients from the Endocrinology clinic).

The sample included patients who were literate, who could communicate, who were 18 and over, and who were diagnosed with Type-II diabetes at least one year ago. The patients were included in the study until the sample size was achieved; hence, the sample was composed of 237 patients who met the research criteria and agreed to participate in the study.

Variables and Data Collection

Data were collected through the Socio-demographic Form, the Diabetes Health Literacy Scale and the Scale for Compliance to the Treatment in Type II Diabetes Mellitus (DM) between January 2019 and July 2019 by conducting face to face interviews administered by the researcher. The patients were informed about the purpose of the study, and their informed consent was received. Data collection took about 15 to 20 minutes for each patient.

The Socio-demographic Form: The form developed by the researcher in line with the related literature was composed of nine questions (15).

The Diabetes Health Literacy Scale: The scale was developed by Ishikawa et al. (14) in 2008. Its validity and reliability were performed by Ağralı and Akyar 2008 (16). The scale has 14 items and 3 sub-scales that are responded on a 4-point Likert scale. The purpose of the scale is to measure the functional, communicative, and critical health literacy levels of individuals with diabetes. The 5-item functional health literacy measures the extent of the problems experienced by individuals when they read the explanations and booklets received from pharmacies and hospitals. Each item is scored as 1 (never), 2 (rarely), 3 (sometimes), and 4 (frequently). In the critical and communicative health literacy sub-scales, there is a directly proportional relationship between the health literacy level and the score while in the functional health literacy sub-scale there is an inversely proportional relationship between the health literacy level and the score. A higher functional health literacy score indicates that health literacy is more problematic in that specific domain. Cronbach's alpha coefficient of the scale is 0.78. Functional, communicative, and critical health literacy Cronbach's Alpha coefficients are 0.84, 0.77, and 0.65 respectively. Cronbach's alpha coefficient was found 0.84 in this study. The functional, communicative, and critical health literacy Cronbach's alpha values are 0.87, 0.80 and 0.88 respectively.

The Scale for Compliance to the Treatment in Type II Diabetes Mellitus: The 30-item scale developed by Demirtaş and Albayrak had 7 sub-scales rated on a 5-point scale (17). The scores to be obtained from the scale range between 30 and 150. The scores obtained are interpreted using the total scale scores. Scores between 30 and 54 indicate a "good level of compliance to the treatment", scores between 55 and 125 indicate a "moderate level of compliance to the treatment", and scores between 126 and 150 indicate a "poor level of compliance to the treatment". There is an inversely proportional relationship between the sub-scale scores and the demonstration of the expected behaviors. In other words, higher scores obtained from the scale indicate decreased compliance to the treatment. Cronbach's alpha coefficient of the scale is 0.77. This study found Cronbach's alpha coefficient as 0.70.

Statistical Analysis

Data obtained from the study were analyzed using SPSS 20 package programming on the computer. Analyses included Kolmogorov Smirnov test, numbers, percentages, Cronbach's Alpha, t-test, Kruskal Wallis, analysis of variance, chi-square test, and correlation test. P-valueslessthan 0.05 were considered statistically significant.

RESULTS

An analysis of the participants' demographic features showed that the average age was 54.63±9.48, the majority of the participants was male (57.4%), 56.1% lived in the city center, 54.4% graduated from primary school, 50.2% had income equal to expenses, 80.2% were married, and 65.8% had a nuclear family. Of all the participants, 64.1% had a family member with diabetes and 35.5% had been diagnosed with diabetes for more than 10 years.

The mean score that the participants received from the diabetes health literacy scale was 38.41±8.59. In addition, the Functional HL sub-scale mean score was 14.28±4.49, the communicative HL sub-scale mean score was 13.25±3.97, and the Critical HL sub-scale mean score was 10.87±3.70 (**Table 1**).

Table 1. Distribution of the participants' Diabetes HL Scale mean scores

Diabetes health literacy scale	Number of items	X±SD	Min-Max
Functional HL	5	14.28±4.49	5-20
Communicative HL	5	13.25±3.97	5-20
Critical HL	4	10.87±3.70	4-16
Total	14	38.41±8.59	14-16

The comparison of the participants' socio-demographic features and Diabetes HL scale mean scores showed that the functional and communicative HL sub-scale mean scores were lower in those who had an education level of university and above, and the difference between the groups was found to be statistically significant ($p<0.05$). The participants who had income more than expenses were found to have significantly lower functional HL mean scores, and the difference between the groups was statistically significant (**Table 2**) ($p<0.05$). A comparison of the participants' HL scale mean scores according to gender, the place where they lived the longest period, having a family member with diabetes, and the duration of diagnosis showed that the difference between the groups was not statistically significant (**Table 2**) ($p>0.05$).

Table 2. Comparison of the participants' Diabetes HL Scale Mean Scores according to their descriptive characteristics

Characteristics	n	Functional HL	Communicative HL	Critical HL	Total
Gender					
Female	101	14.56±4.24	13.36±3.78	11.23±3.60	39.16±7.79
Male	136	14.07±4.68 t=0.830 p=0.407	13.17±4.12 t=0.363 p=0.717	10.60±3.77 t=1.304 p=0.193	37.85±9.12 t=1.167 p=0.245
Place where they lived the longest period					
Village	59	15.23±4.50	12.67±4.03	10.45±3.87	38.37±8.75
Town	45	14.62±4.15	13.22±3.74	10.80±3.28	38.64±5.79
City	133	13.74±4.56 F=2.437 p=0.090	13.52±4.02 F=0.932 p=0.395	11.08±3.77 F=0.589 p=0.556	38.35±9.33 F=0.020 p=0.980
Education level					
Primary school	129	14.93±4.51	12.39±3.77	10.41±3.74	37.75±8.53
Secondary school	46	13.76±4.89	13.67±3.87	10.91±3.87	38.34±9.25
High school	50	13.82±3.84	14.42±3.89	11.58±3.29	39.82±7.66
University and above	12	11.16±3.92 KW=10.054 p=0.018	16.08±4.46 KW=18.211 p=0.000	12.66±3.77 KW=6.934 p=0.074	39.91±10.37 KW=2.559 p=0.465
Income level					
Income less than expenses	101	15.09±4.26	13.12±3.99	10.87±3.93	39.09±8.25
Income equal to expenses	109	13.83±4.73	13.29±4.01	10.78±3.60	37.91±9.13
Income more than expenses	17	12.58±3.22 KW=7.531 p=0.023	13.76±3.76 KW=0.205 p=0.902	11.47±3.14 KW=0.311 p=0.856	37.82±6.41 KW=1.602 p=0.449
Marital status					
Married	190	14.44±4.43	13.31±4.08	10.95±3.76	38.71±8.67
Single	47	13.61±4.72 t=1.133 p=0.258	13.04±3.51 t=0.413 p=0.680	10.53±3.50 t=0.704 p=0.482	37.19±8.22 t=1.090 p=0.277
Family type					
Nuclear family	156	14.19±4.67	13.05±4.07	10.68±3.82	37.93±9.04
Extended family	81	14.44±4.15 t=0.398 p=0.691	13.65±3.76 t=1.108 p=0.269	11.23±3.47 t=1.080 p=0.281	39.33±7.61 t=1.189 p=0.236
Family member with diabetes					
Yes	152	14.47±4.23	13.51±4.11	11.19±3.58	39.17±8.26
No	85	13.94±4.94 t=0.873 p=0.383	12.80±3.69 t=1.326 p=0.186	10.30±3.87 t=0.117 p=0.078	37.04±9.02 t=0.351 p=0.067
Duration of diagnosis					
1-4 years	70	13.68±4.61	12.81±4.15	10.48±3.96	36.98±9.31
5-9 years	83	13.96±4.38	13.75±3.77	11.30±3.43	39.02±8.07
10 years and over	84	15.09±4.44 F=2.217 p=0.111	13.13±4.00 F=1.139 p=0.322	10.77±3.74 F=0.964 p=0.383	39.00±8.42 F=1.377 p=0.254

Table 3. Distribution of the participants' mean scores of the Scale for Compliance to the Treatment in Type II DM

Compliance to the treatment	Number	Percentage	X±SD	Min-Max
Good (30-54)	4	1.7	52.75±1.50	51-54
Moderate (55-125)	233	98.3	83.66±11.79	56-108
Poor (126-150)	0	0	0	0-0
Total	237	100	83.14±12.35	51-108

Table 4. Comparison of the scale for compliance to treatment in type-II DM according to the participants'descriptive characteristics

Characteristics	n	Scale for compliance to the treatment in type II DM total mean score
Gender		
Female	101	82.78±11.86
Male	136	83.41±12.74 t=0.387 p=0.699
Place where they lived the longest period		
Village	59	84.62±13.25
Town	45	84.51±12.38
City	133	82.02±11.90 F=1.251 p=0.280
Education level		
Primary school	129	83.20±12.85
Secondary school	46	84.50±11.20
High school	50	83.64±11.60
University and above	12	75.16±12.64 KW=5.455 p=0.141
Income level		
Income less than expenses	101	85.10±13.61
Income equal to expenses	109	81.77±10.77
Income more than expenses	17	81.05±13.93 KW=5.701 p=0.058
Marital status		
Married	190	83.66±12.14
Single	47	81.02±13.08 t=1.307 p=0.189
Family type		
Nuclear family	156	81.84±12.75
Extended family	81	85.64±11.19 t=2.263 p=0.025
Having a family member with diabetes		
Yes	152	83.79±12.33
No	85	81.97±12.38 t=1.088 p=0.278
Duration of diagnosis		
1-4 years	70	82.38±13.66
5-9 years	83	83.60±11.91
10 years and over	84	83.32±11.74 F=0.196 p=0.822

An analysis of the distribution of the participants' mean scores in the Scale for Compliance to the Treatment in Type II DM showed that the mean score obtained from the Scale for Compliance to the Treatment in Type II DM was 83.14±12.35 (**Table 3**).

When the participants' total mean scores of the Scale for Compliance to the Treatment in Type II DM were analyzed according to their descriptive features, it was found that the participants who lived in a nuclear family received lower mean scores, and the difference between the groups was statistically significant (**Table 4**) ($p<0.05$). The comparison of the participants' mean scores of the Scale for Compliance to the Treatment in Type II Diabetes Mellitus according to gender, the place where they lived the longest period, education level, marital status, and having a family member with diabetes indicated no statistically significant differences between the groups ($p>0.005$).

A negative, significant relationship was found between the Scale for Compliance to the Treatment in Type II Diabetes Mellitus and Diabetes HL Scale communicative and critical sub-scale and total mean scores ($p<0.001$) (**Table 5**).

DISCUSSION

The findings of this study, which aimed to identify the relationship between the health literacy level and compliance to the treatment in patients with diabetes, are discussed with limited literature due to the limited number of studies on this issue in our country.

This study found the Diabetes Health Literacy Scale total mean score as 38.41±8.59. The scores range between 14 and 56, and higher scores indicate higher health literacy levels. Based on these results, the health literacy level of the participants in this study was found to be above-average. Another study that utilized a different tool for identifying diabetes literacy including individuals with diabetes reported the diabetes health literacy mean score as 36.82, indicating a moderate level (7).

This study detected no significant relationships between the functional, communicative, and critical health literacy. A study that utilized the same measurement tool similarly reported no significant relationships between diabetes literacy sub-scales and gender (14). No significant relationship was found between the place where they

Table 5. The relationship between the participants' mean scores in the scale for compliance to the treatment in Type II diabetes mellitus and diabetes HL

Scales	Diabetes HL Scale			
	Functional HL	Communicative HL	Critical HL	Total
The scale for compliance to the treatment in type II diabetes mellitus	r=0.066 p=0.310	r=-0.236 p=0.000	r= -0.262 p=0.000	r=-0.188 p=0.004

lived the longest period and diabetes health literacy, but the scores were found to be lower in villages and higher in cities. This study found no significant differences between the education level and diabetes health literacy total scale scores. On the other hand, functional health literacy and communicative health literacy levels were found to increase significantly with the increase in the education level. Although no significant differences were found between the critical health literacy and education level, it was found that the critical health literacy score increased with the increase in the education level. The literature includes no studies that utilized this scale in patients with diabetes in our country. According to the results of the European Health Literacy Survey, a directly proportional relationship was noted between the general education level and health literacy score (18). Another study reported that starting from adults who graduated from highschool, the average health literacy level was found to increase with each higher education level (3). Although this study found no significant differences, the diabetes health literacy total scale score was found to increase with the education level. This study found a statistically significant relationship between the income level and functional health literacy; those who had income less than expenses were found to have more problematic functional HL. No statistically significant differences were found between the groups in terms of the diabetes health literacy total score, communicative health literacy and critical health literacy sub-scale mean scores. Diabetes health literacy scores of the individuals who had high-income levels were reported to be higher (14). No significant differences were reported between marital status, family structure, and duration of diabetes and health literacy sub-scales.

The participants mean score for the Scale for Compliance to the Treatment in Type II DM was found 83.14±12.35, indicating moderate level compliance. Scores between 55 and 125 indicate a moderate level of compliance to the treatment (17). Another study similar to the present one showed that the mean score for the Scale of Compliance to the Treatment in Type II DM was 107.39±13.55, indicating moderate-level compliance (19). Of all the participating individuals, 98.3% had a moderate level of compliance to the treatment. While the present study involved no participants who had poor compliance to the treatment, 1.7% was found to have good compliance to the treatment. Kav and Bulut, similar to the present study, found that 97.4% of the individuals participating in their study had a moderate level of compliance to the treatment (20). While there were no individuals who had poor compliance to the treatment, the proportion of those who had good compliance was found 2.6%. Review of the related literature indicates differences in the levels of compliance to the treatment among patients with diabetes. In their meta-analysis, Kras et al. (21) reported the compliance to the drug between 38.5% and 93%. Unlike the findings of the present study, some studies conducted in other countries reported high levels of compliance to the treatment among patients. This condition might have resulted from the differences in the health services received by patients as well as the differences in the measurement tools used to measure compliance. As a result, it could be noted that our country needs new practices to increase compliance to the treatment of diabetes.

When the patients' descriptive characteristics and their compliance to the DM treatment were compared, only the family type variable was found to demonstrate significant differences; no significant differences were found between the other variables. Although the DM compliance was higher in women, in those who lived in a city, who had higher education levels, who had income more than expenses, and who were single, no significant differences were found between the groups. Kim et al. (22) also found no significant differences between gender and compliance to the treatment. Kav and Bulut (20) similarly indicated that compliance to the DM treatment was higher in women, in those who lived in a city, who had higher education level, who had income more than expenses, and who were single, but the differences between the groups were not statistically significant. University graduates' compliance to the treatment was found to be better (23). A study conducted in Egypt reported that compliance to the treatment increased with the increase in education level (24). Unlike these studies in the literature reporting an increase in the compliance to the treatment with the increase in education level, some studies in the literature indicate no relationships between education level and compliance to the treatment (25). The participants who had a nuclear family structure were found to have lower scores in the Scale for Compliance to the Treatment in Type II DM, which indicated better compliance to the treatment; this difference was found to be statistically significant. This finding could be related to the fact that individuals living in a nuclear family do not have extra responsibilities such as taking care of parents and thus could spend more time on their own health and treatment. This study found no significant relationships between having a family member with diabetes and compliance to the treatment. The literature also reported no significant relationship between having a family member with diabetes and compliance to the treatment (26). This study found no significant relationship between the duration of diagnosis and compliance to the treatment. A study found that 71.8% of the individuals with more than 19 years of disease duration had good compliance to the treatment (26). Kav and Bulut also reported no significant relationship between the duration of diagnosis and compliance to the treatment (20).

This study found a negative, weak relationship between the diabetes health literacy total scale score, communicative health literacy, and critical health literacy, and compliance to the treatment mean score. In other words, although the relationship is not strong, compliance to the treatment increases with the increase in diabetes health literacy scale total score and communicative and critical health literacy scores. This finding indicates the positive effect of health literacy on compliance to the treatment. Individuals with good diabetes health literacy levels have important opportunities in terms of arranging the insulin dose, interpreting the meaning of blood glucose results, knowing which food to eat or not to eat, counting carbohydrate, and managing the use of drugs like insulin, which could be considered to contribute to the compliance to the chronic disease of diabetes. Similar to the results of the present study, Lai et al. (27) reported a positive, significant relationship between the communicative and critical health literacy and diabetes self-care management while no relationships were found between functional health literacy and diabetes self-care. Another study also reported an increase in individuals' compliance to the treatment with an increase in their health literacy level(24). Studies on individuals with diabetes showed that low health literacy levels had negative effects on compliance to the treatment (28,29). Unlike the present study, Kim et al. (22) reported that individuals with low health literacy demonstrated better compliance to their diet, individual blood glucose follow-ups, and foot care. In addition, another study also reported no relationships between health literacy and compliance to the treatment (30). The reason for these differences between the study findings could be the differences in the sample sizes.

This study found that individuals with high diabetes health literacy showed better compliance to the treatment. In other words, individuals who understand the health information better, who can read and understand the explanations of health professionals and medical training booklets better, and who do not experience communication problems affecting the disease were found to receive the treatment as they are recommended, at appropriate times and doses; namely, their compliance to the treatment was better.

CONCLUSION

This study found the health literacy level as above-average (38.41±8.59) and compliance to the treatment as moderate (83.14±12.35). Income level and education level among the descriptive features were found to affect functional health literacy. This study found that individuals who had a nuclear family structure demonstrated better compliance to the treatment. It was also found that patients with high health literacy levels demonstrated better compliance to the treatment.

In line with these results, as compliance to the treatment was better in patients who had higher diabetes health literacy levels, it could be recommended to increase the patients' diabetes health literacy level with the help of nurses. Nurses should also provide illiterate patients or patients who have low literacy levels and elderly patients with trainings for increasing their health literacy levels. It is also recommended that other factors affecting compliance to the treatment should be investigated.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Date: 29/11/2018, Decision No: 31).

Informed Consent: All patients signed the free and informed consent form.

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 of 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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REFERENCES

1. WHO. Health literacy: The solid facts. 2013.
2. Unıted Natıons Educatıonal Scientific and Cultural Organization, The global literacy challenge a profile of youth and adult literacy at themid-point of the united nations literacy decade 2003-2012.
3. Kutner M,Greenberg E, Jin Y, Paulsen C, White S. The health literacy of America's adults, National Assessment of Adult Literacy 2003.
4. Tanrıöver M, Yıldırım H, Ready FND, Çakır B, Akalın E. Turkey Health Literacy Survey. Saglık-Sen Publications 2014.
5. Okyay P, Abacıgil F. Türkiye sağlık okuryazarlığı ölçekleri güvenirlilik ve geçerlilik çalışması. T.C. Sağlık Bakanlığı 2016; 19-75.
6. Bakan AB, Yıldız M. A study on determining the health literacy levels of individuals aged 21-64. Sağlık ve Toplum 2019; 29: 33-8.
7. Hashempour L,Önal İ.Health and diabetes literacy, Master Thesis, The Case of Hacettepe University Hospitals, 2018.
8. Durna Z. Kronik Hastalıklar ve Bakım, Nobel Tıp Kitapevleri, İstanbul, 2012.
9. Satman I, Omer B,Tutuncu Y, et al. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. EJE 2013; 28: 169-80.
10. Akalın E, Tanrıöver MD,Sayran F. Sürdürülebilir sağlık sistemi için kronik hastalık yönetiminde elektronik sağlık kayıtlarının rolü. TÜSİAD 40 2012; 29-52.
11. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: Its importance in cardiovascular outcomes. Circulation 2009; 119: 3028-35.

12. Wood B.Medication adherence, thereal problem when treating chronic conditions. US Pharmacist 2012; 37: 3-6.
13. Jin J, Sklar GE, Oh VMS, Li SC. Factors affecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag 2008; 4: 269-86.
14. Ishikawa H, Takeuchi T, Yano E. Measuring functional, communicative and critical health literacy among diabetic patients. Am Diabet Assoc 2008; 31: 874-9.
15. Kartal A, Özsoy SA. Effect of planned diabetes education on health beliefs and metabolic control in type 2 diabetes patients. Journal of Hacettepe Universirty Faculty of Nursing 2014; 1: 1-5.
16. Ağralı H, Akyar I.Turkish validation and reliability of health literacy scalefor diabetic patients. Acıbadem Üniversitesi Sağlık Bilimleri Derg 2018; 9: 314-21.
17. Demirtas A, Akbayrak N. Development of an assessment scale for treatment compliance in type 2 diabetes mellitus in Turkish population: Psychometrice valuation. Int J Nurs Sci 2017; 4: 244-51.
18. Sørensen K, Pelikan JM, Röthlin F. Health literacy in Europe: Comparative results of the Europe an health literacy survey (HLS-EU). Eur J Public Health 2015; 25: 1-6.
19. Bal Özkaptan B, Kapucu S, Demirci İ. Relationship between adherence to treatment and acceptance of illness in patients with type 2 diabetes. Çukurova Üniversitesi Tıp Fakültesi Derg 2019; 44: 447-54.
20. Kav S, Bulut Y, Karaaslan Eşer A. et al. Evaluation of the patient compliance in type 2 diabetes mellitus treatment. Ege Üniversitesi Hemşirelik Fakültesi Derg 2018; 34: 64-76.
21. Krass I, Schieback P, Dhippayom T. Systematic review or meta-analysis adherence to diabetes medication: a systematic review. Diabet Med 2015; 32: 725-37.
22. Kim S, Love F, Quistberg DA, Shea JA. Association of health literacy with self management behavior in patients with diabetes. Diabetes Care 2004; 27: 2980-2.
23. Özonuk E, Yılmaz M. Relationship between health literacy and compliance with the treatment among individuals with type 2 diabetes mellitus. Hemşirelikte Eğitim ve Araştırma Derg 2019; 16: 96-103.
24. Shokair FN. Pattern and determinants of compliance of diabetics to health care in Alexandria: A community based study. Bull Alex Fac Med 2010; 34: 200-10.
25. Sweileh WM, Sa'ed HZ, Nab'a RJA. et al. Influence of patients' disease knowledge and beliefs about medicines on medication adherence: Findings from a cross-sectional survey among patients with type 2 diabetes mellitus in Palestine. BMC Public Health 2014; 94: 2-7.
26. Arslan E. Tip 2 Diabetes Mellituslu Hastaların Tedaviye Uyumlarını Etkileyen Faktörler, Tıpta uzmanlık tezi, Dicle Üniversitesi 2011.
27. Lai AY, Ishikawa H, Kiuchi T, et al. Communicative and critical health literacy and self-management behaviors in end-stage renal disease patients with diabetes on hemodialysis. Patient Educat Counsel 2013; 91: 221-7.
28. Osborn CY, Cavanaugh K, Wallston KA. Health literacy explains racial disparities in diabetes medication adherence. J Health Commun 2011 16: 268-78.
29. Bauer AM, Parker MM, Schillinger D. Associations between antidepressant adherence and shared decision making, patient–provider trust, and communication among adults with diabetes: Diabetes study of northern California (DISTANCE). J Gen Intern Med 2014; 29: 1139-47.
30. Thurston MM, Bourg CA, Phillips BB, Huston SA. Impact of health literacy level on aspects of medication nonadherence reported by underserved patients with type 2 diabetes. Diabetes Technology Therapeutics 2015; 17: 187-93.

Original Article

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The frequency of vitamin D deficiency in Ordu and its relationship with chronic diseases

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ABSTRACT

Aim: The aim of this study was to evaluate the frequency of vitamin D deficiency in adult patients admitted to our hospital in Ordu and the relationship between this deficiency and chronic diseases.

Material and Method: In our study, the vitamin D levels of 1432 patients aged 18 yeras and over who applied to the Internal Medicine outpatient clinic between 01.01.2019-31.12.2019 were retrospectively evaluated. Age, gender, chronic diseases were evaluated and vitamin D levels of the patients were measured. Patients with serum vitamin D level of <20 ng/ml are in the vitamin D deficiency group; Patients between 21-30 ng/ml are in the vitamin D insufficiency group; Patients >30 ng/ml were included in the normal vitamin D group.

Results: The study consisted of 1092 females (76.4%) and 340 males (23.6%). We found vitamin D deficiency and insufficiency in approximately 88.3% of the patients. In addition, serum vitamin D levels of female patients included in the study were found to be significantly lower than male patients (p=0.007). There were statistically significant differences between the groups in the number of patients included in the study who had a chronic disease and in the evaluation of their vitamin D levels (insufficient, deficient, normal)(p=0.021, p=0.012, p=0.047, p=0.043, p=0.032, respectively).

Conclusion: With this study, a very high rate of vitamin D deficiency and insufficiency, such as 88.3%, was found in Ordu. In addition, there was a significant relationship between vitamin D deficiency and chronic diseases in our study.

Keywords: Vitamin D deficiency, 25-hydroxy vitamin D, frequency, chronic diseases, mortality

INTRODUCTION

Vitamin D is among the fat-soluble vitamins (1). Vitamin D is a sterol that can be synthesized endogenously and is hormone precursors. Our skin, which is exposed to sunlight, has the ability to synthesize vitamin D. There are two forms of vitamin D, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Of these, vitamin D3 type constitutes its endogenously synthesized form in the skin, and vitamin D2 type constitutes the form taken exogenously with food (2). The most important task of vitamin D is to regulate calcium and phosphorus metabolism and also to provide bone mineralization (3). Vitamin D deficiency causes osteomalacia, osteoporosis, and the risk of bone fractures in patients (4). Many studies have shown that severe vitamin D deficiency is due to insufficient exposure to sunlight, especially in winter months (5,6). However, excessive use of sunscreen creams and insufficient intake of vitamin D with food also cause vitamin D deficiency (7). Again, many studies have shown that vitamin D deficiency is associated with infections, cardiovascular diseases, multiple sclerosis, psychiatric disorders such as depression, diabetes, autoimmune diseases, even breast and colon cancers (8-11). In patients with chronic disease, either insufficient intake of vitamin D with food or the process of chronic disease may cause vitamin D deficiency by disrupting the metabolism of vitamin D. In addition, drugs used in chronic diseases may impair vitamin D metabolism. Again, some studies have shown that vitamin D deficiency in patients with chronic diseases shortens the life span of the patients, increases mortality and causes serious complications in patients. They argued that the reason for this is the loss of anti-inflammatory, anti-oxidant and anti-ischemic properties of vitamin D, which have positive effects on the body, in case of vitamin D deficiency (12,13).

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The aim of our study was to evaluate the frequency of vitamin D deficiency in patients aged 18 years and over who applied to our hospital in Ordu, and to evaluate the relationship of vitamin D deficiency with chronic diseases in these patients. Thus, we think that early detection of vitamin D deficiency in patients with chronic diseases and adequate vitamin D replacement in these patients will have positive effects on the patient's response to treatment and mortality.

MATERIAL AND METHOD

The study was carried out with the permission of Ordu University Clinical Research Ethics Committee (Date: 29.03.2018, Decision no: 2018- 57). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Our study included 1432 patients aged 18 years and older who applied to the Internal Medicine outpatient clinic of Ordu University Training and Research Hospital between 01.01.2019 and 31.12.2019, and these patients had a chronic disease (diabetes mellitus, hypertension, thyroid diseases, heart disease, hyperlipidemia) were evaluated for vitamin D levels. The data of the patients were taken from the archive records retrospectively. Patients using vitamin D and immunosuppressive drugs, patients with primary hyperparathyroidism, patients receiving osteoporosis treatment, pregnant women, nursing mothers, patients with acute and chronic infections, patients with chronic kidney failure, patients using cigarettes and alcohol, patients with insufficient and incomplete archive data patients were not taken. Age, gender, existing chronic diseases and vitamin D levels of the patients were evaluated. Vitamin D levels were recorded at the first admission of patients who had more than one outpatient admission at the time the data of our study were collected. In our hospital, the vitamin D was studied as serum vitamin D level in Abbott Architect i2000-SR auto-analyzer. Patients with serum vitamin D level <20 ng/ml were assigned to the vitamin D deficiency group; Patients with a range of 21-30 ng/ml were assigned to the vitamin D deficiency group; Patients with >30 ng/ml were included in the normal vitamin D sufficiency group.

Statistical Analysis

All data were loaded into SPSS (Version 22.0, Inc., Illinois, Chicago, USA). In the evaluation of the data; number, percentage, mean and standard deviation were used for descriptive statistics. The distribution of data was evaluated with the Kolmogorov-Smirnow test. Student-T test was used to compare the groups. Pearson and Spearman tests were used for correlation analysis. A P value less than 0.05 was considered significant.

RESULTS

In this study, 1432 patients whose vitamin D levels were measured from patients aged 18 years and older who applied to the Internal Medicine outpatient clinic were included. Of these patients, 23.6% (n=340) were male and 76.4% (n=1092) were female. The mean age of the patients participating in the study; It was 36.22±13.46 years. Average age of male patients; 38.43±12.51 years, mean age of female patients; It was 34.63±14.32 years. The number of patients diagnosed with vitamin D deficiency level <20 ng/ml was 1090 (76.1%); The number of patients diagnosed with vitamin D deficiency between 21-30 ng/ml was 176 (12.2%); The number of patients with normal vitamin D with >30 ng/ml was 166 (11.7%). The mean serum vitamin D levels of the patients participating in the study were 14.28±13.61 ng/ml. The mean serum vitamin D levels by gender are; It was found to be 15.3±11.7 ng/ml in women and 17.6±14.2 ng/ml in men. When we evaluate the relationship between the gender of the patients participating in the study and serum vitamin D levels; serum vitamin D levels in female patients were found to be significantly lower than in male patients (p=0.007) (**Table 1**).

Table 1. Statistical comparison of the patients' genders and serum vitamin D levels

Serum vitamin D level	Gender				Total		p value
	Female		Male				
	n	%	n	%	n	%	
Deficiency (<20 ng/ml)	852	78.1	238	21.9	1090	100.0	0.007
Insufficiency (21-30 ng/ml)	110	62.4	66	37.6	176	100.0	
Normal(>30 ng/ml)	130	78.5	36	21.5	166	100.0	

n: number of patients, %: percent,

The median age of the patients participating in the study was calculated as 32 years. When we group our patients according to the age of 32 years; There was no statistically significant difference between the vitamin D levels of patients aged 32 years and younger and patients older than 32 years (p=0.214) (**Table 2**).

Significant differences were found between the groups in the statistical evaluation of the number of patients aged 18 years and older who were included in the study with a chronic disease (diabetes mellitus, hypertension, thyroid diseases, heart disease, hyperlipidemia) and their vitamin D levels (p=0.021, p=0.012, p=0.047, p=0.043, p=0.032, respectively) (**Table 3**).

Table 2. Statistical comparison of serum vitamin D levels of patients over and under 32 years of age.

Age groups	Serum vitamin D level						Total		P value
	Deficiency (<20 ng/ml)		Insufficiency (21-30 ng/ml)		Normal (>30 ng/ml)				
	n	%	n	%	n	%	n	%	
<32 years	532	73.6	92	12.6	98	13.5	722	100.0	0.214
≥32 years	558	79.1	84	11.9	68	9.4	710	100.0	

n: number of patients, %: percent,

Table 3. Statistical comparison of the number of patients with a chronic disease and vitamin D levels among the patients participating in the study

Chronic Diseases	Serum vitamin D level						Total		P value
	Deficiency (<20 ng/ml)		Insufficiency (21-30 ng/ml)		Normal(>30 ng/ml)				
	n	%	n	%	n	%	n	%	
Diabetes Mellitus	87	35.0	100	40.3	61	24.5	248	100.0	0.021
Hypertension	178	39.3	202	44.6	72	15.9	452	100.0	0.012
Thyroid status	489	34.1	543	37.9	400	27.9	1432	100.0	0.047
Euthyroid	317	35.9	332	40.1	203	23.9	852	100.0	0.036
Hypothyroidism	96	39.0	114	46.3	136	55.2	346	100.0	0.041
Hyperthyroidism	76	32.4	97	41.4	61	26.0	234	100.0	0.028
Heart disease	153	49.0	145	46.4	114	36.5	312	100.0	0.043
Hyperlipidemia	79	39.8	88	44.4	31	15.6	198	100.0	0.032

n: number of patients, %: percent,

DISCUSSION

Vitamin D is a very important vitamin for bone metabolism. It is a necessary vitamin for both the normal development of the bone and the protection of the bone. Vitamin D deficiency or insufficiency has adverse effects on ossification of the cartilage matrix, osteoblastic activity, calcium and phosphorus metabolism, bone remodeling process, and bone density (14). In some studies, patients with a vitamin D threshold value of <20 ng/ml were found to have vitamin D deficiency; When patients with a range of 21-30 ng/ml were accepted as vitamin D deficiency, an average of 75-92% of the patients were found to have vitamin D deficiency and insufficiency (15,16). Erol and et al. (17) found the mean vitamin D level to be 10.6±6.5 ng/ml in their study and found the vitamin D level to be below 20 ng/ml in 92.2% of the patients. In our study, we found the mean serum vitamin D levels of the patients to be 14.28±13.61 ng/ml, and we found the vitamin D level to be below 20 ng/ml in 76.1% of the patients. The reason why vitamin D level is so low in our country is; nutritional deficiencies, lifestyle and environmental factors play a role (18). In a study by Uçar and et al. (19), they found 51.8% of vitamin D deficiency and 20.7% of vitamin D deficiency. However, unlike our study, they did not find a difference between the sexes in terms of vitamin D levels. In our study, we found vitamin D deficiency and insufficiency in approximately 88.3% of patients aged 18 years and older who applied to our outpatient clinic in Ordu. In terms of gender, there were more vitamin D deficiency and insufficiency in the female patient group. In this case, Öğüş and et al. (20) found a higher rate of vitamin D deficiency and insufficiency in the female patient group than in the male patient group, similar to our study. The fact that more vitamin D deficiency has been detected in women can be attributed to the fact that women spend more time at home and as a result, they are not exposed to enough sun rays. In our study, we interpreted that the reason why vitamin D deficiency and insufficiency is so high in Ordu is the lack of exposure to sufficient sun rays due to the fact that the weather is cloudy and constantly rainy for most of the year due to weather conditions. However, in a study conducted in Asian societies where there is sufficient exposure to sunlight, vitamin D insufficiency and deficiency were also found. It has been shown that the reason for this is that exposure to sufficient sun rays is not sufficient for normal vitamin D levels, however, age factor, intake of foods containing sufficient calcium, amount of adipose tissue and adequate physical exercise have positive effects on vitamin D levels (15,16).

Despite this, although adequate sun exposure has positive effects on vitamin D levels, there is a serious problem of vitamin D deficiency all over the world due to the harmful effects of long-term sun exposure and the increase in sun protection and the widespread use of sunscreens has occurred. In particular, Australia has become the country with the lowest vitamin D level due to the measures taken by the local people, such as using too much sunscreen and wearing long-sleeved clothes, due to the recent increase in skin cancers in Australia, where the sun's rays are sufficient (11). In a study conducted in Pakistan, a very high rate of vitamin D deficiency, such as 98.8%, was found, and they attributed this to reasons such as insufficient exposure to sunlight, malnutrition, decreased

physical activity and working in closed workplaces for a long time (21). Again, in a study conducted on patients with extensive bone and joint pain, vitamin D deficiency was found to be 71.1% (22). In our study, we found a high rate of vitamin D deficiency and insufficiency, such as 83.3%. We thought that the reason for such high levels of vitamin D deficiency and insufficiency in our region may be due to inadequate sun exposure, closed dressing style, living in high altitude plateaus, low socioeconomic status, nutritional deficiency and decreased physical activity.

Vitamin D deficiency has been found to be associated with rickets in children, osteoporosis and osteomalacia in the elderly, cardiovascular diseases, diabetes mellitus, hyperlipidemia, thyroid diseases, some cancers, and many chronic diseases (3,16). In particular, vitamin D has been shown to be an important determinant of mortality due to its anti-inflammatory, anti-oxidant and anti-ischemic properties (12,13,23). In our study, there was a significant relationship between the patients with a chronic disease (diabetes mellitus, hypertension, thyroid diseases, heart disease, hyperlipidemia) and the vitamin D levels of the patients. Those with chronic disease had low vitamin D levels. In 75.4% of diabetes patients, 84% of hypertension patients, 60.6% of hypothyroid patients, 73.9% of patients with hyperthyroidism, 95.5% of patients with heart disease, and 84% of patients with hyperlipidemia, the vitamin D level was found to be below 30 ng/ml which is accepted as normal level. We believe that such a high rate of vitamin D deficiency and insufficiency in patients with chronic diseases is due to the lack of adequate and balanced nutrition in these patients, the negative effects of the drugs they use due to their diseases on vitamin D metabolism, decreased physical activity performance and not being exposed to adequate sunlight.

CONCLUSION

A high rate of vitamin D deficiency and insufficiency was detected in the patients who applied to our hospital, and considering that this situation would be related to dietary factors, insufficient sunlight exposure and insufficient exercise, it was suggested that adequate vitamin D supplementation and dietary supplementation should be given to the patients. We think that awareness raising about exercise will have positive effects on the mortality of chronic diseases.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ordu University Clinical Research Ethics Committee (Date: 29.03.2018, Decision no: 2018-57).

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 author has no conflicts of interest to declare.

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

Author Contributions: All of 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.

REFERENCES

1. IOM (Institute of Medicine). Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press; 2011.
2. Meer IM, Middelkoop BJC, Boeke AJP, et al. Prevalence of vitamin D deficiency among Turkish, Moroccan, Indian and sub-Sahara African populations in Europe and their countries of origin: an overview. Osteoporos Int 2011; 22: 1009-21.
3. Lips P. Vitamin D status and nutrition in Europe and Asia. J Steroid Biochem Molecul Biol 2007; 103: 620-5.
4. WHOQOL Group. The Development of the World Health Organisation quality of life assessment: International perspectives. Heidelberg: Springer Veriag 1994; 3: 41-57.
5. Champe PC, Harvey RA, Ferrier DR. Biyokimya. Çeviri Editörü: Ulukaya E. Lippincott's Illustrated Reviews Serisinden. 3. Baskı. Nobel Tıp Kitapevleri. 2007.
6. Schoor MN, Lips P. Worldwide vitamin D status. Best Pract Res Clin Endocrinol Metab 2011; 25: 671-80.
7. Hekimsoy Z, Dinç G, Kafesçiler S, et al. Vitamin D status among adults in the Aegean region of Turkey. BMC Public Health 2010; 10: 782-8.
8. Cannell JJ, Vieth R, Umhau JC, et al. Epidemic influenza and vitamin D. Epidemiol Infect 2006; 134: 1129-40.
9. Schottker B, Haug U, Schomburg L, et al. Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study. Am J Clin Nutr 2013; 97: 782-93.
10. Holick MF. Vitamin D: A millenium perspective. J Cell Biochem 2003; 88: 296-07.
11. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr 2008; 87: 1080-6.
12. Yap KS, Northcott M, Hoi AB, Morand EF, Nikpour M. Association of low vitamin D with high disease activity in an Australian systemic lupus erythematosus cohort. Lupus Sci Med 2015; 2: 64.
13. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012; 380: 219-29.
14. Christodoulou S, Goula T, Ververidis A, Drosos G. Vitamin D and bone disease. Biomed Res Int 2013; 1: 1-6.
15. Kumar GT, Chugh R, Eggersdorfer M. Poor vitamin D status in healthy population in India: a review of current evidence. Int J Vitam Nutr Res 2015; 85: 1-7.
16. Atalay SG, Atalay R, Alkan BM, et al. Vitamin D deficiency in adults with musculoskeletal pain. Turk J Osteoporos 2015; 21: 101-4.

17. Erol AM, Çelik C, Hacıoğlu K, et al. The relationship between vitamin D level and lipid profile in patients admitted to the Physical Medicine and Rehabilitation outpatient clinic. Ege Med J 2015; 54: 173-6.
18. Açıkgöz A, Günay T, Uçku R. Vitamin D requirements and supplementation during pregnancy. TAF Prevent Med Bull 2013; 12: 597-608.
19. Uçar F, Taşlıpınar MY, Soydaş AÖ, Özcan N. 25-OH Vitamin D levels in patients admitted to Ankara Etlik Training and Research Hospital. Eur J Basic Med Sci 2012; 2: 12-5.
20. Öğüş E, Sürer H, Kılınç AŞ, et al. Evaluation of Vitamin D levels by months, gender and age. Ankara Med J 2015; 15: 1-5.
21. Roomi MA, Farooq A, Ullah E, Lone KP. Hypovitaminosis D and its association with lifestyle factors. Pak J Med Sci 2015; 31: 1236-40.
22. Pearce SHS, Cheetham TD. Diagnosis and management of vitamin D deficiency. BMJ 2010; 340: 5664.
23. Chowdhury R, Kunutsor S, Vitezova A, et al. Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. BMJ 2014; 348: 1903.

Original Article

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An analysis on the adjuvant efficacy of intravenous or perineural administered dexamethasone in erector spina plane block applied to patients who had thoracotomy: a prospective randomized double-blind study

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ABSTRACT

Aim: Thoracic surgery is one of the surgical procedures that necessitates effective pain management both before and after the procedure. Because of the adverse effects of opioids in thoracic surgeries, regional anesthesia has been widely used for postoperative analgesia. One of the most recent techniques used with this indication is erector spina plane block (ESPB). Many studies in regional anesthesia have shown that adding dexamethasone to local anesthetics as an adjuvant agent prolongs the analgesic effect. The purpose of the present study was to assess the effect of dexamethasone, which is used as a perineural and intravenous adjuvant, on the duration and level of analgesia of ESPB used in thoracic surgeries.

Material and Method: This prospective, randomized controlled study included 60 patients who would have a thoracotomy under general anesthesia and ESP for peri-operative analgesia. Patients were divided into three groups: those who received perineural dexamethasone (Group PN), those who received IV dexamethasone (Group IV), and those who did not receive any dexamethasone at all (Group C-Control). Numerical rating scale (NRS) scores, rescue analgesic drug use and block times were recorded at the postoperative 2nd, 6th, 12th, 24th and 36th hours.

Results: There was no statistically significant ($p>0.05$) difference in blocking times or additional analgesic use between the three groups. There was no statistically significant ($p>0.05$) difference in the NRS scores when the patients' pain levels were measured in all three groups. 36th hour NRS scores and additional analgesic use were higher in the group that did not receive IV or perineural dexamethasone.

Conclusion: NRS scores and rescue analgesic use were similar between ESPB groups with intravenous or perineural addition of 4 mg dexamethasone and ESPB group administered without dexamethasone. However, the NRS score average in the group C was greater than 3, particularly in the 36th hour NRS data, whereas the NRS scores in the group PN and group IV were less than 2.

Keywords: Erector spina plane block, perineural dexamethasone, intravenous dexamethasone, thoracotomy, postoperative analgesia

INTRODUCTION

Thoracic surgeries, whether open or closed (video assisted), are among the most painful surgical procedures and necessitate effective analgesia (1). The pain that develops as a result of insufficient analgesia prevents the patient from breathing deeply and coughing, resulting in respiratory distress such as atelectasis, hypoxia, and pneumonia (2).

Opioids used as traditional analgesics have the potential for a number of unwanted side effects (such as nausea, vomiting, constipation, sedation, urinary retention, and pruritus), tolerance, and dependence. Regional anesthesia and peripheral blocks, which are commonly used in thoracic surgeries, are more effective at controlling postoperative pain than other analgesia strategies and they also reduce the use of opioid drugs (3).

Thoracic epidural analgesia (TEA) and thoracic paravertebral block (TPVB) are the most commonly used pain management techniques following thoracic surgery. They are, however, technically challenging to implement and have a high failure rate (up to 15 percent in TEA). Furthermore, both methods have significant risks, including pneumothorax, dural puncture, hematoma, infection, and nerve injury (4,5). In recent years, facial plane blocks have brought benefits such as ease of application, effective analgesia, and a low complication rate. The most recent of these methods is the erector spina plan block (ESPB), which was described in 2016 by Forero et al. (6).

Many researchers have been looking for the best analgesic adjuvant that both extends the duration of analgesia and

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has fewer side effects after peripheral nerve block. Even though many agents failed this test (opioids, ketamine, clonidine, etc.), it has been demonstrated in some studies that the addition of dexamethasone to local anesthetics, both perineural and intravenously, prolongs the analgesic effect (7,8).

There are studies in the literature regarding the adjuvant efficacy of dexamethasone, which is used perineural or intravenously. In our study, we aimed to evaluate the effect of the adjuvant efficacy of dexamethasone on the level and duration of analgesia in ESPB, which has been defined recently in thoracic surgeries.

MATERIAL AND METHOD

This prospective, randomized controlled and double-blind study was carried out with the permission of Health Sciences University Clinical Researches Ethics Committee (Date: 03.12.2020, Decision No: 20-110). Informed consent was obtained from all patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The Consolidated Standards of Reporting Trials flow diagram was used for enrollment and allocation of patients (**Figure 1**).

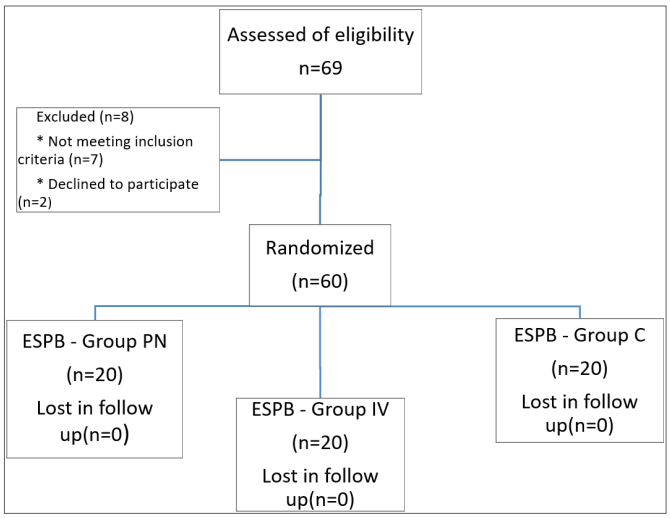


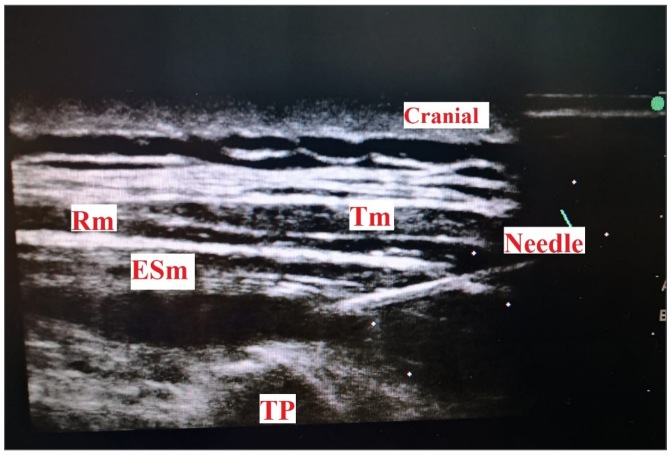
Figure 1. Study flowchart. ESPB, erector spinae plane block.
PN: Perineural, IV: Intravenous, C: Control

In the present study, sixty ASA I-III patients, aged 18-70 years, who will undergo thoracotomy surgery under general anesthesia and are scheduled to receive ESP for peri-postoperative analgesia, were included. Patients in the study were divided into three groups: those who received perineural dexamethasone (Group PN), those who received IV dexamethasone (Group IV), and those who did not receive any dexamethasone at all (Group C-Control).

Patients aged younger than 18 years, older than 70 years, with ASA physical status classification IV, infection of the skin at the site of needle puncture area, with known allergies to any of the study drugs, receiving antithrombotic treatment and whose coagulation parameters are abnormal were excluded from the study.

In the premedication room, patients were informed about ESPB. Data on demographics were collected. Each patient was sedated with 0.03 mg kg-1 midazolam. In the operating room all patients had received standardized monitoring which included SpO_2, ECG, noninvasive blood pressure monitoring.

The patient, whose hemodynamics were deemed stable, was placed in a sitting position. Following sterilization of the procedure area, the USG (SonoSite M-Turbo HFL50x/15-6 MHz Lineer Transducer SonoSite, Inc. Bothell, WA 98021 USA) probe was dressed sterile with a camera sheath. A 4 cm depth-adjusted linear probe was placed in the parasagittal plane, about 3 cm lateral to the T5 spinous process (axillary fold level), under USG guidance. After observing the T5 transverse process with an in-plane approach, an 80 mm long block needle (Stimuplex B. Braun R) was craniocaudally inserted through the skin. When the trapezius, rhomboid, and erector spina muscles were passed and the needle rested on the transverse process (about 3 cm in depth), 1 mL of 0.9 percent NaCl test dose was administered between the erector spina muscle fascia and the vertebral transverse process, the muscle fascia was opened, and the needle location was confirmed (**Picture 1**).



Picture 1. Ultrasonographic image and anatomical landmarks

In group C, 30 mL of 0.25 percent bupivacaine was injected into the erector spina plane, followed by ESPB. In the group PN, the erector spina plan was given 30 ml of 0.25 percent bupivacaine and 4 mg of dexamethasone, and ESPB was used. In the group IV, 30 mL of 0.25 percent bupivacaine was injected into the erector spina plane and ESPB, and 4 mg of dexamethasone was injected intravenously. All blockages were performed by the same anesthesiologist

who was in charge of the thoracic surgery room. The study was conducted in a double-blind fashion, with neither the patient nor the anesthesia team, who administered general anesthesia and followed up on the patient, knowing which group the patient belonged to.

Following the blockade, the patient was placed in the supine position and intubated after anesthesia induction (intravenous propofol 2 mg/kg, rocuronium 0.5 mg/kg, fentanyl 1 mcg/kg). In addition, maintenance anesthesia (50-50 percent O_2 - air and 2% sevoflurane) was planned by connecting to a mechanical ventilator.

At the end of the surgery, all of the patients received paracetamol 1 g IV and petidin (Meperidin, Dolantin) 30 mg as a standard for postoperative analgesia. For preventing postoperative nausea and vomiting ondansetron (8 mg IM) was also administered to all patients.

After being awakened at the end of the procedure, the patients were transferred to the post-operative care unit. Patients with an Aldrete score of 9-10 were transferred to their wards after connecting an intravenous tramadol patient-controlled analgesia device (5mg/ml concentration, 20mg bolus dose, 30-minute lock-in time).

Numerical rating scale (NRS) scores were recorded at 2-6-12, 24 and 36 hours after surgery, as well as additional analgesic medication and administration time if necessary. After the first evaluation hour with NRS >4, patients in both groups were started on IV analgesia treatment (paracetamol 1 gr IV 3x1, dexketoprofen 50 mg IV as an additional analgesic). If the VAS was 4 and the patient did not require analgesics, the paracetamol dose was skipped.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in the descriptive statistics of the data. The Kolmogorov-Smirnov test was used to determine variable distribution. In the analysis of quantitative independent data, ANOVA and Kruskal-wallis were employed. The Chi-square test was used to analyze qualitative independent data. The analysis was carried out using the SPSS 27.0 program. The results were evaluated at the 95% confidence interval and the significance level at $p<0.05$.

The calculation for the strength of the present study was performed on the page https://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/samplesizecalculators.aspx by referring to the " Dexamethasone as a local anesthetic adjuvant in bilateral ultrasound guided erector spinae plane block can provide a long-lasting analgesia in laparotomic abdominal surgery. Fusco P, et al. Minerva Anestesiol. 2019; 85:1144-5." study. A power analysis was carried out, assuming Type I error=0.05 and Type II error=0.2 (80% power to detect this difference), then 20 patients were required in each group.

Randomization was performed according to computer-generated random number tables and allocation to treatment group was done using the sealed opaque envelope technique.

RESULTS

The study included 60 patients, 30 of whom were women and 30 of whom were men. When demographic information, BMI values, and ASA classification distributions were compared, there was no statistically significant difference between the groups C, PN, and IV ($p>0.05$) (**Table 1**).

Table 1. Demographic data of patients

	Group PN n % Median	Group IV n % Median	Group C n % Median	p
Age	62.0	58.0	56.5	0.456A
Sex				0.449X²
Female	12 60.0%	8 40.0%	10 50.0%	
Malea	8 40.0%	12 60.0%	10 50.0%	
Height	163.5	167.5	168.5	0.610A
Weight	73.0	72.5	75.0	0.793A
BMI	26.1	25.2	26.0	0.704A
ASA				0.676X²
I	1 5.0%	3 15.0%	4 20.0%	
II	16 80.0%	13 65.0%	14 70.0%	
III	3 15.0%	4 20.0%	2 10.0%	

A ANOVA/ K Kruskal-wallis / X² Ki-kare test

There was no statistically significant ($p> 0.05$) difference in blocking times or rescue analgesic use between the three groups (**Table 2**). Although NRS scores and rescue analgesic use at 36th hour were not statistically significant, they were lower in favor of PN and IV groups (**Graph 1**). Especially in 36th hour NRS data, NRS score average was above 3 in Group C, NRS scores were around 2 and similar in PN and IV groups.

Table 2. Comparison of Intergroup NRS Scores, Block time and Rescue Analgesic Use

	Group PN Mean±ss n %	Group IV Mean±ss n %	Group C Mean±ss n %	p
Block time (sn)	171.7±22.5	178.6±22.0	174.1±23.1	0.675K
Rescue (-)	18 (90%)	17 (85%)	15 (75%)	0.432X²
Analgesic (+)	2 (10%)	3 (15%)	5 (25%)	0.432X²
NRS Scores				
2nd hour	2.15±1.53	1.75±1.07	2.10±1.02	0.443K
6th hour	1.85±1.07	1.95±1.19	1.85±1.09	0.944K
12th hour	1.80±1.20	1.50±0.69	1.60±0.94	0.759K
24th hour	1.60±0.82	1.80±1.01	2.20±1.36	0.372K
36th hour	2.10±1.07	2.40±1.60	3.30±2.05	0.102K

A ANOVA/ K Kruskal-wallis / X² Ki-kare test

There was no statistically significant (p> 0.05) difference in the NRS scores when the patients' pain levels were measured in all three groups. NRS scores were similar at the 2nd, 6th, 12th, 24th, and 36th hours (**Table 2**) (**Figure 2**).

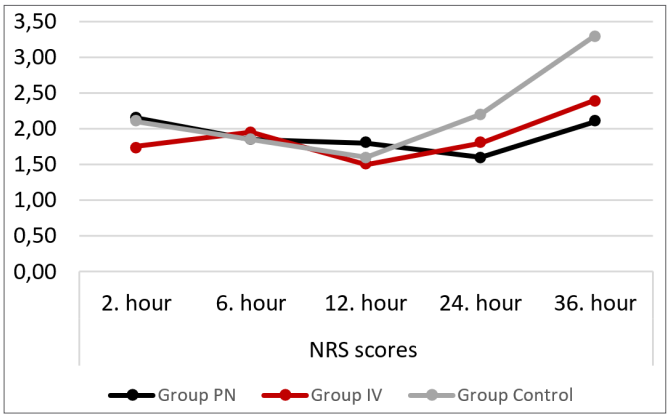


Figure 2. NRS scores and timeline

DISCUSSION

The objective of the present study was to assess the effect of dexamethasone administered intravenously or perineurally as an adjuvant in ultrasound guided ESPB in patients undergoing thoracotomy surgery. There was no statistically significant difference in NRS scores, or additional analgesic need between the ESP block groups that received 4 mg dexamethasone intravenously (IV) or perineurally (PN) versus those that did not receive dexamethasone (C). However, while the NRS score average in the group C was above 3, particularly in the 36th hour NRS data, the NRS scores in the groups PN and IV were around 2 and similar.

Effective pain management following thoracic surgery is important because it has a greater impact on mortality and morbidity than other major surgeries by reducing the stress response and serious pulmonary complications that might occur as a result of changes in lung functions following thoracic surgery (9,10).

The authors recommend a multimodal analgesia approach that includes regional and systemic analgesia techniques for pain that develops after a thoracotomy (11,12). Different regional anesthesia techniques are used in thoracic surgery, the most common of which are TEA, TPVB, and infraclavicular block. Nevertheless, because of difficulties in application, susceptibility to complications, and failed attempts, these methods might not be preferred for postoperative analgesia (4,5,13). As a result, ESPB, which is simple to administer under ultrasound guidance, has a low complication rate, and whose efficacy has been demonstrated in numerous studies, was used on the patients in the present study (14,15).

Ultrasound-guided ESPB is an interfacial plane block developed in 2016 by Forero et al. (6) to treat thoracic neuropathic pain. Even though it was initially defined for use in chronic pain, it has since been used as a postoperative analgesia method in a variety of surgical procedures ranging from shoulder to hip (16). Many studies have been conducted to investigate the postoperative analgesic efficacy of ESPB in thoracic surgeries. It has been agreed that it provides effective postoperative analgesia and reduces complications such as atelectasis by allowing the patient to breathe comfortably and cough without pain (6,14,15).

Many adjuvants, including neostigmine, tramadol, or clonidine, have been investigated for their ability to extend the duration of action of local anesthetics used in regional anesthesia, but negative results have been obtained (17). Dexamethasone was first used perineurally 12 years ago, and it has since been the subject of numerous clinical studies. The mechanism by which dexamethasone prolongs block time is not completely understood. Mechanisms proposed include reduced nociceptive C-fiber activity via glucocorticoid receptors, an effect via inhibitory potassium channels, a local vasoconstrictive effect, and a systemic anti-inflammatory effect (18,19). Some studies have been conducted on the adjuvant effect of dexamethasone, which is used intravenously at moderate doses, due to its systemic anti-inflammatory effect.

Crystallization might occur during in vitro studies when ropivacaine, rather than bupivacaine, is combined with dexamethasone due to the high pH of dexamethasone and the incompatibility of ropivacaine with alkaline solutions (20). Furthermore, systemic dexamethasone administration in moderate doses is a recommended option for effective postoperative analgesia, regardless of whether it is associated with peripheral nerve block (21). Based on this data, bupivacaine and moderate doses of dexamethasone were chosen as local anesthetics in ESPB applications of the present study.

According to a recent meta-analysis, combining perineural dexamethasone with long-acting local anesthetics increases the duration of analgesia by 8 hours when compared to placebo (22).

In their randomized controlled study, Desmet et al. (23) investigated both routes of administration and discovered that the duration of analgesia they produced was comparable (24,25). In a meta-analysis involving 914 patients and 11 randomized controlled trials, Baeriswyl M. et al. (18) found that perineural dexamethasone slightly prolonged the duration of analgesia without causing any side effects. The duration of analgesia increased by 17 percent when dexamethasone was injected perineurally (mean 3.0 hours) compared to systemic administration, according to the same study.

While some studies concluded that perineural dexamethasone was superior in terms of analgesia, others discovered statistically significant but clinically insignificant differences (26-28). In the present study, NRS scores up to the 24th hour and the use of additional analgesics were comparable in all three groups; however, the 36th-hour NRS scores were lower in the groups PN and IV, but this difference was not statistically significant.

The majority of ESPB research focuses on the analgesic effects in the first 24 hours after surgery (29-32). In addition to the adjuvant effect of dexamethasone, its analgesic effect at 36 hours was evaluated in the present study. Even though the NRS scores and use of additional analgesics were comparable up to the 24th hour, the mean of the 36th hour NRS scores was higher in the group C that did not use dexamethasone. During the 36th-hour evaluation, additional analgesics were given to 5 patients in the group C who did not receive dexamethasone, serious pain was observed in two patients, and the NRS score was 7 in one patient and 8 in the other.

The results of the present study can be evaluated within some limitations. According to previous research, the adjuvant effects of low-dose (4 mg) and high-dose (8-10mg) dexamethasone, administered perineurally or intravenously, were also comparable. Furthermore, by controlling the NRS and additional analgesic times every hour and/or by increasing the number of cases, more valuable information can be obtained about whether dexamethasone used as an adjuvant prolongs the duration of analgesic effect.

CONCLUSION

In the present study, all three groups had similar mean NRS scores (Group PN:1.6, Group IV:1.6, Group C:1.9) and rescue analgesic use (Group PN:2/20, Group IV:3/20, Group C:5/20) in the first 24 hours. ESPB blockade provided effective and adequate analgesia to patients in all three groups.

However, when the 36th-hour NRS scores and additional analgesic use were considered, lower mean±ss NRS scores and less rescue analgesic use were found in the group PN (2.10±1.07) and group IV (2.40±1.60) compared to the group C (3.30±2.05), but this was not statistically significant.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Clinical Researches Ethics Committee (Date: 03.12.2020, Decision No: 20-110).

Informed Consent: All patients signed the free 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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Author Contributions: All of 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.

REFERENCES

1. Homma T, Doki Y, Yamamoto Y, et al. Risk factors of neuropathic pain after thoracic surgery. J Thorac Dis 2018; 10: 2898–907.
2. Xie C, Ran G, Chen D, Lu Y. A narrative review of ultrasound-guided serratus anterior plane block. Ann Palliat Med 2021; 10: 700-6.
3. Pirsaharkhiz N, Comolli K, Fujiwara W, et al. Utility of erector spinae plane block in thoracic surgery. J Cardiothorac Surg 2020; 15: 1-6.
4. Romero A, Garcia JEL, Joshi GP. The state of the art in preventing postthoracotomy pain. Semin Thorac Cardiovasc Surg 2013; 25: 116–24.
5. Moustafa MA, Alabd AS, Ahmed AMM, Deghidy EA. Erector spinae versus paravertebral plane blocks in modified radical mastectomy: Randomised comparative study of the technique success rate among novice anaesthesiologists. Indian J Anaesth 2020; 64: 49–54.
6. Forero M, Adhikary SD, Lopez H, Tsui C, Chin KJ. The erector Spinae plane block: a novel analgesic technique in thoracic neuropathic pain. Reg Anesth Pain Med 2016; 41: 621–7.
7. Hewson D, Bedforth N, McCartney C, Hardman J. Dexamethasone and peripheral nerve blocks: back to basic (science). Br J Anaesth 2019; 122: 411-2.
8. Mchardy PG, Singer O, Awad IT, et al. Comparison of the effects of perineural or intravenous dexamethasone on low volume interscalene brachial plexus block: a randomised equivalence trial. Br J Anaesth 2020; 124: 84-91.
9. Goto T. What is the best pain control after thoracic surgery? J Thorac Dis 2018; 10: 1335-8.
10. Cassi LC, Biffoli F, Francesconi D, Petrella G, Buonomo O. Anesthesia and analgesia in breast surgery: the benefits of peripheral nerve block. Eur Rev Med Pharmacol Sci 2017; 21: 1341–5.
11. Szewczyk J, Nguyen BH, Villamizar N, Nguyen DM. Achieving pain control with opioid-sparing multimodal analgesic strategy–doing more with less by enhanced recovery after thoracic surgery protocol: A Review. J Anesthesiol Pain Ther 2020, 1.3.
12. Wenk M, Schug SA. Perioperative pain management after thoracotomy. Curr Opin Anaesthesiol 2011; 24: 8-12.
13. Niesen AD, Jacob AK, Law LA, Sviggum HP, Johnson RL. Reg Anesth Pain Med 2020; 45: 813-7.
14. Seelam S, Nair AS, Christopher, Upputuri O, Naik V, Rayani BK. Efficacy of single-shot ultrasound-guided erector spinae plane block for postoperative analgesia after mastectomy: a randomized controlled study. Saudi J Anaesth 2020; 14: 22-7.
15. Gürkan Y, Aksu C, Kus A, Yörükoğlu UH. Erector spinae plane block and thoracic paravertebral block for breast surgery compared to IV-morphine: a randomized controlled trial. J Clin Anesth 2020; 59: 84-8.

16. Peker K, Peker SA. The effect of erector spinae plane block on cost of percutaneous nephrolithotomy surgery. J Health Sci Med 2020; 3: 409-14
17. Axelsson K, Gupta A. Local anaesthetic adjuvants: neuraxial versus peripheral nerve block. Curr Opin Anaesthesiol 2009; 22: 649–54.
18. Baeriswyl M, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Efficacy of perineural vs systemic dexamethasone to prolong analgesia after peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth 2017; 1; 119: 183-91.
19. Oğurel T, Örnek K, Oğurel R, Onaran Z. The effect of intracameral dexamethasone used at the end of cataract surgery on macular edema in eyes with diabetic retinopathy. J Health Sci Med 2019; 2: 18-23
20. Watkins TW, Dupre S, Coucher JR. Ropivacaine and dexamethasone: a potentially dangerous combination for therapeutic pain injections. J Med Imaging Radiat Oncol 2015; 59: 571–7
21. Desmet M, Vanneste B, Reynvoet M, et al. A randomised controlled trial of intravenous dexamethasone combined with interscalene brachial plexus blockade for shoulder surgery. Anaesthesia 2015; 70: 1180–5.
22. Albrecht E, Kern C, Kirkham KR. Perineural vs intravenous administration of dexamethasone: more data are available. Br J Anaesth 2015; 114: 160.
23. Desmet M, Braems H, Reynvoet M, et al. I.V. and perineural dexamethasone are equivalent in increasing the analgesic duration of a single-shot interscalene block with ropivacaine for shoulder surgery: a prospective, randomized, placebocontrolled study. Br J Anaesth 2013; 111: 445–52.
24. Kawanishi R, Yamamoto K, Tobetto Y, et al. Perineural but not systemic low-dose dexamethasone prolongs the duration of interscalene block with ropivacaine: a prospective randomized trial. Local Reg Anesth 2014; 7: 5–9.
25. Leurcharusmee P, Aliste J, Van Zundert TC, et al. A multicenter randomized comparison between intravenous and perineural dexamethasone for ultrasound-guided infraclavicular block. Reg Anesth Pain Med 2016; 41: 328–33.
26. Aliste J, Leurcharusmee P, Engsusophon P, et al. A randomized comparison between intravenous and perineural dexamethasone for ultrasound-guided axillary block. Can J Anaesth 2017; 64: 29-36.
27. Holland D, Amadeo RJJ, Wolfe S, et al. Effect of dexamethasone dose and route on the duration of interscalene brachial plexus block for outpatient arthroscopic shoulder surgery: a randomized controlled trial. Can J Anaesth 2018; 65: 34-45.
28. Kahn RL, Cheng J, Gadulov Y, Fields KG, YaDeau JT, Gulotta LV. Perineural low-dose dexamethasone prolongs interscalene block analgesia with bupivacaine compared with systemic dexamethasone: a randomized trial. Reg Anesth Pain Med 2018; 43: 572-9.
29. Fu J, Zhang G, Qiu Y. Erector spinae plane block for postoperative pain and recovery in hepatectomy: A randomized controlled trial. Medicine 2020; 99: e22251.
30. Mostafa SF, Abdelghany MS, Abu Elyazed MM. Ultrasound-guided erector spinae plane block in patients undergoing laparoscopic bariatric surgery: a prospective randomized controlled trial. Pain Pract 2021; 21: 445-53.
31. Luo R, Tong X, Yan W, Liu H, Yang L, Zuo Y. Effects of erector spinae plane block on postoperative pain in children undergoing surgery: A systematic review and meta-analysis of randomized controlled trials. Pediatric Anesthesia, 2021, 31: 1046-55.
32. Herman JA, Urits I, Kaye AD, Urman RD, Viswanath O. Erector Spinae Plane Block (ESPB) or Quadratus Lumborum Block (QLB-II) for laparoscopic cholecystectomy: Impact on postoperative analgesia. J Clin Anesth 2020; 66: 109958.

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Effectiveness of internal compression therapy in primary safen vein failure

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ABSTRACT

Aim: The aim of this study is to evaluate the effectiveness of internal compression therapy (ICT), a new technique used in the treatment of chronic venous insufficiency (CVI), and to share the early results.

Material and Method: Between September 2018 and June 2019, 27 patients with superficial venous insufficiency due to saphenofemoral junction (SFJ) insufficiency and who underwent ICT were included in the study. Demographic data, venous color doppler ultrasonography (RDUS) results, CEAP (clinical etiology, anatomy, pathophysiology) classification, venous clinical severity score (VCSS) and visual analog scale (VAS) results were retrospectively analyzed from the files of the patients.

Results: It was determined that 14 of the 27 patients were female and 13 were male in the study. While the mean CEAP classification scores were 3.9±0.5 before the procedure, it was 2.3±0.7 at the 3rd month after the procedure ($p<0.001$). While the mean duration of venous reflux before the procedure was 4.7±0.3 seconds, pathological reflux was detected in 2 patients at the 3rd month after the procedure ($p<0.001$). While the mean VCSS score was 11.2±3.3 before the procedure, it was 5.4±1.2 at 3 months ($p<0.001$). While the mean VAS score was 6.5±1.3 preoperatively, the mean VAS score was 2.7±1.4 at 3 months after the procedure ($p<0.001$). No complications were observed in any of the patients.

Conclusion: We think that ICT can be used as an alternative treatment method in the treatment of superficial venous insufficiency due to valve dysfunction in SFJ.

Keywords: Vena saphenous magna, venous insufficiency, internal compression therapy

INTRODUCTION

Lower extremity chronic venous insufficiency (CVI) and varicose veins are an important health problem that is very common in the population, impairs quality of life and can lead to serious complications (1,2). CVI, which affects a significant part of the society, has been found to be between 20-40% in many studies (3).

Although CVI is most commonly seen as superficial venous insufficiency, it may occur as deep venous insufficiency or perforating venous insufficiency, or in some cases, it may appear as combinations of these insufficiency (4).

CVI clinic has a very broad spectrum according to the underlying factors. It may appear as a cosmetic problem in the form of telangiectasia, or it may cause serious skin changes such as ulcers (5). The main symptoms are pain, swelling, night cramps, warmth and burning sensation, tiredness, restlessness, itching and tingling (6). The basic pathology constituting CVI is an increase in venous pressure, that is, venous hypertension (7). This hypertension consists of insufficiency of the valves in the veins, occlusion in the veins or a combination of these (8).

Most treatment strategies are more conservative. Methods such as compression stockings, exercises and venoactive drugs are used in the treatment. However, these treatments cannot provide adequate or long-term protection in patients. The purpose of the treatment of CVI is the elimination of reflux (9). For many years, only ligation and external valvuloplasty (EVP) could be performed in the vena saphenous magnada (VSM), especially in reflux at the level of SFJ, and surgical methods such as stripping were applied to the VSM as standard treatment. However, in recent years, endovenous interventions such as laser ablation (EVLA), radiofrequency ablation (RFA) and n-butyl cyanoacrylate embolization have found widespread use (10).

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One of these methods is ICT, which is a newly developed technology and can be applied percutaneously interventionally. In this method, a mixture of hyaluronic acid and n-butyl-cyanoacrylate (n-BCA) is placed in the form of a gel implant around the insufficiency deep venous and/or SFJ terminal valve and between the fascia, which is a rigid support tissue. The procedure is also called percutaneous valvuloplasty. Thus, coaptation of the valves is achieved by reducing the circumference of the vessel with an exoskeleton formed with a non-absorbable biopolymer around the vessel wall, thus bringing the valves closer to each other (11,12). The use of ICT, which is a percutaneously applied valvuloplasty technique, instead of traditional surgical treatments in significant saphenofemoral insufficiency, and the preservation of VSM for grafts that may be needed in future cardiovascular surgeries are seen as one of the important advantages of ICT (13,14).

In this study, we aimed to share our short-term experience and results in our clinic of the ICT method, which has been used recently as an alternative to classical surgical and endovascular treatment methods in the treatment of superficial venous insufficiency of VSM.

MATERIAL AND METHOD

In this study, the files of all patients who had valvular leakage at the SFJ and underwent ICT for primary saphenous vein insufficiency between September 2018 and June 2019 in the Department of Cardiovascular Surgery of Kırıkkale University Medical Faculty Hospital were retrospectively reviewed. The study was conducted in accordance with the principles stated in the Declaration of Helsinki. This study was carried out with the permission of Kırıkkale University Faculty of Medicine Non-Invasive Scientific Research Ethics Committee (Date: 29.04.2021, Decision no: 2021.04.17).

All patients signed the informed consent form before the procedure. The files of the patients who had a reflux time of 4 seconds or more on CDUS, had a VSM diameter of less than 5.5 mm, were diagnosed with primary saphenous vein insufficiency and underwent ICT were reviewed. A total of 27 patients were included in the study, except for those who lacked data in their files and did not give permission to work in their consent.

Patients with post-thrombotic or congenital superficial venous disease, previous intervention for venous insufficiency, and deep thrombosis were not treated. Again, no intervention was performed in those with any deep and perforating vein insufficiency.

The demographic characteristics of the patients, the reflux in the SFJ and the diameter of the VSM in the preoperative and postoperative 3rd month RDUS results were examined.

Demographic characteristics, preoperative and postoperative 3rd month CDUS results were recorded from the files of the patients. The venous system was evaluated with CDUS, and the location and duration of reflux and the diameter of the VSM were evaluated. Reflux of 0.5 seconds or more in superficial veins, deep femoral veins, and deep calf veins is considered pathological. Reflux of 0.35 seconds or more in perforating veins is considered pathological. (15,16). In the study, CDUS examinations of the patients were evaluated based on the reports made by the Radiology Clinic. (13–5 and 9–4 MHz multifrequency linear probe, Acuson Antares, Siemens Medical Solutions USA, Inc. instrument)

The CEAP, VCSS and VAS data we used in the follow-up were evaluated before and after the procedure at 3 months. Complications that may develop during and after the procedure (bleeding, infection, ecchymosis, pigmentation, phlebitis or deep vein thrombosis) and the duration of the ICT procedure were recorded.

CEAP Classification

CEAP classification was used for the diagnosis and evaluation of CVI by considering all the findings. In CEAP classification, C: represents clinical appearance, E:etiological factors, A:anatomical distribution, P:pathophysiological status (17).

VAS

VAS scoring was used to determine the severity of symptoms. It is applied by asking patients to rate their pain intensity on a 10-unit scale, with a value of "0" indicating that they have no complaints, and a value of "10" indicating that their complaints are very severe (18).

VCSS

VCSS system, which is based on scoring up to 3, was used to evaluate the treatment efficacy of venous disease. In VCSS system, patients of clinical complaints, findings (pain, varicose veins, edema, skin pigmentation, inflammation, induration, active ulcer number, active ulcer duration, active ulcer diameter) and previous conservative treatments (compression stocking use and elevation) are evaluated (19).

Process

The procedure was performed in the operating room under local anesthesia and with the help of RDUS. A mixture of hyaluronic acid vial and n-butyl-cyanoacrylate vial (RD Global-Invamed, Ankara, Turkey) was formed and an average of 2.1 cc polymer was injected with 19 G needles around the VSM valves at SFJ. After it was seen that adequate coaptation was achieved, the procedure was terminated. The treated extremity was put on an

elastic bandage for compression, and the bandage was removed 48 hours later. All patients were discharged on the same day.

Statistical Analysis

The analysis of the data used in the study was performed using the SPSS for Windows 21.0 package program (SPSS Inc. Chicago, IL, USA). Categorical variables were expressed as percentage (%), continuous variables as mean±standard deviation (mean±std). The Kolmogorov-Smirnov test was used to evaluate the normal distribution of the data used in the study. Student's t-test was used to compare numerical variables. The chi square test was used to compare categorical variables. A P value less than 0.05 was considered statistically significant.

RESULTS

Of the 27 patients, 14 were female and 13 were male. The mean age was 45.7±8.3 (35-59) years. The mean procedure time was 17±3 minutes.

While the reflux time was 4.7±0.3 seconds before the procedure, it was 0.4±0.1 seconds at the 3rd month after the procedure. Pathological reflux was detected in a total of 2 (7.4%) patients. This result was statistically significant (p<0.001). The data are shown in **Table 1**.

Table 1. Perioperative SFJ reflux time

	Preoperative (n=27) mean±std	Postoperative (n=27) mean±std	P
Reflux time (s)	4.7±0.3	0.4±0.1	<0.001

SFJ: Safenofemoral junction, std: Standard deviation

While the mean CEAP classification scores of the patients were 3.9±0.5 before the procedure, it was 2.3±0.7 at the 3rd month after the procedure. While the mean VCSS values were 11.2±3.3 before the procedure, it was found to be 5.4±1.2 at the 3rd month after the operation. While the mean VAS score was 6.5±1.3 before the procedure, the mean VAS score was 2.7±1.4 3 months after the procedure. These results are statistically significant (p<0.001). The data are shown in **Table 2.**

Table 2. Perioperative CEAP, VCSS, VAS values

	Preoperative (n=27) mean±std	Postoperative (n=27) mean±std	P
CEAP	3.9±0.5	2.3±0.7	<0.001
VCSS	11.2±3.3	5.4±1.2	<0.001
VAS	6.5±1.9	2.7±1.4	<0.001

CEAP: Clinical etiology, anatomy, pathophysiology, VCSS: Venous clinical severity score, VAS: Visual analog scale, std: Standard deviation

Bleeding, infection, ecchymosis, pigmentation, phlebitis or deep vein thrombosis were not observed in any of the patients after the procedure. In addition, no significant change was detected in the mean VSM diameters.

DISCUSSION

In our study, in which we evaluated the results of the ICT method in patients with chronic superficial venous insufficiency, a significant improvement was found in CEAP classification, VAS and VCSS scores by evaluating the data we obtained at the end of the 3-month follow-up. These results show us that the ICT method stands out as an alternative treatment to other methods in which VSM is preserved in venous insufficiency due to SFJ reflux.

In recent years, minimal incisions and/or percutaneous pathological venous structures can be treated even with local or tumescence anesthesia, but the VSM structure cannot be preserved in these methods (occlusion, obliteration, striping). This may cause problems in the future when VSM is required to be used as a graft (20). This leads to the search for new treatments. One of these is EVP, a reconstructive surgery method that reduces the diameter of the VSM by using different materials (dacron, PTFE) from the outside to correct the coaptation of the valves in the SFJ (21). A new procedure, ICT, uses a polymer composed of cyanoacrylate and hyaluronic acid, developed according to the effects of compression materials. This polymer is injected percutaneously around the femoral and/or SFJ under RDUS guidance. In this way, the diameter of the vessel is reduced and the function of the valve with insufficiency is restored. This procedure is also called percutaneous valvuloplasty (22).

Although the application of this EVP procedure has increased recently (15%), studies are still scarce, and when the literature is examined, it is reported that different results are obtained in interventions performed on patients with primary saphenous vein insufficiency (23). In a study conducted by Saraç et al. (24) on 83 patients with isolated saphenous vein insufficiency, they reported that in the results of two year surgical EVP, symptomatic improvement was detected in 51 (61.4%) patients, and additional procedures were performed in the remaining 32 patients. In addition, Muhlberger et al. (25) EVP in their study of 210 patients; reported that the procedure was effective in 95.24% of the patients and the VCSS decreased from 4.76 preoperatively to 1.77 6 months after the operation. The findings in this study are similar to our study. Although the procedures in these studies are similar in mechanism, they are performed with surgical intervention. It is a more invasive method compared to ICT.

Complications such as infection, bleeding, hematoma, venous stenosis, deep vein thrombosis, thrombophlebitis and reoperation can be seen after the EVP procedure (26). In their ten years study, Joh et al.

(27) reported the diffuse thrombosis rate of VSM as 12.9%. In addition to these studies, Günaydın et al. (28) performed percutaneous valvuloplasty in 44 patients with primary VSM failure. There were no complications in any patient, venous reflux completely disappeared in 37 (84%) patients in their four month follow-up, mild reflux in 2 (4.5%) patients, 1 (2.2% reported that moderate reflux was observed in the patient. Our results show parallelism to this study and only 2 (7.4%) patients had pathological reflux. In addition, no complications were observed in our study, and we attribute this result to the fact that it is a less invasive procedure performed with CDUS.

Due to the lack of CEAP classification in detecting post-treatment changes, evaluating response to treatment, and comparing the efficacy of different treatment modalities, scoring systems related to clinical severity of the disease were needed. The VCSS system, which evaluates the clinical complaints and findings of patients and their conservative treatments due to CVI, is used to evaluate the treatment effectiveness of venous disease (29). Eroğlu and Acıpayam (30), in their study on 12 patients who underwent ICT due to primary superficial venous insufficiency, showed that the CEAP classification was CEAP 2 (1-4) before the procedure, while it was CEAP 3 (3-4) in the follow-up one month later. They also reported that the VCSS was 6 at the follow-up one month later, while the VCSS score was 10 before the procedure. In our study, we also obtained similar results in terms of reflux time, CEAP classification and VCSS scoring.

Pain in CVI is one of the most common symptoms that negatively affects the work and social life of the person by impairing the quality of life (31). After CVI treatment, VAS, which is a practical evaluation method, can be used in the evaluation of pain to quantify some values that cannot be measured numerically in deciding the effectiveness of the treatment (32). In our study, the mean VAS score was 6.51±1.3 before the procedure, while the mean VAS score was 2.36±1.34 6 months after the procedure. This result is consistent with the literature as an indication that the ICT method improves the quality of life in patients (33).

We think that the ICT procedure is a fast and effective method in the treatment of patients with chronic venous insufficiency due to saphenofemoral junction valve insufficiency, and that it can be applied under day care conditions has an important advantage over other methods.

The limitation of this study is that it is retrospective and single-centered. Studies with a larger patient population and longer follow-up are needed.

CONCLUSION

In this study, it has been shown that ICT is a fast and effective percutaneous treatment method and improves the patient's clinic in a short time that can be used in superficial venous insufficiency, which reduces and eliminates venous reflux in SFJ by preserving VSM.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of Kırıkkale University Faculty of Medicine Non-Invasive Scientific Research Ethics Committee (Date: 29.04.2021, Decision No: 2021.04.17).

Informed Consent: All patients signed the free 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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Author Contributions: All of 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.

REFERENCES

1. Ross DS. Venous stasis ulcers: a review. Northeast Florida Medicine 2012; 63: 29-51.
2. Bolat A, Gültekin Y. Vena safena magnanın anatomik varyasyonu derin ven trombozu için bir risk faktörü müdür? KÜ Tıp Fak Derg 2021; 23: 343-50.
3. Allan PL, Bradbury AW, Evans CJ, et al. Patterns of refluxandseverity of varicoseveins in the general population--Edinburgh VeinStudy. Eur J Vasc Endovasc Surg 2000; 20: 470-7
4. Eroglu E, Yasim A. A Randomised clinical trial comparing n-butyl cyanoacrylate, radiofrequency ablation and endovenous laser ablation for the treatment of superficial venous incompetence: two year follow up results. Eur J Vasc Endovasc Surg 2018; 56: 553-60.
5. Nicolaides AN, Allegra C, Bergan J, et al. Management of chronic venous disorders of the lower limbs: Guidlines according to scientific evidence. International Angiology 2008; 27: 1–59.
6. Burnand KG. The physiology and hemodynamics of chronic venous insufficiency of the lower limb. In: Gloviczki P, Yao JS (eds). Handbook of Venous Disorders. 2nd ed. New York, NY: Arnold; 2001: 49-57.
7. Pappas PJ, Durán WN, Hobson RW. Pathology and cellular physiology of chronic venous insufficiency. In: Gloviczki P, YaoJS, eds. Handbook of Venous Disorders. 2nd ed. New York, NY: Arnold; 2001: 58-67.
8. Gschwandtner ME, Ehringer H. Microcirculation in chronic venous insufficiency. Vasc Med 2001; 6: 169-79.
9. Puggioni A, Kalra M, Carmo M, Mozes G, Gloviczki P. Endovenous laser therapy and radio frequency ablation of the great saphenous vein: analysis of early efficacy and complications. J Vasc Surg 2005; 42: 488-93.

10. Santler B, Goerge T. Chronic venous insufficiency - a review of pathophysiology, diagnosis, and treatment. J Dtsch Dermatol Ges 2017; 15: 538-56.
11. Hafız E, Şen E. A new application of external valvuloplasty using interventional injection of N-butyl cyanoacrylate for malfunctioning venous valves. J Surg Med 2020; 4: 775-8.
12. Yavuz T, Acar, Yavuz K, Ekingen E. A Retrospective study of deep vein insufciency treatment device: ICT. Ann Vasc Dis 2020; 3: 255–60.
13. Lane RJ, Cuzzilla ML, Coroneos JC. The treatment of varicose veins with external stenting to the saphenofemoral junction. Vasc Endovascular Surg 2002; 36: 179-92.
14. Eroğlu E, Yasim A, Arı M, et al. Mid-term results in the treatment of varicose veins with n-butyl cyanoacrylate. Phlebology. J Venous Dis 2017; 32: 665-9.
15. Labropoulos N, Tiongson J, Pryor L, et al. Definition of venous reflux in lowerextremity veins. J Vasc Surg 2003; 38: 793-8.
16. Duran E. Kalp ve Damar Cerrahisi, 1st ed.. İstanbul, Çapa Tıp Kitabevi; 2004.
17. Padberg FT Jr. CEAP classification for chronic venous disease. Dis Mon. 2005; 51: 176–82.
18. Gracely RH. Methods of testing pain mechanisms in normal man. In: Wall RD, Melzack R (eds). Textbook of Pain. 2nd ed. Singapore: Churchill Livingstone; 1989:257-69.
19. Kakkos SK, Rivera MA, Matsagas MI, et al. Validation of the new venous severity scoring system in varicose vein surgery. J Vasc Surg 2003; 38: 224-8.
20. Muhlberger D, Brenner E, Brockhoff H, et al. External valvuloplasty of the saphenofemoral junction in insufficient great saphenous veins - six weeks results of a prospective multicentre trial. Vasa 2020; 49: 411-7.
21. Camilli D, Platone A, Ruggeri M, et al. Use of a novel device in reconstructive venous surgery: preliminary results. Int J Angiol 2020; 29: 245-9.
22. Yavuz T, Acar AN, Yavuz K, Ekingen E. A retrospective study of deep vein insufficiencyt treatment device: ICT. Ann Vasc Dis Vol 2020; 13: 1-6.
23. Geier B, Voigt I, Marpe B, et al. External valvuloplasty in the treatment of greater saphenous vein insufficiency: a five year follow up. Phlebology 2003; 18: 137-42.
24. Saraç A, Talay S, Özkan M. İzole büyük safen ven yetmezliğinde eksternal valvüloplasti uygulaması ve uzun dönem sonuçlarımız. Turk J Vasc Surg 2012; 21: 175-80.
25. Mulhlberger D, Brenner E, Frings N, et al. Functional repair of the great saphenous vein by external valvuloplasty reduces the vein's diameter: 6-month results of a multicentre study. J Int Med Research 2020; 49: 1-9.
26. Geier B, Voigt I, Marpe B. External valvuloplasty in the treatment of greater saphenous vein insufficiency: A five-year follow up. Phlebology 2003; 18: 137-42.
27. Joh JH, Lee KB, Yun WS, Lee BB, Kim YW, Kim DI. External banding valvuloplasty for incompetence of the great saphenous vein:10 year results. Int J Angiol 2009; 18: 25-8
28. Gunaydin S, Budak AB, Gunertem OE, Ozisik K. Midterm clinical outcome of minimally ınvasive vein-restoring treatment method for chronic venous ınsufficiency. J Vasc Surg 2018; 68: 160-1.
29. Beebe-Dimmer JL, Pfeifer JR, Engle JS, Schottenfeld D. Theepidemiology of chronic venous insufficiency and varicose veins. AnnEpidemiol 2005; 15: 175-84.
30. Eroğlu E, Acıpayam M. As a New method for treatment of venous insuffciency; vein restoration treatment (Vrt). KSU Med J 2020; 15: 11-5.
31. Chiesa R, Marone EM, Limoni C et al. Chronic venous insufficiency in Italy: the 24-cities cohort study. Eur J Vasc Endovasc Surg 2005; 30: 422-9.
32. Gücü A, Erdolu B, Ay D, et al. The Evaluation of patient satisfaction with visual analog scale after treatment of varicosities with endovenous laser ablation: case series. Turk J Vasc Surg 2014; 23: 29-33.
33. Bademci MŞ, Kocaaslan C, Aldağ M, Öztekin A, Denli Yalvaç EŞ, Aydın E. Evaluation of early patient satisfaction with visual analogue scale in the treatment of isolated great saphenous vein insufficiency with n-butyl cyanoacrylate ablation. Medeniyet Med J 2018; 33: 212-7.

Original Article

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Is USG-guided aspiration more effective than physiotherapy in the treatment of Baker's cyst?

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ABSTRACT

Aim: Previous publications have described various therapeutic modalities for symptomatic cysts, including non-steroidal anti-inflammatory drugs, cystostomy, physical therapy, and exercises. The objective of thise study was to elucidate the effectiveness of shrinking the cyst without steroidal injection and to compare aspiration with classic physiotherapy and exercises.

Material and Method: This randomized, controlled trial involved 40 patients with Baker's cyst. The participants were randomized into two groups, (I) an aspiration group (n=20) and (II) a control group (n=20). In the aspiration group, Baker's cyst content was aspirated percutaneously under USG guidance, while no aspiration was performed in the control group. Pain was evaluated with a visual analog scale, while the Lysholm knee scoring scale and Cincinnati knee rating system were employed to determine functional status. Quality of life and disability were evaluated using the Nottingham Health Profile and the Western Ontario and McMaster Universities Arthritis Index .

Results: Differences were observed in USG measurements (width, length, and area) and clinical parameters before and after treatment in both groups. However, although these differences were greater in the aspiration group, they were not statistically significant.

Conclusion: Our results indicate that cyst aspiration performed with USG provides no additional effect to those of physical exercises and cold application. Exercise therapy and cold application should be considered before proceeding with an invasive procedure.

Keywords: Baker's cyst, cyst aspiration, cold pack, knee exercises, physical therapy, ultrasonography

INTRODUCTION

Popliteal cysts (PCs) were first described by Adams in 1840. However, after Baker's report of 1877, these cysts were collectively defined as Baker's cyst (BC) (1). There are six bursas around the popliteal fossa in the knee (1), all of which are expandable. The most frequently expanding bursa is the gastrocnemius semimembranosus bursa, also known as the PC or BC (2). Rauschning and Lindgren classified cysts in the popliteal region into two categories (3,4). In case of primary or idiopathic BCs, the cyst has a valvular connection with the joint space. This type of cyst is frequently seen in children and young adults and does not cause joint symptoms. Secondary or symptomatic cysts are directly related to the joint and are often symptomatic.

BCs on the knees in adult patients are often accompanied by an undefined pain and mass behind the knee. Patient also describe complaints related to intra-articular pathologies that are more associated with movement limitation in the knee, particularly during physical activity. At physical examination, the inside of the popliteal region is palpable as a round, smooth-faced, fluctuating mass that becomes apparent during extension and disappears during flexion (Foucher's sign) (5). These position-dependent changes are used for differentiating BC from other masses.

Ultrasonography (USG) and magnetic resonance imaging (MRI) are used to determine whether a popliteal region mass is solitary or cystic. Previous studies have shown that the diagnostic findings of USG are compatible with those of arthrography (6). USG is particularly valuable in differentiating between popliteal artery aneurysm, venous insufficiency, and solitary masses. MRI is a non-invasive method used for identifying accompanying pathologies, but is expensive and not easily available.

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Study Hypothesis

Previous publications have described various therapeutic modalities for symptomatic cysts, including non-steroidal anti-inflammatory drugs, cystostomy, physical therapy, and exercises.

Research to date has investigated pain, knee functions, and disability in BC. However, no studies have evaluated all these symptoms (pain, knee functions, and disability) in a single trial. This study was therefore intended to examine these parameters in the same patient population.

The objective of thise study was to determine the effectiveness of shrinking the cyst without steroidal injection and to compare aspiration with classic physiotherapy and exercises.

MATERIAL AND METHOD

This prospective, randomized study was conducted at the Atatürk University Medical Faculty Department of Physical Therapy and Rehabilitation. This study was carried out with the permission of Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Date: 03.12.2015, Decision No: 08-24). The clinical trial registry number was NCT04785014 (ClinicalTrials.gov Identifier: NCT04785014). Informed consent was obtained from all participants. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

Forty patients with symptoms of swelling at the back of the knee were included in the study. The sample size was determined with a 95% confidence interval using the G*POWER 3.1.9.7 website. Diagnosis of BC was based on the patient's medical history and USG assessment. All patients were evaluated by means of gray-scale USG using an Esaote MyLab 60 USG device with a linear probe of 7.5 MHz. The transverse diameter (width-parallel to the knee joint), longitudinal, and cyst areas were recalculated at USG examination.

The inclusion criteria were (1) diagnosis of BC confirmed via standard USG evaluation, (2) swelling or tension at palpation of the posterior aspect of the knee at physical examination, and (3) varying degrees of flexion-extension of the knee joint. Patients with (1) a history of malignancy, (2) coagulation disorders, (3) any neurological deficit, (4) receiving anticoagulant therapy, (5)with a history of previous knee surgery, or with (6) acute local or systemic infections were excluded.

After screening, 40 eligible participants were randomly divided into two groups by consecutive alternate allocation based on time of admission. The aspiration group (n=20) consisted of patients aspirated with USG-guidance, and the control group (n=20) of patients undergoing no aspiration procedure.

Outcome Measures

Prior to intervention, demographic data including sex, age, body mass index, and the affected side were collected. Pain was evaluated with a visual analog scale (VAS), and Lysholm's knee scoring scale and the Cincinnati knee rating system were employed to determine the functional status of the knee. Quality of life and disability were evaluated using the Nottingham Health Profile (NHP) and the Western Ontario and McMaster Universities Arthritis Index (WOMAC). The NHP is a questionnaire designed to measure the patient's view of his health status. All participants were evaluated before the interventions, and after one and three months.

Intervention

In the aspirated group, the popliteal fossa areas were sterilized, and BC content was aspirated from the popliteal fossa percutaneously under USG guidance with a 21-gauge needle (**Figure 1**). If the BC was septal, aspiration was performed from several different levels of the cyst so that the content could be completely emptied. In contrast, no aspiration was performed on the control group. Additionally, the participants in both groups were trained to perform exercises and were also advised to practice cold treatment for 15 min in the morning and evening for two weeks (wrapping a towel around the knee for 15 min).

Exercise Program

Both groups received exercises including range of motion exercises (extension/flexion), stretching of hamstrings, non-weight bearing exercises for gastrocnemius/soleus, muscle re-education in the form of quadriceps sets, straight leg raise, hip adduction, multiangle isometrics, ankle pumps, and heel slides.

No patient received any additional treatment during the three-month follow-up period. The success of the procedure was defined as a reduction in BC width, length, and area on sonographic measurements and decreases in the Lysholm knee scoring scale, Cincinnati knee rating system, VAS, WOMAC knee osteoarthritis index, and NHP scores.

Statistical Analysis

Statistical analysis was performed on Statistical Package for the Social Sciences for Windows version 22.0 software (SPSS,Chicago,IL,USA). Numerical variables were expressed as mean±standard deviation. The independent sample t-test was used to compare the ages of the aspirated and non-aspirated groups. The Mann-Whitney U test was applied to compare the genders of the aspirated and non-aspirated groups. One-Way ANOVA for repeated measures was used to determine differences in clinical and ultrasonographic measurements between baseline, and the first, and third-months. p-values < 0.05 were regarded as statistically significant.

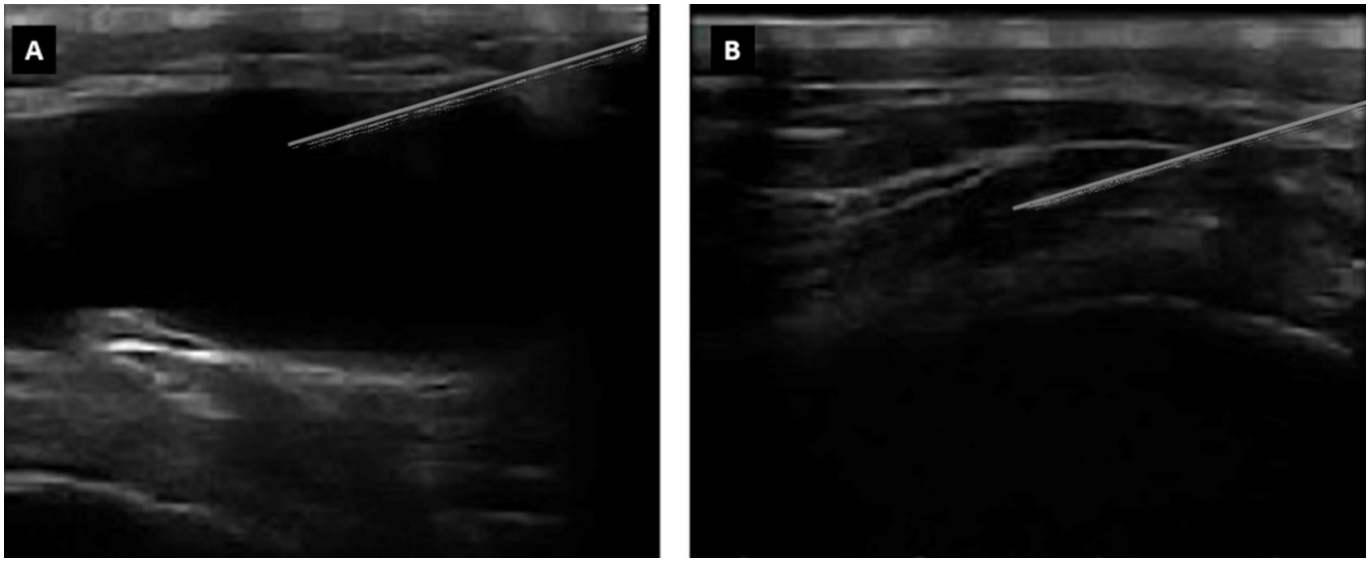

Figure 1. A-USG-guided percutaneous injection into a Baker's cyst, **B**-Aspiration of the content of a Baker's cyst

RESULTS

The study involved 40 patients (11 male, 29 female) with a mean age of 55.9±9.6 years (**Table 1**). Initial, BC width was 20.8 ±9.1 mm, length was 27.22±8.8 mm, and area was 455.75±241.9 mm² in the aspiration group. Significant differences were observed in both USG measurements (width, length, and area) and clinical parameters in both patient groups on the first and third months. While this difference was greater in the aspiration group, it was not statistically significant in the non-aspiration group. The length of the BC's decreased in both the aspirated and non-aspirated patients (Wilks' Lambda=0.79, F(2.37)=4.79, p=0.014).

A greater decrease in the length of the cysts was observed in the patients in the aspirated group, but this was not statistically significant (Wilks' Lambda=0.97, F(2.37)=.414, p=0.664). Similarly, the BC widths decreased in both the aspirated and non-aspirated patients (F(2-76)=11.24, p=0.000<0.5). Although the cyst widths decreased more in the aspirated group, the difference was again not significant (F (2-76) =.111, p=0.895>0.5). BC areas in the two groups are shown in **Table 2**. The cyst areas decreased in both groups, but not statistically significantly (F (2-76)=.460, p=0.633>0.5). VAS, WOMAC, and NHP scores also decreased in both aspirated and non-aspirated patients (**Tables 3** and **Table 4**). Although the scores decreased more in the aspirated group, this was also not statistically different. Lysholm knee and Cincinnati knee scores increased in both aspirated and non-aspirated patients (**Tables 3** and **Table 4**). Similarly, no significant difference was observed between the two groups in terms of Cincinnati knee scores or Lysholm knee scores.

Table 1. Patients' demographic parameters

	aspirated (mean±SD)	Non-aspirated (mean±SD)	p
Age (year)	59.55±8.6	52.25±9.4	0.015[a]
Gender (M/F)	6/14	5/15	0.73[b]
BMI	30.61±3.9	28.49±3.1	0.07[a]

BMI: Body Mass Index; F: Female, M: Male, SD: Standard deviation, [a]:Independent samples t-test; [b]: Chi-square (2×2) independence test

Table 2. Baker's cyst areas in the two groups

Area of BC	Groups	mean	SD	N
Baseline				
	Non-aspirated	213,1000	105,68269	20
	aspirated	455,7500	241,92841	20
	Total	334,4250	221,47847	40
First month				
	Non-aspirated	149,6655	81,73168	20
	aspirated	352,5000	240,75856	20
	Total	251,0828	205,04337	40
Third month				
	Non-aspirated	149,5610	99,59434	20
	aspirated	371,1500	248,59993	20
	Total	260,3555	218,01641	40

Table 3. Evaluation of parameters in the aspiration group at baseline, and at the first and third months

	Baseline (mean±SD)	First month (mean±SD)	Third month (mean±SD)	p
VAS	7.3±1.8	5.5±2.5	5.5±2.9	.001<p (.493)
Lysholm knee scoring scale,	48.3±17.3	60.6±23.6	64.7±24.1	.001<p (.180)
Cincinnati knee rating system,	10.4±7.2	14.6±8.6	15.8±8.3	.001<p (.121)
NHP scores.	206.6±92.8	146.2±95.3	139.2±96.6	.001<p (.273)
WOMAC	68.3±18.1	51.2±29.3	48.6±27.3	.001<p (.219)

Table 4. Evaluation of parameters in the non-aspirated group at baseline, and at the first and third months

	Baseline, (mean±SD)	First month (mean±SD)	Third month (mean±SD)	p
VAS	5.2±2.4	3.9±2.8	4.3±2.9	p< .001 (.000)
NHP scores	202.4±98.9	170.9±88.9	139.7±75.3	p< .001 (.000)
WOMAC	53.2±24.5	49.3±28.6	46.1±26.1	.001<p (.009)
Lysholm knee scoring scale,	61.6±17.2	68.6±16.8	69.9±17.6	p< .001 (.000)
Cincinnati knee rating system,	14.5±9.2	15.9±8.9	17.6±7.7	p< .001 (.000)

DISCUSSION

Synovial effusion in osteoarthritis (OA) and other intra-articular pathologies leads to an increase in intracavitary pressure, the first phase of the mechanism involved in BC formation (7). BC is a fluid-filled mass representing a distention of a pre-existing bursa in the popliteal fossa, most commonly the gastrocnemius-semimembranosus bursa. In contrast to other known periarticular bursae, this bursa is unique in that it communicates with the knee joint through an opening in the joint capsule behind the medial femoral condyle. This opening may create a valve-like mechanism in the presence of effusion. This mechanism may thus lead to the formation of these cysts in adults.

Numerous therapeutic options have been reported for popliteal cysts, particularly considering the underlying cause and associated conditions (8-14). Asymptomatic BCs and incidentally located cysts do not require any treatment. However, aspiration of the knee joint may be useful in the presence of knee effusion. Acebes et al. evaluated the sonographic changes occurring in BC after single intra-articular corticosteroid injection in patients with OA of the knee accompanied by BC. The authors concluded that USG is an ideal imaging method, not only in the diagnosis of BC but also in the evaluation of the response to treatment (7). USG was employed in the present study, since it provides procedural safety and also it is non-invasive, inexpensive, and easily accessible.

Many cases of relapse after treatment as well as successful steroid injection have been published in the literature (15). These relapses were mostly explained in terms of cysts possibly having a complex structure. Hypothesizing that aspiration alone may perhaps be sufficient, this study was intended to determine whether aspiration can be superior to conventional cold therapy and exercises.

Cold pack and exercise methods are more non-invasive and should be applied initially since they are easier for use by a physician. Cold pack therapy is a non-pharmacological method used in musculoskeletal injuries and many surgical procedures. Cold therapy produces its effect primarily by removing heat energy conduction from the injury site (16). Cold therapy produces effects such as a decrease in blood flow, reductions in edema and hemorrhage, hypoxia, a decrease in enzymatic activity, and tissue damage (17). It has also been demonstrated to significantly increase the pain threshold and pain tolerance by reducing nerve conduction velocity and muscle spasm (18). No additional drug therapy was given to our study groups, and the study design was thus unaffected.

Calvisi et al. (19) suggested that arthroscopic surgery is an effective method in the treatment of cysts and related joint diseases. That study evaluated 22 patients with BC associated with intra-articular pathologies. Over the two-year follow-up period, clinical improvement was achieved in 96% of patients, 64% of cysts disappeared on MRI, 27% of cysts were in remission, and 9% of cysts persisted. The authors concluded that arthroscopic techniques can improve BC-related symptomatology and may lead to complete loss or shrinkage of the cyst. The participants in our study were not complicated by intra-articular knee pathologies. However, surgical treatment may be considered in case of BC accompanied by intra-articular knee pathologies that require surgery, such as meniscus tears and anterior cruciate ligament tears.

Previous studies have generally used only one additional questionnaire together with VAS scores. The present study yielded a more objective evaluation by using scales that had previously been employed separately. Complaints, limitations, functional movements, and quality of life were all assessed. This resulted in a more objective approach to the patients, since rehabilitation involves approaching the patient an integral whole.

CONCLUSION

Cyst aspiration is an invasive procedure. Our results indicate that cyst aspiration performed with USG provides no additional effect to those of physical exercises and cold application. Exercise therapy and cold application should therefore be considered before proceeding with an invasive procedure.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Date: 03.12.2015, Decision No: 08-24).

Informed Consent: All patients signed the free 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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REFERENCES

1. Handy JR. Popliteal cysts in adults: a review. Semin Arthritis Rheum 2001; 31: 108-18.
2. Baker WM. On the formation of synovial cysts in the leg in connection with disease of the knee-joint. 1877.Clin Orthop Relat Res 1994; 299: 2-10.
3. Burleson RJ, Bickel WH, Dahlin DC. Popliteal cyst; a clinicopathological survey. J Bone Joint Surg Am 1956; 38-A: 1265-74.
4. Gristina AG, Wilson PD. Popliteal cysts in adults and children. a review of 90 cases. Arch Surg 1964; 88: 357-63.
5. Canoso JJ, Goldsmith MR, Gerzof SG, Wohlgethan JR. Foucher's sign of the Baker's cyst. Ann Rheum Dis 1987; 46: 228-32.
6. Scheible W. Diagnostic ultrasound. In: Diagnosis of bone and joint disorders (2nd ed) Resnick D, Niwa-yama G, eds. Phildelphia Saunders 1988; 1: 247-9
7. Acebes JC, Sanchez-Pernaute O, Diaz-Oca A, Herrero-Beaumont G. Ultrasonographic assessment of Baker's cysts after intra-articular corticosteroid injection in knee osteoarthritis. J Clin Ultrasound 2006; 34: 113-7.
8. Good AE. Rheumatoid arthritis, Baker's cyst, and "thrombophlebitis". Arthritis Rheum 1964; 7: 56-64.
9. Macfarlane DG, Bacon PA. Popliteal cyst rupture in normal knee joints. Br Med J 1980; 281: 1203-4.
10. Takano Y, Oida K, Kohri Y, et al. Is Baker's cyst a risk factor for pulmonary embolism? Intern Med 1996; 35: 886-9.
11. Kirkham B, Churchill M, Dasgupta B, Wedderburn L, Spencer J, Macfarlane DG. Anterolateral rupture of popliteal cysts in rheumatoid arthritis. Ann Rheum Dis 1991; 50: 187-8.
12. Dash S, Bheemreddy SR, Tiku ML. Posterior tibial neuropathy from ruptured Baker's cyst. Semin Arthritis Rheum 1998; 27: 272-6.
13. Scott WN, Jacobs B, Lockshin MD. Posterior compartment syndrome resulting from a dissecting popliteal cyst. Case report. Clin Orthop Relat Res 1977; 122: 189-92.
14. Nakano KK. Entrapment neuropathy from Baker's cyst. JAMA 1978; 239: 135.
15. Köroglu M, Callıoglu M, Eris HN, et al. Ultrasound-guided percutaneous treatment and follow-up of Baker's cyst in knee osteoarthritis. Eur J Radiol 2012; 81: 3466-71.
16. Cooling efficiency of 4 common cryotherapeutic agents. J Athl Train 2007; 42: 343–8.
17. Cina-Tschumi B. (Evidence-based impact of cryotherapy on postoperative pain, swelling, drainage, and tolerance after orthopedic surgery). Pflege 2007; 20: 258–67.
18. Algafly AA, George KP. The effect of cryotherapy on nerve conduction velocity, pain threshold and pain tolerance. Br J Sports Med 2007; 41: 365–9.
19. Calvisi V, Lupparelli S, Giuliani P. Arthroscopic all-inside suture of symptomatic Baker's cysts: a technical option for surgical treatment in adults. Knee Surg Sports Traumatol Arthrosc 2007; 15: 1452-60.

Original Article

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Serum 25-hydroxy vitamin D, vitamin B12 and folic acid levels in myasthenic crisis

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ABSTRACT

Aim: Myasthenia gravis (MG) is an autoimmune disease often caused by autoantibodies against postsynaptic acetylcholine receptors (AChR). It is known that vitamin D (VD), vitamin B12 and folic acid have some effects on the immune system. The aim of this study is to evaluate whether there is a difference in serum VD, vitamin B12 and folic acid levels in MG patients during the myasthenic crisis period compared to the non-crisis period.

Material and Method: 32 patients followed up with the diagnosis of MG in Atatürk University Faculty of Medicine, Department of Neurology were included in the study. Serum 25(OH)D, vitamin B12 and folic acid levels were measured by taking blood from the antecubital vein in two different time periods, during the myasthenic crisis and during the non-crisis period, and periods were compared among themselves.

Results: During the myasthenic crisis period, 25(OH)D level was 11.54 (1.08-50.33) ng/mL, vitamin B12 level was 299.5 (104-964) pg/mL, and folic acid level was 9.54±5.08 ng/mL. In the non-crisis period, 25(OH)D level was 18.74 (6.63-30.19) ng/mL, vitamin B12 level was 266 (119-678) pg/mL and folic acid level is 10.26±3.5 ng/mL. During the myasthenic crisis period, 25(OH)D vitamin levels of the patients were statistically significantly lower than the non-crisis period ($p<0.05$). There was no difference between the two periods in terms of vitamin B12 and folic acid ($p>0.05$).

Conclusion: Low VD levels can be a facilitating factor in worsening myasthenic symptoms and entering myasthenic crisis. The use of VD supplements in MG patients with low VD levels may be beneficial in terms of protection from myasthenic crisis. Despite the limitations of our study, such as the small number of patients and the fact that 25(OH)D levels were not adjusted for seasonal effects, this study is the first study showing that VD levels are lower in the myasthenic crisis period than in the non-crisis period.

Keywords: Myasthenia gravis, myasthenic crisis, 25-hydroxy vitamin D, vitamin B12, folic acid

INTRODUCTION

Myasthenia gravis (MG) is a chronic autoimmune disease caused by autoantibodies that develop against postsynaptic acetylcholine receptors (AChR) frequently at the neuromuscular junction. Most commonly, anti-AChR and anti-muscle specific tyrosine kinase (MuSK) antibodies are positive. Various degrees of muscle weakness that occurs and fluctuates in the ocular, bulbar muscles and extremity and respiratory muscles is the most important clinical feature of the disease. Myasthenic crisis can be defined as a life-threatening worsening of symptoms such as dysphagia and respiratory distress in MG. Myasthenic crisis may occur in some patients as the first manifestation of MG. The risk of myasthenic crisis is high in the first years of the disease. The risk of myasthenic crisis in patients with MG is 2-3% per year (1). Conditions such as the use of certain drugs, infection, pregnancy, surgical operation, physical stress, discontinuation of immunosuppressive drugs or reducing their dose may cause myasthenic crisis in MG patients.

Vitamin D (VD) is a steroid hormone with a cytosolic receptor. The main function of VD is to regulate calcium homeostasis and bone formation via the parathyroid glands, kidneys and intestine. Besides these critical functions in calcium metabolism, it has been shown to play a role in the modulation of the immune system (2). 25-hydroxyvitamin D (25(OH)D) is the most commonly

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measured circulating form of VD (3). The half-life of 25(OH)D is 14-21 days and it is a marker which reflects the body's VD levels and reserves. 25(OH)D level above 30 ng/mL is considered normal, between 20-30 ng/mL is considered insufficient, and below 20 ng/mL is considered as deficiency (4).

On the other hand, B group vitamins mainly serve as cofactors of enzymes involved in energy metabolism and the synthesis of organic molecules. Thanks to these functions, they play an significant role in the immune system, which consists of cells with high turnover. This is especially true for folic acid and vitamin B12, which have some functions in the nucleotide synthesis of proteins and deoxyribonucleic acid (DNA) (5,6).

Folic acid and vitamin B12 metabolism are closely related as methylcobalamin is required for the regeneration of tetrahydrofolate. Folic acid has been reported to be effective on some immune system functions (6-8).

The number of studies on vitamin levels in MG is limited. According to our research, there are no studies on VD, vitamin B12 and folic acid levels which have some effects on the immune system during myasthenic crisis. Our aim in this study is to evaluate whether there is a difference in serum VD, vitamin B12 and folic acid levels of MG patients during the myasthenic crisis period compared to the non-crisis period, and to evaluate the effect of this situation on the myasthenic crisis as a trigger.

MATERIAL AND METHOD

The study was carried out with the permission of Ethics Board of Atatürk University, Faculty of Medicine (Date: 06/33, Decision No: 30.09.2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Forty patients followed up with the diagnosis of MG in the Neurology Department of Atatürk University Faculty of Medicine were included in the study. Those younger than 18 years of age, pregnant, using corticosteroids, ocular MG patients, and using VD, vitamin B12 and folic acid supplements were excluded from the study. 3 patients were excluded from the study at their own request, due to pregnancy in 1 patient, and 4 patients using vitamin D, vitamin B12 or folic acid. The study was continued with 32 MG patients. Based on the presence of MG clinical features and neurological examination findings, detection of elevated levels of antibodies (anti-AChR or anti-MuSK antibodies), and/or electrophysiological studies (≥10% decremental response on repetitive nerve stimulation or increased jitter on single fiber electromyography), patients are given MG diagnosis was made. Anti-AChR and anti-MuSK antibody tests were performed by enzyme-linked immunoassay method. Myasthenic crisis was defined as the life-threatening worsening of myasthenic symptoms such as dysphagia and dyspnea and the need for intravenous immune globulin (IVIG), plasmapheresis or mechanical ventilation due to this worsening.

Blood was taken from the antecubital vein from the patients during two different periods which are during the myasthenic crisis and the non-crisis period. All samples were collected at 9:00 am after 12 hours of fasting. Standart straight biochemistry tubes were used to collect blood samples. After waiting for half an hour, the blood samples were centrifuged at 5000 rpm for five minutes and serum samples were obtained. Serum samples were placed in Eppendorf tubes and stored at -80°C until analysis of VD, vitamin B12 and folic acid levels. 25(OH)D, vitamin B12 and folic acid levels were measured by chemiluminescence method in Beckman Coulter UniCel Dxl 800 brand device.

Normal range of 25(OH)D level was 25-80 ng/mL, normal range for vitamin B12 level was 126.5-505 pg/mL and normal range for folic acid level was 3.1-19.9 ng/mL.

Body mass index was calculated by dividing the patient's body weight in kilograms by the square of the patient's height in meters (kg/m^2).

Statistical Analysis

Summary statistics of all participants were obtained based on the means and standard deviations for normally distributed data and, medians and min-max for non-normal distributed data. The distribution of normality was assessed with the D'Agostino-Pearson test. Continuous variables with normal distribution belonging to two groups were compared using the student t-test whereas non-normal distributed data were compared using the Wilcoxon test. A two-tailed p-value < 0,05 was considered statistically significant. All statistical analyzes were performed using Statistical Package for the Social Sciences (SPSS 20.0).

RESULTS

Thirty two MG patients were included in the study. Sixteen of the patients were male and 16 were female. The mean age of female patients was 43.3±16.8, and the mean age of male patients was 46.1±17.1. Anti-AChR antibody in 31 patients and anti-MuSK antibody in 1 patient were positive. Detailed clinical and demographic characteristics of the patients are given in **Table 1**.

Table 1. Clinical and demographic characteristics of the patients

Features	Number (n=32)
Gender (n,%)	
Woman	16 (50)
Man	16 (50)
Age (median±SD)	
Woman	44.3±14.8
Man	46.1±15.4
Disease Duration (years)	6.2±2.7
Antibody (n,%)	
Anti-AChR Positive	30 (93.8)
Anti-MuSK Positive	2 (6.2)
Treatment (n,%)	
Pyridostigmine	3 (9.3)
Pyridostigmine, Mycophenolate mofetil	5 (15.6)
Pyridostigmine, Azathioprine	17 (53.1)
Rituximab	2 (6.2)
Monthly IVIG	5 (15.6)
Body mass index (kg/m²) (median±SD)	
Man	26.03±2.2
Woman	25.11±4.1

n: number, Anti-AChR: anti-acetylcholine receptor antibody, Anti-MuSK: anti-muscle specific tyrosine kinase antibody, IVIG: intravenous immunoglobulin

25(OH)D level was determined as 11.54 (1.08-50.33) ng/mL during the myasthenic crisis period and as 18.74 (6.63-30.19) ng/mL in the non-crisis period (**Table 2, Figure 1a**) . During the myasthenic crisis period, 25(OH)D vitamin levels of the patients were statistically significantly lower than the non-crisis period ($p<0.05$).

Vitamin B12 level was found to be 299.5 (104-964) pg/mL in the myasthenic crisis period and 265 (119-678) pg/mL in the non-crisis period (**Table 2, Figure 1b**). No significant difference was observed between vitamin B12 levels in myasthenic crisis and non-crisis periods ($p>0.05$).

Folic acid level was found to be 9.54±5.08 ng/mL during the myasthenic crisis period and 10.26±3.5 ng/mL during the non-crisis period (**Table 2, Figure 1c**). In our study, no significant difference was observed in folic acid levels of MG patients in the crisis and non-crisis periods ($p>0.05$).

Table 2. Serum vitamin D, vitamin B12, folic acid levels of patients during myasthenic crisis and non-crisis periods

Level	Myasthenic Crisis Period	Non-Crisis Period	P
25(OH)D (ng/mL)	11.54 (1.08-50.33)	18.74 (6.63-30.19)	0.01*
Vitamin B12 (pg/mL)	299.5 (104-964)	266 (119-678)	0.15
Folic acid (ng/mL)	9.54±5.08	10.26±3.5	0.54

25(OH)D: 25-hydroxy vitamin D, *Statistical significance level according to Wilcoxon test

DISCUSSION

Aricha et al. (9) showed in their study which is performed with mice with experimental autoimmune myasthenia gravis disease that peripherally circulating regulatory T cells (Treg) control self-reactive T cells, leading to inhibition of the autoimmune response and play an important role in the disease process.

It is known that VD directly inhibits effector T cells and induces Treg cells to reduce the production of inflammatory cytokines. Low levels of VD have been demonstrated in some autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis and multiple sclerosis attacks (10–12). Low 25(OH)D levels have been found in coronavirus disease (COVID-19) patients and it is stated that this may be associated with musculoskeletal symptoms that may occur in COVID-19 (13).

Likewise, it has been shown that VD levels are lower in MG patients than in healthy individuals and that VD supplementation in MG patients has beneficial effects on fatigue scores (14-16). However, these studies do not reflect the myasthenic crisis period.

In our study, 25(OH) vitamin D levels of the patients were found to be lower in the myasthenic crisis period compared to the non-crisis period. The fact that VD levels are lower in MG patients compared to healthy controls and that they are found to be lower in the myasthenic crisis period than in the non-crisis period may indicate that low VD levels may be an important factor in

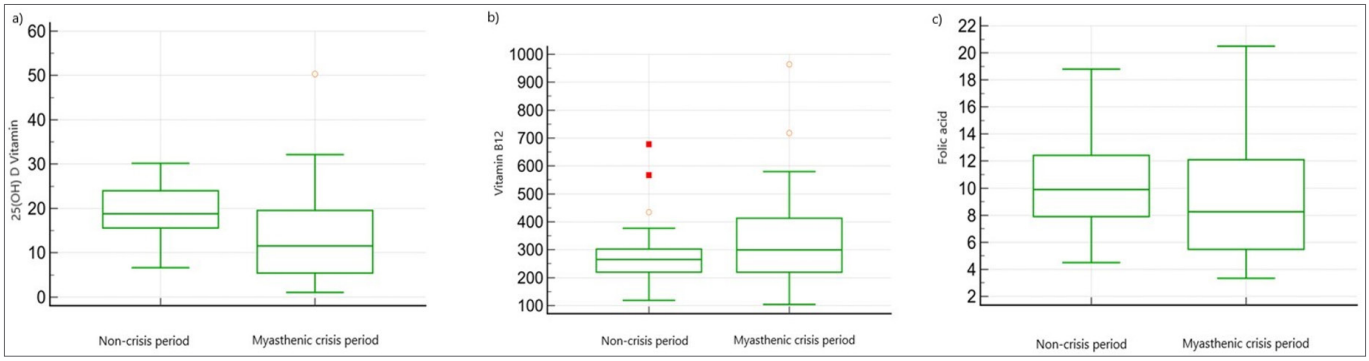

Figure 1. Serum vitamin D, vitamin B12, folic acid levels in myasthenic crisis and non-crisis periods

worsening myasthenic symptoms and myasthenic crisis. We think that low serum 25(OH) vitamin D levels in patients with MG may have reduced the inhibitory effect of Treg cells on self-reactive T cells, leading to an increase in autoimmune response and aggravation of myasthenic symptoms. In this respect, we speculate that the use of VD supplements in MG patients with low VD levels may be beneficial in terms of protection from myasthenic crisis. We believe that large-scale studies on this subject will be more beneficial. According to our evaluation, this is the first study showing that VD levels are lower in the myasthenic crisis period than in the non-crisis period.

MG may be associated with autoimmune diseases such as SLE, rheumatoid arthritis and Hashimoto's thyroiditis at a rate of 5-10% (17). The association of MG with pernicious anemia has also been reported very rarely (18,19). Anti-parietal cell and anti-intrinsic factor antibody positivity has been demonstrated in some MG patients (20,21).

However, B vitamins also have direct regulatory effects on the immune response (22). In particular, vitamin B12 has been shown to play an important role by upregulating these cells for the cytotoxic immune response mediated by both natural killer cells and CD8 (+) T cells (23). In our study, no significant difference was observed between vitamin B12 levels in myasthenic crisis and non-crisis periods. While MG is primarily a CD4 (+) T cell-dependent disease, the fact that vitamin B12 is mostly involved in natural killer and CD8(+) T cell-dependent immunogenic functions, the rare association of MG-pernicious anemia and the low number of patients in the study may have played a role in this result.

Folic acid deficiency has been associated with reduced maturation of dendritic cells (DC), lower secretion of IL-12, TNF-α, IL-6 and IL-1β by DCs, and impaired differentiation of CD4(+) T lymphocytes (6,7). In addition, high-dose oral folic acid administration in mice with atopic dermatitis has been shown to reduce T cell proliferation and reduce the inflammatory response by suppressing the secretion of proinflammatory and Th2 cytokines (IL-4, IL-5, IL-9, IL-13, IL-17, IL-33) (8). Methotrexate, a structural analogue of folic acid, is an immunosuppressive drug that acts as an antimetabolite by selectively inhibiting the dihydrofolate reductase enzyme. There are conflicting results in studies on the efficacy of methotrexate in MG patients. In some studies, it has been stated that the use of methotrexate in MG patients leads to improvement in myasthenic symptoms or a decrease in corticosteroid requirement in 38-87% of patients. The mechanism by which methotrexate provides improvement over folic acid in MG patients was not mentioned in any of these studies (24,25). Pasnoor et al. (26), in their randomized double-blind placebo-controlled study, reported that the use of methotrexate in MG patients did not reduce the dose of prednisolone needed and did not improve clinical MG scores.

The fact that no significant difference was observed in the folic acid levels of MG patients during the crisis and non-crisis periods in our study indirectly confirms the results of this study. Although our study was not primarily conducted on the pathophysiology of folic acid in MG patients, this result may indicate that the role of folic acid in the pathophysiology of MG may be limited. We believe that more extensive research on this subject will be beneficial.

CONCLUSION

In our study, VD levels were found to be significantly lower in the myasthenic crisis period than the non-crisis period. This result may indicate that low VD levels may be an important factor in worsening myasthenic symptoms and experiencing a myasthenic crisis. We speculate that the use of VD supplements in MG patients with low VD levels may be beneficial in preventing myasthenic crisis. There was no significant difference between vitamin B12 and folic acid levels between myasthenic crisis and non-crisis periods. Despite the limitations of our study, such as the small number of patients and the fact that 25(OH) D levels were not adjusted for seasonal effects, this study is the first study showing that VD levels are lower in the myasthenic crisis period than in the non-crisis period.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Board of Atatürk University, Faculty of Medicine (Date: 06/33, Decision No: 30.09.2021).

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.

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

Author Contributions: All of 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.

REFERENCES

1. Rabinstein AA, Mueller-Kronast N. Risk of extubation failure in patients with myasthenic crisis. Neurocrit Care 2005; 3: 213

2. Szodoray P, Nakken B, Gaal J, et al. The complex role of vitamin D in autoimmune diseases. Scand J Immunol 2008; 68: 261-9.
3. Holick M.F. Vitamin D deficiency. N Engl J Med 2007; 357: 266–81.
4. Doğan M, Doğan AG. Vitamin D yetersizliği ve eksikliğine güncel yaklaşım. J Health Sci Med 2019; 2: 58-61.
5. Depeint F, Bruce WR, Shangari N, Mehta R, O'Brien PJ. Mitochondrial function and toxicity: role of B vitamins on the one-carbon transfer pathways. Chem Biol Interact 2006; 163: 113-32.
6. Elmadfa I, Meyer AL. The role of the status of selected micronutrients in shaping the immune function. Endocr Metab Immune Disord Drug Targets 2019; 19: 1100-15.
7. Wu CH, Huang TC, Lin BF. Folate deficiency affects dendritic cell function and subsequent T helper cell differentiation. J Nutr Biochem 2017; 41: 65-72.
8. Makino E, Fukuyama T, Watanabe Y, et al. Subacute oral administration of folic acid elicits anti-inflammatory response in a mouse model of allergic dermatitis. J Nutr Biochem 2019; 67: 14-9.
9. Aricha R, Feferman T, Scott HS, Souroujon MC, Berrih-Aknin S, Fuchs S. The susceptibility of Aire(-/-) mice to experimental myasthenia gravis involves alterations in regulatory T cells. J Autoimmun 2011; 36: 16-24.
10. Mok CC, Birmingham DJ, Ho LY, Hebert LA, Song H, Rovin BH. Vitamin D deficiency as marker for disease activity and damage in systemic lupus erythematosus: a comparison with anti-dsDNA and anti-C1q. Lupus 2012; 21: 36-42.
11. Varenna M, Manara M, Cantatore FP, et al. Determinants and effects of vitamin D supplementation on serum 25-hydroxy-vitamin D levels in patients with rheumatoid arthritis. Clin Exp Rheumatol 2012; 30: 714-9.
12. Smolders J, Menheere P, Kessels A, Damoiseaux J, Hupperts R. Association of vitamin D metabolite levels with relapse rate and disability in multiple sclerosis. Mult Scler 2008; 14: 1220-4.
13. Dügeroğlu H. Evaluation of 25-hydroxy vitamin D levels in COVID- 19 positive patients J Health Sci Med 2021; 4: 931-5.
14. Kang SY, Kang JH, Choi JC, Song SK, Oh JH. Low serum vitamin D levels in patients with myasthenia gravis. J Clin Neurosci 2018; 50: 294-7.
15. Justo ME, Aldecoa M, Cela E, et al. Low vitamin D serum levels in a cohort of myasthenia gravis patients in Argentina. Photochem Photobiol 2021; 10.1111/php.13432. doi:10.1111/php.13432
16. Askmark H, Haggård L, Nygren I, Punga AR. Vitamin D deficiency in patients with myasthenia gravis and improvement of fatigue after supplementation of vitamin D3: a pilot study. Eur J Neurol 2012; 19: 1554-60.
17. Richman DP, Agius MA. Acquired myasthenia gravis: immunopathology. Neurol Clin 1994; 12: 273-84.
18. Chang KH, Lyu RK, Ro LS, Wu YR, Chen CM. Coexistence of pernicious anemia and myasthenia gravis--a rare combination of autoimmune diseases in Taiwan. J Formos Med Assoc 2006;105: 946-9.
19. Khademolhosseini S, Springsted E, Pourshahid S, Giri B. Coexistence of pernicious anemia and myasthenia gravis presenting as dyspnea. Cureus 2021; 13: e15295.
20. Krol TC. Myasthenia gravis, pernicious anemia, and Hashimoto's thyroiditis. Arch Neurol 1979; 36: 594-5.
21. Zittoun J, Tulliez M, Estournet B, Goulon M. Humoral and cellular immunity to intrinsic factor in myasthenia gravis. Scand J Haematol 1979; 23: 442-8.
22. Wintergerst ES, Maggini S, Hornig DH. Contribution of selected vitamins and trace elements to immune function. Ann Nutr Metab 2007; 51: 301-23.
23. Tamura J, Kubota K, Murakami H, et al. Immunomodulation by vitamin B12: augmentation of CD8+ T lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. Clin Exp Immunol 1999; 116: 28-32.
24. 24.Hartmann J, Rivner MH. Methotrexate in myasthenia gravis. Clin Neurophysiol 2009; 120: e123–e124.
25. Koźmiński P, Halik PK, Chesori R, Gniazdowska E. Overview of dual-acting drug methotrexate in different neurological diseases, autoimmune pathologies and cancers. Int J Mol Sci 2020; 21: 3483.
26. Pasnoor M, He J, Herbelin L, et al. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. Neurology 2016; 87: 57-64.

Original Article

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Analysis of "code blue" application and results: a single center experience

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ABSTRACT

Aim: This study was prepared to analyze the "Code Blue" application and results in Hitit University Erol Olçok Training and Research Hospital.

Material and Method: Whole of the code blue calls issued in our hospital in 2019 were retrospectively examined and evaluated within the framework of the necessary legal permissions. In this context, arrival time of the code blue team at the scene, CPR performance, duration, results of application and demographic information of patient, place, date and time data were collected. The obtained data were analyzed using the SPSS (Statistical Package for Social Science).

Results: Between 01.01.2019 and 31.12.2019 a total of 748 code blue notifications were evaluated. The average time for the blue code team to reach the patient was 2.06 minutes. Code blue call was made mostly in intensive care units, by nurses and in January. Patients who underwent code blue intervention 55.89% of them were male and 44.11% were female. Code blue calls were requested the most was the range of 61-80 ages. The oldest patient who received CPR was 105 years old, and the youngest was 2 years old. Besides, code blue call reason is most respiratory+cardiac arrest (243), cardiac arrest (199) and respiratory arrest (109). The results of the whole code blue interventions in 2019, it was figured out that 401 of the patients were dead, 135 of them were taken into intensive care, 173 of them were monitored in the service, 25 people were transferred to the emergency, 12 calls were wrong calls and 2 calls for exercise.

Conclusion: The internationally determined intervention period for the patient to not lose his vital functions to survive is 2 -5 minutes. As a result, code blue application in our hospital has been successfully implemented in accordance with the standards, with effective and rapid intervention.

Keywords: Code blue, cardiopulmonary arrest, survival, patient safety

INTRODUCTION

Today much progress has been made in terms of patients, patient rights and quality of care all over the world. For this purpose, new regulations and rules are being implemented by different countries. Although many countries have different standards and practices, "code blue" which indicates cardiac or respiratory arrest is used as a common medical emergency code throughout the world. And, code blue was used for the first time in the USA. In our country, code blue applications started to be implemented for the first time in 2008 within the scope of health transformation with service quality standards. Its implementation has been made compulsory in all health institutions in the scope of the Regulation on Ensuring Patient and Employee Safety made by the Ministry of Health with the regulation no 27214 and 9489 in 2009 and 2011, respectively (1).

Code blue is the international emergency code applied by a professional team to secure the basic life support process of patients who develop cardiac and/or respiratory arrest and need emergency medical attention. Patients whose basic life functions at risk such as breathing and circulation need immediate intervention is done by code blue team. That professional team at all levels receives training at regular intervals and constantly controlled has been constituted with blue code standards. In this way, critical interventions are carried out professionally by a trained and specific team according to certain standards. Besides, the emergency number of code blue is set as "2222" by the Ministry of Health.

Code blue team formed with experienced doctors, nurses and other health personnel trained in cardiopulmonary

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resuscitation (CPR). After the emergency code blue call, the code blue team arrives at the scene as soon as possible and applies CPR immediately when necessary. All information in this process is recorded in the code blue notification form. Thus, the whole process and its results become traceable.

MATERIAL AND METHOD

The study was carried out with the permission of Scientific Researches Ethics Committee of Hitit University (Date: 29.06.2020, Decision No: 2020/73). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In recent years, studies on the code blue application and its results have been carried out in many different hospitals. Hence, the strengths and weaknesses that arise in practices in different hospitals are revealed. By evaluating the results which are important in terms of guiding other hospitals, the failing aspects of the processes and the steps to be taken for improvement can be determined. In this study, the code blue application and results in 2019 at the Hitit University Erol Olçok Training and Research Hospital were analyzed.

This study was carried out at Hitit University Erol Olçok Training and Research Hospital which was replaced in its new location in 2017 and enlarged (422 rooms and 650 beds) in line with the needs. Code blue application was first started in our hospital in 2011. And this study was conducted by retrospectively analyze the code blue notification forms and records for 2019. The code blue notification form includes the patient's age, gender, scene and time of the event, arrival time of code blue team, patient intervention time and results.

Statistical Analysis

The data were analyzed with the SPSS statistical package program, and error controls, tables and statistical analyzes were made. In statistical evaluations, percentage, mean, chi-square test for categorical data according to the characteristics of the variables, t-test/Mann Whitney-U test, One-Way ANOVA/ Kruskall Wallis tests were used for measurement data. Tukey's HSD test/Mann Whitney U test will be used to determine the differences between groups in these tests. Pearson correlation analysis will be used in case of normal distribution, in the contrary case Spearman correlation analysis will be used. Means (Mean.) were given together with standard deviation (SD) (Mean±SD), $p<0.05$ was considered statistical significance. In addition, all other information, documents and experiences gained during the code blue implementation process were evaluated.

RESULTS

In this study, 748 code blue calls were assessed between January 1, 2019 - December 31, 2019. Among them, 330 (44.11%) were female and 418 (55.89%) were male. And, the age ranges of patients who were given a blue code call are as in **Figure 1**. The number of patients between the ages of 61-80 constitutes 51.87% (388) of the total number of patients. On the other hand, the number of patients in the 0-20 age range is only 4%. As can be seen from Figure1, there are many critical cases in patients over 60 years and that cases should be carefully considered. Besides, The youngest age at which CPR was applied in the code blue call was a 2 years old baby boy (alive) and the oldest age was a 105 years old female (ex).

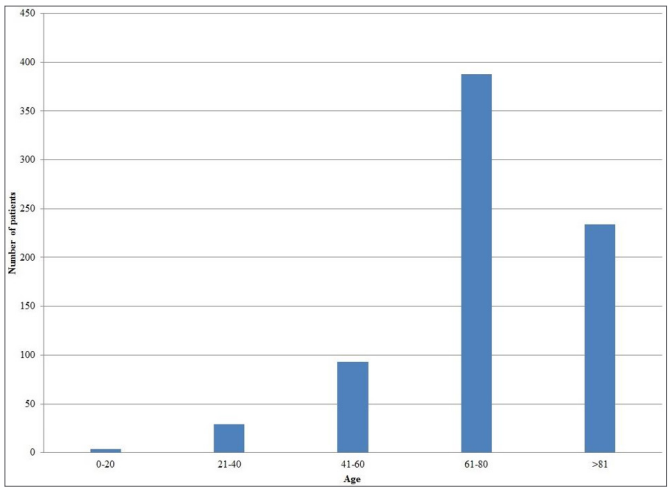

Figure 1. Age range of patients

The monthly distribution of response times to code blue calls is shown in **Figure 2**. Average response time is 2.06 minutes and it can be seen from figure this rate partially below 1 minute and in some cases reaches to 3 minutes.

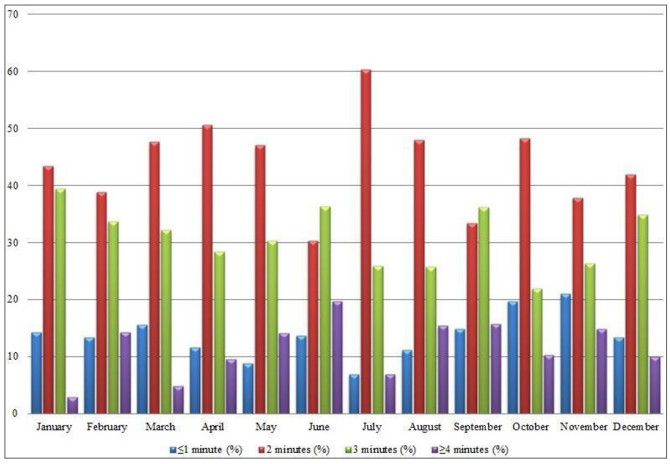

Figure 2. Monthly intervention (response) time

When obtained data were analyzed periodically, average response time was 1.99 minutes for the shortest 1st quarter and 2.16 minutes for the longest 2nd quarter. **Table 1** shows the average intervention times on a periodic (quarterly) basis.

When the total annual cases are examined, the intervention rate under <1 minute is 13.65%, the rate of intervention in <2 minutes is 43.98%, the rate of intervention in <3 minutes is 30.99%, and the rate of >4 is 11.5%. Results show that the intervention time periods are within the internationally predetermined time intervals. A statistically significant relationship was found between the intervention time and the quarters ($\chi2$=27,573; p=0,001). 81 cases (38.4%) that were intervened in <1 minutes were in the 4th quarter, 194 cases (29.0%) that were intervened in <2 minutes in the 4th quarter, 129 cases (27.0%) that were intervened in <3 minutes in the 1st quarter and It was determined that 56 cases (32.0%) that were intervened in 4 minutes/more were in the 2nd quarter. In addition, it was observed that nearly half (50.8%) of the code blue calls from intensive care services, such as internal medicine intensive care, coronary intensive care, surgical intensive care and angio intensive care services. Also, 42% of the code blue calls from services. And that calls were mostly made by nurses.

With the information given in **Table 2**, code blue calls were analyzed according to units. A statistically significant difference was found in terms of the number of codes blue calls according to the units (p=0.018). As a result of pairwise comparisons with Bonferroni correction made to determine which group the significant difference originated from; Statistically significant difference was determined between the code blue numbers coming from the service, polyclinic and single units. The number of codes blue coming from the service is statistically significantly higher than those coming from polyclinic and single units.

Table 2. Comparison of code blue calls by units

Unit	Code blue calls		Statistical analysis* probability
	$\bar{x}$±S.S	Median [Min-Max]	
Service	37.11±55.17	10.0 [1.0-213.0]	$\chi2$=7.996
Polyclinic	1.80±0.84	2.0 [1.0-3.0]	p=0.018
Single units	3.78±2.68	3.0 [1.0-9.0]	[1-2.3]

* "Kruskal-Wallis H" test ($\chi2$-table value) statistics are used to compare the measurement values of three or more independent groups in non-normally distributed data.

The results given to the blue code calls in our hospital are shown in **Table 3**. 93 (12.4%) of the code blue call requests were not intervened and the remaining 655 (87.6%) requests were intervened in the form of CPR, intubation or drug treatment.

When the blue code calls were analyzed in 3-month periods (quarter): a statistically significant relationship was found between the intervention status and the quarters ($\chi2$=16.683; p=0.001) as seen in **Table 4**. It was determined that 46 codes blue (49.5%) given in the non-intervention group were given in the 4th quarter, while in the intervention group, 164 codes blue (25.0%) were given in the 1st quarter. In the non-intervention group, the rate of code blue calls in the 4th quarter was found to be significantly higher than in the 1, 2 and 3rd quarters. It was determined that approximately 25% of the codes blue were given in each period when the distributions were homogeneous in the intervention group.

Table 1. Relationship between intervention time and quarterly

	n	%	n	%	n	%	n	%	n	%	
Quarterly											
1.	51	24.2	154	23.1	129	27.0	23	13.1	357	23.3	
2.	42	19.9	158	23.7	120	25.2	56	32.0	376	24.6	$\chi2$=27.573
3.	37	17.5	162	24.2	99	20.8	43	24.6	341	22.3	p=0.001
4.	81	38.4	194	29.0	129	27.0	53	30.3	457	29.8	

*Pearson-$\chi2$ crosstabs were used to examine the relationships between two qualitative variables.

Table 3. Summary of code blue calls

Not-intervened	8	3	4	2	3	13	5	1	8	10	14	22	93
CPR+intubation +drug treatment	79	44	41	43	65	48	50	54	43	63	63	62	655
Number of processed calls	87	47	45	45	68	61	55	55	51	73	77	84	748
Observation in the service	31	9	16	14	10	10	12	13	8	26	20	4	173
Transferrring to intensive care service	10	11	6	3	12	7	7	6	11	11	11	40	135
EX	42	24	21	28	40	36	34	34	27	34	43	38	401
Transferring to emergency polyclinic	4	3	1	0	6	1	1	2	3	1	2	1	25
Wrong call	0	0	1	0	0	6	1	0	2	1	1	0	12
Practice	0	0	0	0	0	1	0	0	0	0	0	1	2
Total	87	47	45	45	68	61	55	55	51	73	77	84	748

Table 4. Analysis of relationship between intervention and quarters

	n	%	n	%	n	%	
Quarter							
1.	15	16.1	164	25.0	179	23.9	
2.	18	19.4	156	23.8	174	23.3	χ2=16.683
3.	14	15.1	147	22.5	161	21.5	p=0.001
4.	46	49.4	188	28.7	234	31.3	

*Pearson-χ2 crosstabs were used to assess the relationship between two qualitative variables.

A statistically significant relationship was found between the type of intervention and the quarters (χ2=29.495; p=0.001) as seen in **Table 5**. It was determined that 56 interventions (32.4%) was followed-up in the service, in the 1st quarter, 62 interventions (45.9%) transferred to the intensive care unit in the 4th quarter, 14 interventions (35.9%) of the other types were in the 2nd quarter, and 115 interventions (28.7%) with Exitus were in the 4th quarter. It was determined that the interventions follow-up periods in the service were predominantly in the 1st quarter, the interventions transferred to the intensive care unit and exitus were predominantly in the 4th quarter, and other types of interventions were predominantly in the 2nd quarter.

DISCUSSION

Code blue application which stands out as a very important application in reducing the life risks of patients is mandatory in our country by the Ministry of Health. In addition, code blue application has been an important criterion in terms of health worker, patient safety and service quality standards. As it is known, code blue is a system that regulates the necessary emergency intervention to the patient in case of cardiopulmonary arrest (2). This intervention being done quickly and by a professional team directly affects the patient's chance of survival (3). As a result of the Petrie et al. study is meaningful at this point, patients mortality rate was found to be approximately 100% in cases whose response time exceeded 8 minutes (4). Another remarkable results of the studies are that the chance of survival and the rate of discharge of the patients increase with the early defibration of the code blue team (5-9). Besides, it has been found that the response rate to CPR is between 15-40% in literature, and that intervention in the first 3 minutes increases the patient's chance of survival more (6). Considering the gender status of the patients with code blue, it is seen that it is between 55-70% in male and 30-45% in females (7,9,10). If our study is compared with the literature, it will be seen that the results are similar. As a result of the code blue application carried out throughout 2019, 418 (55.89%) of 748 patients who intervened were male and 330 (44.11%) were female. It is thought that the lower incidence of coronary diseases in women than men indicates the lower number of code blue cases (11, 12). On the contrary, it is possible to see opposite examples in the literature. Such as, 60.08% of patients who underwent code blue intervention are women in Gurman et al. (13) study. In the literature, code blue response time is around 2-3 minutes (14-17). Tosyalı et al. investigated seven code blue studies between 2008 and 2014 to carry out an average response time of 1404 patients was 3.02 minutes which decreased from year to year (18). However, Ozuturk et al. (11) achieved an average arrival time to the scene of 1.10 minutes for 225 patients. But it should also be clarified that the factors affecting the duration are also directly related to the physical structure of the hospital and the locations of the polyclinics. Although the code blue response time is relatively high in big hospitals, the average time of our hospital is 2.06 minutes. Also in our study, interventions were performed for 11 patients in less than 1 minute, 200 patients within 1 minute, 271 patients within 2 minutes, 139 patients within 3 minutes, 21 patients within 4 minutes, and 14 patients within <6 minutes. In CPR applications, the shortest CPR duration is 2 minutes to a 90-year-old intensive care patient/woman (intervention is performed twice, the first is 45 minutes, then intervened again 5-10 minutes later), the longest CPR duration is 50 minutes to 61 years old oncology patient/man .

CONCLUSION

In this study, the application and results of the code blue in Hitit University Erol Olçok Training and Research Hospital were analyzed. With this study, it is aimed to make a positive contribution to the literature by examining and analyzing 748 code blue calls in detail. Within the scope of our literature review, this study evaluated the highest number of calls and results among the code blue studies conducted in our country. In addition, the results are similar between hospitals

Table 5. Assessing the relationship between the type of intervention and the quarters

	n	%	n	%	n	%	n	%	n	%	
Quarter											
1.	56	32.4	27	20.0	9	23.1	87	21.7	179	23.9	
2.	34	19.3	22	16.3	14	35.9	104	25.9	174	23.3	χ2=29.495
3.	33	19.1	24	17.8	9	23.1	95	23.7	161	21.5	p=0.001
4.	50	28.9	62	45.9	7	17.9	115	28.7	234	31.3	

*Pearson-χ2 crosstabs were used to assess the relationship between two qualitative variables.

in general regarding the code blue application in our country, but it is also observed that there is a significant difference in the data obtained according to the parameter differences. In this context, a comprehensive code blue research should be carried out for the whole of Turkey in the future, and the results should be shared and necessary analyzes should be made.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Scientific Researches Ethics Committee of Hitit University (Date: 29.06.2020, Decision No: 2020/73).

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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REFERENCES

1. Ministry of Health, Regulation on Ensuring Patient and Employee Safety, Official Gazette, 2011, R.G: 06/04/2011, number: 27897.
2. Möhnle P, Huge V, Polasek J, et al. Survival after cardiac arrest and changing task profile of the cardiac arrest team in a tertiary care center. Scientific World J 2012; 2012: 294512.
3. İncesu E. Return to life is "blue code" retrospective evaluation of notification reports of blue code section by Seydisehir State Hospital. Usaysad Derg 2018; 4: 26-39.
4. Petrie DA, De Maio V, Stiell IG, Dreyer J. Factors affecting survival after prehospital asystolic cardiac arrest in a basic life support - defibrillation system. CJEM 2001; 3:186-192.
5. Saghafinia M, Motamedi MH, Piryaie M, et al. Survival after in hospital cardiopulmonary resuscitation in a majör referral center. Saudi J Anaesth 2010; 4: 68-71.
6. Herlitz J, Rundqvist S, Bång A, et al. Is there a difference between women and men in characteristics and outcome after in hospital cardiac arrest. Resuscitation 2001; 49: 15-23.
7. Özmete, Ö. Bir üniversite hastanesinde mavi kod uygulamaları. Cukurova Med J 2017; 42: 446-50.
8. Çiçekci, F., Atıcı S. Mavi Kod çağrısına bağlı kardiyopulmoner resüsitasyon uygulamaları sonuçlarının değerlendirilmesi. Genel Tip Derg 2013; 23.
9. Oğuztürk H, Turtay MG, Tekin YK, Sarıhan E. Cardiac arrests in the emergency ward and our experiences on the cardiopulmonary resuscitation. Kafkas J Med Sci 2011; 1: 114-7.
10. Mendes A, Carvalho F, Dias C, Granja C. In-hospital cardiac arrest: factors in the decision not to resuscitate. the impact of an organized in-hospital emergency system. Rev Port Cardiol 2009; 28: 131-41.
11. Özütürk B, Muhammedoğlu N, Dal E, Çalışkan B. Evaluation of blue code interventions outcomes. Haseki Tıp Bülteni 2014; 2276: 204-8.
12. Villamaria JF, Pliego FJ, Wehbe-Janek H, et al. Using simulation to Orient Code Blue Teams to a new hospital facility. Simul Healthc 2008; 3: 209-16.
13. Gürmen ES, Demir B. Investigation of the suitability and outcome of the Blue Code Call System at an University Hospital. Van Tıp Derg 2019; 26: 353-7.
14. Esen O, Esen HK, Öncül S, Gaygusuz EA, Yılmaz M, Bayram E. Code Blue practices and evaluation of results in a training and research hospital. J Kartal TR 2016; 27: 57-61.
15. Sık G, Çıtak A. Evaluation of Code Blue Implementation and Its Outcomes in Pediatric Patients JARSS 2020; 28: 47-51.
16. Murat E, Toprak S, Doğan DB, Mordoğan F. Evaluation of code blue implementation outcomes. Med Sci 2014; 3: 1002-12.
17. Özgür Y, Albayrak MD, Results of the blue code application in chest diseases and chest surgery training and research hospital. J DEU Med 2020; 34: 35-42
18. Tosyalı C, Numanoğlu M. Mavi kod uygulaması algılaması. Sağlıkta Performans ve Kalite Dergisi 2015; 9: 66-77.

Original Article

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Anesthesia management in geriatric patients which were interventional bronchoscopy due to central airway obstruction; retrospective analysis

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ABSTRACT

Aim: In the endobronchial treatment of tumors that cause obstruction in the tracheobronchial system; Applications such as cryo-recanalization and argon plasma coagulation (APC) are widely used. Patients presenting with central airway obstruction (CAO) require urgent intervention, sharing the airway with the bronchoscopist, severe shortness of breath in patients, and the presence of comorbid diseases make it difficult for anesthetists. This situation becomes more complicated due to pharmacokinetic and pharmacodynamic changes in geriatric patients. In this article, it is aimed to present the anesthesia method in geriatric patients who underwent interventional bronchoscopy due to central airway obstruction.

Material and Method: The files of geriatric patients who underwent interventional procedures for central airway obstruction between January 2021 and September 2021 were reviewed retrospectively. The treatments applied to the patients and the applied anesthetic protocols were recorded.

Results: Forty-five geriatric patients who underwent interventional procedures for CAO were identified. 74% of the patients were male. 95.6% of the patients were in the American Society of Anesthesiologists (ASA) III or ASA IV risk group, which we can refer to as the high risk group. It was observed that rapid and short-acting propofol and remifentanil were used in induction and maintenance of anesthesia, rocuronium was used as muscle relaxant, and sugammadex was used to eliminate the residual effect of the muscle relaxant.

Conclusion: Airway management is very complex in severe life-threatening airway stenosis. This situation requires a more comprehensive preoperative evaluation, selection of appropriate short-acting anesthetics, and effective anesthetic monitoring, especially in geriatric patients. In addition, the anesthetist and bronchoscopist should be prepared and in constant communication against complications that may develop.

Keywords: Airway obstruction, anesthesia, geriatrics, interventional pulmonology, rigid bronchoscopy

INTRODUCTION

Rigid bronchoscopy, cryorecanalization and argon plasma coagulation (APC) applications are increasingly used to remove or reduce tumors that cause obstruction in the endobronchial system (1). Dilatation, stent placement, laser and electrocautery are other methods used to reduce or eliminate obstruction (2). General anesthesia is usually required during rigid bronchoscopy (3). However, patients with central airway obstruction (CAO) require urgent intervention, sharing the airway with the bronchoscopist, severe shortness of breath in patients and the presence of comorbid diseases complicate the work of anesthesiologists.

In addition, the fact that the patients are in the geriatric age group makes the work even more complicated and difficult. Geriatric patients are known to be more sensitive to anesthetic agents. It is possible to achieve the desired effect with fewer drugs in geriatric patients, and the drug effect is generally prolonged in the elderly population (4). This difference in geriatric patients is mainly due to the difference in kidney and liver metabolism and, accordingly, changes in pharmacokinetic and pharmacodynamic responses (5-7). Therefore, anesthesia management is very important in geriatric patients presenting with CAO. In this study, it was aimed to present our anesthesia management experience in the treatment of severe airway stenosis in geriatric patients.

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MATERIAL AND METHOD

The study was initiated with the approval of the Ankara Keçiören Training and Research Hospital Ethics Committee (Date: 28.09.2021, Decision No: 2012-KAEK-15/2357), our study was conducted in the 3rd level chest diseases and chest surgery center (Ankara Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration. The files of patients who underwent interventional procedures due to CAO reviewed retrospectively between January 2021 and September 2021.

Patients aged 65 and over, with ASA score of I-IV and with central airway obstruction were included in the study.

Patients under 65 years of age, patients with ASA score of V and above, and without central airway obstruction were excluded from the study.

Diagnosis, age, body mass index, gender, history of smoking and alcohol use, ASA score, pre-procedural dyspnea, presence of hemoptysis, mallampati score, concomitant diseases, lesion localizations and treatments, applied anesthetic protocols were recorded.

Data were analyzed using IBM SPSS 25.0 (Armonk, NY: IBM Corp.) statistical package software. Frequency, percentage and standard deviation were used for descriptive statistics

Anesthesia Protocol Applied in CAO

The patients were evaluated in the anesthesia outpatient clinic at least one day before the interventional procedure. After the ASA physical scores were determined, the patients who signed the written informed consent form underwent an interventional procedure.

Invasive pressure monitoring was also provided by monitoring the patients after routine preparations and performing radial artery cannulation. A 37 Fr and 39 Fr double lumen endobronchial intubation tube was kept ready in case of endobronchial bleeding. After 3 minutes of preoxygenation with 100% oxygen, 1 mg/kg 2% lidocaine, 50 mg ranitidine, 1 mg/kg methylprednisolone and 2 mg/kg propofol were administered intravenously (iv). Patients were given 40 mcg remifentanil and 0.9 mg/kg rocuronium iv. After the rigid bronchoscope was inserted into the trachea of the patients by the bronchoscopist, it was connected to the anesthesia circuit and ventilated with balloon ventilation. Anesthesia maintenance was adjusted as propofol 4-6 mg/kg/hour and remifentanil 2-3 mcg/kg/min as IV infusion. During the procedure, the hemodynamic parameters of the patients were monitored continuously and their arterial blood gases (ABG) values were followed every 10 minutes.

After the procedure was completed, 4 mg/kg sugammadex was given iv and the rigid bronchoscope was removed. After recovery, the patients were taken to the intensive care unit. Patients who were followed up with nasal O2 and had no complications and had an SpO2 value above 90% in room air were sent to the service 2 hours after the procedure.

RESULTS

Between January 2021 and September 2021, a total of 111 patients underwent interventional procedures for CAO. 47 of them were in the geriatric age group. 2 patients were excluded from the study due to missing data (**Figure**).

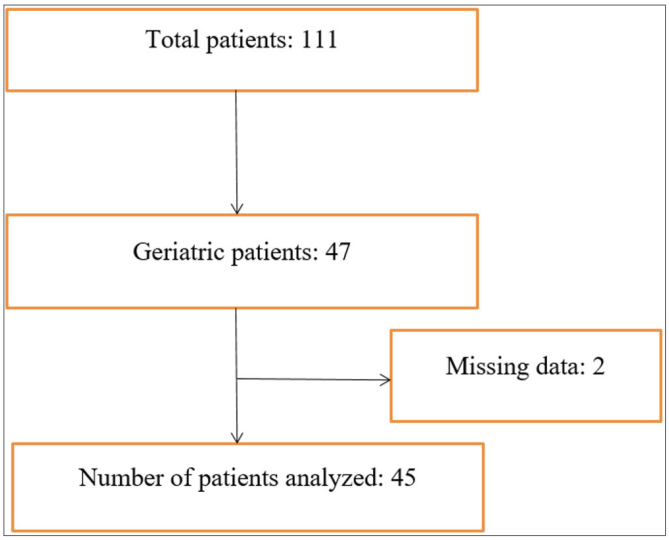

Figure. Flow chart of the patients

Demographic characteristics of patients in the geriatric age group are given in **Table 1**. 74% of the patients were male. 95.6% of the patients were in the ASA III or ASA IV risk group, which we can refer to as the high risk group. In one patient, an interventional procedure was performed under emergency conditions. While 62.2% of the patients had a history of smoking, 93.4% did not have a history of alcohol use (**Table 1**).

Table 2 shows whether the patients had dyspnea and hemoptysis before the procedure, whether they needed nasal oxygen or ventilator, their tracheostomy status and mallampati scores. While 44.4% of the patients were dependent on nasal oxygen, only 2.2% were using a home ventilator. Mallampati score was 2 or 3 in 91.1% of the patients (**Table 2**).

Additional diseases of the patients are listed in **Table 3**. **Table 4** shows the localization of the pathology causing CAO, the diagnosis of the patients and the procedures for the patients.

Table 1. Demographic characteristics of the patients

	n (%)
Gender	
Female	12 (26%)
Male	33 (74%)
Age (± SD)	71.2±5.29
BMI (± SD)	25.81±4.67
ASA	
II	2 (4.4%)
III	26 (57.8%)
IV	16 (35.6%)
IV-E	1 (2.2%)
Smoking	
Yes	11 (24.4%)
No	17 (37.8%)
left	17 (37.8%)
Alcohol use	
Yes	2 (4.4%)
No	42 (93.4%)
Left	1 (2.2%)

SD: Standart deviation; BMI: Body mass index; ASA; Amerikan Anestezistler Birliği; E: Emergency

Table 3. Additional Diseases of the Patients

	n (%)
Lung cancer	15 (33.3%)
Chronic obstructive pulmonary disease	14 (31.1%)
Past Covid-19 Infection	6 (13.3%)
Hypertension	17 (37.8%)
Coronary Artery Disease	14 (31.1%)
Arrhythmia	2 (4.4%)
Diabetes Mellitus	10 (22.2%)
Hypothyroidism	1 (2.2%)
Previous Cerebrovascular Event	3 (6.7%)
Chronic renal failure	1 (2.2%)
Extrapulmonary Cancer	9 (20%)

Table 2. Clinical characteristics of the patients

	n (%)
Dyspnea	33 (73.3%)
Nasal oxygen	20 (44.4%)
Hemoptysis	5 (11.1%)
Home ventilator	1 (2.2%)
Tracheostomy	3 (6.7%)
Mallampati	
I	3 (6.7%)
II	26 (57.8%)
III	15 (33.3%)
IV	1 (2.2%)

Table 4. Diagnosis of the patients, localization of pathology, procedure performed

	n (%)
DIAGNOSIS	
EBL	35 (77.7%)
Tracheal Stenosis	6 (13.3%)
Tracheal Fistula	2 (4.4%)
Foreign Body	2 (4.4%)
LOCALIZATION	
Trachea	14 (31.1%)
Right Main Bronchus	12 (26.6%)
Left Main Bronchus	17 (37.7%)
Bilateral	2 (4.4%)
APPLIED TREATMENT	
APC	3 (6.6%)
MTR	1 (2.2%)
APC+MTR	24 (53.3%)
Dilation	3 (6.6%)
Cryoextraction	4 (8.8%)
Cryoextraction + APC	2 (4.4%)
Cryoextraction + APC + MTR	2 (4.4%)
Biopsy	4 (8.8%)
Foreign Body removal	2 (4.4%)

EBL: Endobrochial lesion; APC: Argon plasma coagulation; MTR: Mechanical tumor resection

DISCUSSION

In geriatric patients who will undergo rigid bronchoscopy due to severe CAO, general anesthesia is often required to prevent the patient from moving. For this purpose, rapid and short-acting propofol and remifentanil are appropriate choices for induction and maintenance of anesthesia, considering the physiological, pharmacokinetic and pharmacodynamic changes in geriatric patients. It may be preferable to use fast-acting rocuronium to accelerate the passage of the bronchoscope through the vocal cords. We think that sugammadex will be a good choice for rapid recovery and elimination of the residual effect of the muscle relaxant.

The fact that both physicians use a common airway and there are air leaks during ventilation requires continuity of communication between the anesthetist and bronchoscopist during the procedure.

Interventional pulmonology has made significant advances in the diagnosis and treatment of pulmonary pathologies in recent years (8). Along with these developments, the anesthesia method to be applied is also important. In the literature, performing rigid bronchoscopy under deep sedation where spontaneous breathing is preserved is reported as an alternative to general anesthesia. However, the possibility of hypoventilation in deep sedation, laryngospasm, insufficient relaxation of the laryngeal muscles, coughing or movement of the patient complicates the insertion of the rigid bronchoscope into the trachea and the work of the team (9). However, geriatric patients presenting with CAO usually have a high rate of comorbidities. Therefore, the possibility of complications related to anesthesia is high (10,11).

A safe and controlled airway should be established before the interventional procedure. Alternative airway

equipment such as small-diameter intubation tube, double-lumen intubation tube (DLT) and high-frequency jet ventilator should be ready for acute complications such as bleeding, pneumothorax, and airway obstruction (9). Massive bleeding, especially during the procedure, is a serious life-threatening complication. In this case, DLT, which is frequently applied in our clinic, can be life-saving.

Especially in cases with severe stenosis with limited reserves, hypoxia and cardiopulmonary arrest may develop after the compensation mechanisms are depressed (12). In addition, it should be kept in mind that masses located in the anterior mediastinum may cause tracheal obstruction and sudden cardiovascular collapse during induction due to compression in the supine position (13). For these reasons, the anesthesia method to be preferred should create a rapid and sufficient level of anesthesia, and at the same time, short-acting anesthetic drugs that will provide rapid recovery should be selected (14).

Total intravenous anesthesia (TIVA) should be considered as the first option in the maintenance of anesthesia instead of inhalation anesthesia for reasons such as air leaks in ventilation with a rigid bronchoscope and the need for apnea periods during the procedure (9). Propofol and remifentanil infusion are frequently used together in TIVA due to the short half-life and rapid recovery of patients.

The adequacy of ventilation should be checked with SpO2 and end-tidal CO2 monitoring. The presence of hypercapnia is a strong indicator for inadequate ventilation (14). However, the presence of air leaks requires the end-tidal CO2 value to be measured with an accurate technique. Transcutaneous CO2 has been used for hypercapnia monitoring in recent years. However, in cases where this technique cannot be applied, it is very important to monitor acid-base balance, pCO2 and pO2 with ABG analysis at regular intervals. Invasive arterial monitoring will be useful for close ABG monitoring and instant hemodynamic evaluation.

Bispectral index monitoring can be used as an appropriate method for the evaluation of depth of anesthesia (15,16). In addition, TOF (train of four) monitoring may be useful in these patients for the evaluation of neuromuscular blockade efficiency (17). It was seen that these techniques were not used in our study, but we think that the use of these two techniques would be beneficial in terms of increasing anesthesia safety.

Reversing the effect of post-procedure muscle relaxants with neostigmine is a frequently used method. Sugammadex, on the other hand, reverses the effect of muscle relaxation faster than neostigmine. In addition, cholinergic side effects are not observed and residual muscle relaxant effects are less common (18,19).

CONCLUSION

As a result, anesthesia management in airway stenosis becomes complicated because the anesthetist and bronchoscopist use the airway together and the procedure is high-risk. Addition of physiological, pharmacokinetic and pharmacodynamic changes and comorbidities in geriatric patients to this situation can put a strain on the anesthetist. Therefore, a comprehensive preoperative evaluation, selection of appropriate short-acting anesthetics, effective anesthetic monitoring, and good perioperative communication with the operating team are very important in preventing complications in geriatric patients.

ETHICAL DECLARATION

Ethics Committee Approval: The study was initiated with the approval of the Ankara Keçiören Training and Research Hospital Ethics Committee (Date: 28.09.2021, Decision No: 2012-KAEK-15/2357).

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 of 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.

REFERENCES

1. de Lima A, Kheir F, Majid A, Pawlowski J. Anesthesia for interventional pulmonology procedures: a review of advanced diagnostic and therapeutic bronchoscopy. Can J Anaesth 2018; 65: 822-36.
2. Okiror L, Jiang L, Oswald N, et al. Bronchoscopic management of patients with symptomatic airway stenosis and prognostic factors for survival. Ann Thorac Surg 2015; 99: 1725-30.
3. Bakan M, Topuz U, Umutoglu T, et al. Remifentanil-based total intravenous anesthesia for pediatric rigid bronchoscopy: comparison of adjuvant propofol and ketamine. Clinics (Sao Paulo) 2014; 69: 372-7.
4. Kanonidou Z, Karystianou G. Anesthesia for the elderly. Hippokratia 2007; 4: 175-7.
5. Cavalieri TA. Managing pain in geriatric patients. J Osteopathic Med 2007; 107: E10-E16.
6. Gloth FM 3rd. Pain management in older adults: prevention and treatment. J Am Geriatr Soc 2001; 49: 188-99.
7. Cavalieri TA. Pain management in the elderly. J Am Osteopath Assoc 2002; 102: 481-5.
8. Arias S, Lee HJ. The future of interventional pulmonology. Semin Respir Crit Care Med 2014; 35: 6.

9. Dincq AS, Gourdin M, Collard E, et al. Anesthesia for adult rigid bronchoscopy. Acta Anaesthesiol Belg 2014; 65: 95-103.
10. Chadha M, Kulshrestha M, Biyani A. Anaesthesia for bronchoscopy. Indian J Anaesth 2015; 59: 565-73.
11. Putz L, Mayné A, Dincq AS. Jet Ventilation during Rigid Bronchoscopy in Adults: A Focused Review. Biomed Res Int. 2016; 2016: 4234861.
12. Ramaswamy AH, Kurdi MS, Shaikh SI, Deva RS, Raza SU. Awake rigid bronchoscopy for post intubation tracheal stenosis. Anaesth Pain & Intensive Care 2014; 18: 299-301.
13. Bolliger CT, Mathur PN, Beamis JF, et al. ERS/ATS statement on interventionalpulmonology. European Respiratory Society/ American Thoracic Society. Eur Respir J 2002; 19: 356-73.
14. Salman Önemli C, Çatal DA. Trakeal Stenozun Rijit Bronkoskop ve Balon Dilatasyonla Tedavisinde Total İntravenöz Anestezi Kullanımı: Dört Olgunun Sunumu. GKDA Derg 2015; 21, 4: 174-9.
15. Avidan MS, Zhang L, Burnside BA, et al. Anesthesia awareness and the bispectral index. N Engl J Med 2008; 358: 1097-108.
16. Zorrilla-Vaca A, Healy RJ, Wu CL, Grant MC. Relation between bispectral index measurements of anesthetic depth and postoperative mortality: a meta-analysis of observational studies. Can J Anaesth 2017; 64: 597-607.
17. Arıkan M, Ulus F, Sazak H, Şavkıoğlu E, Pehlivanoğlu P, Cengiz Z. Yaşlılığın rokuronyum ile sağlanan nöromüsküler bloğa etkisinin train of four (TOF) ve posttetanik count (PTC) ile değerlendirilmesi. Ortadoğu Tıp Dergisi 2011; 3: 61-5.
18. Honing G, Martini CH, Bom A, et al. Safety of sugammadex for reversal of neuromuscular block. Expert Opin Drug Saf 2019; 18: 883-91.
19. Brueckmann B, Sasaki N, Grobara P, et al. Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study. Br J Anaesth 2015; 115: 743-51.

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The effects of D-dimer high rates on prognosis and mortality in chronic obstructive respiratory disease

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ABSTRACT

Aim: We aim to answer the question of "Can D-dimer be an indicator of prognosis and mortality in COPD exacerbations?" by doing retrospective research on the prognosis and mortality of patients who had high D-dimer levels in COPD exacerbations with no thromboembolism detected.

Material and Method: Our research is retrospective and cross-sectional. A total of 115 patients who had applied to our hospital between January 2018 and January 2019 with COPD acute exacerbations and who had higher D-dimer levels detected than the 0.44 mg/L upper limit of our hospital's laboratory are included in this research. All patients have been previously diagnosed with COPD by a pulmonologist and have been undergoing treatment. Patients under the age of 18, patients whose information was not accessible through their files, pregnant patients, patients who have not been diagnosed with COPD by a pulmonologist, patients who had been diagnosed with lung malignancy through pathology, patients where pulmonary embolism was detected through pulmonary CT angiography, patients with renal function test disorder and patients with known renal failure are not included in this study.

Results: A total of 115 patients were included in the study. Patients who developed mortality had statistically significant lower levels of OSAS, higher rates of pneumonia, anemia, and liver failure, higher numbers of applications to emergency services in 1 year, higher numbers of hospitalizations due to COPD acute exacerbations in 1 year, higher numbers of intensive care unit admissions due to COPD acute exacerbations in 1 year and lower survival time. In addition, patients who developed mortality had statistically significant lower rates of group B and C and higher rates of group D according to the classification of Global Initiative of Chronic Obstructive Lung Disease (GOLD). Although the D-dimer levels were higher in patients who developed mortality, there were no statistically significant differences between groups. No significant cut-off value for D-dimer was calculated.

Conclusion: As a result, although our study has found higher D-dimer levels in patients who develop mortality, these results were not statistically significant.

Keywords: COPD, D-dimer, mortality, prognosis

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airway obstruction and it causes chronic airway inflammation (1,2). COPD is one of the most common reasons for mortality, hospitalization, and repeated visits to hospitals worldwide (1,3). It is the 3rd most common cause of death in the world and 4th in Turkey (4). Due to its high mortality, morbidity rates, and high costs, a global initiative named Global Initiative for Chronic Obstructive Lung Disease (GOLD) and a burden group called Burden of Obstructive Lung Disease (BOLD) have been established against COPD (4,5). The studies conducted by these groups show that the COPD prevalence and burden keeps increasing and it might turn into larger scales in the future (4,5). COPD characteristically progresses with acute exacerbations and these exacerbations increase mortality and morbidity (1-3). Acute exacerbations are related to the mortality rates of patients in hospitals and their prognosis in the long term (6). This creates a need for laboratory biomarkers that can be correlated with acute exacerbations and that should be easily accessible (6-9). COPD acute exacerbations can occur due to pneumonia, additional diseases, seasonal or thromboembolism-related incidents (1-3,10). In the course of COPD, it is common for thromboembolism incidents to occur which are related to hypoxemia and

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carbon dioxide retention caused by hypercoagulation (11). It is known that D-dimer is a biomarker for in vivo thrombin and plasmin activation which are used in the prediction and prognosis of thromboembolism incidents (11). However, only a few studies have researched the prognostic importance of D-dimer on acute exacerbated COPD patients who have high rates of D-dimer with excluded pulmonary thromboembolism. In our study we planned to research the effects D-dimer has on prognosis and 1-year survival on patients who have high D-dimer rates detected during COPD acute exacerbations and who have excluded pulmonary thromboembolism.

MATERIAL AND METHOD

Patients who have applied to our hospital between January 2018 and January 2019 with COPD acute exacerbations and who had higher D-dimer levels detected than the 0.44 mg/L upper limit of our hospital's laboratory have been scanned and 115 patients who have met the requirements of our study have been included in the study. All patients have been previously diagnosed with COPD by a pulmonologist and have been undergoing treatment. Patients under the age of 18, patients whose information was not accessible through their files, pregnant patients, patients who have not been diagnosed with COPD by a pulmonologist, patients who had been diagnosed with lung malignancy through pathology, patients where pulmonary embolism was detected through pulmonary CT angiography, patients with renal function test disorder and patients with known renal failure are not included in this study.

D-dimer levels were limited to an upper limit of 0.44 mg/L according to our hospital's cut-off value. Complete blood count, routine biochemistry, C Reactive protein, arterial blood gas, thorax X-Ray screening have been performed on all patients as part of the standard protocol and have been evaluated in terms of pulmonary thromboembolism (PTE) according to Modified Wells criteria (12). All patients who had a Pulmonary CT (Computed Tomography) angiography and embolism were excluded. In patients with contrast agent allergies, the embolism was excluded by V/Q (ventilation/perfusion scintigraphy).

Demographic data of patients such as their age, gender, use of cigarettes, or comorbid diseases were recorded. Whether the patients received additional corticosteroid, antibiotic, nasal oxygen, or non-invasive mechanical ventilation treatments during their hospitalizations were analyzed and the intensity of the acute exacerbations was determined. Patients were classified as mild acute exacerbations, those who did not receive these treatments, moderate acute exacerbations, those who had steroids and antibiotics and severe acute exacerbations, those who received steroids, antibiotics, nasal O2, and non-invasive mechanical ventilation treatments. The prognosis of the patients was evaluated according to the number of their applications to the emergency service in 1 year, their hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year, and their admission to intensive care units with COPD acute exacerbations in 1 year. The patients were classified according to GOLD criteria and grouped as A-B-C-D (13).

The data will be evaluated in the IBM SPSS Statistics 25.0 package program. Unit number (n), percentage (%), average±standard deviation (), Median (Q1-Q3) values will be provided as part of descriptive statistics. In the evaluation of categorical variables, the Pearson Chi-Square test will be used. For the continuous variables' evaluation Shapiro Wilk, normality test, and Q-Q graphics will be used. When comparing the continuous variables of two groups, the Unpaired T-Test will be used for variables with normal distribution and the Mann-Whitney U test will be used for variables with non-normal distribution. While comparing the continuous variables of three or more groups, the homogeneity of variances with normal distribution will be analyzed with the Levene Test. If the variances are homogenous single direction variance analysis will be used and if the variances are not homogenous the Welch Test will be used. For non-normal distributed variables Kruskal-Wallis analysis will be applied. As a multi comparison test, for the normally distributed variables, if the variances are homogenous Tukey HSD and if the variances are not homogenous Games-Howell will be used, and for the non normally distributed variables Dunn-Bonferroni test will be used. To determine the relationship between two numeric values, normally distributed variables will use Pearson, and non-normally distributed variables will use Spearman correlation analysis. To identify risk factors, the logistic regression model will be analyzed. For univariate analyses, any variables with $p<0.1$ value will be included in the logistic regression model. The appropriateness of the logistic regression model will be analyzed with the Hosmer-Lemeshow test. The diagnostic performance of the test will be evaluated by drawing ROC (receiving operating characteristics) curves. The threshold value will be determined with the Youden index and the sensitive, specific, positive predictive and negative predictive values will be calculated based on the predetermined threshold value. ($p<0.05$ value will be considered statistically significant.)

Necessary permissions for our study were granted by the decision (Date: 26.10.2021 Decree no. 2012-KAEK-15/4207) of the Clinical Studies Ethics Comittee of Health Sciences University Ankara Keçiören Educational and Research Hospital.

RESULTS

The demographic data, general features, and comorbidity situations of the patients included in this study are shown in **Table 1**. The average age for the patients was 68.57±10.16 and 79 of the patients (68.7%) were male. During their hospitalization 96.5 % (n=111) received systemic steroids, 87.0% (100 patients) received antibiotics, 96.5% (111 patients) received nasal oxygen and 24.3% (28 patients) received non-invasive mechanical ventilation treatment.

Table 1. Demographic data, general features and comorbidity situations

Patient Features (n=115)	Rates n (%)
Gender	
Female	36 (31.3%)
Male	79 (68.7%)
Age (Year)	68.57±10.16
Smoking	
Non-smoker	24 (20.9%)
Active Smoker	19 (16.5%)
Quit	72 (62.6%)
Diabetes Mellitus	42 (36.5%)
Hypertension	53 (46.1%)
Obstructive Sleep Apnea Syndrome (OSAS)	15 (13.0%)
Coronary artery Disease	29 (25.2%)
Congestive Heart Failure	19 (16.5%)
Cardiac Arrhythmia	5 (4.3%)
Dementia	1 (0.9%)
Previous Cerebrovascular Accident	2 (1.7%)
Epilepsy	1 (0.9%)
Malignancy	1 (0.9%)
Moderate-Severe Kidney Failure	3 (2.6%)
Pneumonia	80 (69.6%)
Systemic Steroid Use During Hospitalization	111 (96.5%)
Antibiotic Use During Hospitalization	100 (87.0%)
Oxygen Support Need During Hospitalization	111 (96.5%)
Non-Invasive mechanical ventilation support use During Hospitalization	28 (24.3%)
COPD exacerbation intensity	
Mild Acute Exacerbation	-
Moderate Acute Exacerbation	4 (3.5%)
Severe Acute Exacerbation	111 (96.5%)
Number of applications to the emergency service in 1 year	3 (1-112)
Number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year	2 (1-18)
Number of admission to intensive care units with COPD acute exacerbations in 1 year.	0 (0-6)
Decompensated Respiratory Failure in Application Artery Blood Gas Analysis	98 (85.2%)
GOLD Classification	
B	21 (18.3%)
C	49 (42.6%)
D	45 (39.1%)
Creatinin	0.82 (0.51-19)
D-dimer	1.4 (0.1-13.2)
Survival Time (Month)	28.97 (1.53-39)

Continuous variables are expressed as either the mean±Standard deviation (SD) or median (minimum-maximum value) and categorical variables are expressed as either frequency (percentage).

Acute exacerbation intensity was determined after analyzing whether the patients have received intravenous methylprednisolone, antibiotic, nasal oxygen, or non-invasive mechanical ventilation treatments during their hospitalization. No patients with mild acute exacerbations were hospitalized. The number of patients with moderate acute exacerbations was 4 (3.5%) and the number of patients with severe acute exacerbations was 111 (96.5%).

Among the patients that were included in this study, Pulmonary CT angiography examination to 110 (95.7%) of patients and Pulmonary ventilation/ perfusion (V/Q) examination to 15 (13.0%) patients were made. Pulmonary thromboembolism (PTE) was excluded in all patients. All patients that have received V/Q examination were reported with a low possibility of PTE.

Patients were evaluated according to GOLD criteria and classified as A-B-C-D groups. Among the patients that have applied to the hospital, group A patients were non-existent. 21 (18.3%) Group B, 49 (42.6%) Group C and 45 (39.1%) Group D patients were present. The average survival time for the patients included in this study was 28.97 (1.53-39) months.

In **Table 2**, the mortality rates of 115 patients with COPD acute exacerbations, who were included in this study, were compared in terms of related factors. According to the table, in patients that have developed mortality, the frequency of OSAS (p=0.008) was lower, frequency of pneumonia (p=0.033) was higher, the number of applications to the emergency service in 1 year, the number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year and the number of admission to intensive care units with COPD acute exacerbations in 1 year were higher and the survival time was lower (respectively p=0.003, p=0.003, p<0.001 ve p<0.001) on statistically significant levels. In addition, with patients that have developed mortality and were classified according to GOLD classification, the rate of Group B and C patients were lower and the rate of Group D patients was higher and these rates were statistically significant (p<0.001).

Although D-dimer levels were higher in patients that have developed mortality, no statistically significant differences were found between the groups (p=0.128) (**Figure**).

To determine the factors that predict survival in COPD patients with acute exacerbations, univariate cox regression analysis was applied. As we had a monitoring period we have used cox regression instead of logistic regression. It was seen that the variants with p<0.05 value were able to predict or foresee survival (**Table 3**).

Table 2. The comparison of mortality rates in terms of related factors

Patient features (n:115)	Mortality (+) (n : 43)		Mortality (-) (n : 72)		p
	n	%	n	%	
Gender					0.544
Female	12	(27.9%)	24	(33.3%)	
Male	31	(72.1%)	48	(66.7%)	
Age (year)	70.77±10.90		67.26±9.53		0.073
Smoking					0.794
Non-smoker	10	(23.3%)	14	(19.4%)	
Active smoker	6	(14.0%)	13	(18.1%)	
Quit	27	(62.8%)	45	(62.5%)	
Diabetes mellitus	16	(37.2%)	26	(36.1%)	0.906
Hypertension	19	(44.2%)	34	(47.2%)	0.752
Obstructive sleep apnea syndrome	1	(2.3%)	14	(19.4%)	0.008
Coronaryartery disease	11	(25.6%)	18	(25.0%)	0.945
Congestive heart failure	8	(18.6%)	11	(15.3%)	0.642
Cardiac arrhythmia	1	(2.3%)	4	(5.6%9	0.649
Dementia	1	(2.3%)	-		0.374
Pneumonia	35	(81.4%)	45	(62.5%)	0.033
Systemic steroid use during hospitalization	43	(100%)	68	(94.4%)	0.295
Antibiotic use during hospitalization	39	(90.7%)	61	(84.7%)	0.357
Oxygen support need during hospitalization	42	(97.7%)	69	(95.8%)	0.999
Non-invasive mechanical ventilation support use during hospitalization	15	(34.9%)	13	(18.1%)	0.042
Moderate-severe kidney failure	-		3	(4.2%)	0.292
COPD exacerbation intensity					0.999
Moderate acute exacerbation	1	(2.3%)	3	(4.2%)	
Severe acute exacerbation	42	(97.7%)	69	(95.8%)	
Number of applications to the emergency service in 1 year	5 (1-112)		3 (1-22)		0.003
Number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year	2 (1-18)		2 (1.11)		0.003
Number of admission to intensive care units with COPD acute exacerbations in 1 year.	0 (0-6)		0 (0.3)		<0.001
Application artery blood gas analysis					0.727
Decompensated	7	(16.3%)	10	(13.9%)	
Compensated	36	(83.7%)	62	(86.1%)	
Gold classification					<0.001
B	2	(4.7%)	19	(26.4%)	
C	14	(32.6%)	35	(48.6%)	
D	27	(62.8%)	18	(25.0%)	
Creatinin (mg/dL)	0.8 (0.53-19)		0.84 (0.51-1.67)		0.422
D.Dimer (mg/L)	1640 (600-11900)		1305 (100-13200)		0.128
Survival Time (Month)	15.8 (1.53-36.87)		30.77 (23.27-39)		<0.001

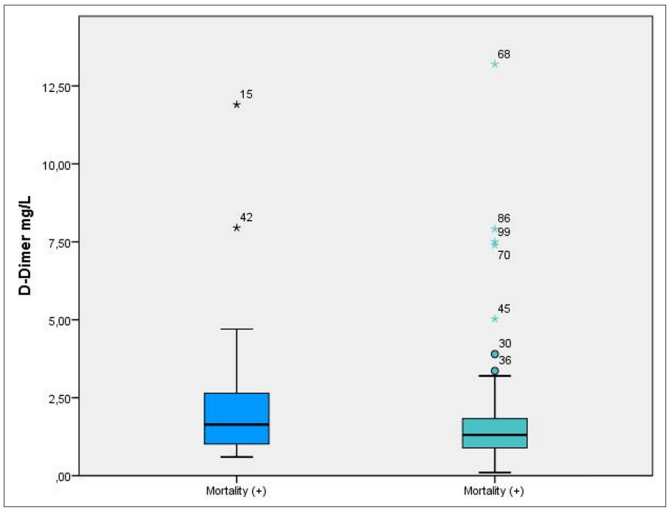

Figure. Box plotsgraphicforD-dimer in terms of mortality development.

Pneumonia existence, increase in the number of hospitalization in the pulmonary diseases unit with COPD acute exacerbations and the number of admission to intensive care units with COPD acute exacerbations, non-existence of OSAS, and survival rates of D compared to B according to GOLD classification is lower and all these predict mortality.

The p-value of <0.25, which was marked with bold, in the univariate cox regression analysis has been included in the multivariate cox regression analysis as well. D-dimer, which is the main subject of the study, was not included in the multivariate analysis as no p>0.25 value has been detected in the univariate analysis. In the multivariate analysis, the backward LR method has been used. In the table below, the first step results of all the variants included in the analysis are given first and then the 5th step results, which are the most significant model, are given (**Table 4**). An increase in the number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations and the number of admission to intensive care units with COPD acute exacerbations are considered as the predictive or foreseeing incidents in the decrease of survival. Pneumonia remains outside of the limit of significance.

Table 3. The univariate coxregression analysis that was applied to identify the variables that predict survival in COPD patients

Univariate cox regression	Wald	p	HR	95.0% CI for HR
Age	3.526	0.060	1.030	(0.999-1.063)
Gender (ref: female)	1.008	0.315	1.408	(0.722-2.745)
Smoking (ref: non-smoker)				
Active smoker	0.107	0.744	0.844	(0.306-2.327)
Quit	0.035	0.852	0.933	(0.451-1.930)
D-dimer level	0.596	0.440	1.051	(0.927-1.191)
Creatinin level	2.687	0.101	1.101	(0.981-1.235)
Diabetes mellitus	0.002	0.962	1.015	(0.547-1.884)
Hipertansion	0.078	0.780	0.918	(0.503-1.676)
Obstructive sleep apnea syndrome (OSAS)	4.447	0.035	0.118	(0.016-0.860)
Coronaryartery disease	0.004	0.952	1.021	(0.515-2.026)
Congestive heart failure	0.331	0.565	1.254	(0.581-2.707)
Cardiac arrhythmia	0.351	0.554	0.549	(0.076-3.993)
Dementia	0.852	0.356	2.551	(0.349-18.624)
Pneumonia	4.630	0.031	2.328	(1.078-5.024)
Systemic steroid use during hospitalization	0.919	0.338	1.732	(0.040-3.091)
Antibiotic use during hospitalization	1.366	0.242	1.851	(0.659-5.195)
Oxygen support need during hospitalization	0.208	0.648	1.588	(0.218-11.576)
Non-invasiv emechanical ventilation support use during hospitalization	2.894	0.089	1.724	(0.920-3.230)
COPD exacerbation intensity (ref: moderate acute exacerbations)	0.208	0.648	1.588	(0.218-11.576)
Moderate-severe kidney failure	0.559	0.455	0.048	(0.000-139.927)
Number of applications to the emergency service in 1 yearwith COPD acute exacerbations	3.656	0.056	1.012	(1.000-1.024)
Number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year	5.084	0.024	1.093	(1.012-1.180)
Number of admission to intensive care units with COPD acute exacerbations in 1 year.	13.424	<0.001	1.446	(1.187-1.761)
Application artery blood gas analysis (ref: decompensated)	0.005	0.944	0.972	(0.432-2.187)
GOLD Classification				
C	3.047	0.081	3.746	(0.850-16.500)
D	10.361	0.001	10.832	(2.539-46.212)

Wald: test statistics, HR: hazardradio, CI: ConfidentalInterval

Table 4. The multivariate cox regression test which was applied in order to identify the variables that predict survival in COPD patients.

Multivariate cox regression		Wald	p	HR	95.0% CI for HR	
Step 1	Age	16.157	<0.001	1.080	1.040	1.121
	Creatinin level	3.462	0.063	1.123	0.994	1.269
	Pneumonia	3.474	0.062	2.575	0.952	6.963
	Antibiotic use during hospitalization	0.487	0.485	.639	0.181	2.251
	Non-Invasive mechanical ventilation support Use During Hospitalization	1.202	0.273	1.460	0.742	2.875
	Number of applications to the emergency service in 1 year	0.820	0.365	1.011	0.987	1.037
	Number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year	2.738	0.098	1.150	0.975	1.356
	Number of admission to intensive care units with COPD acute exacerbations in 1 year.	14.673	0.000	1.632	1.270	2.096
Step 5	Age	14.521	<0.001	1.071	1.034	1.109
	Pneumonia	2.853	0.091	1.990	0.895	4.420
	Number of hospitalizations in the pulmonary diseases unit with COPD acute exacerbations in 1 year	11.386	0.001	1.204	1.081	1.342
	Number of admission to intensive care units with COPD acute exacerbations in 1 year.	16.485	<0.001	1.662	1.301	2.125

Wald: test statistics, HR: hazardradio

When the study population was divided into two according to the median (median 1400 mg/L) of D-dimer value, the Kaplan-Meier curve was used to determine the survival rate between the groups, and the log-rank tests were applied to find out whether there are any differences between the groups in terms of survival. According to the D-dimer median value,there are no statistically significant differences between the groups in terms of survival (p>0.05). Whether D-dimer can make a distinction between those who develop mortality and those who don't and whether a cut-off value can be given to determine mortality for D-dimer has been evaluated. According to the results, the area that remains below the curve for mortality in the D-dimer level is 0.585 and this value has no statistical significance (p=0.128). Therefore a D-dimer cut-off value could not be calculated.

In addition, after dividing the groups into two according to the D-dimer median, there have been no statistically significant differences between the two groups in terms of the comparison made between demographic features, additional diseases, and all variables that are present in **Table 1** and **2**.

DISCUSSION

The studies in the literature show that D-dimer levels can be related to many diseases and it can be used in the prognosis (14-20). The thrombotic incidents that occur in COPD are explained by carbon dioxide retention and hypercoagulation (11,21,22). It is known that thromboembolism is one of the most common causes of COPD acute exacerbations (1-3). D-dimer is used as a biomarker for thromboembolism incidents (11).

In a study conducted by Christian H. Nickel et al. (14), the 90-day survival of patients with high D-dimer levels that have been applied to emergency services has been examined. It has been observed that these patients were diagnosed with venous thromboembolism, cancer, anemia, or infection and 8.1% of the patients were confirmed dead within the first 90 days. In another study, 30 days and 365 days survival of the patients were examined and it has been observed that 9 patients with high D-dimer levels died within 30 days and 60% of the patients with high D-dimer levels died within 365 days (15). In our study, while the patients who developed mortality had higher D-dimer levels, there were no statistically significant differences between the groups.

In a study conducted by Guoping Hu et al. (11), D-dimer is detected to be a risk factor in terms of hospital mortality and 1-year mortality. Oren Fruchter et al. (6) have also discovered in a study that high D-dimer levels were significant when showing mortality. The study we have conducted shows that there is a relation between mortality and pneumonia, an increase in hospitalization and admission to intensive care units in 1 year due to COPD acute exacerbations, non-existence of OSAS, and being in Group D in GOLD classification. The increase in age, increase in hospitalization in 1 year with COPD acute exacerbations, and admission to intensive care units in 1 year due to COPD acute exacerbations are situations that predict a decrease in survival. While pneumonia has a significant difference between groups that develop mortality and groups that do not, it has been determined in the multivariate analysis that it carried no significance. A study conducted by Oren Fruchter et al shows that the GOLD phase and mortality are related, which conforms with our study. Alongside this, high D-dimer levels were found to be relatedto mortality (6).

Guoping Hu et al.(11) have determined the D-dimer cut-off value as 985 ng/dL, and Oren Fruchter et al. (6) have determined it as 1.52 mg/dL. In another study that was conducted on COPD patients with venous thromboembolism, D-dimer cut-off value was determined as 0.95 pg/mL (22). Our study has evaluated whether D-dimer can make a distinction between groups that develop mortality and groups that don't and whether a cut-off value can be given to identify mortality. D-dimer levels were not statistically significant while identifying mortality. In the groups that have been divided according to the D-dimer value median (median 1400), no statistically significant differences could be detected between the groups in terms of survival.

It is known that biomarkers can be affected by multiple factors (1,2,6). In our study, we have tried to exclude these factors as much as possible and tried to solely focus on finding COPD acute exacerbation effects for D-dimer. The reasons why D-dimer was found to be related to mortality and why the cut-off value could be calculated could be affiliated with the high levels of D-dimer other factors had or the inefficacy of the methods which were applied to exclude thromboembolism. In other studies, the inclusion of patients with thromboembolism could be considered as a situation that could increase D-dimer levels with no relation to COPD acute exacerbations.

Limitations

The fact that our study is single-centered and the analysis was retrospective creates limitations. The respectively low number of cases might have affected the analysis. In our study, all patients who had high levels of D-dimer and pulmonary thromboembolism were excluded by pulmonary CT angiography. None of the patients had clinical evidence of peripheral venous thromboembolism. However, this was not verified with a Doppler ultrasonography and this might have created a limitation as well. Our study has only included patients with COPD acute exacerbations and some of the patients were identified with pneumonia. This could have increased mortality in the patients and might have affected the increase in D-dimer levels. We believe it is necessary to conduct prospective studies with more patients where pneumonia is also excluded.

CONCLUSION

While D-dimer levels were higher in patients who developed mortality in the follow-up period after COPD acute exacerbations, there could be no statistical significance found when determining mortality. While other studies in the literature prove otherwise, it should

be noted that biomarkers can be affected by many clinical incidents and therefore it does not seem likely to have a prognosis in COPD acute exacerbations with only one biomarker.

ETHICAL DECLARATION

Ethics Committee Approval: Necessary permissions for our study were granted by the decision (Date: 26.10.2021, No. 2012-KAEK-15/4207) of the Clinical Studies Ethics Comittee of Health Sciences University Ankara Keçiören Educational and Research Hospital.

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 of 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.

REFERENCES

1. Spannell, F, Giulietti F, Cocci G, et al. Acute exacerbation of chronic obstructive pulmonary disease in older adults: predictors of in-hospital mortality and need for post-acute care. J Am Med Directors Association 2019; 20: 893-98.
2. López-López L, Torres-Sánchez I, Romero-Fernández R, et al. Impact of previous physical activity levels on symptomatology, functionality, and strengths during an acute exacerbation in COPD patients. Multidisciplinary Digital Publishing Institute. In Healthcare 2018; 4: 139.
3. Jo YS, Rhee CK, Kim KJ, Yoo KH, Park YB. Risk factors for early readmission after acute exacerbation of chronic obstructive pulmonary disease. Therapeutic Advances in Respiratory Disease 2020; 14.
4. Türk Toraks Derneği Kronik Obstrüktif Akciğer Hastalığı Tanı ve Tedavi Uzlaşı Raporu 2014; 3: 7.
5. Rodriguez-Roisin R, Rabe KF, Vestbo J, Vogelmeier C, AgustíA. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 20th anniversary: a brief history of time. Eur Respir J 2017; 50: 1700671.
6. Fruchter O, Yigla M, Kramer MR. D-dimer as a prognostic biomarker for mortality in chronic obstructive pulmonary disease exacerbation. Am J Med Sci 2015; 349: 29-35.
7. Beyaz A, Atilla N, Arpağ H, Bozkuş F, Kahraman H, Uğuz FA. The effect of C-reactive protein, procalcytonine, nuetrophil/ lymphosite levels on mortality and duration of hospital stay in pneumonia. Anatolian Curr Med J 2021; 3: 15-9
8. Biçer HS, Çırak Z, Özkan E, Taştan YÖ, Özçelik F, Kaplan M. A new biomarker for early diagnosis in patients with sepsis in intensive care units: presepsin. J Med Palliat Care 2020; 1: 19-22
9. Kim SH, Ahn HS, Park JS, et al. A proteomics-based analysis of blood biomarkers for the diagnosis of COPD acute exacerbation. Int J Chron Obstruct Pulmon Dis 2021; 16: 1497
10. Çelikhisar GDİ, Arslan S, Arman Y, Altun Ö, Çelikhisar H,Tükek T. The relationship between sarcopenia and nesfatin-1 and ghrelin levels in patients with chronic obstructive pulmonary disease. J Health Sci Med 2021;4: 402-7
11. Hu G, Wu Y, Zhou Y, et al. Prognostic role of D-dimer for in-hospital and 1-year mortality in exacerbations of COPD. Int J Chron Obstruct Pulmon Dis 2016; 11: 2729.
12. Konstantinides S V, Meyer G, Becattini C, et al. 2019 ESC Guidelines For The Diagnosis And Management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS) The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Heart J 2020; 41: 543-603.
13. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med 2017; 195: 557-82.
14. Nickel, Christian H,Cooksley T, et al. The diagnosis and outcomes of emergency patients with an elevated D-dimer over the next 90 days. Am J Med 2021: 260-6.
15. Nickel CH, Kellett J, Cooksley T, Bingisser R, Henriksen DP, Brabrand M. Combined use of the national early warning score an D-dimer levels predict 30-day and 365-day mortality in medical patients. Resuscitation 2016; 49-52
16. Tang N, Pan Y, Xu C, Li D. Characteristics of emergency patients with markedly elevated D-Dimer Levels. Scientific Reports 2020; 10: 1-5
17. Ichkawa Y, Wada H, Ezakİ M, et al. Elevated D-dimer levels predict a poor outcome in critically ill patients. Clin Applied Thrombosis/Hemostasis 2020; 1076029620973084.
18. Gülpek M, Tuksavul F, Uslu Ö, Güçlü S. Kronik obsturüktif akciğer hastalığı olgularının akut atakta plazma fibrinojen ve D-dimer düzeyleri. İzmir Göğüs Hastanesi Derg 2016; 16: 1-13
19. Hansen ES, Rinde F, Edvardsen MS, et al. Elevated plasma D-dimer levels are associated with risk of future incident venous thromboembolism. Thromb Res 2021; 208: 121-6.
20. Cai YQ, Zhang XB, Zeng HQ, Prognostic value of neutrophil-to-lymphocyte ratio, lactate dehydrogenase, D-dimer, and computed tomography score in patients with coronavirus disease 2019. Aging (Albany NY) 2021; 13: 20896.
21. 17- Kyriakopoulos C, Gogali A, Kostikas K, Konstantinidis A. Hypercoagulable state in COPD-A comprehensive literature review. Diagnostics 2021; 11: 1447
22. Akpinar EE, Hoşgün D, Doğanay B, Ataç GK, Gülhan M. Should the cut-off value of D-dimer be elevated to exclude pulmonary embolism in acute exacerbation of COPD? J Thoracic Dis 2013; 5: 430.

Original Article

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Comparison of volumetric and bidimensional measurement of the thymic gland to determine interobserver variability

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ABSTRACT

Aim: Thymic measurements should be interpreted relative to normal measurement values according to age groups and gender. Thymic gland measurement may vary between radiologists. In our study we wanted to determine the interobserver variability of thymic size measurements on CT by comparing volumetric calculations to commonly used bidimensional measurements.

Material and Method: The chest CT scans of 156 patients who had any oncological problems or disorders influencing the thymic size were retrospectively evaluated. The shape (quadrilateral or triangular), anteroposterior (AP) and transverse (TR) diameters, as well as the thickness of each lobe and thymus volume were measured independently by two radiologists. Interobserver variability was determined according to these parameters by Pearson correlation test.

Results: The shape of the thymic gland was triangular in 72% (n:113) and quadrilateral in 28% (n: 43) of all subjects. According to the results of the correlation test, a moderate relationship in terms of AP length, a weak relationship in terms of TR length, a negligible relationship in terms of right lobe thickness and a weak relationship in terms of left lobe thickness were obtained, but a very strong relationship was found between the two radiologists for volumetric measurements.

Conclusions: Volumetric measurements can be used as a basis for thymic imaging, reducing the differences among radiologists, and unnecessary and advanced examinations can be avoided.

Keywords: Thymus gland, volumetric measures, bidimensional measures, computerized tomography

INTRODUCTION

The thymus differs in size, shape and density in each individual. The thymic gland changes with time, reaching its maximum size in puberty due to increased sex hormones during adolescence and then shrinking in adulthood as a result of involution by fat tissue (1,2). In addition to these physiological changes, gender, physical differences, smoking, stress, and severe illnesses/disorders and treatments affecting the thymus make it challenging for radiologists to determine if a gland is "normal" using cross-sectional imaging (3). As the thymus appears in a variety of shapes, including pyramidal, triangular, arrow head, and quadrilateral, any space-occupying lesion can be confused with the gland (4-7). Consequently, there can be misdiagnosis or failure to diagnose normal from abnormal results in follow-up examinations, biopsies and thymectomies (8,9).

Multi-detector row Computed Tomography (MDCT) scanners provide novel information about the thymus due to contiguous thin slices, multiplanar reformats, 3D quantification and volumetrics. CT characteristics, bidimensional measurements and volumetric calculations of the thymus have been reported in the literature (10,11). Measurements on CT are subject to interobserver variability and there are ongoing studies defining the intra- and interobserver variability of thickness, diameter and density values (12). This study aimed to evaluate the interobserver variability of thymic bidimensional and volumetric measurements of chest CTs.

MATERIAL AND METHOD

The study was approved by Marmara University Non-Interventional Clinical Researchs Ethics Committee (Date: 12.04.2019, Decision No: 09.2019.350) and by the relevant committee or the Helsinki Declaration of Principles.

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Patient Selection

In this study the chest CT scan of patients who were admitted to our hospital for any reason other than oncological problems between March 2018 and July 2020 were evaluated retrospectively. Any known disorders influencing the size of the thymus, patients with mediastinal mass, hematoma, patients undergoing chemotherapy and patients with thymus showing complete fat replacement were excluded (n:100).

Equipment and CT Examination

All examinations were performed on a 256 slice scanner (Somatom Definition Flash, Siemens, Erlangen, Germany) with the following scan parameters: CARE Dose 4D for automatic exposure control for 120 kV and 50 mAs, 5 mm slices acquired with 128x0.6 mm setting, 0.5 pitch and 0.28 second rotation time. FOV was adjusted to patient size, a 512x512 matrix was used and the mean scan time was 4.2 seconds. Additional 0.75 mm axial reconstructions were generated as well as 10 mm multi-planar reformat (MPR) images in sagittal, coronal and axial planes for every examination. All patients received a bolus of 80 to 100 ml of intravenous contrast matter at a rate of 3 to 4 ml/s. The enhanced CT scan commenced 60 seconds after the administration of the contrast medium.

Image Interpretation

All patient data were examined separately on a PACS system (Novapacs, Novarad Corporation, USA) by two radiologists with 6 and 17 years of expertise, respectively, in radiology, and each radiologist documented their findings. The radiologists were free to adjust the window level and width and review sagittal and coronal images as well. The shape of the thymus was classified in two groups as quadrilateral or triangular (**Figure 1**). The axial CT images that provided the largest images of the thymus in terms of overall size and length were determined. The anteroposterior (AP) and transverse (TR) diameters of the gland were measured on this axial image from the thickest point of the gland using the caliper tool on the PACS system (**Figure 2**). The thickness of each lobe was also measured. The axial CT image with the largest area of each thymic lobe was selected for this (**Figure 3**).

Thymic gland volumes were measured using a software application (syngo.CTPulmo 3D, Siemens, Erlangen) after the chest CT images of patients were transferred to the Siemens Syngo Multimodality Workplace. Automated volume calculation was developed on the basis of 3D active contouring. Both radiologists manually traced the contour of the thymus on each CT slice and created this 3D contour to determine the thymic volume (**Figure 4**). Each case had an average of five slices (3-7). Volume was determined by multiplying the sum of all slices with the 3D image reconstruction and volume-rendering tool. The processing time was approximately 5 min per case. Results of each case in terms of volume were summarized by arithmetic mean and corresponding standard deviation as well as minimum and maximum values.

Statistical Analysis

The data of all patients were evaluated in SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) system version 21. Data distribution analysis of volume and all measurement values were performed. As a result of this analysis, normal distribution was determined for all parameters. Then, a non-parametric bi-variate correlation test (Pearson correlation test) was used to determine the correlation between the two radiologists. According to the results, p and r values were calculated. $p<0.05$ was considered statistically significant. r values were considered as having a very strong relationship for +.70 or higher, a strong relationship for +.40 to +.69, a moderate relationship for +.30 to .39, a weak relationship for .20 to .29 and no or negligible relationship for 0 to .19

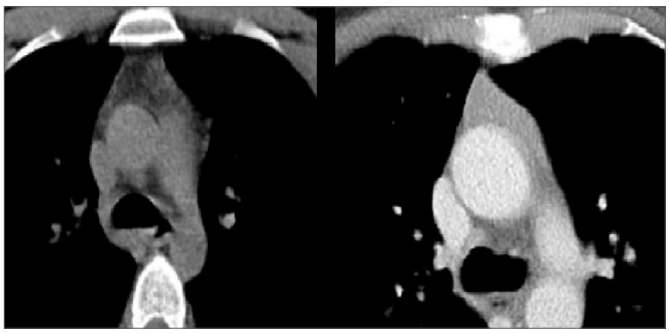

Figure 1. CT image example of quadrilateral (a) and triangular (b) shapes of the thymus.

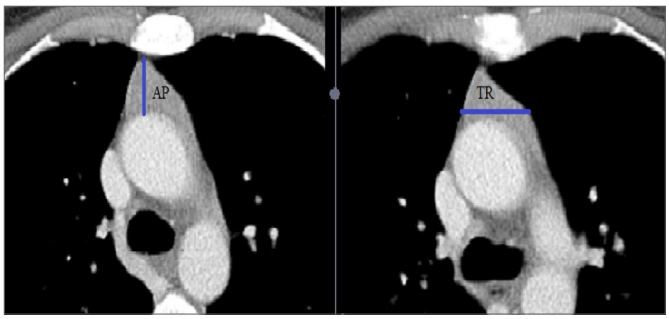

Figure 2. The measurements of anteroposterior (AP) and transverse (TR) diameters from the thickest point of the gland on axial CT images.

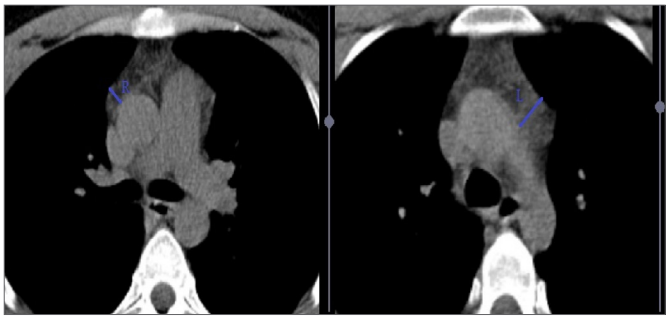

Figure 3. The axial CT image with the largest area of thymic lobe was selected for measuring the thickness of each lobes.

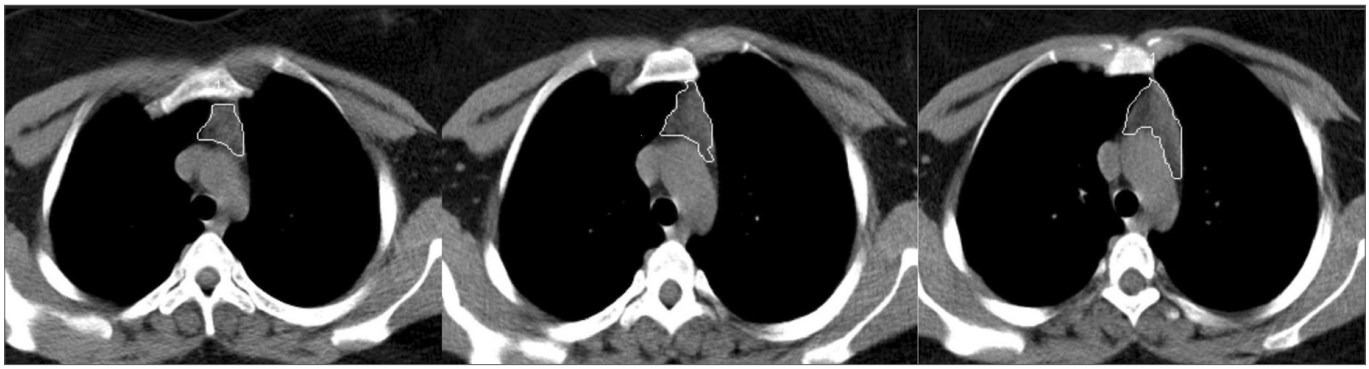

Figure 4. The volumetric contours of the thymus on CT slice.

RESULTS

One hundred and fifty-six patients (67 females, 89 males) were included in the study. The median age was 33.2 years (range: 17–79 years). The shape of the thymus gland was triangular in 72% (n:113) and quadrilateral in 28% (n: 43) of all subjects enrolled in the study.

The thymic size measurements of the two radiologists including the AP and transverse diameters of the thymus, thickness of each lobe and volume of the gland are summarized in **Table 1.** According to the results of the Pearson correlation test, although a statistically significant relationship was found among the radiologists in all measurement parameters, a moderate relationship in terms of AP length (r=0,376), weak relationship in terms of TR length (r=0,204), negligible relationship in terms of right lobe thicknes (r=0,184) and weak relationship in terms of left lobe thicknes (r=0,299) were obtained. In addition, a very strong relationship was found between the two radiologists for volumetric measurements (r=0,957). p and r values are given in **Table 2.**

DISCUSSION

In our study, the interobserver variability in thymic size measurement on CT was investigated by comparing two radiologists' volumetric calculations to commonly used bidimensional measurements. To the best of our knowledge, this study is the first to determine the interobserver variability of thymic volumetric calculations on CT compared to the variability of routinely used bidimensional measurements such as the transverse and AP diameters and thickness of each lobe. Our results showed a very strong relationship between the volumetric measurements of the two radiologists, which were more accurate than bidimensional measurements for thymic evaluation.

Each radiologist determined the image to be measured independently when performing bidimensional measurements. When the data were obtained, it was seen that only 40% of the selected axial images were in agreement. Araki et al. (3) found that the rate at which two radiologists chose the same image was 49%,

Table 1. Thymic bidimensional size measurements and volumetric calculations on CT.

Radiologist	Tr length (mm)	AP length (mm)	Right Lobe Thickness (mm)	LeftLobe Thickness (mm)	Volume (cm3)
Radiologist 1					
N	156	156	156	156	156
Minimum	8.80	10.40	3.10	3.70	4.00
Maximum	47.00	56.00	22.10	19.00	30.60
Mean	18.6878	19.4115	7.5199	8.1808	12.8671
Std. Deviation	4.97460	6.65665	3.11039	2.60013	5.79009
Radiologist 2					
N	156	156	156	156	156
Minimum	8.20	11.70	3.30	5.10	4.40
Maximum	43.90	58.70	21.90	23.40	32.20
Mean	22.9564	28.1256	9.3942	10.2538	12.9503
Std. Deviation	6.72529	8.23478	2.85086	2.87455	5.67049

Table 2. r and p values of thymus size and volumetric measurements of the thymus.

Group Variable	AP length	Tr length	Right Lobe	Left Lobe	Volume
Pearson Correlation (r)	0.376	0.204	0.184	0.299	0.957
p value	<0.001	0.011	0.022	<0.001	<0.001

Table 3. Thymus shape according to gender.

	Triangular (n)	Quadrilateral (n)
Male (89)	65 (73%)	24 (27%)
Female (67)	48 (72%)	19 (28%)

which is similar to our results. In their study, it was stated that there would be more agreement between the measurements if the image sections were chosen independently by the radiologists. The independence of the selected image sections in our study resulted in more consistent bidimensional measurements compared to other studies.

McErlean et al. (13) mentioned the importance of selecting the image by both of the radiologists before hand and suggested that measurements should be made in consecutive series in order to minimize measurement differences. We believe that since the volumetric measurements included the measurement of all images containing the thymus, the incompatibility between the radiologists' preferences for the selected image is unimportant; thus, unnecessary advanced examinations will be prevented. Our suggestion is in line with Simanovsky et al. (10), who performed a study that included volumetric measurements of the thymus with the aim of preventing unnecessary advanced examinations and recurrent radiation exposure.

On the other hand, Araki et al. (7) noted increased coherence between radiologists performing measurements on pre-determined images in patients with increased left lobe thickness. We suggest that when volumetric measurements are preferred over image selection, no matter whether it is one image or consecutive images, results would not be affected by the shape of the thymus or the status of thymus lobes.

Considering the physiological and pathological processes that result in the thymus shrinking or enlarging, which are mentioned both in our study and in the literature, we suggest that volumetric measurements would be more accurate than bidimensional measurements in terms of interobserver variability.

Our study has some limitations. First, this was a retrospective study and second, the number of patients included in the study was not large. Future studies with more subjects are needed to systematize the volumetric measurement method and hence contribute to the literature.

CONCLUSION

Interobserver variability of thymic bidimensional measurements was determined by our study as well as by previous studies. Our study suggests that changes in thymic volume can be accurately mapped with the noninvasive method of volumetric measurement, which can be used as a basis for thymic imaging and can reduce the differences among radiologists, thus avoiding unnecessary advanced examinations.

ETHICAL DECLARATION

Ethics Committee Approval: The study was approved by Marmara University Non-Interventional Clinical Researchs Ethics Committee (Date: 12.04.2019, Decision No: 09.2019.350)

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 of 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.

REFERENCES

1. Aw D, Silva AB, Palmer DB. Immunosenescence: emerging challenges for an ageing population. Immunology 2007; 120: 435–46.
2. Elmore S. Enhanced histopathology evaluation of thymus. Toxicol Pathol 2006; 34: 656–65.
3. Araki T, Nishino M, Gao W, et al. Normal thymus in adults. appearance on CT and associations with age, sex, BMI and smoking. Eur Radiol 2016; 26: 15-24.
4. Baron R, Lee J, Sagel S, et al. Computed tomography of the normal thymus. Radiology 1982; 142: 121–5.
5. Francis I, Glazer G, Bookstein F, et al. The thymus: reexamination of age-related changes in size and shape. Am J Roentgenol 1985; 145: 249–54.
6. Ackman JB, Kovacina B, Carter BW, et al. Sex difference in normal thymic appearance in adults 20-30 years of age. Radiology 2013; 268: 245–53.
7. Araki T, Sholl LM, Gerbaudo VH, et al. Imaging characteristics of pathologically proven thymic hyperplasia: identifying features that can differentiate true from lymphoid hyperplasia. AJR Am J Roentgenol 2014; 202: 471–8.
8. Singla S, Litzky LA, Kaiser LR, et al. Should asymptomatic enlarged thymus glands be resected? J Thorac Cardiovasc Surg 2010; 140: 977–83.
9. Ackman JB, Mino-Kenudson M, Morse CR. Nonsuppressing normal thymus on chemical shift magnetic resonance imaging in a young woman. J Thorac Imaging 2012; 27: 196–8.
10. Simanovsky N, Hiller N, Loubashevsky N, et al. Normal CT characteristics of the thymus in adults. Eur J Radiol 2012; 81: 3581-6.
11. Prodhomme O, Seguret F, Martrille L, et al. Organ volume measurements: comparison between MRI and autopsy findings in infants following sudden unexpected death. Arch Dis Child Fetal Neonatal Ed 2012; 97: 434-8.
12. Araki T, Sholl LM, Gerbaudo VH, et al. Thymic measurements in pathologically proven normal thymus and thymic hyperplasia: intraobserver and interobserver variabilities. Acad Radiol 2014; 21: 733-42.
13. McErlean A, Panicek DM, Zabor EC, et al. Intra- and interobserver variability in CT measurements in oncology. Radiology 2013; 269: 451-9.

Original Article

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Exploring radiation safety knowledge among nurses

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ABSTRACT

Aim: As part of the medical team, nurses often take part in both controlled and supervised radiation fields. For this reason, nurses need to know about radiation and radiation safety. This study is aimed to determine the knowledge level of nurses in a tertiary pediatric hospital about radiation safety through a questionnaire.

Material and Method: Within the scope of the survey conducted, the age, gender and years of experience data of the participants were collected. In addition, they have been asked whether they have received radiation safety training throughout their professional life and whether they want to receive such training now. Basic questions about radiation safety and questions to measure the general level of information about radiation are also addressed.

Results: The link of the survey was delivered to 583 nurses in the study center and 313 nurses completed the questionnaire. 53.67% of the nurses stated that they do not know the name of the beam used for x-ray imaging. 64.28% of the nurses stated that they did not receive such education in their professional life. 78.57% of all participants stated that they wanted to receive a training how to protect themselves while X-ray is being performed in their environment.

Conclusion: A significant number of nurses do not receive radiation safety training. Those who received such an education state that they are not satisfied with the training. Nurses want to receive radiation safety training. Trainings with regular and appropriate content can increase nurses' radiation safety knowledge and awareness.

Keywords: Awareness nurse, knowledge, radiation, safety

INTRODUCTION

Radiation safety is a necessity that must be ensured not only for patients exposed to radiation but also for staff working in this environment. National and international institutions have already determined the limits of iatrogenic radiation exposure. However, it is likely to be beneficial for individuals working in ionizing radiation environments to know basic radiation safety and fundamental concepts of radioactivity both for their own health and compliance with daily radiation safety practices (1,2).

In healthcare institutions, areas with a risk of exposure to doses of 1 mSv radiation or more per year are considered radiation areas. Besides, radiation areas are divided into two as controlled and supervised areas. The risk of radiation exposure is higher, and dosimeters must be used in controlled areas. Although there is a higher risk of radiation exposure in supervised areas, the use of dosimeters is not mandatory (3,4).

Nurses, as part of the healthcare staff, are frequently employed in both controlled and supervised areas (5). For example, nurses working in areas where portable radiographs are utilized intensively (e.g., intensive care units) have increased exposure risk (6,7). Hence, nurses are among the professionals who should know about radiation and radiation safety. By the way, radiation knowledge plays a vital role in ensuring radiation safety (4,8). For this reason, both nurses and other healthcare professionals frequently engage in radiation safety training (6,7). The relevant literature hosts several studies measuring nurses' awareness of radiation and radiation safety. Yet, most of these studies found nurses' awareness of radiation to be insufficient (6,8).

Ultimately, this study aimed to reveal the radiation and radiation safety knowledge of nurses working in a tertiary pediatric hospital through a questionnaire. In this way, the findings may help increase radiation safety awareness and pave the way for relevant training programs.

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MATERIAL AND METHOD

The study was carried out with the permission of Etlik Zübeyde Hanım Gynecology Training and Research Hospital Clinical Researh Ethics Committee (Date: 23.09.2020, Decision No: 2020/136). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The present study was prospective survey research carried out with nurses working in a tertiary pediatric hospital. We obtained ethical approval for the study from relevant bodies. Participation in the study was entirely voluntary, and we included an informed consent section at the beginning of the questionnaire that contains a summary of research purpose, states that the participants' personal information will not be collected, and emphasizes that the participation is on a voluntary basis.

Prior to the study, we performed a pilot study with 20 nurses of varying experience levels to reveal the suitability and comprehensibility of the questions in the survey. Then, we finalized the questionnaire based on the feedback.

Next, we transferred the questionnaire form to the online environment and delivered the relevant electronic link to the participants via a social media platform (WhatsApp). We compiled the responses without any personal information. Filling out the questionnaire more than once was prevented using the internet protocol (IP) address restriction provided by the online platform.

In the study, we collected demographic characteristics of the participants (age, sex, and years of experience). In addition, we inquired whether they had received radiation safety training during their formal education and professional life and whether they would like to receive such training now. Moreover, the questionnaire included basic questions about radiation safety and questions to measure the general radiation knowledge of the participants. Appendix 1 presents the questionnaire.

We analyzed the data using the Statistical Package for Social Sciences (SPSS), Windows 20 (IBM SPSS Inc., Chicago, IL). We referred to the Kolmogorov-Smirnov test to check the normality of data distribution and showed normally distributed data as mean and standard deviation. The distribution of responses was shown as percentages. Finally, we performed the Mann-Whitney U test, student t test and Chi-Square test to compare the responses by age, professional experience, and sex.

A p-value of < 0.05 was considered statistically significant in all analyses.

RESULTS

We delivered the questionnaire link to 583 nurses employed in the center where we conducted the study and got responses from a total of 313 nurses. Among them, 245 (78.2%) were females, and 68 (21.7%) were males. The mean age of the participants was 37.3±11.5, while they had an average of 17.2±6.8 years of work experience.

The survey includes two questions to measure the participants' general radiation knowledge. The results revealed that 53.67% of the nurses did not know the name of the beam used for X-ray imaging. Only 17.89% were able to give an "X-ray" response (**Table 1**). About half of the participants (42.85%) stated knowing about natural radiation.

Table 1. What is the name of the rays used in X-ray research?

Answer	Number (%)
Alfa	67 (21.4%)
X	56 (17.89%)
Gama	22 (7.02%)
I don't Know	168 (53.67%)

More than half of the participants (57.14%) reported being knowledgeable about what they should do to protect themselves while performing an X-ray examination; however, only 31.19% were able to accurately know the minimum distance (1 meter) from an X-ray generator (**Table 2**).

Table 2. The answers given to the questions about what is the distance required to be protected from X-rays in the environment.

Answer	Number (%)
1 meter	100 (31.19%)
3 meter	190 (60.70%)
5 meter	22 (7.02%)

Correct answer is shown in bold (Hellwig BJ, Wilson B. Quality Improvement Related to Radiation Safety of Chest Radiography in the NICU. Radiology management. 2013;35(2).)

We found the rates of those not receiving any training during their education and professional life on how to protect themselves during an X-ray examination to be 46.42% and 64.28%, respectively.

More than half of the participants (56.2%) received training on radiation protection during their education or professional life. Yet, among them, the majority (71.25%) did not consider the training sufficient. Besides, 78.57% of all participants desired to receive training covering what they need to do to protect themselves during an X-ray examination.

We could not find any significant differences between the responses by sex (p=0.07).

We found an inverse and significant relationship between age and knowledge of radiation protection. We divided the participants into two groups, accepting the threshold of 35 years, and compared the responses between the groups. Similarly, we formed two groups by professional experience, as those with less than 15 years of experience and the others, and compared their responses. Findings showed that those below 35 years and with less than 15 years of professional experience gave a significantly higher response of "Yes" to the question "Do you have any information about the methods of protecting yourself when you are needed for an X-ray examination?" (p=0.03). In addition, a significantly larger percentage of these participants gave a correct answer to the question about the minimum distance (1 meter) from an X-ray generator during an examination (p=0.04). Again, those below 35 years and with less than 15 years of professional experience received radiation protection training during their formal education significantly higher than the others (p=0.001). However, the other responses/paramethers (except the knowledge of radiation) did not significantly differ by age and professional experience.

DISCUSSION

Nurses constitute a remarkable part of healthcare personnel and are widely employed in all types of units in hospitals, which may make them vulnerable to occupational radiation exposure. In the literature, a significant number of nurses do not know how to protect themselves from ionizing radiation during their professional life. Besides, most nurses consider their previous education on radiation protection to be insufficient and are willing to receive more comprehensive education on this subject (10,11).

Natural radiation comes out from natural sources, especially from radon gas. Apart from radon gas, one may be exposed to natural radiation through gamma rays, cosmic rays, food, drinks, and air. Artificial radiation, on the other hand, occurs as a result of X-rays and artificial radioactive materials used for medical, agricultural, and industrial purposes. Of these, medical applications account for more than 95% of artificial radiation. The annual dose for artificial radiation is on average 0.3 mSv (12,13).

Radiation caused by medical interventions stands as a problem that should be emphasized for both patients and healthcare personnel, and its effects should be minimized. At this point, the most important and indispensable step of radiation safety is education (14,15).

Recent years have witnessed a plethora of studies aiming to measure healthcare workers' radiation and radiation safety knowledge to design appropriate training programs and increase awareness of radiation safety (16,17). Nurses are also one of the target groups of such studies. In their research, Morishima et al. (17) concluded that 58.2% of the nurses did not know about the types of radiation. Our data overlap the finding in the literature; only a few of our participants were able to specify the name of the ionizing beam used in the X-ray examination as "X-ray." Less than half of the participants knew about natural radiation. Overall, we may assert that the participating nurses have a lack fundamental radiation knowledge (18,19).

Although more than half of the participants knew about protecting themselves from radiation, only about 1/3 knew correctly the minimum distance required to set from an X-ray generator. This situation can be considered an indirect indicator of the lack of knowledge, even for those thinking to have sufficient knowledge about the topic. Similarly, several studies in the literature (6, 14) concluded that most nurses do not know the safe distance to stand from an X-ray generator during an examination.

The literature also emphasizes that nurses are not given adequate radiation safety training, and their level of knowledge often remains poorer than that of physicians and radiologic technologists (10, 20). Similarly, we found a significant part of the participants did not receive radiation safety training during their education or professional life, and the majority of those receiving such training was not satisfied with the training. In addition, 78.57% of the nurses desired to receive radiation safety training. Similar to our data, Morishima et al. (17) found 85.6% of the nurses to report that they would like to attend periodic radiation safety seminars.

In their study, Kim et al. (10) showed that nurses over 40 comply more with radiation safety precautions. Partly different from the literature, our data demonstrated that young nurses had more radiation and radiation safety knowledge than experienced nurses. In addition, the rate of receiving radiation safety training during formal education was found to be high among young nurses, which may refer to that radiation safety training has started to take place more in the curriculum of healthcare professionals in the last two decades. However, in parallel with the literature, both young and experienced nurses tended to consider the relevant training to be insufficient. Overall, it is not prudent to assert there is a need for radiation safety training for nurses of all age groups.

There are some limitations of our study. First, since we carried out the study in a single center, the findings may only present a preliminary situation about the subject. Therefore, multicenter studies with larger samples may be more reliable. Second, the study was carried only with nurses and did not make a comparison with physicians

or other auxiliary healthcare personnel. If we had carried out the study immediately after any radiation safety training, we could have made a robust evaluation of the effectiveness of the training.

CONCLUSION

To conclude, nurses, an essential part of the healthcare staff and often exposed to in-hospital radiation, do not have sufficient knowledge of general radiation and radiation safety. A significant portion of the nurses did not receive radiation safety training, and those who did are not satisfied with the training. Overall, nurses want to receive radiation safety training; therefore, regular and appropriate training may increase nurses' knowledge and awareness of radiation safety.

ETHICAL DECLARATION

Ethics Committee Approval: The study was carried out with the permission of Etlik Zübeyde Hanım Gynecology Training and Research Hospital Clinical Researh Ethics Committee (Date: 23.09.2020, Decision No: 2020/136).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Gökharman DF, Aydın S, Koşar PN. Radyasyon güvenliğinde mesleki olarak bilmemiz gerekenler. SDÜ Sağlık Bilimleri Derg 2016; 7: 35-40.
2. Frane N, Bitterman A. Radiation Safety and Protection 2021 May 29. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.
3. Organization WH. International basic safety standards for protection against ionizing radiation and for the safety of radiation sources. 1994.
4. International Commission on Radiological Protection. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Annals of the ICRP 2007; 37: 2.
5. Cupitt J M, Vinayagam S , McConachie I. Radiation exposure of nurses on an intensive care unit. Anaesthesia 2001; 56: 183.
6. Dianati M, Zaheri A, Talari HR, Deris F, Rezaei S. Intensive care nurses' knowledge of radiation safety and their behaviors towards portable radiological examinations. Nursing Midwifery Studies 2014; 3: e23354.
7. Kang SG, Lee EN. Knowledge of radiation protection and the recognition and performance of radiation protection behavior among perioperative nurses. J Muscle Joint Health 2013; 20: 247-57.
8. World Health Organization. Global Initiative on Radiation Safety in Healthcare Settings. Technical Meeting Report. 2008.
9. Amis Jr ES, Butler PF, Applegate KE, et al. American College of Radiology white paper on radiation dose in medicine. J Am College Radiol 2007 ; 4: 272-84.
10. Kim O, Kim MS, Jang HJ, et al. Radiation safety education and compliance with safety procedures-The Korea Nurses' Health Study. J Clin Nurs 2018; 27 : 2650-60.
11. Ohno K, Kaori T. Effective education in radiation safety for nurses. Radiation Protection Dosimetry 2011; 147: 343-5.
12. Szarmach A, Piskunowicz M, Świętoń D, et al. Radiation safety awareness among medical staff. Polish J Radiol 2015; 80: 57.
13. International Commission on Radiological Protection. Education and training in radiological protection for diagnostic and interventional procedures. ICRP Publication 113. Annals of the ICRP 2009; 39: 5.
14. Sheyn DD, Racadio JM, Ying J, Patel MN, Racadio JM, Johnson ND. Efficacy of a radiation safety education initiative in reducing radiation exposure in the pediatric IR suite. Pediatr Radiol 2008; 38: 669-74.
15. Choi GN, Jeon JS, Kim YW. Radiation exposure dose on persons engaged in radiation-related industries. J Korean Soc Radiol 2002; 6: 27-37.
16. Yoon SJ, Oh JN, Im MH. Knowledge, attitude, and education needs of radiation protection among nursing students and nurses. J Korea Contents Assoc 2016; 16: 563–72.
17. Morishima Y, Chida K, Katahira Y, Seto H, Chiba H, Tabayashi K. Need for radiation safety education for interventional cardiology staff, especially nurses. Acta Cardiologica 2016; 71: 151-5.
18. Alotaibi M, Saeed R. Radiology nurses' awareness of radiation. J Radiol Nurs 2005; 25: 7-12.
19. 19.Rassin M, Granat P, Berger M, Silner D. Attitude and knowledge of physicians and nurses about ionizing radiation. J. Radiol. Nurs 2005; 24: 26-30.
20. Badawy MK, Mong KS, Lykhun UP, Deb P. An assessment of nursing staffs' knowledge of radiation protection and practice. J Radiol Prot 2016; 36: 178-83.

Original Article

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The importance of urotensin II level in the diagnosis of acute mesenteric ischemia

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ABSTRACT

Aim: This study was conducted to investigate the diagnostic importance of Urotensin II (UT-II) levels, which cause vasodilation as a compensation mechanism in the early phase of Acute Mesenteric Ischemia (AMI). For this purpose, human plasma urotensin was studied for the first time in the literature for the early diagnosis of mesenteric ischemia.

Material and Method: The study consisted of 60 patients. The patients were divided into three groups: Group 1: group with mesenteric ischemia (n: 20); Group 2: group with abdominal pain and with no mesenteric ischemia (n: 20); Group 3: control group with no complaints (n: 20). The blood samples were taken from the patients through peripheral venous access, and Urotensin II (UT-II), Aspartate Aminotransferase (AST), Alkaline phosphatase (ALP), Lactate, and D-dimer levels were measured.

Results: While a significant increase was found between Group1 and Group 2 and between Group1 and Group3 in terms of UT-II values ($p<0.05$), no significant difference was found between Group2 and Group3 ($P>0.05$). A significant increase was found between Group1 and Group2 and between Group1 and Group3 regarding AST values ($p<0.05$), but there was no significant difference between Group2 and Group3 ($p>0.05$). There was a significant increase between Group1 and Group3 in terms of D-dimer values ($p<0.05$), but no significant difference was seen between Group1 and Group2 and between Group2 and Group3 ($p>0.05$). There was no significant difference between the groups concerning ALP and Lactate values ($P>0.05$).

Conclusion: It was concluded that UT-II could be used in the diagnosis of AMI but that there was a need for comprehensive studies investigating the changes in ischemia time-related UT-II serum levels.

Keywords: Acute mesenteric ischemia, urotensin-II, D-dimer

INTRODUCTION

Acute Mesenteric Ischemia (AMI) is a vascular pathology of the gastrointestinal system. It is one of the causes of acute abdomen, which is rarely seen but has very high mortality rates in the community. Early diagnosis is one of the most important factors determining mortality. Despite advances in technology and appropriate diagnosis and treatment, mortality remains high (1). Two main pathophysiological mechanisms can lead to mesenteric ischemia: acute thromboembolic vascular occlusion and non-occlusive mesenteric ischemia (NOMI) (2, 3).

Although computed tomography angiography (CTA) gives satisfactory results for the diagnosis of occlusive mesenteric ischemia, the use of CTA is difficult because patients are in intensive care, elderly and immobile. It is very difficult to make a definitive diagnosis of NOMI, which constitutes 20-30% of AMI cases radiologically (4).

The inadequacy of anamnesis, physical examination, and radiological examinations in making the diagnosis and the high mortality rates of the disease have brought up the search for a specific biomarker.

The splanchnic circulation receives 15-35% of cardiac output, depending on nutritional status. However, oxygen extraction is relatively low, taking into account the oxygen-carrying capacity of the portal vein to the liver.

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Therefore, blood flow decreases by more than 50% before the small intestine becomes ischemic (5). In addition, the intestines automatically regulate oxygen availability through enhanced oxygen extraction and perfusion due to early vasodilation. (6) Therefore, we believe that UT-II, a vasodilator peptide, increases in the early period of ischemia.

UT-II is an important molecule in the pathophysiology of human diseases. Many studies have observed increased plasma levels of UT-II, which is a potent vasoconstrictor, in the tissues of numerous disease conditions, including hypertension, preeclampsia, atherosclerosis, heart failure, pulmonary hypertension, diabetes, renal failure, and various metabolic syndromes. (7). However, in recent studies, UT-II has been shown to have a vasodilator effect in some veins such as the pulmonary artery and mesenteric arteries. UT-II has been found to be high in patients with low blood pressure in hemodialysis, and this is thought to be due to its vasodilator characteristic (8). Studies on intravenous infusions of UT-II in animals have also shown that UT-II can cause vasodilation (9).

This study was conducted to investigate whether UT--II levels, which may cause vasodilation as a compensatory mechanism in the early period in patients with AMI, could be used as a diagnostic marker. With this study, human Plasma Urotensin was studied for the early diagnosis of mesenteric ischemia for the first time in the literature.

MATERIAL AND METHOD

The study was initiated with the approval of the Fırat University Non-Interventional Researchs Ethics Committee (Date: 2013, Decision No: 2013/04-06). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

The study was conducted in the General Surgery and Emergency Medicine Clinic. A detailed anamnesis was taken from the patients included in the study, and their physical examinations were done. Blood samples were taken from the patients through peripheral venous access. The tests were done at the Central Laboratory of Medical Faculty. The serum AST, ALP, lactate, and D-dimer levels were measured. In addition, for UT-II measurement, blood samples of 4 ml placed in an EDTA tube were centrifuged for 4 minutes at 5000 rpm. After centrifugation, 1 ml sample was taken from the serum and stored at -20°C until the day when UT-II would be determined. Patient names and numbers were written on each sample and were listed and archived.

Biochemical Examination

1. Urotensin II: UT-II level was studied after the serums previously taken from the patients and stored at -20°C were thawed. Features of the human urotensin II Elisa kit used in our study: Kit brand- (date): Rel Assay Diagnostic Research and Clinical Chemistry; Assay range: 5 pg/mL-1000 pg/mL; Sensitivity: 2.23 pg/mL; Intra assay: CV<10%; inter-assay: CV<12%.

2. Serum AST measurement was performed by using the Olympus AU 2700 (Olympus Inc Corporation, Japan) autoanalyzer and original kits.

3. D-dimer measurement was performed by using Siemens CA1500 SYSMEX device (Siemens Healthcare Diagnostic Inc, USA).

4. Serum ALP measurement was performed by using the Olympus AU 2700 (Olympus Inc Corporation, Japan) autoanalyzer and original kits.

5. Lactate plasma levels were determined by using the Siemens Rapidlab-1265 (Siemens Healthcare Diagnostic Inc, USA) device.

Patient Groups

Group-1 (n=20) - Acute Mesenteric Ischemia Group (AMI group): This group consisted of patients who were diagnosed with mesenteric ischemia by laparotomy or those who were diagnosed by CTA as they could not undergo a laparotomy.

Group-2 (n=20) - Abdominal Pain Group: This group consisted of patients who presented to the emergency department with acute abdomen pain but did not have ischemia or necrosis due to acute mesenteric vascular occlusion, and had other underlying pathologies.

Group-3 (n=20) - Control Group: The control group consisted of subjects who did not have a known pathology to cause abdominal pain.

Statictical Analysis

The data obtained in the study were presented as mean±standard deviation values. One-way analysis of variance (ANOVA) tests, post-ANOVA tests, Tukey B, and Scheffe tests were used to evaluate the intergroup differences. In addition, Pearson and Spearman correlation tests were used to examine the correlations between the data in the groups. $p<0.05$ was accepted as the level of significance.

RESULTS

The study included a total of 60 patients, including 20 patients who were admitted to the General Surgery Clinic of Fırat University Faculty of Medicine between January 2013 and January 2016 with a diagnosis of AMI (Group-1), 20 patients who had non-specific abdominal pain (Group-2), and 20 randomly selected patients with no abdominal pain (Group-3). There were 14 female and 6 male patients in Group 1 with a mean age of 69.6

(40-93), 12 female and 8 male patients in Group 2 with a mean age of 61.6 (42-83), and 12 female and 8 male patients in Group 3 with a mean age of 40.6 (23-73) (**Table 1**).

Table 1. Demographic characteristics of the groups

	Female	Male	Mean age (years)
Group-1	14	6	69.9
Group-2	12	8	61.6
Group-3	12	8	40.6

The statistical findings for the comparison of the gender and biochemical parameters of the patients in Group 1 indicated that there was no statistically significant difference between gender and UT-II, AST, and ALP values. Lactate and D-dimer values were found to be significantly higher in male patients (Mann-Whitney Test; $p<0.05$). There was no statistically significant difference between the age and biochemical parameters of the patients in Group-1 (Summarize Test; $p>0.05$).

While a significant increase was observed between Group1 and Group2 and also between Group1 and Group3 ($p<0.05$) regarding AST values, no significant difference was observed between Group2 and Group3 ($P>0.05$). There was a significant increase between Group1 and Group3 in terms of D-dimer values ($p<0.05$), but no significant difference was observed between Group1 and Group2 and between Group2 and Group3 ($P>0.05$). There was no significant difference between the groups relating to ALP and Lactate values ($P>0.05$). All blood values are given in **Table 2**.

Table 2. Mean values in the groups

	Group-1	Group-2	Group-3
AST (U/L)	76.60±88.96	27.46±13.01	26.05±9.89
LAKTAT (mEq/L)	2.5±1.6	1.8±0.91	2.9±1.2
D-DİMER (ng/mL)	5.8±7.6	0.39±0.28	0.07±0.03
ALP (IU/L)	95.46±28.66	98.81±54.91	83.3±23.2

Urotensin-II (UT-II) values in 6 patients in group 1 were higher than 1280pg/ml, which is the highest value that the device can read. The UT-II values of these six patients were included in the study as 1280 pg/ml. In group 3, UT-II values in two patients were lower than 9,917 pg/ml, which is the lowest value that the device can read. The UT-II values of these two patients were included in the study as 9,917 pg/ml. The mean Urotensin II value was 502.34±471.57 pg/ml in Group-1, 240.87±123.98 pg/ml in Group-2, and 202.48±58.18 pg/ml in Group-3. The difference between the UT-II values of Group2 and Group3 was not significant ($P>0.05$). When Group2 was compared to Group3 and Group1, a significant increase was observed in UT-II values ($p<0.05$) (**Figure 1**).

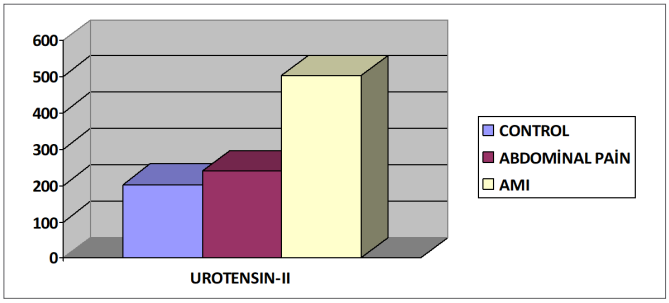

Figure 1. Comparison of UT-II values according to all groups

DISCUSSION

There is no clear protocol for the diagnosis and treatment of acute mesenteric ischemia yet. The most important factor affecting mortality and morbidity is early diagnosis. Therefore, many studies have been conducted for early diagnosis, but a parameter with early diagnostic efficiency to increase the survival rate has not been found yet (10)

The current diagnostic tool with the highest sensitivity and specificity for the diagnosis of AMI is computed tomography angiography (CTA). Nevertheless, even high-tech diagnostic equipment such as CTA can sometimes miss acute obstructive intestinal ischemia (11,12). In addition, there are also misdiagnosed cases in CTA examinations (13). It may not always be possible to make diagnoses with CTA in non-stable patients hospitalized in the intensive care unit and under mechanical ventilation. At the same time, the sensitivity and specificity of BTA are low in NOMI, which makes up 25% of all AMI cases (4).

More than 90% of patients with ischemia have abnormally high leukocyte counts. The second most common abnormal finding is metabolic acidosis with high lactate levels occurring in 88% of the cases (14). Patients may present with lactic acidosis due to dehydration and decreased oral intake. Therefore, the distinction between early ischemia and irreversible intestinal damage based on lactate level alone is unreliable unless accompanied by other clinical evidence. Elevated serum lactate levels of >2 mmol/l have been associated with irreversible intestinal ischemia in the diagnosis of acute AMI (15). Kulaçoğlu et al. (16) found that there was a significant increase in plasma lactate levels in rat models of mesenteric ischemia. Lange et al. (17) found lactate 100% sensitive but 42% specific as a biochemical marker for AMI. Acosta et al. (18) concluded that plasma lactate levels would not be recommended as a diagnostic marker in suspected intestinal ischemia in the experimental AMI they created. In another study, it was concluded that serum lactate measurement was not a specific confirmatory factor for diagnosis (19). As in similar studies, no statistically

significant difference was observed between the groups relating to lactate values in our study.

D-dimer is a degradation product specific to fibrin clots, with a plasma half-life of 4-8 hours. There are studies on dynamic D-dimer levels in AMI (20-22). D-dimer has been reported to be an independent risk factor for intestinal ischemia, reflecting continued clot formation and endogenous degradation via fibrinolysis (23). Kurt et al. (24) found the sensitivity of D-dimer in AMI as 88.8%, specificity as 90%, positive predictive value (PPV) as 88.8%, and negative predictive value (NPV) as 100% in an experimental study and concluded that D-dimer may be practical in the early diagnosis of acute mesenteric ischemia. Acosta et al. (25) showed that D-dimer was significantly higher in patients with AMI than in patients with inflammatory bowel disease and intestinal obstruction. The sensitivity of the D-dimer value has been reported as 100% and the specificity as 36%. Cudnik et al. (26) reviewed data from five studies evaluating D-dimer as a biomarker for AMI, reporting a sensitivity of 96% and a much lower specificity of 40%. In a small series of 10 patients with confirmed AMI, Block et al. (27) noted that D-dimer was positive in all individuals. In our study, we found that D-dimer was significant in the diagnosis of AMI.

As a result of acute mesenteric ischemia, necrosis and ultimately bacterial translocation-related sepsis occur. Septic complications contribute to multiple organ damage. An increase in liver function tests can be observed with liver damage. Diebel et al. (28) observed an increase in liver function tests with liver injury by decreasing portal blood flow. In our study, there was a statistically significant increase in serum AST levels in Group1. These results of ours are in parallel with the findings of Diebel et al.

Urotensin II peptide has been isolated in vascular endothelium, heart, leukocytes, liver, adrenal glands, pituitary, brain, spinal cord, kidney, spleen, leukocytes, small intestine, colon, placenta, and other tissues (29). Stirrat et al. (30) demonstrated that UT-II caused vasodilation in human mesenteric and pulmonary arteries through its receptors on the endothelium. Similarly, Katano et al. (31) showed that the vasodilator effects of UT-II might be dependent on endothelial dysfunction and suggested that this molecule exerted its vasodilatory effects through NO and prostaglandin formation. In our study, UT-II levels in the patients in the AMI group were found to be significantly higher than the patients in the other groups.

Our study has some limitations. For example, the number of patients in our study was low, and we could not measure the stage of ischemia in our patients in group 1 when they presented to our clinic.

The strength of our study is that it is a biomarker study on human serum studied for the first time in the literature.

We have concluded that UT-II can be used in the biochemical diagnosis of AMI. However, there is a need for more studies to investigate the ischemia time-related changes in UT-II serum levels.

ETHICAL DECLARATION

Ethics Committee Approval: The study was initiated with the approval of the Fırat University Non-Interventional Researchs Ethics Committee (Date: 2013, Decision No: 2013/04-06).

Informed Consent: All patients signed the free and informed consent form.

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 of 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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REFERENCES

1. Acosta-Mérida MA, Marchena-Gómez J, Saavedra-Santana P, Silvestre-Rodríguez J, Artiles-Armas M, Callejón-Cara MM. Surgical outcomes in acute mesenteric ischemia: has anything changed over the years? World J Surg 2020; 44: 100–7.
2. Van Noord D, Kolkman JJ. Functional testing in the diagnosis of chronic mesenteric ischemia. Best Pract Res Clin Gastroenterol 2017; 31: 59-68.
3. Bourcier S, Oudjit A, Goudard G, et al. Diagnosis of non-occlusive acute mesenteric ischemia in the intensive care unit. Ann Intensive Care 2016; 6: 112.
4. Clair DG, Beach JM. Mesenteric ischemia. N Engl J Med 2016; 374: 959–68.
5. Rosenblum JD, Boyle CM, Schwartz LB. The mesenteric circulation. Anatomy and physiology. Surg Clin North Am 1997; 77: 289–306.
6. Haglund U, Bergqvist D. Intestinal ischemia—the basics. Langenbeck's Arch Surg 1999; 384: 233–8.
7. Ross B, McKendy K, Giaid A. Role of urotensin II in health and disease. Am J Physiol 2010; 298: 1156–72.
8. Mosenkis A, Kallem RR, Danoff TM, Aiyar N, Bazeley J, Townsend RR. Renal impairment, hypertension and plasma urotensin II. Nephrology Dialysis Transplantation 2011; 26: 609–14.
9. Gardiner SM, March JE, Kemp PA, Davenport AP, Bennett T. Depressor and regionally-selective vasodilator effects of human and rat urotensin II in conscious rats. Br J Pharmacol 2001; 132: 1625–9.
10. Bobadilla JL. Mesenteric ischemia. Surg Clin North Am 2013; 93: 925-40.

11. Bourcier S, Oudjit A, Goudard G, et al. Diagnosis of non-occlusive acute mesenteric ischemia in the intensive care unit. Ann Intensive Care 2016; 6: 112.
12. Kärkkäinen JM, Acosta S. Acute mesenteric ischemia (part I) - Incidence, etiologies, and how to improve early diagnosis. Best Pract Res Clin Gastroenterol 2017; 31: 15-25.
13. Kozuch PL, Brandt LJ. Review article: diagnosis and management of mesenteric ischaemia with an emphasis on pharmacotherapy. Aliment Pharmacol Ther 2005; 21: 201-15.
14. Kougias P, Lau D, El Sayed HF, Zhou W, Huynh TT, Lin PH. Determinants ofmortality and treatment outcome following surgical interventions for acutemesenteric ischemia. J Vasc Surg 2007; 46: 467–74.
15. Nuzzo A, Maggiori L, Ronot M, et al. Predictive factors of intestinal necrosis in acute mesenteric ischemia: prospective study from an intestinal stroke center. Am J Gastroenterol 2017; 112: 597–605.
16. Kulaçoğlu H, Kocaerkek Z, Moran M, Kulah B, Atay Ç, Kulaçoğlu S. Diagnostic value of blood D-dimer level in acute mesenteric ischaemia in the rat: An experimental study. Asian J Surg 2005; 28: 131-5.
17. Lange H, Jackel R. Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. Eur J Surg 1994; 160: 381-384.
18. Acosta S, Nilsson TK, Malina J, Malina M. L-lactate after embolization of the superior mesenteric artery. J Surg Res 2007; 143: 320-8.
19. Meyer T, Klein P, Schweiger H, Lang W. How can the prognosis of acute mesenteric artery ischemia be improved? Results of a retrospektive analysis. Zentralbl Chir Nürnberg 1998; 123: 230-4.
20. Fernández-Ruiz I. Biomarkers: extended predictive value of d-dimer. Nat Rev Cardiol 2018; 15: 198.
21. Yang K, Wang W, Zhang WH, et al. The combination of D-dimer and peritoneal irritation signs as a potential indicator to exclude the diagnosis of intestinal necrosis. Medicine 2015; 94: e1564.
22. Montagnana M, Danese E, Lippi G. Biochemical markers of acute intestinal ischemia: possibilities and limitations. Ann Transl Med 2018; 6: 341.
23. Powell A, Armstrong P. Plasma biomarkers for early diagnosis of acuteintestinal ischemia. Semin Vasc Surg 2014; 27: 170–5.
24. Kurt Y, Akin ML, Demirbas S, et al. D-dimer in early diagnosis of acute mesenteric ischemia secondary to arterial occlusion in rats. Eur Surg Res 2005; 37: 216-9.
25. Kanda T, Fujii H, Tani T. Intestinal fatty acid-binding protein is a useful diagnostic marker for mesenteric infarction in humans. Gastroenterology 1996; 110: 339–43.
26. Cudnik MT, Darbha S, Jones J, Macedo J, Stockton SW, Hiestand BC. The diagnosis of acute mesenteric ischemia: A systematic review and meta-analysis. Acad Emerg Med 2013; 20: 1087-100.
27. Block T, Nilsson TK, Björck M, Acosta S. Diagnostic accuracy of plasma biomarkers for intestinal ischaemia. Scand J Clin Lab Invest 2008; 68: 242-8.
28. Diebel LN, Wilson RF, Dulchavsky SA, Saxe J. Effect of increased intraabdominal pressure on hepatic arterial, portal venous, and hepatic microcirculatory blood flow. J Trauma 1992; 33: 279-82.
29. Acosta S, Nilsson TK, Bjorck M. D-dimer testing in patients with suspected acute thromboembolic occlusion of the superior mesenteric artery. Br J Surg 2004; 91: 991-4.
30. Stirrat A, Gallagher M, Douglas SA. Potent vasodilator responses to human urotensin-II in human pulmonary and abdominal resistance arteries. Am J Physiol Heart Circ Physiol 2001; 280: 925–8.
31. Katano Y, Ishihata A, Aita T, Ogaki T, Horie T. Vasodilator effect of urotensin II, one of the most potent vasoconstricting factors, on rat coronary arteries. Eur J Pharmacol 2000; 402: 5-7.

Original Article

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The effectiveness of concomitant intravaginal laser treatment in patients undergoing mesh excision due to vaginal exposure or extrusion

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ABSTRACT

Objective: To investigate the efficacy of intravaginal laser therapy applied concurrently with mesh excision for the treatment of vaginal polypropylene mesh exposure or extrusion, which is the most common complication after transobturator tape (TOT), on the recurrence of incontinence.

Material and Method: The data of 49 patients who underwent mesh excision due to vaginal mesh exposure or extrusion in our clinic between January 2009 and January 2020 were retrospectively analyzed. The patients were divided into two groups as simultaneous intravaginal laser therapy during the mesh excision (EL, n=23) and only mesh excision (EO, n=26). Data of the patients and long-term stress urinary incontinence (SUI) recurrence rates were determined and the groups were compared.

Results: The mean age of the patients was 50.4±9.9 years and the mean follow-up period was 33.3±22.1 months. SUI recurrence in 1-h pad test was significantly lower in the EL group than the EO group at the 12 th month evaluation (8.7% vs 34.6% p=0.030 respectively). According to multivariate regression analysis operation type was an independent risk factor for SUI recurrence (p=0.021). However, there was no significant difference between the groups in terms of postoperative incontinence quality of life questionnaire (I-QOL) scores (p=0.082).

Conclusion: Concomitant laser treatment applied with the mesh excision for the treatment of vaginal meshexposure or extrusion secondary to TOT surgery provides a significant advantage in preventing the recurrence of SUI.

Keywords: Laser therapy, mesh erosion, incontinence recurrence

INTRODUCTION

Stress urinary incontinence (SUI) is involuntary incontinence caused by increased intra-abdominal pressure such as coughing, laughing, and weight lifting that affects approximately 45-50% of women (1). Surgical treatment methods of SUI include bulking agents, open or laparoscopic pubovaginal sling or Burch colposuspension or mid-urethral sling procedures (2). Mid-urethral sling procedures and minimally invasive methods have become the first choice in the surgical treatment of SUI due to their many advantages such as easy application, cost effective, short learning curve, short operation time and high success rates (3).Despite the many advantages that mid-urethral sling procedures provide, polypropylene mesh (PPM) exposure or extrusion, which is reported to be approximately 3.8-15 %, is the most common complication of these surgeries (4). It has been reported that within 5 years after mid-urethral sling surgeries, 3.7% require additional treatment due to recurrent SUI secondary to mesh excision (5). It has been reported that after partial or total mesh removal performed due to vaginal extrusion, up to 40% of SUI recurs in patients and therefore second anti-incontinence surgery or concomitant surgery is required (6). Recently, more minimally invasive and easily applicable laser therapy methods have been used in the treatment of SUI in order to reduce the complications of sling materials, and success rates comparable to mid-urethral sling procedures have been reported (7,8). Although laser applications are used as the primary treatment method in SUI, there is not enough data in the literature regarding the efficacy of laser treatments applied simultaneously with the mesh removal operation

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performed due to vaginal PPM exposure or extrusionto prevent recurrence of incontinence. Therefore, in this study, we aimed to evaluate the efficacy of erbium-doped yttrium aluminum garnet (Er: YAG) laser therapy, which we applied concomitantly, in preventing SUI recurrence in patients underwent PPM excision due to vaginal mesh exposure or extrusion.

MATERIAL AND METHOD

After obtaining approval from the ethics committee of Health Sciences University Keçiören Training and Research Hospital (Date: 22.06.2021, No:2012-KAEK-15/2335), the data of 56 patients who underwent mesh excision due to vaginal PPM exposure or extrusion secondary to transobturator tape (TOT) surgery in our clinic between January 2009 and January 2020 were retrospectively analyzed. All of the study process was carried out accordance with the ethical rules and the principles of the Declaration of Helsinki. Data of 49 of these patients with a median 1.4 (0.5-2.6) cm mesh exposure or extrusion were available for the study.Seven of the patients who developed mesh extrusion were excluded due to missing data. The patients were divided into two groups as those who received concomitant Er: YAG laser treatment (excision + laser=EL) and those who underwent excision only (EO). All the patients with vaginal mesh exposure or extrusion were informed about possible SUI incontinence recurrence after mesh excision and positive efficacy and possible side effects of laser treatment methods and informed consent forms were obtained. After an informed discussion, decisions for EL or EO procedures were made according to patient's preferences and the physician's recommendations. Patients who received medical treatment after mesh excision due to urge urinary incontinence, over active bladder or with urge-predominant mixed urinary incontinence were excluded. Other exclusion criteria were the presence of severe obesity with a body mass index> 35 during excision, cystocele requiring additional surgery, rectocele, pelvic organ prolapse, previous additional vaginal-gynecological operation, or a history of irradiation. In both groups, all patients received intravaginal estradiol therapy for at least 6 months prior to mesh excision in the preoperative period. Urine analysis and urine culture, preoperative urodynamics (UD), stress and Q-tip test with vaginal examination, and cystoscopy were routinely performed for all patients before mesh excision surgery. Cystocele gradings were classified according to the SWIFT classification (9). One-hour pad test was used to determine the presence of incontinence before and 12 months after the operation. Postoperative 1-h pad test results were taken as a basis for determining SUI recurrence. In 1-h pad test, an increase in pad weight of more than 2 g in one hour was considered as SUI presence (10). To determine quality of life in the postoperative period, we used the Incontinence Quality of Life Questionnaire (I-QOL) form, which is validated for Turkish (11). In the EO group, after 16-18 fr urethral catheterization in lithotomy position under spinal anesthesia, the vaginal erosive mesh area of the patients was identified and marked, and eroded piece of the mesh was separated from the vaginal mucosa with sharp-blunt dissections and removed partially. At this stage, care was taken to protect the vaginal mucosa outside the eroded area and no additional mucosal dissection was performed. The part of the mesh entering both obturator foramen was not removed. Following the procedure, vaginal mucosa was closed with 2/3-zero absorbable suture (Vicryl®) and the procedure was completed. In the EL group, mesh excision was performed similarly to the EO group; then, a single session non-ablative 2940 nm (10J / cm^2 fluence and 7 mm spot size) Er: YAG laser (Asclepion Juliet Er:YAG Lazer,Med-Laser,Turkey) treatment was applied to the anterior vaginal wall following suture closure of the surgical incision line.At this stage, care was taken not to apply laser energy directly above the suture line. Laser energy was applied to the vaginal mucosa and the suburethral area around the suture line.Laser treatment was performed in three phases. In the first phase, full circumference of the vaginal canal was irradiated applying two passes around 650J of laser energy. In the second phase, a 900 angular adapter was used and the anterior vaginal wall was irradiated with a fractionated smooth beam using several longitudinal passes with total 250J of energy. Then, following the second phase, vestibular mucosa and introitus were irradiated directly with fractionated smooth beam in three passes with a 100J of energy.

In the postoperative period, no additional treatment like vaginal estradiol was given to the patients. Patients in both groups were invited for a follow-up at the 12th month and evaluated with 1-h pad-test to determine SUI presence. Patients who did not have SUI in the 1-h pad test before mesh excision and who were found to have SUI in the 1-h pad test at the 12th month after excision were considered to have recurrence of SUI. After the 12th month, the patients were called for a follow-up once a year for 5 years.

Statistical Analysis

All statistical analyses were performed using the SPSS 24.0 (IBM Corp., Chicago) software for Windows. Descriptive statistics are given as "frequency" and "description." For data with normal distribution,

independent samples-t test was used as means and standard deviation. In the univariate analysis, Chi-Square Test was used for nominal data, while the Mann-Whitney U test was used for nonparametric variables. A p-value of <0.05 was considered statistically significant. Univariate regression analysis was performed to predict SUI recurrence. Multivariate regression analysis was performed by creating a model with values of p<0.1 in univariate analysis.

RESULTS

The mean age of the patients was 50.4±9.9 years and the mean follow-up period was 33.3±22.1 months. 23 (46.9%) of the patients were in the EL group and 26 (53.1%) were in the EO group. Mean operation time was 35.6±6.0 minutes and mean hospital stay was 1.1±0.3 days. 17 of the patients (34.6 %) had SUI in the 1-h pad test in postoperative 12th month. The general characteristics of the patients are shown in **Table 1.** The mean age was 51.2±10.7 years in the EL group and 49.8±9.3 years in EO group (p=0.634). The mean follow-up period was 27.7±17.8 months in the EL group and 38.3±24.6 months in EO group (p=0.097). However, the mean operation time was 37.3±5.8 minutes in the EL group and 34.0±5.8 minutes in the EO group (p=0.049).There was no significant difference between the EL and EO groups in terms of excised mesh length (1.73±0.6 cm vs 1.68±0.5 cm, p=0.723). According to the postoperative 1-h pad test, 2 (8.7%) of the patients in the EL group and 9 (34.6) in the EO group had SUI recurrence (p=0.030). However, there was no significant difference between the groups in terms of I-QOL scores at the 12th month (p=0.082) (**Table 2**).

A univariate analysis was performed to predict the factors on SUI recurrence. The parameters for univariate regression analysis were age, BMI, operation time, preoperative pad/day, excised mesh length, and operation type (**Table 3**). Then,a multivariate regression analysis was performed to predict SUI recurrence using operation type (EL or EO), excised mesh length, and BMI variables. According to this model, operation type was an independent risk factor for SUI recurrence (p=0.021) (**Table 4**).

Table 1. Baseline characteristics of the patients (n=49)

Age, mean±SD, years	50.4±9.9
Body mass index, mean±SD, kg/m²	27.5±2.5
Follow-up, mean±SD, months	33.3±22.1
Preoperative vaginal mesh exposure, n (%)	41 (83.7%)
Preoperative vaginal mesh extrusion, n (%)	8 (16.3%)
Operation time, mean±SD, minutes	35.6±6
Hospitalization, mean±SD, days	1.1±0.3
Postoperative I-QOL score, mean±SD	20.9±23.5
Preoperative SUI (1-h pad> 2 gr) n (%)	6 (12.2%)
Postoperative SUI (1-h pad> 2 gr) n (%)	17 (34.6%)
Postoperative SUI recurrence, n (%)	11 (22.4%)
Complications, n (%)	
Vaginal wound infection	6 (12.2%)
Dyspareunia	6 (12.2%)
Total	12 (24.5%)

*SD:Standard deviation, IQO-L: Incontinence Quality of Life Questionnaire, SUI: Stress Urinary Incontinence

Table 2. Comparison of the patients in both groups

	EL (n =23)	EO (n =26)	p
Age, mean±SD, years	51.2±10.7	49.8±9.3	0.634
Body mass index, mean±SD	27.5±2.7	27.4±2.3	0.887
Follow-up, mean±SD, months	27.7±17.8	38.3±24.4	0.097
Operation time, mean±SD, minutes	37.3±5.8	34.0±5.8	0.049*
Hospitalization, mean±SD, days	1.2±0.5	1.1±0.4	0.460
Excised mesh length, mean±SD, cm	1.73±0.6	1.68±0.5	0.723
Postoperative I-QOL score, mean±SD	13.2±16.9	27.8±26.6	0.082
Preoperative SUI (1-h pad>2g) n (%)	2 (8.7%)	4 (15.4%)	0.476
Postoperative SUI (1-h pad>2 g) n (%)	4 (17.4%)	13 (50.0%)	0.041*
Postoperative SUI recurrence, n (%)	2 (8.7%)	9 (34.6%)	0.032*
Complication, n (%)	4 (17.4%)	8 (30.8%)	0.115
Vaginal wound infection	3 (13.0%)	3 (11.5%)	0.873
Dyspareunia	1 (3.8%)	5 (21.7%)	0.057

*SD:Standard deviation, IQO-L: Incontinence Quality of Life Questionnaire, SUI: Stress Urinary Incontinence

Table 3. Univarite regression analyses for predicting SUI recurrence

	R + (n =16)	R - (n =33)	p
Age, mean±SD, years	48.87±10.1	51.27±10.1	0.434
Body mass index, mean±SD	28.37±2.7	27.10±2.4	0.092
Operation time, mean±SD, minutes	33.75±5.6	36.51±6.1	0.132
Preoperative pad / day, mean±SD (n)	0.75±0.9	0.60±0.8	0.535
Excised mesh length, mean±SD,cm	1.90±0.6	1.60±0.5	0.079
Operation type, n (%)	23 (47)	26(53)	0.032*

SUI: Stress urinary incontinence, R+: Recurrence +, R-: Recurrence -, SD: Standard deviation

Table 4. Multivariate regression analysis results for predicting SUI recurrence

Variables	Regression coefficients		95% CI		p
	B	SE	Lower Limit	Upper Limit	
Constant	8.22	4.04			0.042
Operation type	1.8	0.78	0.04	0.77	0.021*
Excised mesh length	1.18	0.68	0.848	12.36	0.086
BMI	0.22	0.41	0.95	1.64	0.117

CI:Confidence intervals, B: Unstandardized beta, SE:Standard error, and BMI: Body-massindex.

DISCUSSION

Mid-urethral sling operations have been considered as the first choice in the surgical treatment of SUI due to the high success rates reported, the ease of application, and other advantages it provides (12). Although autologous transobturator rectus fascia is used in limitedly selected patients with a history of hypersensitivity to polypropylene and similar materials, currently PPM is the most preferred sling material in mid-urethral sling operations due to its ease of application and no need for additional surgical operation (13). Despite their advantages, the most common complication of PPM suspension materials is vaginal mesh exposure and extrusion and intraurethral or intravesical erosion (14). Studies have reported that re-operation is required for PPM erosion at a rate of approximately 2-12% after either retropubic sling, TOT or mini-sling surgeries in the long-term (15). The treatment of mesh exposure secondary to mid-urethral sling operations is partial or total removal of the mesh (16). However, various studies have reported that SUI recurs in approximately 30-60% of patients following the removal of the mesh (17). Jonathan et al. (18) reported the results of 102 patients who underwent revision due to mesh erosion. Accordingly, sling division was performed in 45 patients, mesh excision in 57, and SUI recurrence was observed at a rate of 13% in the division group and 56% in the excision group. Similar to the literature data, in our study, there was no significant difference between the groups in terms of SUI rates in 1-h pad test in the preoperative period, but the SUI recurrence was significantly higher in the EO group than in the EL group. These results support the idea that SUI recurrence is seen at a high rate following mesh excision and that additional surgery is required in these patients due to SUI. Although there is no definite recommendation in the literature, pubovaginal sling and open colposuspension surgeries are some secondary surgical treatment options of SUI developing after mid-urethral sling surgeries (19). Laparoscopic approaches and more minimally invasive methods in which the erosive mesh is removed locally are also shown as alternative surgical treatment options (20). Studies have shown that type-1 and type-3 collagen levels in the pubocervical fascia are significantly lower in patients with SUI and collagen reserves are further reduced as a result of decreased hormonal support with menopause, which triggers SUI by weakening the formations that support the vaginal hammock structure (21). The photothermal laser energy supports the collagen tissue in this area and strengthens the vaginal hammock structure and pelvic floor (22). As a result of these findings, laser therapy procedures have been used frequently as a minimally invasive treatment option and successful results have been reported at a level comparable to mid-urethral sling operations (7,8). Nobou (23) compared the results of TVT, TOT, and laser treatment in 50 patients and stated that the 1-h pad test and International Consultation of Incontinence Questionnaire Short Form (ICIQ-SF) score results showed considerable improvement in all three groups and were comparable to each other (p. <0.001 and p <0.001, respectively). In another recent study including a total of 114 postmenopausal women, Mija et al. (24) compared patients who received Er: YAG laser treatment and patients in the "sham" group who received no treatment in terms of SUI, quality of life, and improvement in sexual functions. The improvement in ICIQ-SF, pelvic organ prolapse, urinary incontinence, sexual questionnaire short form (PISQ-12), and the female sexual function index (FSFI) scores was significantly higher than the ''sham" group, with no serious side effects observed in any patient (p<0.001, p=0.014 and p=0.025 respectively). In another similar study, Andrzej et al. (25) reported the results of 59 patients applied Er: YAG laser treatment. The authors reported that intravaginal laser therapy provided significant improvement in patients with mild and moderate SUI, but did not provide sufficient improvement in patients with severe SUI. In another similar study, Erel et al. (26) reported the results of 82 patients treated with Er: YAG laser therapy for SUI. They found a significant improvement in ICIQ-SF and King's Health Questionnaire (KHQ-UI) scores after laser treatment (p<0.0001 and p <0.0001, respectively). In another study, Ogrinc et al. (27) reported the results of 175 patients (66% with SUI and 34% with mixed urinary incontinence) who received Er: YAG laser treatment. According to their findings, a 77% improvement rate was observed in patients with SUI after intravaginal laser treatment, while there was a 34% improvement in patients with mixed urinary incontinence (MUI). Besides, there were no serious side effects other than minimal discomfort and pain during laser application. Similar to the literature, in our study, the SUI recurrence in the 1-h pad test was found to be significantly lower in the EL group compared to the EO group, but there was no significant difference between the groups in terms of I-QOL scores. Similar to the results reported in the primary treatment of patients with SUI or stress predominant MUI, we also observed that Er: YAG laser treatment contributed significantly to the reduction of SUI recurrence in patients with SUI who underwent mesh excision.The type of operation (EL or EO) performed was the only independent risk factor for SUI recurrence in the multivariate analysis, which also supports this finding. Moreover, we observed that concomitant laser treatment during mesh excision developing secondary to PPM exposure or extrusion did not cause serious

adverse effects, similar to the literature data, and the rates of complications were similar between the EL and EO groups. In our study, we determined no significant difference between the laser group and the excision group in terms of wound infection in the vaginal area where the mesh was excised in the postoperative period. The mean excised mesh length was similar between the groups, suggesting that the length of the excised part of the mesh had no effect on SUI recurrence. The mesh sections removed from our patients were not very long, which may have affected this finding. This points out that intravaginal laser treatment with concomitant applied during mesh excision can be performed safely as in primary SUI treatment, significantly reducing the need for additional surgery due to recurrent SUI. On the other hand, although there was no significant difference between the groups in our study, dyspareunia was less in the EL group in the postoperative period. The lack of a statistical difference between the groups in terms of dyspareunia may be related to the small number of patients in our study. In studies with larger samples, the rate of dyspareunia is likely to be significantly lower in the laser group, which is consistent with the idea that intravaginal laser therapy contributes positively to sexual functions. Although there are many recent studies reporting positive results for the effectiveness of laser treatment in the primary treatment of SUI, there is not enough data on preventing SUI recurrence with laser therapy in patients who underwent mesh excision. We think more prospective and randomized studies with larger samples are needed in this area. Therefore, we believe that our study will make a significant contribution to the literature.

The most important limitation of our study is absence of randomization due to its retrospective nature. Another limitation is that SUI severity could not be differentiated as mild, moderate or severe in a 1-h pad test before excision or laser operations. In addition, the absence of long-term incontinence recurrence rates of the groups due tothe short follow-up time can be considered as another important limitation.

CONCLUSION

Intravaginal laser treatment can be applied effectively and safely simultaneously with the vaginal mesh excision that develops secondary to TOT surgery,as in primary SUI patients. Laser treatments contribute significantly to the reduction of SUI recurrence in patients undergoing mesh excision, and significantly reduces the need for additional anti-incontinent surgical intervention for the treatment of SUI recurrence.

ETHICAL DECLARATION

Ethics Committee Approval: Ethical approval was obtained from the ethics committee of Health Sciences University Keçiören Training and Research Hospital (Date: 22.06.2021, Decision No:2012-KAEK-15/2335).

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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REFERENCES

1. Takahashi S, Takei M, Nishizawa O, et al. Clinical guidelines for female lower urinary tract symptoms. Tokyo: The Neurogenic Bladder Society; 2013: 6–168.
2. Jarvis GJ. Surgery for genuine stress incontinence. Br J Obstet Gynaecol 1994; 101: 371–4.
3. Henriksson L, Ulmsten U. A urodynamic evaluation of the effects of abdominal urethrocystopexy and vaginal sling urethroplasty in women with stress incontinence. Am J Obstet Gynecol 1978; 131: 77–82.
4. Keršič M, Keršič M, Kunič T, et al. Single-incision mini-sling for the treatment of female stress urinary incontinence: is it actually inferior to transobturator vaginal tape and tension-free vaginal tape? Gynecol Minim Invasive Ther 2020; 9: 123-30.
5. Kenton K, Stoddard AM, Zyczynski H, et al. 5-year longitudinal follow-up after retropubic and transobturator midurethral slings the urinary incontinence treatment network. J Urol 2015; 193: 203–10.
6. Ramart P, Ackerman AL, Cohen SA, Kim JH, Raz S. The risk of recurrent urinary incontinence requiring surgery after suburethral sling removal for mesh complications. Urology 2017; 106: 203-9.
7. Fistonić N.Fistonić I.Guštek Š.F et al.Minimally invasive, non-ablative Er:YAG laser treatment of stress urinary incontinence in women–a pilot study.Lasers Med Sci 2016; 31: 635-43.
8. Pardo J, Sola VR, Morale AA. Treatment of female stress urinary incontinence with Erbium-YAG laser in non-ablative mode. Eur J Obstet Gynecol Reprod Biol 2016; 204: 1-4.
9. Swift S. Current opinion on the classification and definition of genital tract prolapse. Curr Opin Obstet Gynecol 2002; 14: 503-7.
10. Orgensen L, Lose G, Anders J. One-hour pad weighing test for objective assessment of female incontinence. Obstet Gynecol 1987; 69: 39-43.
11. Eyigor S, Karapolat H, Akkoc Y, Yesil H, Ekmekci O. Quality of life in patients with multiple sclerosis and urinary disorders: reliability and validity of Turkish-language version of Incontinence Quality of Life Scale. J Rehabil Res Dev 2010; 47: 67-71.
12. Burkhard FC, Bosch JLHR, Cruz F et al. EAU Guidelines. Edn. presented at the EAU Annual Congress Copenhagen 2018. ISBN 978-94-92671-01-1. 2018.

13. Niknejad K, Plzak LS, 3rd, Staskin DR, Loughlin KR. Autologous and synthetic urethral slings for female incontinence. Urol Clin North Am 2002; 29: 597-611.
14. Gomes CM, Carvalho FL, Bellucci CHS, et al. Update on complications of synthetic suburethral slings. Int Braz J Urol. 2017; 43: 822-34.
15. Berger AA, Tan-Kim J, Menefee SA. Long-term risk of reoperation after synthetic mesh midurethral sling surgery for stress urinary incontinence. Obstet Gynecol 2019; 134: 1047-55.
16. Welk B, Al-Hothi H, Winick-Ng J. Removal or revision of vaginal mesh used for the treatment of stress urinary incontinence. JAMA Surg 2015; 150: 1167-75.
17. Ismail S, Chartier-Kastler E, Reus C, Cohen J, Seisen T, Phé V. Functional outcomes of synthetic tape and mesh revision surgeries: a monocentric experience. Int Urogynecol J 2019; 30: 805-13.
18. Shaw J, Wohlrab K, Rardin C. Recurrence of stress urinary incontinence after midurethral sling revision: a retrospective cohort study. Female Pelvic Med Reconstr Surg 2017; 23: 184-7.
19. Bakali E, Johnson E, Buckley BS, Hilton P, Walker B, Tincello DG. Interventions for treating recurrent stress urinary incontinence after failed minimally invasive synthetic midurethral tape surgery in women. Cochrane Database Syst Rev 2019; 4: 9.
20. Yoshizawa T, Yamaguchi K, Obinata D, et al. Laparoscopic transvesical removal of erosive mesh after transobturator tape procedure. Int J Urol 2011; 18: 861–3.
21. Han L, Wang L, Wang Q, Li H, Zang H. Association between pelvic organ prolapse and stress urinary incontinence with collagen. Exp Ther Med 2014; 7: 1337–41.
22. El-Domyati M, Abd-El-Raheem T, Medhat W, Abdel-Wahab H, Anwer MA. Multiple fractional erbium: yttrium-aluminum-garnet laser sessions for upper facial rejuvenation: clinical and histological implications and expectations. J Cosmet Dermatol 2014;13: 30–7.
23. Okui N. Comparison between erbium-doped yttrium aluminum garnet laser therapy and sling procedures in the treatment of stress and mixed urinary incontinence. World J Urol 2019; 37: 885-9.
24. Blaganje M, Šćepanović D, Žgur L, Verdenik I, Pajk F, Lukanović A. Non-ablative Er:YAG laser therapy effect on stress urinary incontinence related to quality of life and sexual function: A randomized controlled trial. Eur J Obstet Gynecol Reprod Biol 2018; 224: 153-8.
25. Kuszka A, Gamper M, Walser C, Kociszewski J, Viereck V. Erbium:YAG laser treatment of female stress urinary incontinence: midterm data. Int Urogynecol J 2020; 31: 1859-66.
26. Erel CT, Inan D, Mut A. Predictive factors for the efficacy of Er:YAG laser treatment of urinary incontinence. Maturitas 2020; 132: 1-6.
27. Ogrinc UB, Senčar S, Lenasi H. Novel, minimally invasive laser treatment of urinary incontinence in women. Lasers Surg Med 2015; 47: 689–97.

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Comparison of thoracic epidural analgesia and thoracic paravertebral block in pain management after thoracotomy

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ABSTRACT

Aim: Thoracotomy is among the most painful surgical incisions and causes severe acute pain in the postoperative period. Many analgesic methods have been suggested for thoracotomy pain treatment. Thoracic epidural analgesia (TEA) and thoracic paravertebral block (TPVB) are common regional methods for post-thoracotomy pain. In this study, we aimed to compare the efficacy and the side effects of TEA and TPVB methods applied for post-thoracotomy analgesia.

Material and Method: After ethical committee approval, we retrospectively analyzed postoperative analgesia records of patients, who underwent thoracotomy, received TEA or TPVB for postoperative analgesia between 01.01.2019 and 01.01.2021. Visual analog scale (VAS) scores of the patients who received analgesic treatment for 24 hours postoperatively after TEA or TPVB application were evaluated.

Results: Data of 474 patients were found eligible for analysis. Demographic data of patients, VAS scores, patient satisfaction, and additional analgesic requirements were not statistically significant between the groups ($p>0.05$). Nausea-vomiting, hypotension, headache, itching, and sweating was statistically significantly higher in the TEA group when compared to patients who underwent TPVB ($p<0.05$).

Conclusion: In the present study, in the early postoperative pain management after thoracotomy; it was observed that preemptive TPVB and postoperative IV patient-controlled analgesia (PCA) and TEA provided similar VAS scores and additional analgesic requirements. On the other hand, postoperative complications were observed less frequently in patients who underwent TPVB with postoperative IV PCA compared to TEA. Therefore, TPVB may be a good alternative to prevent acute pain after thoracotomy.

Keywords: Pain, postoperative acute pain, thoracic epidural analgesia, thoracic paravertebral block, thoracotomy

INTRODUCTION

Thoracotomy causes significant trauma to pain-sensitive structures such as muscle layers, fascia, neurovascular bundles, bone, joints, and parietal pleura. For this reason, it is among the most painful surgical incisions and causes severe acute pain in the postoperative period (1,2). Acute pain, on the other hand, increases postoperative morbidity and prolongs hospital stay (3). If thoracotomy-related pain is not adequately treated, chronic pain may develop after thoracotomy and may prevent patients from regaining their normal activities for a long time (4,5).

Many analgesic methods have been suggested for thoracotomy pain treatment. Some of these are thoracic epidural analgesia (TEA), thoracic paravertebral block (TPVB), plane blocks, intercostal nerve blocks, pleural blocks, as well as systemic and intrathecal analgesics (6-8). Although the risk of spinal hematoma is not as high as in thoracic epidural catheterization, a normal coagulation profile is also required in block applications (9). TEA is still considered the gold standard technique for post-thoracotomy pain (10-12). The paravertebral space is a wedge-shaped space that extends on either side of the vertebral column and contains formations such as the spinal nerve, dorsal ramus, rami communicantes, and sympathetic chain (6). Administration of local anesthetic to the paravertebral area produces unilateral analgesia, somatic and sympathetic block, and this application is suitable for unilateral surgical procedures of the thoracic region (12). TPVB can be applied unilaterally or bilaterally. TEA affects bilaterally. Therefore, the TPVB technique, unlike TEA, can be used

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to avoid the contralateral sympathetic block. Thus, it minimizes the possibility of hypotension and maintains blood pressure (13). There are studies suggesting that complications such as postoperative nausea-vomiting, hypotension, and urinary retention are less common after TPVB application compared to TEA application (14,15).

In this study, we aimed to compare the efficacy and the side effects of TEA and TPVB methods applied for post-thoracotomy analgesia in postoperative acute pain.

MATERIAL AND METHOD

The study was initiated with the approval of the Keçiören Training and Research Hospital Clinical Researchs Ethics Committee (Date: 11.05.2021, Decision No: 2012-KAEK-15/2307). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

The data of the patients who had elective thoracic surgery between 01.01.2019 and 01.01.2021 in our clinic were analyzed retrospectively. Patients, who underwent thoracotomy, received TEA or TPVB for postoperative analgesia, were 18-80 years old, and were in the American Society of Anesthesiologists (ASA) I, II, and III physical status. The visual analog scale (VAS) values at the rest of the patients who received analgesic treatment for 24 hours postoperatively after TEA or TPVB application were evaluated. All patients were informed about the application and their informed consent was obtained. We excluded patients who were under the age of 18, or over the age of 80, or did not undergo thoracotomy, or were operated under emergency conditions, or had chronic pain before the operation, and constantly used analgesics. Postoperative kinking, catheter dislocation, and occlusion associated with the epidural catheter were defined as "catheter failure". The patients were divided into 2 groups: TPVB and TEA (**Figure 1**).

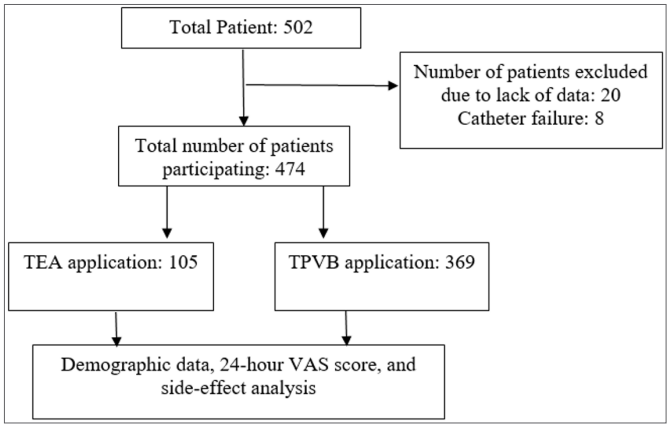

Figure 1. Flow chart of the patients. TEA: Thoracic Epidural Analgesia. TPVB: Thoracic Paravertebral Block.

TEA and TPVB Protocols in Participating Patients

In the preoperative anesthesia outpatient clinic, TEA and TPVB were explained in detail to the patients who were planned for thoracotomy. If the patients gave consent, TEA was preferred first. Most of the patients preferred TPVB application instead of TEA. Intravenous (IV) patient-controlled analgesia (PCA) was applied to the patients who did not accept either of these methods.

For the patients in the TEA group, in the sitting position, after the skin was cleaned with the strict antisepsis rules and covered, skin anesthesia was performed with 3 ml 2% prilocaine. The epidural space was entered from the T5-T6 or T6-T7 vertebral spaces with an 18-Gauge Tuohy needle using the median approach and hanging drop method. Four cm of the catheter was left in the epidural space. To exclude vascular and intrathecal injection, a test dose (5 µg/ml (1:200.000) adrenaline and 3 ml 2% lidocaine) was administered through the epidural catheter and the patients were placed in the supine position. The bilateral block was evaluated with a pin-prick test. In the intraoperative period; for epidural analgesia, 67.5 ml of 0.5% bupivacaine, 201.5 ml of saline, and 10 mg/1 ml of morphine were mixed with a 270 ml elastomeric infusion pump. A concentration of 0.125% bupivacaine infusion was started and was given epidurally for 3 days postoperatively, starting with an elastomeric pump at a rate of 4 ml/h. In our study, we considered the first 24-hour follow-up to compare with TPVB.

For general anesthesia induction, 2 mg/kg propofol, 0.1 mg/kg vecuronium, and 1µg/kg fentanyl were administered intravenously (IV). Anesthesia was maintained in both groups with 50% – 100% O2 – air mixture and 2% sevoflurane administration with remifentanil infusion (0.01-0.20 mcg/kg/min). If the continuation of neuromuscular blockade is necessary, IV 0.03 mg/kg vecuronium was administered. At the end of the surgery, 50 mg IV dexketoprofen and 100 mg IV tramadol were administered for analgesia, and 10 mg IV metoclopramide as an antiemetic.

For the patients in the TPVB group; under general anesthesia, after the skin was cleaned with strict antisepsis rules and covered in the lateral decubitus position, the ultrasound (US) probe was placed 2-3 cm lateral to the T5 spinous process just before the surgery. After imaging the transverse process, musculature up to the transverse process, paravertebral area, internal intercostal membrane, and pleura, the needle was advanced to the paravertebral area in the cauda-cranial direction with the in-plane technique. Analgesic treatment of the patients was continued with postoperative IV PCA. Postoperative analgesia was provided by the IV PCA method in the surgical intensive

care unit. According to our PCA protocol; 400-500 mg of tramadol was added into 100 ml of isotonic sodium chloride. Thus, a concentration of 4-5 mg/ml tramadol was obtained. It was adjusted to be 10 mg/hour basal infusion, 5-20 mg bolus, 20-30 minutes lock-in time, and 4 hours limit of 100 mg. IV PCA treatment was applied for 24 hours.

A paracetamol dose of 1 g every 8 hours and a dexketoprofen dose of 50 mg twice daily were administered intravenously for multimodal analgesia. 50 mg IV tramadol was given as an "additional analgesic" to patients with a VAS value of 4 and above.

Age, gender, body mass index (BMI), ASA physical status, diagnosis, the type of surgery, duration of anesthesia, VAS values in postoperative 24 hours, analgesic treatment given, additional analgesic need, patient satisfaction, and side effects related to analgesic treatment were recorded. Patient satisfaction was determined as satisfied, moderately satisfied, and dissatisfied.

Statistical Analyses

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by the Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean±standard deviation (SD) and median (minimum-maximum value). Categorical data were described as a number of cases (%). Statistical analysis differences in not normally distributed variables between two independent groups were compared by the Mann Whitney U test. Categorical variables were compared using Pearson's Chi-Square Test or Fisher's Exact test. It was accepted $p < 0.05$ as a significant level on all statistical analyses.

RESULTS

The data of 502 patients who underwent elective thoracic surgery and underwent TEA or TPVB between 01.01.2019 and 01.01.2021 were analyzed retrospectively. 28 of these patients were excluded from the study due to a lack of data. Data of 474 patients were found eligible for analysis.

In terms of demographic data when patients were compared, no statistically significant difference was observed in both groups ($p > 0.05$), (**Table 1**).

In terms of VAS scores, patient satisfaction, and additional analgesic requirement; there was no statistically significant difference between TEA and TPVB groups ($p>0.05$) (**Table 2**, **Figure 2**, **Figure 3**).

Table 1. Demographics Characteristics of Patients

	TPVB (n:369)	TEA (n:105)	p
Age			0.835
Mean±SD	53.66±15.70	55.44±12.52	
Median (min-max)	58 (18-80)	56 (20-78)	
Gender			0.058
Female	116 (31.4%)	17 (21.9%)	
Male	253 (68.6%)	88 (78.1%)	
BMI			0.07
Mean±SD	26.92±4.29	26.04±4.49	
Median (min-max)	26.64 (18-35)	26.04 (18-35)	
ASA			0.139
ASA II	123 (33.3%)	27 (25.7%)	
ASA III	246 (66.7%)	78 (74.3%)	
Diagnosis			0.120
Lung cancer	283 (76.7%)	79 (75.2%)	
Bronchiectasis	14 (3.8%)	11 (10.5%)	
Hydatid Cyst	24 (6.5%)	6 (5.7%)	
Pleural thickening/effusion	29 (7.9%)	4 (3.8%)	
Interstitial Lung Disease	2 (0.5%)	-	
Other	17 (4.6%)	5 (4.8%)	
Operation type			0.777
Thoracotomy	286 (77.5%)	80 (76.2%)	
VATS + Thoracotomy	83 (22.5%)	25 (23.8%)	
Operation			0.085
Lung Resection	221 (59.9%)	71 67.6%)	
Pneumonectomy	37 (10%)	15 (14.3%)	
Exploration-Decortication	45 (12.2%)	9 (8.6%)	
Cystotomy	23 (6.2%)	6 (5.7%)	
Other	43 (11.7%)	4 (3.8%)	
Anesthesia Duration			0.056
Mean±SD	268.2±72.14	259.5±29.63	
Median (min-max)	270 (82-660)	245 (190-325)	

Continuous variables were expressed as mean±standard deviation (SD) and median (minimum-maximum value). Categorical variables were expressed as frequency (percentage). Continuous variables were compared with Mann Whitney U-Test, and categorical variables were compared using Pearson's Chi-Square Test or Fisher's Exact Test. Statistically significant $p<0.05$ are in bold. ASA: American Society of Anesthesiologists. TPVB: Thoracic Paravertebral Block. TEA: Thoracic Epidural Analgesia. BMI: Body Mass Index. VATS: Video-Assisted Thoracoscopic Surgery.

Table 2. Patients' visual analog scale scores, additional analgesic requirements and patient satisfaction

		TPVB (n:369)	TEA (n:105)	p
VAS 1st hour	Mean±SD Median (min-max)	4.12±1.30 4 (0-8)	3.90±1.11 4 (2-7)	0.061
VAS 2nd hour	Mean±SD Median (min-max)	3.59±1.21 4 (0-7)	3.48±1.02 3 (2-6)	0.344
VAS 6th hour	Mean±SD Median (min-max)	3.11±1.14 3 (0-7)	2.99±0.95 3 (1-6)	0.318
VAS 12th hour	Mean±SD Median (min-max)	2.56±0.89 2 (0-6)	2.52±0.82 2 (1-5)	0.664
VAS 24th hour	Mean±SD Median (min-max)	2.03±0.93 2 (0-5)	1.95±0.79 2 (1-4)	0.270
Additional Analgesic Requirements		84 (22.8%)	19 (18.1%)	0.306
Patients satisfaction	Moderately satisfied	79 (21.4%)	29 (27.6%)	0.181
	Satisfied	290 (78.6%)	76 (72.4%)	

Continuous variables were expressed as the mean±standard deviation (SD) and median (minimum-maximum value,) and categorical variables are expressed as either frequency (percentage). Continuous variables were compared with Mann Whitney U Test, and categorical variables were compared using Pearson's Chi-Square Test or Fisher Exact Test. Statistically significant p-values are in bold. TPVB: Thoracic Paravertebral Block. TEA: Thoracic Epidural Analgesia. VAS: Visual Analog Scale

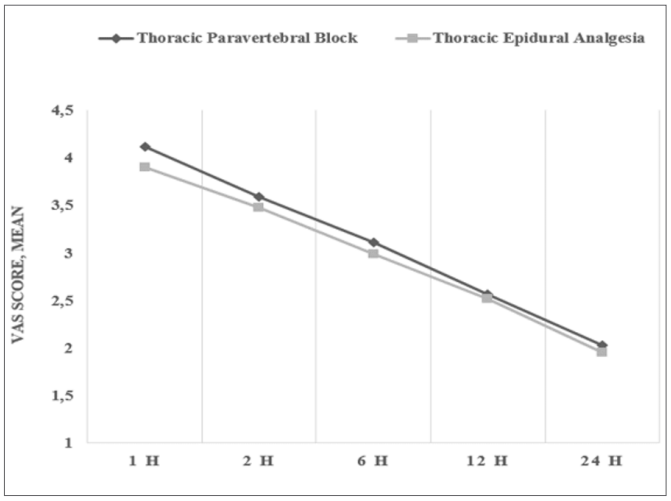

Figure 2. Mean Visual Analog Scale levels of patients over time. VAS: Visual Analog scale.

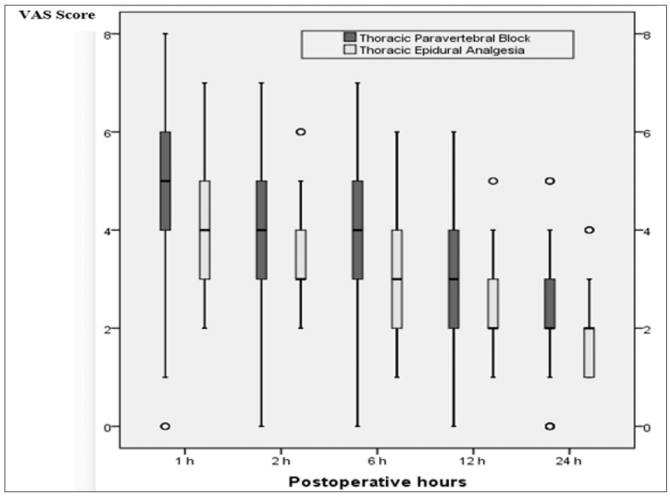

Figure 3. Median, minimum and maximum Visual Analog Scale levels of patients over time. VAS: Visual Analog Scale.

For patients who underwent TEA; nausea-vomiting, hypotension, headache, itching, and sweating were statistically significantly higher compared to patients who underwent TPVB ($p < 0.05$). In terms of bradycardia, there was no statistically significant difference between the groups ($p > 0.05$), (**Table 3**).

Table 3. Evaluation of the patients in terms of side effects

	TPVB (n:369)	TEA (n:105)	p
Nausea/vomiting	6 (1.6%)	12 (11.4%)	**<0.001**
Hypotension	20 (5.4%)	13 (12.4%)	**0.013**
Bradycardia	1 (0.3%)	2 (1.9%)	0.125
Headache	-	7 (6.7%)	**<0.001**
Itching	-	5 (4.8%)	**<0.001**
Sweating	-	4 (3.8%)	**<0.001**
Respiratory depression	-	-	-

Categorical variables were expressed as either frequency (percentage). Variables were compared using Pearson's Chi-Square Test or Fisher Exact Test. Statistically significant p-values are in bold. TPVB: Thoracic Paravertebral Block. TEA: Thoracic Epidural Analgesia.

DISCUSSION

In our study, in early postoperative pain management after thoracotomy; we observed that preemptive TPVB and postoperative IV PCA application, and TEA administered with postoperative fixed infusion provided similar VAS scores and additional analgesic requirements. On the other hand, postoperative complications were observed less frequently in patients who underwent TPVB and IV PCA compared to TEA.

Thoracotomy is among the most painful surgical procedure. If not treated effectively, it increases postoperative pulmonary complications such as pain-related atelectasis, pulmonary embolism, and pneumonia in the early postoperative period (1). As a result, it increases postoperative morbidity and prolongs hospital stay (2). Another significant problem after thoracotomy is the development of chronic pain, and this may prevent patients from regaining their normal activities for a long time (3,4). Therefore, effective perioperative analgesia is one of the most vital elements in thoracotomy (6,7). Effective postoperative analgesia is the method in which multimodal techniques are applied. Multimodal analgesia provides both comprehensive analgesias and limits the side effects via lower dose usage of opioid analgesics. One of the most important components of multimodal analgesia is regional techniques (6-8). TEA and TPVB are regional methods that have been used for many years in pain after thoracotomy (10,11).

TEA is a regional analgesia method that is still used as the gold standard for post-thoracotomy pain. There are studies showing that TPVB, which has been widely applied in recent years, provides a similar or even more effective analgesic effect than TEA (12,16-19). The analgesic effect due to TPVB occurs with unilateral somatic and sympathetic block effects. By providing a block in the upper and lower dermatomal area in the application area, pain levels that may occur along the thoracotomy line can be achieved as in TEA (12,19). In our study, it was found that similar pain scores were obtained with TEA and the rates of additional analgesics used were similar. These results are consistent with the literature and we think that TPVB is an effective analgesic method in acute pain after thoracotomy.

Undesirable complications such as hypotension, bradycardia, nausea-vomiting, and urinary retention that may occur due to sympathetic block after TEA limit its use (13,20). In addition; the increase in the use of anticoagulants due to the increase in the elderly patient population and cancer surgery applications in recent years has led to alternative methods due to catastrophic complications such as epidural hematoma that may develop after TEA (6,21,22). The most frequently used of these applications is the TPVB application. In TPVB, the somatic effect due to the block is prominent and a limited

level of sympathetic block develops. In addition, it is safe in terms of avoiding epidural hematoma and similar complications due to its distance from the epidural area (14,15,17,18). In our study, complication rates were also quite limited in the TPVB group compared to TEA, and this shows that TPVB can be used safely in post-thoracotomy pain.

Acceleration of postoperative recovery (ERAS) protocols, which have become an important issue in thoracic surgery in recent years, especially support opioid-free and low complication rate analgesia protocols (23,24). The purpose of ERAS protocols is to reduce the complication rate by making the least intervention with the least complication and to ensure that the patients are discharged quickly and without problems (25,26). It is claimed that paravertebral blockade provides analgesia equivalent to epidural analgesia (27). In our study, only local anesthetic administration and postoperative analgesia with tramadol, a weak opioid, in TPVB application may be a suitable alternative in the ERAS protocol, since it reduces the complications that may develop with potent opioids.

We have some limitations in our study. First of all, our study is single-center and retrospective. In addition, the effects of these two methods on chronic pain could not be evaluated because the long-term records of the patients could not be reached.

CONCLUSION

In our study, in early postoperative pain management after thoracotomy; it was observed that preemptive TPVB with postoperative IV PCA application and TEA provided similar VAS scores and additional analgesic requirements. On the other hand, postoperative complications were observed less frequently in patients who underwent TPVB and postoperative IV PCA compared to TEA. As stated in the ERAS protocols, TPVB can provide equivalent analgesia to TEA. Therefore, TPVB may be a good alternative to prevent acute pain in the post-thoracotomy period.

ETHICAL DECLARATION

Ethics Committee Approval: The study was initiated with the approval of the Keçiören Training and Research Hospital Clinical Researchs Ethics Committee (Date: 11.05.2021, Decision No: 2012-KEAK-15/2307).

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 of 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.

REFERENCES

1. Tamura T, Mori S, Mori A, et al. A randomized controlled trial comparing paravertebral block via the surgical field with thoracic epidural block using ropivacaine for post-thoracotomy pain relief. J Anesth 2017; 31: 263-70.
2. Sentürk M, Ozcan PE, Talu GK, et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. Anesth Analg 2002; 94: 11-5.
3. Khalil AE, Abdallah NM, Bashandy GM, Kaddah TA. Ultrasound-guided serratus anterior plane block versus thoracic epidural analgesia for thoracotomy pain. J Cardiothorac Vasc Anesth 2017; 31: 152-8.
4. Ochroch EA, Gottschalk A. Impact of acute pain and its management for thoracic surgical patients. Thorac Surg Clin 2005; 15: 105-21.
5. Rogers ML, Henderson L, Mahajan RP, Duffy JP. Preliminary findings in the neurophysiological assessment of intercostal nerve injury during thoracotomy. Eur J Cardiothorac Surg 2002; 21: 298-301.
6. Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy--a systematic review and meta-analysis of randomized trials. Br J Anaesth 2006; 96: 418-26.
7. Joshi GP, Bonnet F, Shah R, et al. A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. Anesth Analg 2008; 107: 1026-40.
8. Schnabel A, Reichl SU, Kranke P, Pogatzki-Zahn EM, Zahn PK. Efficacy and safety of paravertebral blocks in breast surgery: a meta-analysis of randomized controlled trials. Br J Anaesth 2010; 105: 842-52.
9. Madabushi R, Tewari S, Gautam SK, Agarwal A, Agarwal A. Serratus anterior plane block: a new analgesic technique for post-thoracotomy pain. Pain Physician 2015; 18: E421-4.
10. Barbera C, Milito P, Punturieri M, Asti E, Bonavina L. Serratus anterior plane block for hybrid transthoracic esophagectomy: a pilot study. J Pain Res 2017; 4: 73-7.
11. Özden Omaygenç D, Çıtak N, İşgörücü Ö, et al. Comparison of thoracic epidural and intravenous analgesia from the perspective of recovery of respiratory function in the early post-thoracotomy period in lung cancer surgery. Turk Thorac J 2021; 22: 31-6.
12. Karmakar MK. Thoracic paravertebral block. Anesthesiology 2001; 95: 771-80.
13. D'Ercole F, Arora H, Kumar PA. Paravertebral block for thoracic surgery. J Cardiothorac Vasc Anesth 2018; 32: 915-27.
14. Fang B, Wang Z, Huang X. Ultrasound-guided preoperative single-dose erector spinae plane block provides comparable analgesia to thoracic paravertebral block following thoracotomy: a single center randomized controlled double-blind study. Ann Transl Med 2019; 7: 174.
15. Wojtyś ME, Wąsikowski J, Wójcik N, et al. Assessment of postoperative pain management and comparison of effectiveness of pain relief treatment involving paravertebral block and thoracic epidural analgesia in patients undergoing posterolateral thoracotomy. J Cardiothorac Surg 2019; 14: 78.

16. Yeung JH, Gates S, Naidu BV, Wilson MJ, Gao Smith F. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. Cochrane Database Syst Rev 2016; 2: CD009121.
17. Detterbeck FC. Efficacy of methods of intercostal nerve blockade for pain relief after thoracotomy. Ann Thorac Surg 2005; 80: 1550-9.
18. Kotzé A, Scally A, Howell S. Efficacy and safety of different techniques of paravertebral block for analgesia after thoracotomy: a systematic review and metaregression. Br J Anaesth 2009; 103: 626-36.
19. Richardson J, Sabanathan S, Jones J, Shah RD, Cheema S, Mearns AJ. A prospective, randomized comparison of preoperative and continuous balanced epidural or paravertebral bupivacaine on post-thoracotomy pain, pulmonary function and stress responses. Br J Anaesth 1999; 83: 387-92.
20. Kupersztych-Hagege E, Dubuisson E, Szekely B, et al. Epidural hematoma and abscess related to thoracic epidural analgesia: a single-center study of 2,907 patients who underwent lung surgery. J Cardiothorac Vasc Anesth 2017; 31: 446-52.
21. El Shora HA, El Beleehy AA, Abdelwahab AA, et al. Bilateral paravertebral block versus thoracic epidural analgesia for pain control post-cardiac surgery: a randomized controlled trial. Thorac Cardiovasc Surg 2020; 68: 410-6.
22. Conlon NP, Shaw AD, Grichnik KP. Postthoracotomy paravertebral analgesia: will it replace epidural analgesia? Anesthesiol Clin 2008; 26: 369-80.
23. Simpson JC, Bao X, Agarwala A. Pain management in enhanced recovery after surgery (ERAS) protocols. Clin Colon Rectal Surg 2019; 32: 121-8.
24. Gupta R, Van de Ven T, Pyati S. Post-thoracotomy pain: current strategies for prevention and treatment. Drugs 2020; 80: 1677-84.
25. Batchelor TJP, Ljungqvist O. A surgical perspective of ERAS guidelines in thoracic surgery. Curr Opin Anaesthesiol 2019; 32: 17-22.
26. Nicholson A, Lowe MC, Parker J, Lewis SR, Alderson P, Smith AF. Systematic review and meta-analysis of enhanced recovery programmes in surgical patients. Br J Surg 2014; 101: 172-88.
27. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg 2019; 55: 91-115.

Original Article

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Childhood renal tumors: surgical treatment and results

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ABSTRACT

Aim: Renal tumors in children are rare. Wilms' tumor (WT) is the most common renal tumor in childhood. The aim of this study is to investigate the data on the demographic factors, treatment, and follow-up results of pediatric patients who were operated on for renal tumors and determine the factors affecting mortality.

Material and Method: Patients who were operated for renal tumor in our clinic in 2005-2020 were evaluated retrospectively. Age at diagnosis, gender, complaint, localization of the involved kidney, additional anomalies, tumor size, tru-cut biopsy performed, tumor stage, distant metastasis, applied treatments, pathology, treatment complications, and follow-up period were examined.

Results: Of the 47 patients, 25 were female and 22 were male. The mean age was 45.46 (2–204) months. The tumor was located in the right in 21 cases, left in 23 cases and bilateral in three cases. The mean length of the tumor was 11.73 cm. At the time of diagnosis, there was metastasis in 15 cases (31.9%). While metastasis were the most common seen in lung (24.3%), bone-cell metastases were seen in clear cell carcinoma (33.3%) and brain metastases were seen in rhabdoid tumor (50%). Tru-cut biopsy was performed in 15 (31.9%) cases and biopsy was diagnostic in ten cases. Histopathologically, 41 cases had WT (87.23%), three cases were clear cell carcinoma (6.3%), two cases had anaplasia rhabdoid tumor (4.2%), and one case had metanephric adenoma. Relaps occured in nine cases (19.14%) during the follow-up period. Histopathologically, one case was a clear cell carcinoma, one case was a rhabdoid tumor, and seven cases were unilateral WT. The survival rate of our series was 89,4%.

Conclusion: The most common renal tumor in childhood was WT. Surgery have no effect on survival; the most important survival factors were detecting the existence of rhabdoid tumors and anaplasia histopathologically. Therefore, during the follow-up and treatment of renal tumors in childhood, pathological examination should be of primary importance and followed up with the pediatric oncologists.

Keywords: Renal tumors, children, surgery, Wilms tumor, rhabdoid tumor, clear cell carcinoma

INTRODUCTION

Renal tumors in children constitute 6-7% of all childhood tumors and are rare. Such tumors are usually detected incidentally when the child is bathed by the parent when the mass is palped or during routine physical examination or screening of children with known clinical syndromes predisposed to renal disease (1). Wilms' tumor (WT) is the most common renal tumor in childhood. Also, WT is the second most common intra-abdominal solid tumor after neuroblastoma in children. The mean age of diagnosis of WT is around 3 years; it is common in children aged 1–4 years old (2). Other renal tumors are clear cell sarcoma of the kidney, congenital mesoblastic nephroma, cystic partially differentiated nephroblastoma, malignant rhabdoid tumor (MRT), renal cell carcinoma, renal medullary carcinoma, intrarenal neuroblastoma, and renal lymphoma (3). Although non-WT kidney tumors constitute 10% of childhood renal tumors, they have higher morbidity and mortality rates than WT (4). There is debate on and differences in the follow-up and treatment of these rare and heterogeneous tumors. For example, while cystic tumors have a good prognosis, malignant rhabdoid tumors have an aggressive course.

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This study aimed to investigate the data on the demographic factors, treatment, and follow-up results of pediatric patients who were operated on for renal tumors and determine the factors affecting mortality.

MATERIAL AND METHOD

This study was approved by the 2. Clinical Researchs Ethics Committee of Ankara City Hospital, under number E2-21-436 and 10/13/2021 dated. All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles. Data on 50 children who were treated for renal tumors at in our hospital between January 2005–January 2020 were retrospectively analyzed from the hospital computer records and files. Three cases were excluded from the study because they were operated on in another hospital. The cases were evaluated in terms of age at diagnosis, gender, complaint, localization of the involved kidney, additional anomalies, tumor size, tru-cut biopsy performed, tumor stage, distant metastasis, applied treatments, pathology, treatment complications, and follow-up period. In all cases; tru-cut biopsy, neoadjuvant chemotherapy, timing of surgery, and subsequent treatment requirement were decided within TPOG protocols in the pediatric oncology council, which consists of a pediatric surgeon-oncologist-radiologist-radiation oncologist, and pathologist.

RESULTS

A total of 47 children, 25 girls and 22 boys, who were operated on in our clinic for renal tumors were included in the study. The mean age of diagnosis of the cases was 45.46 (2–204) months. The mean age at diagnosis of the 41 patients with WT was 48.8 (2–204) months. The mean age of those with non-WT was 34 (4–60) months. The tumors were located on the left side in 23 cases, on the right in 21 cases, and bilaterally in three cases. Congenital anomalies, including Beckwith-Wiedeman syndrome (in one case), Ochoa syndrome (one case), and chromosomal breakage syndrome (one case), were detected.

The oncology council decided to perform a tru-cut biopsy for diagnosis in 15 (31,9%) of the cases. The tru-cut biopsy results were reported as consistent with necrosis in five cases, diagnostic in ten cases, WT in eight cases, clear cell carcinoma in one case, and rhabdoid tumor in one case. Based on the treatment plans of the oncology council, surgery was performed in 32 (68.08%) cases after neoadjuvant chemotherapy while surgery was performed initially in 15 (31,9%) cases. Neoadjuvant chemotherapy procedure was vincristine and dactinomycin for 4 weeks in patients without metastasis, and vincristine, dactinomycin and doxorubicin for 6 weeks in patients with metastasis. Total nephroureterectomy was performed in 38 cases with unilateral tumors; Lymph node dissection was performed in 12 cases. The mean length of the tumor was 11.73 cm (4–20 cm). The dimensions of bilaterally located tumors and the surgery performed are also shown (**Table 1**).

The most common tumor was WT with 41 cases. Other pathological diagnoses were clear cell carcinoma in three cases, rhabdoid tumor in two cases, and metanephric adenoma in one case. Anaplasia was observed in five patients with WT (**Table 2**).

The pathology results showed favorable histology in 37 cases (78.72%) and unfavorable histology in 10 cases (21.27%). Distant metastases were detected in 15 cases (27.6%) at time of diagnosis and the cases were considered as stage IV according to the TPOG staging. The organs with metastases and their pathological diagnoses are shown in **Table 3**.

Table 1. The datas of bilateral WT

Bilateral Wilms' Tumor Case	Tumor size (cm)	Neodajuvant chemotherapy	Distant metastasisorgan	Surgery	Follow-up
First Case One- year-old girl	Right: 9 cm Left: 4.5 cm	Performed	None	Bilateral mass excision	6 month CT RT Recovered
Second Case 3-year- old boy	Right: 3.5 cm Left: 7.5 cm	Performed	Lung	Right kidney Mass excision Left kidney total nephrectomy	6 month CT RT Recovered
Third Case 3.5-year-old girl	Right: 1.5 cm Left: 10 cm	Performed	None	Right kidney wedge resection Left kidney Total nephrectomy	6 month CT RT Relapse

Table 2. The mortality according to histopathological diagnoses

Tumor	n (%)	Mean age	G/B	Recover	Relapse	Ex
Wilms tumor	41 (87.23%)	4.06 years	21/20	34	7	3 (7.3 %)
Clear cell carcinoma	3 (6.38%)	2.8 years	2/1	1	1	-
Rhabdoid tumor	2 (4.25%)	0.9 years	2/0	-	1	2 (100%)
Metanephric adenoma	1 (2.12%)	1.25 years	0/1	1	-	-
Total	47	3.78 years	25/22	36 (76.5%)	9 (19.1%)	5 (10.6%)

Table 3. The pathological diagnoses of tumors, metastase and tumor stage according to pathology

Pathological diagnosis	Distant metastasis	Tumor stage
Wilms' tumor (n= 41)	Lung (n=10) Lung and Liver (n=2) Brain (n=1)	Stage I: 7 patient (17.07%) Stage II: 16 patient (39.02 %) Stage III: 4 patient (9.7%) Stage IV: 10 patient (24.3%) Stage V: 4 patient (9.7%)
Clear Cell Carcinoma (n=3)	Bone (n=1)	Stage I: 0 Stage II: 1 patient (33.3%) Stage III: 1 patient (33.3%) Stage IV: 1 patient (33.3%)
Rhabdoid tumor (n=2)	Brain and Lung (n=1)	Stage III: 1 patient Stage IV: 1 patient
Metanephric adenoma (n=1)		Stage 1: 1 patient

While the most common lung metastasis (24,3%) was seen in WTs, bone metastasis (33.3%) was evident in clear cell carcinoma, while lung and combined brain metastasis were evident in rhabdoid tumors (50%).

Bilateral WT were detected in three cases. Demographic data, treatments, histopathological diagnoses, and follow-up processes of the cases are shown in the table 1. The mean age of patients with bilateral WT was 2.5 (1–3.5) years; two females (66%) and one male (33%).

The mean follow-up period of the cases was 48 (4–65) months. During the follow-up period, relapse developed in nine cases (19.14%). Histopathologically, one case was a clear cell carcinoma, one case was a rhabdoid tumor, and seven cases were unilateral WT. Six cases were unfavorable and three cases were favorable. In the treatment of relapsed tumors, reoperation and excision of the mass were performed in five cases. Chemotherapy was performed in four cases. Three (33.3%) of the patients died in the treatment process.

Chemotherapy was performed in the cases for an average of 7.8 (4–12) months post-op. In the postoperative period, 40% of the cases were administrated Vincristine + Actinomycin-D + Doxurabucin, 60% of them were administrated Vincristine + Actinomycin. Radiotherapy was administered in addition to post-op chemotherapy in 20 cases.

Five patients died in our study. Two had rhabdoid tumors, two had stage IV anaplasic WT, and the other had a stage III relapsed WT. The mortality rates according to histopathological diagnoses are shown in Table 2. The 5-year surveillance of the cases in our series was 89.3%.

DISCUSSION

Renal tumors are among the most common malignant solid tumors in children, accounting for 5%–6% of all malignant childhood tumors, with WT being the most common renal malignancy (5). In this study, as per the literature, we observed that 87.23 % of our cases received a diagnosis of WT, followed by clear cell sarcoma of the kidney (CCSK) (6.38%), malignant rhabdoid tumor of the kidney (MRT) (4.25%), and metanephric adeoma (2.12%).

In the literature, synchronous or metachronous bilateral WT rate was reported as 5–10% of children with WT (6). In our study, bilateral synchronous WT were detected at a rate of 8.5 %, which was in accordance with the literature.

While renal tumors are common in boys in European studies, they are also frequently seen in girls in National Wilms Tumor Study Group (NWTS) (7). In our study, we found that the female/male ratio was 1.13:1. In the National WT study of the Turkish Pediatric Oncology Group (TPOG), the median age of patients was 3 years (8). The mean age at diagnosis of the patients in our study was 45.84 months (2–204 months). The mean age at diagnosis of 38 patients with WT was 48.8 months (2–204 months). The mean age of non-WT patients was 25 months (4–60 months). Although it has been reported in the literature that the mean age of non-WT patients tends to be higher, the mean age of patients with a diagnosis of WT was found to be statistically higher than those with a diagnosis of non-WT in our study. (p=0.04) (9) (10).

WAGR (WT, aniridia, genitourinary anomalies, and mental retardation), Denys-Drash syndrome, and Beckwith-Wiedemann syndrome may be associated in 5–10 % of cases with WT (11) (12). In our study, one patient with WT (2.6%) had Beckwith-Wiedemann syndrome. Also, we observed one case of Ochoa syndrome, which was seen for the first time in the literature and previously reported by Emir et al. (13), and one case of chromosomal breakage syndromes (WT together with hepatocellular carcinoma).

Different methods are preferred in Europe and America for the treatment of childhood renal tumors. While preoperative chemotherapy is preferred by The International Society of Paediatric Oncology (SIOP) protocol in Europe, initial surgery followed by chemotherapy are prefered by the COG protocol in the USA. The aim of pre-surgical chemotherapy in SIOP is to prevent the spread of peritoneal cancer and reduce the stage of the disease (14). No differences in the overall survival rates for the SIOP and COG approaches were evident (15). In our study, the SIOP protocol was applied to 32 cases (68.08%) by performing a tru-cut biopsy and pre-op chemotherapy, while the COG protocol was applied to 15 cases (31.9%) by performing surgery first.

In bilateral WT patients, preoperative chemotherapy has the advantage of reducing tumor volume, and the treatment response may provide a valuable prognostic indicator. (16) In our study, in accordance with the literature, neoadjuvant chemotherapy was given to all patients with bilateral WT.

The standard surgery in the SIOP and COG protocols for WT is open nephrectomy, whereas nephron-sparing surgery (NSS) has been recommended as the treatment of choice for bilateral WT (17). In our study, total open nephroureterectomy was performed in 38 cases. Lymph node dissection was performed in 12 cases. In two of the bilateral cases, NSS was performed on one kidney and total ureterenephrectomy on the other kidney. Bilateral NSS was performed in one case.

In developed countries, with the development of multimodal surgery, chemotherapy, and radiotherapy treatments for childhood kidney tumors, survival rates have increased up to 90% (7). Although most patients with WT survive, patients with relapsed and anaplastic histology WT have poor survival rates; fewer than 15% achieve durable survival (18).

Anaplasia is defined by the presence of polyploid atypical mitotic figures, a large nuclear size, and hyperchromasia (19). The stage of the disease and the histopathology of the tumor are the two main risk factors. In histopathological evaluation, a WT is classified into two histology groups: (i) good (favorable) and (ii) poor (unfavorable) according to the presence of anaplasia. The presence of anaplasia indicates that the tumor has a 'poor histology'. Anaplasia is seen in 5–10% of cases. Anaplasia refers to cellular resistance to treatment rather than a tendency towards metastasis or a poor treatment course for the tumor and is considered a predictor of a poor prognosis (20).

The present overall relapse rate was 14% with an overall post-relapse survival rate of 44% (20). In our study, the relapse rate was 19.5%. Although the relapse rate was higher than reported in the literature, the post-relapse survival rate was 66%. The most significant risk factor for relapse was unfavorable WT histology. In studies with larger series, the recurrence rate was 15% in patients with a favorable WT histology and 50% in patients with anaplastic WT (19) (21). In our study, we found a recurrence rate of 8.1% in patients with a favorable WT histology and a recurrence rate of 60% in patients with anaplastic WT.

It has been reported that tumor stage is a critical prognostic factor (22). In our study, of the four patients who did not survive, two had stage III tumors and two had stage IV tumors.

WT most commonly metastasizes to the lungs, regional lymph nodes and liver, and less commonly to the brain and bone (23-25). 80% of hematogenous metastases occur in the lungs or the liver alone or together with the lungs in 15% of patients (24). In our study, similar to the literature, we found that metastases of WT cases were most common in the lungs with 76.9%.

Clear cell sarcoma of the kidney (clear cell sarcoma) is the second most common kidney tumor. It is usually seen in boys aged 3–5 years. Metastases are most commonly found in the lungs and bones. In previous studies, it was determined that the 1–10 year surveillance rate was 57-83%. In our study, the 5-year surveillance of three cases with clear cell sarcoma was 100%.

Malignant rhabdoid tumors of the kidney are malignant tumors that are most commonly located in the kidneys and/or brain, and are usually seen in infants and young children, with a frequency of 2% of all cancer types. A brain tumor is seen together with a kidney tumor. Despite treatment, there is a poor prognosis for his type of tumor: the mortality rate is 80%, and the cure rate is low (3). Similar to the literature, the two rhabdoid tumor cases we detected in our data were seen in children under the age of one in whom brain metastases were detected; the mortality rate was 100%.

Despite its merits, the present study has two main limitations. First, as in all retrospective studies, our study was dependant on secondary data, which may have been subject to biases or errors in collection. Second, the present study was single-centered and featured a short post-op follow-up period.

CONCLUSION

The results showed that most common renal tumor in childhood was WT, which was similar to the findings in the literature. Surgical procedure appeared to have no effect on survival; the most important survival factors were detecting the existence of rhabdoid tumors and anaplasia histopathologically. Therefore, during the follow-up and treatment of renal tumors in childhood, pathological examination should be of primarary importance and followed up with the pediatric oncologists.

ETHICAL DECLARATION

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Clinical Researchs Ethics Committee (Date: 10.13.2021, Decision No: E2-21-436).

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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REFERENCES

1. Malkan AD, Loh A, Bahrami A, et al. An approach to renal masses in pediatrics. Pediatrics 2015; 135: 142-58.
2. Kieran K, Ehrlich PF. Current surgical standards of care in Wilms tumor. In Urologic Oncology: Seminars and Original Investigations 2016; 34: 13-23.
3. Saula PW, Hadley GP. Pediatric non-Wilms' renal tumors: a third world experience. World J Surg 2012; 36: 565-72.
4. Ünal E, Yilmaz E, Özcan A, et al. Twenty children with non-Wilms renal tumors from a reference center in Central Anatolia, Turkey. Turk J Med Sci 2020; 50: 18-24.
5. Pritchard-Jones K, Dome JS (eds.). Renal Tumors of Childhood: Biology and Therapy, Pediatric Oncology. SpringerVerlag Berlin Heidelberg; 2014. doi:10.1007/978-3-662-44003-2_3.
6. Tan XH, Zhang DY, Liu X, et al. Retrospective analysis to determine outcomes of patients with bilateral Wilms tumor undergoing nephron sparing surgery: 15-year tertiary single-institution experience. Pediatr Surg Int 2018; 34: 427-33.
7. Pan C, Cai JY, Xu M, et al. Renal tumor in developing countries: 142 cases from a single institution at Shanghai, China. World J Pediatr 2015; 11: 326-30.
8. Genç B, Özkan MA. Çocukluk çağı böbrek tümörleri. Kanser Gündemi Dergisi 2016; 4: 1-2.
9. Bozlu G, Çıtak EÇ. Evaluation of renal tumors in children. Turk J Urol 2018; 44: 268-73.
10. Miniati D, Gay AN, Parks KV, et al. Imaging accuracy and incidence of Wilms' and non-Wilms' renal tumors in children. J Pediatr Surg 2008; 43: 1301-7.
11. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014; 64: 83-103.
12. Dumoucel S, Gauthier-Villars M, Stoppa-Lyonnet D, et al. Malformations, genetic abnormalities, and Wilms tumor. Pediatr Blood Cancer 2014; 61: 140-4.
13. Emir S, Kan R, Demir HA, Cakar N, Güler M. Occurrence of Wilms tumor in a child with urofacial (OCHOA) syndrome. Pediatr Hematol Oncol 2011; 28: 616-8.
14. Metzger ML, Dome JS. Current therapy for Wilms' tumor. Oncologist 2005; 10: 815-26.
15. Kembhavi SA, Qureshi S, Vora T, et al. Understanding the principles in management of Wilms' tumour: can imaging assist in patient selection? Clin Radiol 2013; 68: 646-53.
16. Venkatramani R, Malogolowkin M, Davidson TB, May W, Sposto R, Mascarenhas L. A phase I study of vincristine, irinotecan, temozolomide and bevacizumab (vitb) in pediatric patients with relapsed solid tumors. PLoS One 2013; 8: e68416.
17. Ritchey ML, Shamberger RC, Haase G, Horwitz J, Bergemann T, Breslow NE. Surgical complications after primary nephrectomy for Wilms' tumor: report from the National Wilms' Tumor Study Group. J Am Coll Surg 2001; 192: 63-8.
18. Mavinkurve-Groothuis AM, van den Heuvel-Eibrink MM, Tytgat GA, et al. Treatment of relapsed Wilms tumour (WT) patients: experience with topotecan. A report from the SIOP Renal Tumour Study Group (RTSG). Pediatr Blood Cancer 2015; 62: 598-602.
19. Spreafico F, Bellani FF. Wilms' tumor: past, present and (possibly) future. Expert Rev Anticancer Ther 2006; 6: 249-58.
20. Cunningham ME, Klug TD, Nuchtern JG, et al. Global Disparities in Wilms Tumor. J Surg Res 2020; 247: 34-51.
21. Lovvorn HN 3rd, Pierce J, Libes J, et al. Kenyan Wilms Tumor Consortium. Genetic and chromosomal alterations in Kenyan Wilms Tumor. Genes Chromosomes Cancer 2015; 54: 702-15.
22. Davidoff AM. Wilms' tumor. Curr Opin Pediatr 2009; 21: 357-64.
23. Berger M, Fernandez-Pineda I, Cabello R, et al. The relationship between the site of metastases and outcome in children with stage IV Wilms tumor: data from 3 European pediatric cancer institutions. J Pediatr Hematol Oncol 2013; 35: 518e24.
24. Verschuur A, Van Tinteren H, Graf N, Bergeron C, Sandstedt B, Kraker J. Treatment of pulmonary metastases in children with stage IV nephroblastoma with risk-based use of pulmonary radiotherapy. J Clin Oncol 2012; 30: 3533-59.
25. Iaboni DSM, Chi YY, Kim Y, Dome JS, Fernandez CV. Outcome of Wilms tumor patients with bone metastasis enrolled on national Wilms tumor studies 1-5: a report from the children's Oncology group. Pediatr Blood Canc 2019; 66: e27430.

Original Article

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The evaluation of asecond line drug susceptibilities and molecular epidemiological profiles of multidrug resistance *Mycobacterium tuberculosis* isolates isoleted from different region of Turkey

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ABSTRACT

Introduction: This study was planned to determine the second line drug resistance and molecular epidemiological profiles of multidrug resistant *Mycobacterium tuberculosis* isolates isolated from different geographical regions of Turkey.

Material and Method: In our study, 63 MDR *M. tuberculosis* isolates were evaluated for the drug susceptibility sent from different tuberculosis laboratories of Turkey. Secondary antituberculosis drugs resistance was evaluated by indirect proportion method. Epidemiological origins were evaluated by using IS6110-RFLP and spoligotyping methods.

Results: Cycloserine, ethionamide, capreomycin, thiacetozone, ofloxacin, kanamsin and paraaminosalicylic acid resistance rates were 15.87%, 19.04%, 7.93%, 6.34%, 11.11%, 12.69% and 6.34.%, respectively. According to spoligotyping results, 11 different patterns were obtained, including 52 isolates consisting of 5 clusters and 11 patterns consisting of a single isolate. When we compared our results with the spoligotype database in the world; 42 of 52 isolates forming 5 clusters were identified as predefined spoligotypes (LAM7-TUR, LAM9, T clade). 10 isolates showed the characteristics of the U spoligotype family. Of the 11 isolates that produced 11 different patterns, 8 were Haarlem and T spoligotypes. It was found that 2 isolates had the characteristics of Orphan and 1 isolate had the characteristics of BOV family.

Conclusion: In our study, LAM7-TUR, LAM9, T clade spoligotype families are common in our country and in the world were determined.

Keywords: *M. tuberculosis*, multi-drug resistance, IS6110 RFLP, spoligotyping

INTRODUCTION

Tuberculosis (TB) is one of the most common infectious diseases worldwide. Approximately 1.5 billion people worldwide are infected with TB bacilli, 10 million new cases occur each year and 3 million people die from TB (1). Development of multiple drug resistance (MDR) to TB drugs is a major problem worldwide. Multidrug-resistant tuberculosis (MDR-TB) is called TB caused by strains of Mycobacterium. *M. tuberculosis* (MTB) resistant to INH and RIF. It is man-made and is considered to be the heaviest form of resistant TB because resistance to the two most effective drugs of treatment develops (2-4). The MDR-TB problem has been experienced in developing countries where inadequate treatment programs have been implemented for years.

In recent years, it has been observed in developed countries due to HIV prevalence. Second line drugs should be added to the treatment. Factors in the development of second line drug resistance are the education level of the community and health personnel, health infrastructure, cooperation of related units and the determinant factors in the development of MDR-TB (2,5-7). The rates of resistance to a single drug or a greater number of TB drugs vary according to societies and regions. Single drug resistance is reported as 20% and multiple drug resistance is reported as 10% in developing countries. This rate is even higher in patients who previously received TB treatment. For effective treatment, drug susceptibility tests, detection of resistant

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cases and initiation of second line antiTB drugs are of great importance in terms of treatment and prevention of spread of the disease (1,8-10).

Many new methods have been developed to accelerate the diagnosis of TB. These include radiometric methods, DNA probes, mycolic acid chromatography, PCR and serological tests (11,12). Each country has to establish TB treatment programs according to epidemiological characteristics and requirements, prevalence of primary resistance, attitudes and behaviors of patients regarding TB treatment, health infrastructure and economic strength, and determine appropriate treatment regimens and methods of application for these different clinical situations. As a result of the studies, it has been shown that the clinical and epidemiology of TB has changed and resistance to multiple drugs has disrupted the efficacy of the regimens used in the treatment (1,3,10). Innovations in molecular biology have opened new horizons in the diagnosis of TB cases and epidemiological studies. Today, geographic distribution maps of TB are made using molecular epidemiological typing methods such as spoligotyping, IS 6110-RFLP (Restriction fragment length polymorphysm), MIRU etc. This can give information about disease control, which different strains are present, their drug resistance status, and what precautions can be taken? (13-17).

In this study, it was aimed to determine the epidemiologic origins of MDR-TB strains isolated from different geographical regions by second line drug resistance profile and molecular epidemiologic methods (spoligotyping, IS6110 RFLP) by indirect proportion method.

MATERIAL AND METHOD

Ethics committee approval is not required for this study, as there is no study conducted on individuals or containing biological material.

Patients and Bacterial Strains

This study performed in collobaration between İnönü University Faculty of Medicine Departmant of Microbiology between November 2006 and November 2007. The study was carried out within the scope of TÜBİTAK SBAGHD63 project with the official permission of the Refik Saydam Hygiene Center. The 63 isolates used in the study consisted of MTB strains isolated from sputum samples taken from patients with suspected tuberculosis with clinical, symptomatic and radiological findings in Kayseri, Trabzon, İzmir, Elazığ, Denizli, Çorum and Ankara provinces of our country. A value above 15 mm was recorded in PPD confirmation tests of all patients, and positive results were obtained with AARB staining in smear tests. MDR-TB was detected in all patients according to the indirect proportion drug susceptibility test results. In the study (7) TB isolates, which were found to have multiple drug resistance from the isolates sent for external quality control in the sensitivity tests from the Supranational TB Laboratory (Roma, Italia), were evaluated as controls.

Bacteriology and Drug Susceptibility Testing

All patient specimens submitted for acid-fast culture were processed by the N-acetyl-L cysteine-NaOH decontamination procedure recommended by the BACTECTM MGITTM 960 TB system manufacturer (Becton Dickinson) (18-20). Isolates grown in MGIT tube were also subcultured on Löwenstein Jensen (LJ) medium at 37°C. Fresh cultures on LJ medium were used as a source of the organisms. Differentiation of the MTBC and non-TB mycobacteria were performed by BD MGIT™ TBC Identification Test. Testing for susceptibility to rifampicin (RIF), isoniazid (INH), streptomycin (SM), and ethambutol (EMB) was performed by the BACTECTM MGITTM 960 TB drug susceptibility test kit. Drug susceptibility testing against rifampicin (R), isoniazid (I), streptomycin (S), and ethambutol (E) was performed by using standard proportion method on LJ medium (11,12).

DNA Extraction

A loopful of bacteria colonies was suspended in 400 µl 1× TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), and inactivated at 80°C for 20 minutes. Bacterial DNA was extracted by the standard cetyl-trimethyl ammonium bromide (CTAB) (Merck, Darmstadt, Germany) method, as described previously. The pellet of DNA was dried at room temperature, resuspended in 1× TE buffer and stored at 4°C until use (21).

Molecular Typing

Spoligotyping was performed by using a commercially available kit (Isogen Bioscience BV, Maarssen, The Netherlands) according to the instructions supplied by the manufacturer as previously described (26). The spoligotiyping method was performed according to manufacturer instructions (27,28). The DNA concentration was estimated spectrophotometrically. The spacers between the direct repeats in the target region were amplified by using Dra biotinylated at the 5' and DRb primers. The amplified DNA was hybridized to a set of 43 immobilized oligonucleotides derived from the spacer sequences of *M. tuberculosis* H37Rv and *M. bovis* BCG P3 by reverse line blotting. Detection of hybridizing DNA was done by enhanced chemiluminescence (ECL; Enhanced Chemo-Luminescence Detection kit; Amersham, Little Chalfont, England), followed by exposure to X-ray film (Hyperfilm ECL, Amersham), in accordance with the instructions of the manufacturer. *M. tuberculosis* strain H37Rv and the Pasteur strain

of *M. bovis* BCG P3 were used as reference strains for spoligotyping. The spoligotyping results were entered in a binary format as Excel spreadsheets and were compared to the World Spoligotype Database of the Institute Pasteur de Guadeloupe (29). An isolate was assigned a shared type if the same spoligotype was found for isolates obtained from two or more patients in the world. If no matching spoligotype was identified in the database, the isolate was defined as unique. The shared types formed by a unique isolate in the database and a Turkish isolate, or two or more Turkish isolate alone, were defined as new shared types. IS6110 RFLP was performed according to reference literatures (22-27).

Statistical Analysis

Descriptive statistics were calculated as count and percent. Spoligotyping and IS6110 RFLP typing test results were shared as cluster and group name.

Tablo 1. Critical drug concentration (CC) and critically resistant (CR) bacteria rate of tuberculosis drugs in LJ medium

Drug	%1 CP için CC (µg/ ml)	%10 CP için CK (µg/ ml)
İsoniazid	0.2	-
Rifampicin	40	-
PAS	0.5	0.25
Cycloserine	40	30
Etionamide	30	20
Kanamycin	30	20
Capreomycin	40	20
Ofloxacin	2	-
Tiasetozone	-	10.0

Table 2. Second line drug resistance test results of MTB isolates

Drugs	Isolates	
	Number	%
Sensitive to all	32	50.79
Drug resistance		
Resistant to only one drug		
Cycloserine (CYC)	4	6.34
Etionamide (ETN)	4	6.34
Capreomycin (CAP)	2	3.17
Tiasetozone (TIA)	3	4.76
Oflaxacin (OFL)	3	4.76
Kanamycin (KAN)	4	6.34
Paraaminosalicylic acid (PAS)	0	-
Total	20	31.74
Resistant to only two drug		
ETN+KAP	1	1.58
TİA+OFL	1	1.58
CYC+ETN	2	3.17
Total	4	6.34
Resistant to only three drug		
ETN+ KAP+KAN	1	1.58
ETN+KAN+PAS	1	1.58
SKS+OFL+PAS	1	1.58
KAP+KAN+PAS	1	1.58
SKS+ETN+OFL	2	3.17
Total	6	9.52
Resistant to four drugs		
SKS+ETN+KAN+PAS	1	1.58
Total (Resistance)	31	49.20

RESULTS

All 63 isolates used in this study were resistant to first line drugs rifampicin and isoniazid. The results of the second line drug susceptibility tests of these isolates are given in **Table 2**. According to the test results, 32 (50.79%) of 63 isolates were susceptible to 7 minor drugs and 31 (49.20%) were resistant to at least one drug. While 20 isolates were resistant to one drug (31.74%), 4 were resistant to two drugs (6.34%), 6 were resistant to three drugs (9.52%) and 1 (1.58%) to four drugs.

Of 63 isolates, 32 (50.79%) were susceptible to 7 minor drugs and 31 (49.20%) were resistant to at least one drug. Among the resistant isolates; While 20 isolates were resistant to one drug (31.74%), 4 were resistant to two drugs (6.34%), 6 were resistant to three drugs (9.52%) and 1 (1.58%) to four drugs. No resistance was detected in all 7 drugs. When the resistance rate for each second line drug was evaluated in general, the highest resistance was found to be 12 (19.04%) against etionamide and the lowest resistance to PAS in 4 isolates (**Table 3**).

The spoligotyping results of 63 isolates were shown in **Table 4**.

Table 3. Number and percentage of 63 minor MDR-resistant strains found to be resistant to 7 second line antituberculosis drugs by indirect proportion method

Drugs	Number of resistant strains	Percent (%)
Cycloserine (CYC)	10	15.87
Etionamide (ETN)	12	19.04
Capreomycin (CAP)	5	7.93
Tiasetozone (TIA)	4	6.34
Oflaxacin (OFL)	7	11.11
Kanamycin (KAN)	8	12.69
Paraaminosalicylic acid (PAS)	4	6.34

Table 4. Spoligotypes of isolate clusters

Cluster	Size of cluster	Isolates of Percentage[a]	Spoligotype pattern	Spoligotype family[b]
A	1	1.58	760177777720771	H3
B	1	1.58	774777777420771	H4
C	1	1.58	776023037760771	Orphan
D	1	1.58	777737774020771	H1
E	1	1.58	777737777760700	T3
F	1	1.58	777777000437771	Orphan
G	16	25.39	777777404760771	LAM7-TUR
H	1	1.58	7777776007607 71	T1
I	4	6.34	777777607760771	LAM9
J	1	1.58	777777637760771	T
K	1	1.58	777777760000731	U
L	10	15.87	777777770000771	U
M	1	1.58	777777774020771	H1
N	2	3.17	777777777720771	H3
O	20	30.15	777777777760771	T1
P	1	1.58	777777777777400	BOV

a LAM: Latino–American, and Mediterranean familiies
[b]7 isolates could not be typed by spoligotyping The RFLP pattern of 5 isolates contained more than 6 bands.

16 spoligotypes were detected by this method. Eleven isolates (17.46%) formed separate spoligotype, 52 (82.53%) isolates formed 5 clusters (G, I, L, N, O). Sixteen samples (cluster G) showing the same spoligotype were identified as the LAM-7 TUR spoligotype family. The largest spoligotype cluster (20 isolates, cluster 0) matched the T1 family. Four isolates in cluster J were identified as LAM 9 spoligotype. 2 isolates in cluster N, 1 isolate in cluster B and 1 isolate in cluster are defined as Haarlem 3, Haarlem 4, Haarlem 1 spoligotype, respectively. The isolates (1 isolate) in clusters A and M shared the key characteristics of the Haarlem family. Although 1 isolate in cluster K and 10 isolate in cluster L have characteristic spoligotip characteristics of U family, filling of 15-24 spacers in the K cluster and 25-32 spacers in the L cluster requires more detailed identification for the U family. One isolate in the P cluster showed the characteristic features of the BOV (Bovis) family with the absence of 33-43 spacers. The isolates (1 isolate) in clusters C and F were defined as orphan. 63 MDR tuberculosis isolate was also genotyped by IS6110-RFLP method. No results were obtained due to low DNA concentration in 32 isolates. 3 clusters were formed in 31 isolates.

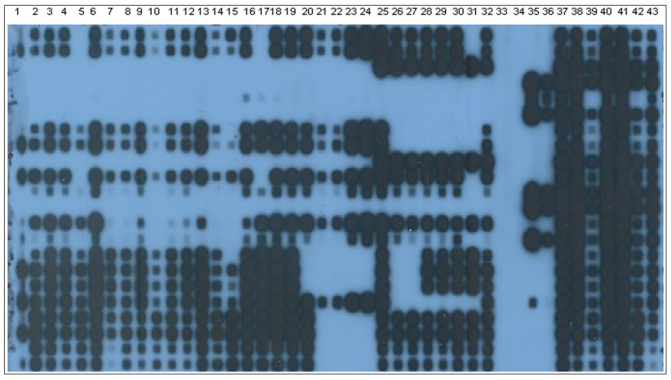

Figure 1. Evaluation of MTB isolates by spoligotyping method

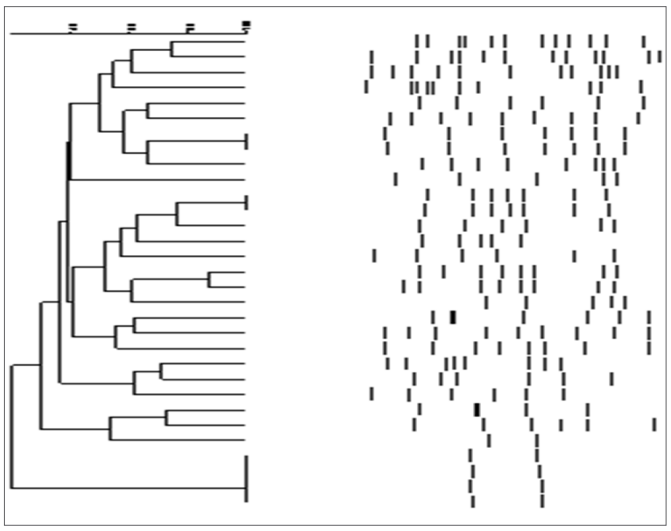

Figure 2. Evaluation of MTB isolates by IS 6110 RFLP method

DISCUSSION

Multi drug-resistant tuberculosis remains an important threat all over the World. It is the development of resistance to drugs used against the disease that presents TB as a problem for today and the future. The most important reason for this is treatment failure. Drug regimens were given to patients who were the result of insufficient TB control programs in the past and drugs were used unattended, causing drug resistance rates to increase. In the regulation of follow-up and treatment of patients, it is important to know the drug resistance rates in the community and to determine the individual resistance status. In the direction of Directly Observed Treatment (DOT) and DGT-plus (DOT-plus) strategies, which have been on the agenda in recent years, and due to the major and minor antiTB-resistant cases that are increasingly encountered in daily practice, drug susceptibility tests have become more important today, laboratory methods used to determine drug sensitivity and studies on this subject have been accelerated (1-5).

In Turkey, susceptibility tests to second generation drugs are carried out only in the National Tuberculosis Reference and Research Laboratory. Therefore, there are limited data on second line drug sensitivity rates. In most of the studies, only a few of these drugs were included in the study and it was not stated how much strains in these studies were MDR- MTB isolate.

In our study, the susceptibility of 63 multi-drug resistant MTB strains were isolated from different geographic regions to 7 minor antiTB drugs was determined according to the indirect proportion method in the Löwenstein-Jensen medium, which is accepted as the reference method. While 32 (50.79%) of 63 isolates were sensitive to 7 minor drugs, 31 (49.20%) were found resistant to at least one drug. In the evaluation made among the resistant isolates; while 20 isolates were resistant to one drug (31.74%), 4 were resistant to two drugs (6.34%), 6 to three drugs (9.52%) and 1 (1.58%) to four drugs. Among the isolates examined, resistance to 7 drugs was not detected. When the resistance rate for each minor drug is generally evaluated; resistance rates for CYC, ETN, CAP, TIA, OFL, KAN and PAS, respectively; 15.87%, 19.04%, 7.93%, 6.34%, 11.11%, 12.69% and 6.34% were found. The highest resistance in our study was found in ETN (19.04%).

In another study in the same center conducted by Kayalı et al. (28) ; second-line drug resistance rates for ETN, CYC, KAN, PAS,OFL, TIA, and CAP in a different set of MDR-TB samples were found as 22%, 8%, 6%, 6%, 2%, and 0%, respectively. Our results were similar to this study.

Şimşek et al. (29) in their evaluation of 122 MDR MTB isolates using the E-test method; found that 119 (98%)

isolates were susceptible to CAN, OFL, ETN and linezolid (LIN), while 3 (2%) were resistant to ETN and CAN. The Etest method is a standardized gradient method and is a more reliable test. The fact that our rates are higher may be due to the difference in method.

Second line drug susceptibility varies in different regions of the world, this situation is similar in Turkey.

Bektöre et al. (30) investigated the susceptibility status of 81 MDR-TB isolates isolated from MDR-TB patients living in Istanbul, Izmir and Manisa to first- and second-line anti-TB drugs with the fully automated BACTEC MGIT960 system; determined the rates of resistance to second-line anti-TB drugs as 1.2% for Amikacin (AMK) and CAN, 2.5% for OFL and levofloxacin (LVX), 14.8% for CPM, 37% for ETN, and did not detect resistance to LIN. ETN resistance rate in our study was found to be similar to this study.

There are studies showing that resistance to izoniazide (INH) associated with mutations in the inhA gene. Considering that the isolates studied are INH resistant, our conclusion supports this hypothesis. However, in our study, strains sensitive to etionamide were also detected. This suggests that INH resistance developing with other mechanisms does not cause resistance development against etionamide. In the study conducted by Çiçek et al. (31). With the method of probing in MB 7H10 agar for the detection of sensitivity against minor drugs in 100 strains of MTB, ethionamide resistance was found to be 4%, but it was found that all strains of MTB, which are resistant to multi drug, are sensitive to ethionamide.

This situation can be explained by its role in different mechanisms in INH resistance. This rate is quite low compared to ETN resistance, which was found to be 19.04% in our study. This difference suggests that all MTB isolates used in our study may be due to the fact that they are MDR. The resistance rate we found in the strains of MDR- MTB against TIA is 6.34%.

The most studied secondline antiTB drug in our country is TIA. In the first studies carried out by the national reference center in our country; Tumer and Savran (32) used the properation method to determine the resistance to TIA. While 8% of 2345 strains of MTB were found to be resistant to TIA in 1992, this ratio was found to be 6% in 1639 isolates in 1993. Osmanlıoğlu (33) determined the average resistance to TIA as 8% in cultures sent to the RSHMB tuberculosis national reference laboratory in 1990 from all regional TB laboratories. However, no information is given about the extent to which these origins are MDR- MTB. In a study conducted by Kayalı (28), while 50 MDR-MTB isolates were found to be 2% in TIA resistance by the method of proportions, this rate was higher in our study (6.34%). In this study, resistance to OFL was determined as 11.11%. The development of cross resistance among the commonly used quinolone group antibiotics can be held responsible for this situation. Özkütük et al. (34) found 5% OFL resistance in their studies evaluating 40 MDF-TB strains with BACTEC 460 TB radiometric semi-automated culture system.

In our study, the 11.11% resistance we found in MDR -MTB isolates suggests that quinolones may be developed as a result of the empirical starting of quinolones in patients with TB over time. The rate of resistance to PAS was found to be 6.34%. Çiçek et al. (31) found 12% resistance for PAS. Strains of MDR -MTB were found to be sensitive to PAS. In this study, the resistances of CYC, CAP and CAN were found as 15.87%, 7.93% and 12.69%, respectively. Pfyffer et al. (35) conducted a three-phase study in 1999. While phase I had strains sensitive to all drugs, phase 2 had strains known to be susceptible and resistant to drugs, and phase 3 had a large working group, mostly composed of resistant strains. Resistance to CYC was found to be 7.85% in phase 3. In the same study, resistance to CAN and CAP was 45% and 30% in phase 2, respectively; found to be 8.26% in phase 3. The values we detected in our study are higher.

Since TB is a highly contagious and drug resistant disease, it requires better surveillance programs and a rapid diagnosis of the disease. It is thought that there are geographical differences in terms of epidemiological differences between strains. In epidemiological studies, comparing the strains isolated from different geographic regions with each other and monitoring individual strains, It suggests that strains associated with transmission routes, high virulence and multiple drug resistance can be detected worldwide (36).

With the introduction of molecular methods to routine use, epidemiology studies have become easier. Typing of bacterial strains, TB prevalence and spread are the most important topics studied. In studies conducted with spoligotyping and IS6110 methods, MTB isolates were sensitively typed (37,38).

Thanks to the data obtained from these studies, it is planned to establish treatment protocols quickly and control the disease according to the epidemiological origin. In this study, epidemiological origins of strains of 63 MDR-TB isolates sent from different geographical regions (Kayseri,Trabzon, İzmir, Elazığ, Denizli, Çorum, Ankara) of Turkey were investigated by spoligotyping and IS6110 RFLP method.

No results were obtained due to low DNA concentration in 32 isolates. 3 clusters were formed in 31 isolates. All isolates were studied by spoligotiping method to better identify clusters of related strains. Spoligotyping was used as the second method, especially in strains with 6

or fewer copies of IS6110. The spoligotypes of the two samples detected by two bands with IS6110 method were the same. The combined use of the two methods reduced the fraction of clustered strains.

In this study, the percentage of clusters we determined using the IS6110 and spoligotiping method was found to be similar to the clusters recently characterized by the combination of IS6110 and pTBN12 fingerprint methods. 16 spoligotype were determined by spoligotiping method. 11 isolates (17.46%) were separate spoligotip and 52 (82.53%) isolates formed 5 clusters. Sixteen samples showing the same spoligotype were from the LAM-7 TUR spoligotip family. The largest spoligotip cluster matched the T1 subset. 4 isolates were identified as LAM 9 spoligotype. Two isolates were defined as Haarlem 3, 1 isolate Haarlem 4, 1 isolate Haarlem 1 spoligoty. Two isolates shared key characteristics of the Haarlem family. Although the 11 U family has the characteristic spoligotip features, the exact definition needs to be confirmed by the world database.In our study, the LAM-7 TUR spoligotip family unique to our country was identified. The data obtained from our study showed compatibility with other similar studies conducted in our country (39-46).

U family is a spoligotip defined in Eastern Europe and especially in Russia according to Spol4B program 64. The fact that it belongs to the province of Trabzon in 11 isolates supports that it will belong to the spoligotip U family determined in this group due to its geographical proximity. In our study, while 1 isolate showed the character characteristics of the BOV family, 2 isolates were found to be orphan (47).

In a study recently reported by Karagöz et al. (39) in our country; 13 different spoligotypes were defined by the spoligotyping method, and a total of 188 strains (94.0%) were included in the cluster. The most prominent spoligo family was the T family (43.0% of the strains). The other group consisted of LAM (26.0%), H (8.0%), X and S (both 6.0%), and U (5.0%). The study also found a Beijing profile of 6.0%.

In another study in Turkey, Cavusoğlu et al. (48) were investigated genotype distribution of *M. tuberculosis* in Aagean region in 470 *M. tuberculosis* isolates from 470 patients in 1996-2014. In this study, they reported that among the 470 *M. tuberculosis* strains, 132 different spoligopatterns were identified and 46 different cluster for 384 strains were determined. The most predominant spoligotypes were determined as T1(n:116, 24.7%), and LAM7-TUR (n:38, 8.1%) followed by H3 (5.7%), T1(4.7%) and Unknown (4.3%), respectively. MDR –TB was determined in 12 isolates, of which six were Beijing.

In our study, similar results were obtained with these studies.

The limitation of this study is that comprehensive studies with more samples are needed to identify definitive epidemiological groups across the country.

CONCLUSION

As a result; control and treatment of MTB infections is critical worldwide. Mapping of isolated strains according to geographical regions is important for controlling the disease and knowing whether the disease is an infection or reactivation.

At this stage, epidemiological studies are valuable. It is concluded that it would be beneficial to carry out these studies with internationally accepted methods that determine the genotype of the strains. Extensive studies with more isolates are needed to assess the effectiveness and transmission of the tuberculosis control strategy. In susceptibility tests, the factors of the method used can affect the results. The main differences are in practice differences, inoculum amount, medium used and drug concentrations. Therefore, it is not possible to talk about complete standardization in comparing the results obtained in different centers. Despite this, studies can have information about resistance rates in different regions.

ETHICAL DECLARATION

Ethics Committee Approval: Ethics committee approval is not required for this study, as there is no study conducted on individuals or containing biological material.

Informed Consent: There is no need for informed consent since there is no study on individuals or containing biological material.

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 of 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.

REFERENCES

1. WH0. Global tuberculosis report 2019. Geneva: World HealthOrganization, 2020. https: //www.who.int/tb/publications/global_report/en/
2. WHO Consolidated Guidelines on Tuberculosis Module 4: Treatment Drug-resistant Tuberculosis Treatment. Geneva, World Health Organization, 2020. https: //apps. who.int/iris/bitstream/handle/10665/332397/9789240007048-eng.pdf
3. World HealthOrganization. Guidelines for the programmatic management of drug-resistant tuberculosis—2014.

4. McBryde ES, Meehan MT, Doan TN, et al. The risk of global epidemic replacement with drug resistant *M. tuberculosis* strains. Int J Infect Dis 2017; 56: 14–20.
5. Dheda K, Gumbo T, Maartens G, et al. The epidemiology, pathogenesis, transmission, diagnosis, andmanagement of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. Lancet Respir Med 2017; 5: 291–360.
6. Suchindran S, Brouwer ES, Van Rie A. Is HIV infection a risk factor for multi-drug resistant tuberculosis? A systematic review. PLoS One 2009; 4: e5561.
7. Kendall EA, Fofana MO, Dowdy DW. Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis. Lancet Respir Med 2015; 3: 963–72.
8. Uçar E, Kılıç A, Ceyhan I, et al. Ülkemizin yedi farklı bölgesinden 2003-2006 yılları arasında izole edilen *Mycobacterium tuberculosis* suşlarının majör antitüberküloz ilaçlara direnç oranları. Mikrobiyol Bült 2010; 44: 11-9.
9. Türkiye'de Verem Savaş Raporu 2019. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü, 2019.
10. World Health Organization WHO treatment guidelines for drug-resistant tuberculosis 2016 update. WHO/HTM/TB 2016. 04. World Health Organization, Geneva, 2016.
11. Handbook on TB laboratory diagnostic methods in the European Union. Technıcal Document.https: //www.ecdc.europa.eu/ sites/ default/ files/ documents/ tuberculosis - laboratory-diagnostic-methods-eu.pdf.2016.
12. Ulusal Tüberküloz Tanı Rehberi. T.C. Sağlık Bakanlığı Türkiye Halk Sağlığı Kurumu Başkanlığı Mikrobiyoloji Referans Laboratuvarları Daire Başkanlığı Ankara – 2014.
13. Basil MV, Nair D. Molecular epidemiology of tuberculosis: Opportunities&challenges in disease control. Indian J Med Res 2017; 146: 11–14.
14. Cannas A, Mazzarelli A, DiCaro A, Delogu G, Girardi E. Molecular typing of *Mycobacterium tuberculosis* strains: A fundamental tool for tuberculosis control and elimination. Infect Dis Rep 2016; 8: 6567.
15. Jagielski T, Minias A, vanIngen J, et al. Methodological and clinical aspects of the molecular epidemiology of *Mycobacterium tuberculosis* and other mycobacteria. Clin Microbiol Rev 2016; 29: 239–90.
16. Oudghiri A , Chaoui I, Elmzibri M. Molecular epidemiology of tuberculosis: a review of tools and applications. J InfectDis Ther 2018; 6: 386.
17. Kato-Maeda M, Metcalfe JZ, Flores L. Genotyping of *Mycobacterium tuberculosis*: application İn epidemiologic studies. Future Microbiol 2011; 6: 203-16.
18. Kubica GPW, Dye E, Cohn ML, Middlebrook G. Sputum digestion and decontamination with N-acetyl-L-cysteine-sodiumhydroxide for culture of mycobacteria. Am Rev Respir Dis 1993; 87: 775-80.
19. Becton Dickinson. MGIT For BACTEC ™ MGIT 960 ™ TB System 2006.
20. Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results.Eur Respir J 2005; 25: 564-9.
21. Kocagöz T, Yılmaz E, Özkara Ş, et al. Detection of *Mycobacterium tuberculosis* in sputum samples by polymerase chain reaction using a simplified procedure. J Clin Microbiol 1993; 31: 1435-8.
22. van Soolingen D, Hermans PW, de Haas PE, Soll DR, van Embden JD. Occurrence and stability of insertion sequences in *Mycobacterium tuberculosis* complex strains: evaluation of an insertion sequence-dependent DNA polymorphism as a tool in the epidemiology of tuberculosis. J Clin Microbiol 1991; 29: 2578–86.
23. Kamerbeek J, Schouls L, Kolk A, et al. Simultaneous detection and strain differentiation of *Mycobacterium tuberculosis* for diagnosis and epidemiology. J Clin Microbiol 1997; 35: 907–14.
24. Aranaz A, Liebana E, Mateos A, Dominguez L, Cousins D. Restriction fragment length polymorphism and spacer oligonucleotide typing: a comparative analysis of fingerprinting strategies for *Mycobacterium bovis*. Vet Microbiol 1998; 61: 311–24.
25. www.pasteur-guadeloupe.fr: 8081/sıtvıt_online
26. Roring S, Brittain D, Bunschoten AE, et al. Spacer oligotyping of *Mycobacterium bovis* isolates compared to typing by restriction fragment length polymorphism using PGRS, DR and IS6110 probes. Vet Microbiol 1998; 61: 111–20.
27. Sola C, Horgen L, Maisetti J, Devallois A, Goh KS, Rastogi N. Spoligotyping followed by double-repetitive-element PCR as rapid alternative to IS6110 fingerprinting for epidemiological studies of tuberculosis. J Clin Microbiol 1998; 36: 1122–4.
28. Kayalı R, Çöplü N, Ceyhan İ, Ocak F, Çitil BE, Esen B. Çok ilaca dirençli *Mycobacterium tuberculosis* suşlarının minör antitüberküloz ilaçlara duyarlılığının saptanması. Mikrobiyol Bült 2006, 40: 1-7.
29. Şimşek H, Tarhan, G , Cesur S. Evaluation of second-line antituberculosis drug susceptibilities of multidrug-resistant *Mycobacterium tuberculosis* complex isolates by E-test method. Mikrobiyol Bult 2015; 49: 47-55.
30. Bektöre B, Haznedaroğlu T, Baylan O, et al. Investigation of Extensive Drug Resistance in Multidrug Resistance Tuberculosis Isolates. Mikrobiyol Bul 2013; 47: 59-70.
31. Çiçek SC, Çavuşoğlu C, Burhanoğlu D, Özkalay N, Badak ZF, Bilgiç A. Susceptibility of *Mycobacterium tuberculosis* strains to first-line and second-line antituberculosis drugs in Ege University hospital. Turk J Med Sci 2001; 31: 395-400.
32. Tumer F, Savran Ş. Memleketimizde 1992-93 yıllarında tüberküloz ilaçlarına direnç durumu 20. Turk tüberküloz ve göğüs hastalıkları kongresi 7-9 Nisan 1994 Antalya, 380-386.
33. Osmanlıoğlu G. Türkiye'de tüberküloz ilaçlarında direnç durumu 19. Tüberküloz ve göğüs hastalıkları kongresi. Sivas, 1991; l58.
34. Ozkutuk N, Surucuoglu S, Gazi H, Coskun M, Ozkutuk A, Ozbakkaloglu B. Second-line drug susceptibilities of multidrug-resistant *Mycobacterium tuberculosis* isolates in Aegeanregion-Turkey. Turk J Med Sci 2008; 38: 245-50.
35. Pfyffer EG, Bonato AD, Ebrahimzadeh A et al. Multicenter laboratory validation of susceptibility testing of *Mycobacterium tuberculosis* against classical second-line and newer antimicrobial Drugs by using the radyometric BACTEC 460 Technique and the proportion Method with Solid media. Clin Microbiol 1999; 37: 3179-86.
36. WH0. Guidelines for surveillance of drug resistance in tuberculosis. 5th Edition, Geneva: World Health Organization, 2015.
37. Cannas A, Mazzarelli A, DiCaro A, Delogu G, Girardi E. Molecular typing of *Mycobacterium tuberculosis* strains: a fundamental tool for tuberculosis control and elimination. Infect Dis Rep 2016; 8: 6567.
38. Basil MV, Nair D. Molecular epidemiology of tuberculosis: Opportunities & challenges in disease control. Indian J Med Res 2017; 146: 11–4.
39. Karagöz A, Hidayet Tütün H, Altintaş L, Alanbayi U, Yıldırım D, Kocak N. Molecular typing of drug-resistant *Mycobacterium tuberculosis* strains from Turkey. J Glob Antimicrob Resist 2020; 23: 130-4.
40. Pourostadi M, Rashedi J, Poor BM, et al. Role of Molecular Epidemiology on Tuberculosis Control in the Middle East Countries: a Systematic Review and Meta-Analysis.Tanaffos 2018; 17: 223–32.
41. Kısa O, Tarhan,G, Gunal S, et al. The distribution of spoligotyping defined genotypic lineages among drug-resistant *M. tuberculosis* complex clinical isolates in Ankara, Turkey, Plos One 2012; 7: e30331.

42. Durmaz R, Ozerol IH, Durmaz B, Gunal S, Senoglu A, Evliyaoglu E. Primary drugresistance and molecular epidemiology of *Mycobacterium tuberculosis* isolates from patients in a population with high tuberculosis incidence in Turkey. Microb Drug Resist 2003; 9: 361-6.
43. Gencer B, Shinnick MT. Molecular genotyping of *Mycobacterium tuberculosis* Isolates from Turkey. Am J Infec Dis.2005; 1: 5–11.
44. Durmaz R, Zozio T, Gunal S, Allix C, Fauville-Dufaux M, Rastogi N. Population-based molecular epidemiological study of tuberculosis in Malatya. Turk J Clin Microbiol 2007; 45: 4027-35.
45. Durmaz R, Zozio T, Gunal S, et al. Genetic diversity and major spoligotype families of drug-resistant *Mycobacterium tuberculosis* clinical isolates from different regions of Turkey. Infect Genet Evol 2007; 7: 513–9.
46. Otlu B, Durmaz R, Gunal S, et al. Beijing/W and major spoligotype families of *Mycobacterium tuberculosis* strains isolated from tuberculosis patients in Eastern Turkey. New Microbiol 2009; 32: 255–63.
47. Sinkov V, Ogarkov O, Mokrousov I, Bukin Y, Zhdanova S, Heysell SK. New epidemic cluster of pre-extensively drug resistant isolates of *Mycobacterium tuberculosis* Ural family emerging in Eastern Europe. BMC Genomics 2018; 19: 762.
48. Cavuşoğlu C, Yılmaz FF, Onmus IRD, Bozdemir T, Taslı H, Limoncu MH. Genotype distribution of *Mycobacterium tuberculosis* in the Aegean Region and associated demographic factors. Turk J Med Sci 2017; 47: 1593-601.

Original Article

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Is there a correlation between complete blood count parameters and nutritional risk score 2002, geriatric nutritional risk index and nutric score in geriatric patients admitted to intensive care unit

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ASBTRACT

Aim: Malnutrition is a common condition especially in geriatric patients admitted to intensive care. There are various screening tools to be used in the evaluation of nutritional status in geriatric patients hospitalized in intensive care. However, a laboratory test has not been found yet for nutritional status assessment. With this study, we aimed to investigate whether there is a correlation between NLR, PLR, and complete blood count parameters at the time of admission to the intensive care unit and NRS-2002, GNRI, and mNutric Score measured in the intensive care unit.

Material and Method: This retrospective study was performed in a tertiary intensive care unit of a Chest Diseases Hospital. Patients aged 65 and over were included in the study. Demographic data, length of stay in intensive care, complete blood count on the day of admission to the intensive care unit, albumin value, NLR, PLR, NRS-2002, GNRI, and mNutric Score values were recorded.

Results: A total of 218 geriatric patients were analyzed. It was determined that 72.5% of the patients were at medium/high risk in terms of nutritional risk according to the GNRI classification, 76.6% were at high risk according to NRS-2002, and 84.9% were at high risk according to the mNutric score. According to the GNRI, the MPV values were statistically significantly higher ($p<0.05$). According to the biserial correlation analysis, there is a statistically significant correlation between GNRI and MPV in the positive direction ($p<0.05$). The cut-off value for MPV was determined as 7.895 in terms of nutritional risk assessment

Conclusion: It was observed that the majority of geriatric patients in the intensive care unit were at high risk for malnutrition according to nutritional scores. It was determined that the MPV value of the patients in the intermediate/high-risk group for GNRI was significantly higher and there was a positive correlation between MPV and GNRI. The cut-off value for MPV was determined as 7.895 in terms of nutritional risk assessment. We think that MPV can be used practically in nutritional risk scoring in geriatric patients hospitalized in the intensive care unit.

Keywords: Complete blood count, geriatric nutritional risk index, intensive care, nutric score, nutritional risk score-2002, mean platelet volume

INTRODUCTION

Malnutrition is a common condition especially in geriatric patients admitted to intensive care (1). There are various screening tools to be used in the evaluation of nutritional status in geriatric patients hospitalized in intensive care (1). Nutritional status assessment in these patients is frequently performed with geriatric nutritional risk index (GNRI), nutritional risk score-2002 (NRS-2002), and modified nutrition risk in the critically ill score (mNUTRIC Score) (1-6). However, a laboratory test has not been found yet for nutritional status assessment. However, the nutritional status of the patients affects the length of stay in the hospital and intensive care unit and is a determinant in prognosis and mortality (7,8). Therefore, it is important to evaluate the nutritional status quickly and practically, especially in geriatric patients.

The complete blood count is performed in almost all patients for whom blood tests are requested and it is a practical method. In some studies, it has been shown that neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are parameters that can determine the prognosis in patients (9-11). However, we could not find any research on whether there is a correlation

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between the scoring used in the nutritional status assessment of geriatric patients admitted to the intensive care unit and the parameters of the complete blood count. With this study, we aimed to investigate whether there is a correlation between NLR, PLR, and complete blood count parameters at the time of admission to the intensive care unit and NRS-2002, GNRI, and mNutric Score measured in the intensive care unit. If a correlation is detected, a more practical nutritional status assessment can be made in geriatric patients.

MATERIAL AND METHOD

Our study was performed in a tertiary intensive care unit after the approval of the Keçiören Training and Resarch Hospital Clinical Researchs Ethics Committee (Date: 11.05.2021, Decision No: 2012-KAEK-15/2306). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

The data of patients admitted to the intensive care unit with respiratory failure between January 2018 and December 2018 were scanned retrospectively from patient files. Demographic data such as age, gender, height, weight, body mass index, length of stay in intensive care, complete blood count on the day of admission to the intensive care unit, albumin value, NLR, PLR, NRS-2002, GNRI, and Nutric Score values were recorded. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. NRS-2002 is routinely calculated by the nutrition team for each patient admitted to the intensive care unit. NRS-2002 is calculated based on the patient's body mass index, weight loss in the last 3 months, appetite status, and severe disease status. Nutric score calculation is based on patient's age, Apache-II score (Acute Physiology and Chronic Health Evaluation-II), SOFA score (Sequential Organ Failure Assessment Score), number of co-morbidities, Interleukin-6(IL-6), and the length of hospital stay before admission to the intensive care unit (12). In our study, the modified Nutric score (mNutric score) calculated without taking into account IL-6 was used. GNRI was calculated from the formula [1.489 X albumin (g/L)] + [41.7 (kilo/ideal weight)] (13). Ideal weight was calculated with the formula [(Height-100) –(Height-150/4)] for men and with the Formula [(Height-100) –(Height-150/2,5)] for women (13). The nutritional risk status of the patients was determined as follows: GNRI≥ 92; (low risk/No risk), GNRI< 92; (Moderate Risk/High Risk), NRS-2002≤4; (Low Risk), NRS-2002>4; (High Risk), Nutric score≤4; (Low Risk), Nutric score>4;(High Risk) (1,13-15). If the weight of the patients was more than their ideal weight, the weight/ideal weight ratio was accepted as 1 (13). Patients under the age of 65, patients with a diagnosis of hematological malignancy, patients hospitalized in the intensive care unit for less than 24 hours, and those with insufficient data required for the study were excluded from the study.

Statistical Analysis

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by the Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean±SD for normal distributions, and median (interquartile range) for skewed distributions. Categorical data were described as the number of cases (%). Statistical analysis differences in normally distributed variables between two independent groups were compared by Student's t-test, Mann Whitney U tests were applied for comparisons of the not normally distributed data. Concordance between nutritional scores was evaluated by Cohen's Kappa Analysis. İt was evaluated degrees of the relation between variables with point biserial correlation. It was accepted p-value<0.05 as a significant level on all statistical analysis.

RESULTS

The number of patients hospitalized in the intensive care unit with respiratory failure was 348. 232 patients were 65 years of age or older. 3 patients were excluded because they stayed in the intensive care unit for less than 24 hours, and 11 patients were excluded because their data were missing. A total of 218 patients were analyzed (**Figure 1**).

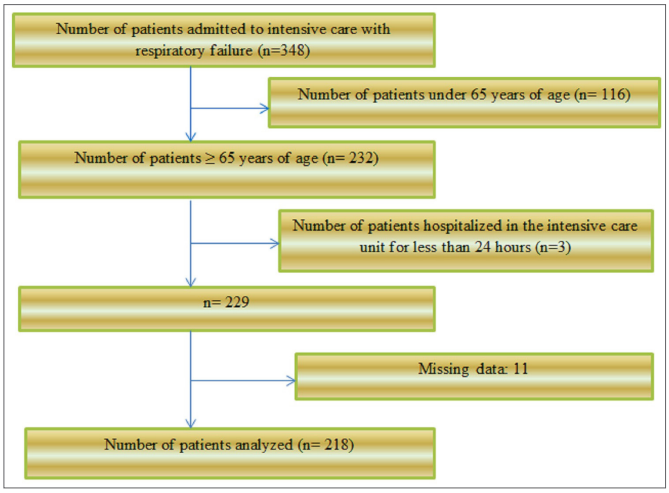

Figure 1. Flow chart of the patients.

The demographic data of the patients, their diagnoses, the status of receiving mechanical ventilator support, and the length of stay in the intensive care unit are given in **Table 1**.

It was determined that 72.5% of the patients were at medium/high risk in terms of nutritional risk according to the GNRI classification, 76.6% were at high risk according to NRS-2002, and 84.9% were at high risk according to the mNutric score.

According to the GNRI, the RBC, hemoglobin, and hematocrit values of the medium/high-risk group were statistically significantly lower than the no-risk/low-risk group, while the MCH, MCHC, and MPV values were statistically significantly higher (p<0.05) (**Table 2**).

Table 1. The demographic data of the patients, their diagnoses, the status of receiving mechanical ventilator support and the length of stay in the intensive care unit

n:218	AllPatients
Gender, n (%)	
Male	121 (55.5%)
Female	97 (44.5%)
Age, mean±SD	78.28±7.43
BMI (kg/m^2), mean±SD	25.38±5.83
Mechanical Ventilator Support, n (%)	101 (46.3%)
Type 1 Respiratory Failure, n (%)	82 (37.6%)
Type 2 Respiratory Failure, n (%)	136 (62.4%)
Diagnosis of malignancy, n (%)	
No	189 (86.7%)
Lung malignancy	23 (10.6%)
COPD, n (%)	143 (65.6%)
ICU stay,days, median (IQR)	3.5 (4)

Continuous variables are expressed as either the mean±Standard deviation (SD) or median (interquartile range) and categorical variables are expressed as either frequency (percentage).
BMI: Body mass index, ICU: Intensive care unit, COPD: chronic obstructive pulmonary disease, IQR: interquartile range

Table 2. NLR, PLR and hemogram values of patients according to GNRI risk classification

	GNRI Risk		P
	No-risk/Low-risk (n:60)	Medium/High-risk (n:158)	
WBC, ×10^3/µL	10.35(5.75)	10.95(7.50)	0.319
Lymphocyt count, ×10^3/µL	0.82(1.07)	0.84(0.96)	0.993
Monocyte count, ×10^3/µL	0.44(0.54)	0.47(0.59)	0.518
Neutrophil count, ×10^3/µL	8.81(5.00)	8.94(7.44)	0.160
Eosinophil count, ×10^3/µL	0.01(0.04)	0.01(0.07)	0.427
Basophil count, ×10^3/µL	0.03(0.05)	0.03(0.05)	0.811
RBC, ×10^6/µL	4.57±0.88	4.06±0.85	<0.001
Hemoglobin, g/dL	11.85(3.25)	10.90(2.80)	0.009
Hematocrit, %	39.51±7.98	35.42±7.06	<0.001
MCV, fL	86.30 (10.40)	88.10 (8.80)	0.430
MCH, pg	27.05 (3.95)	28.20 (3.60)	0.040
MCHC, g/dL	30.91±1.62	31.67±1.60	0.002
RDW, %	17.85 (4.65)	16.85 (3.50)	0.209
Platelet ×10^3/µL	241.70±98.77	228.55±95.98	0.371
MPV, fL	8.22 (1.95)	8.80 (1.68)	0.016
PCT, %	0.20±0.08	0.20±0.08	0.956
PDW, %	17.55 (1.85)	17.40 (2.40)	0.494
NLR	9.54 (12.54)	10.01 (12.90)	0.501
PLR	319.29 (316.39)	240.82 (290.49)	0.423

Continuous variables are expressed as either the mean±Standard deviation (SD) or median (interquartile range) and categorical variables are expressed as either frequency (percentage).Continuous variables were compared with student t test or mann whitney u test, and categorical variables were compared using Pearson'schi-square test or fisher exact test. Statistically significant p-values are in bold.
NLR: neutrophil / lymphocyte rate; LMR: lymphocyte/monocyte rate; PLR: platelet/lymphocyte rate; WBC: White blood cell; RBC: Red blood cell; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; MPV: mean platelet volume; PCT: platelet crit; PDW: platelet distribution width. GNRI: geriatric nutritional risk index

There are no statistically significant difference between the groups in terms of NLR, PLR, and hemogram values according to NRS-2002 and mNutric score risk groups (p > 0.05).

According to the biserial correlation analysis, there is a statistically significant correlation between GNRI and RBC and Hematocrit in the negative direction, and between MCHC and MPV in the positive direction (p<0.05) (**Table 3**).

Table 3. Correlation Analysis between Nutritional Scoring and NLR, PLR and Hemogram Values

		GNRI Risk	NRS -2002	mNutric Score
WBC, ×10^3/µL	r	0.024	-0.119	0.066
	p	0.720	0.079	0.331
Lymphocyt Count, ×10^3/µL	r	-0.109	0.009	0.037
	p	0.108	0.891	0.590
Monocyte Count, ×10^3/µL	r	0.046	-0.075	0.083
	p	0.501	0.269	0.220
Neutrophil Count, ×10^3/µL	r	0.087	-0.139	0.051
	p	0.203	0.041	0.454
Eosinophil Count, ×10^3/µL	r	0.030	-0.038	0.032
	p	0.662	0.572	0.637
Basophil Count, ×10^3/µL	r	-0.068	0.053	0.054
	p	0.320	0.433	0.427
RBC, ×10^6/µL	r	-0.254	-0.005	-0.031
	p	<0.001	0.938	0.646
Hemoglobin, g/dL	r	-0.025	0.048	0.022
	p	0.711	0.477	0.749
Hematocrit, %	r	-0.243	0.021	-0.007
	p	<0.001	0.754	0.913
MCV, fL	r	0.049	0.048	0.039
	p	0.471	0.481	0.569
MCH, pg	r	0.075	-0.107	0.039
	p	0.270	0.115	0.567
MCHC, g/dL	r	0.207	0.017	-0.019
	p	0.002	0.801	0.783
RDW, %	r	-0.080	-0.098	0.024
	p	0.241	0.147	0.728
Platelet, ×10^3/µL	r	-0.061	-0.023	-0.109
	p	0.371	0.732	0.107
MPV,fL	r	0.137	0.041	0.033
	p	0.044	0.551	0.624
PCT, %	r	0.004	-0.011	-0.105
	p	0.956	0.874	0.121
PDW, %	r	-0.029	-0.001	0.015
	p	0.675	0.989	0.828
NLR	r	0.069	-0.036	-0.046
	p	0.312	0.594	0.501
PLR	r	0.031	0.041	-0.094
	p	0.653	0.547	0.169

NLR: neutrophil / lymphocyte rate, LMR: lymphocyte/monocyte rate, PLR: platelet/lymphocyte rate, WBC: White blood cell, RBC: Red blood cell, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width, MPV: mean platelet volume, PCT: platelet crit, PDW: platelet distribution width, GNRI: geriatric nutritional risk index, NRS: Nutritional risk score, mNutric: modified nutrition risk in critically ill

In the ROC analysis, the area under the curve (AUC) for MPV was calculated as 0.606 and was found to be statistically significant (p<0.05). When the cut-off value of 7.895 was accepted as the cut-off value in terms of MPV level, the sensitivity was calculated as 77.8 %, the specificity as 43.3 %. (**Table 4**) (**Figure 2**)

Table 4. ROC Curve Analysis Results by Geriatric Nutritional Risk Index for Mean Platelet Volume

	MPV
AUC	0.606
AUC for 95% CI	(0.519-0.593)
P values	0.016
CutOff	7.895
Sensitivity	77.8%
Specificity	43.3%
PPV	78.3%
NPV	42.6%
LR+	1.37
LR-	0.52

AUC: area under curve, PPV: positivepredictivevalue, NPV: negativepredictivevalue, LR+: positivelikelihoodrati, LR-: negativelikelihoodratio

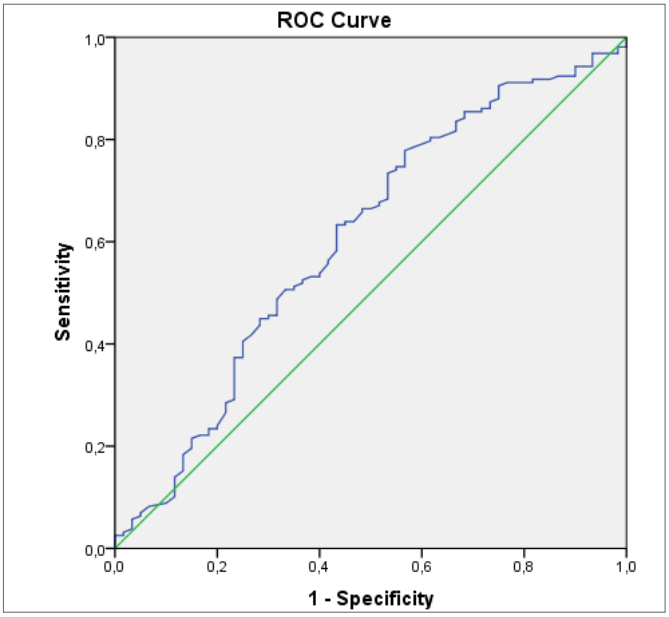

Figure 2. ROC curve for Mean Platelet Volume. ROC: Receiver Operating Characteristic

DISCUSSION

In our study, it was seen that the majority of patients hospitalized in the intensive care unit with respiratory failure were at high risk for malnutrition according to nutritional scores. According to NRS-2002 and mNutric Score, there was no difference in NLR, PLR, and hemogram values between low and high-risk patients. However, according to GNRI, the MPV values of the medium/high-risk group were found to be statistically significantly higher than the no-risk/low-risk group. In addition, there is a low level of statistically significant correlation between GNRI and MPV in the positive direction. As a result of the ROC analysis, a cut-off value of 7.895 was determined for MPV.

The number of geriatric patients hospitalized in the intensive care unit with respiratory failure is gradually increasing (1). Geriatric patients are handled differently from other patients due to increased comorbidity and pharmacokinetic and pharmacodynamic differences (16,17). Studies indicate that advanced age is a risk factor for morbidity and mortality (18-20). We think that nutritional evaluation in geriatric patients should be handled differently. Malnutrition is an important condition that is frequently encountered in the elderly population and leads to muscle weakness and the development of various infections if not detected and treated in a timely manner (1). Therefore, it is very important to detect malnutrition or the risk of malnutrition quickly, especially in geriatric patients. NRS-2002 is not specifically designed for intensive care patients. The mNutric score, on the other hand, does not contain any nutritional parameters (21). However, both scorings are used for nutritional risk assessment in intensive care patients (1,3,21). Nutric score has a limited prediction for the initiation of early nutritional therapy in the admission of patients to the intensive care unit(22). In addition, both NRS-2002 and mNutric Score were investigated to predict mortality in intensive care patients (1,3). It is not possible to obtain detailed information about the nutritional status of geriatric patients admitted to the intensive care unit. The information provided by their relatives may not be sufficient. It is stated that GNRI can be used easily and objectively as a malnutrition screening tool in geriatric patients (1). GNRI, on the other hand, is a screening tool that integrates serum albumin and BMI for nutritional assessment in geriatric patients (23). Studies indicate that GNRI can also be used as a prognostic indicator in many diseases (24-26). For this reason, the effect of GNRI on nutritional assessment and mortality in geriatric patients hospitalized in the intensive care unit was investigated and it was stated that it could predict mortality in patients hospitalized in the intensive care unit with respiratory failure (1). However, recently, studies have been carried out to evaluate the prognosis of patients using laboratory parameters (9,13,27). It is known that NLR and PLR, which can be calculated especially with hemogram parameters, are used in the evaluation of prognosis in various diseases (9-11). However, there are limited studies evaluating the relationship between hemogram parameters and nutritional status (28,29). In a study examining the relationship between lymphocyte count and nutritional status in geriatric patients, it was stated that lymphocyte count could be used as a nutritional marker in hospitalized geriatric patients (28). In another

study, it was stated that lymphocyte count was not a good nutritional marker in geriatric patients (29). However, these studies were not conducted specifically for geriatric patients admitted to the intensive care unit. Our study is the first in the literature to evaluate the nutritional status with hemogram parameters in geriatric patients hospitalized in the intensive care unit with respiratory failure. In our study, similar to the result of Kuzuya M, et al (29), no relationship was found between lymphocyte count and nutritional assessment in geriatric patients.

In our study, there was no difference between the groups in terms of NLR, PLR, and hemogram values according to NRS-2002 and mNutric score risk groups. However, according to GNRI, the RBC, hemoglobin, and hematocrit values of the medium/high-risk group were lower than the no-risk/low-risk group, while the MCH, MCHC, and MPV values were found to be significantly higher. While there is no difference according to NRS-2002 and mNutric score risk groups, the difference in laboratory parameters according to GNRI risk groups may be due to the fact that GNRI is a screening tool designed specifically for the geriatric age group.

MPV is evaluated as an indicator of platelet function (30). It is also stated that it is associated with the inflammatory process and reflects the severity of the disease (31-35). MPV value may increase in chronic respiratory diseases and various diseases (36). In a study, it was stated that high MPV levels were associated with increased mortality in geriatric patients (37). In our study, it was determined that the MPV value of the patients in the intermediate/high-risk group for GNRI was significantly higher and there was a positive correlation between MPV and GNRI. In addition, as a result of the ROC analysis, a cut-off value of 7.895 was determined for MPV. The cut-off value of 7,895 that we have obtained can be used in a practical way in determining the nutritionally intermediate/high-risk patients in geriatric patients admitted to the intensive care unit.

There are some limitations in our study. First of all, our study is a single-center and retrospective study. Accordingly, the nutritional treatments applied to the patients and the changes in the nutritional status of the patients after these treatments could not be evaluated. In addition, the prognosis of the patients after the intensive care unit could not be evaluated.

CONCLUSION

As a result, the majority of patients hospitalized in the intensive care unit with respiratory failure in our clinic are geriatric patients. It was observed that the majority of geriatric patients in the intensive care unit were at high risk for malnutrition according to nutritional scores. In our study, it was determined that the MPV value of the patients in the intermediate/high-risk group for GNRI was significantly higher and there was a positive correlation between MPV and GNRI. In addition, the cut-off value for MPV was determined as 7.895 in terms of nutritional risk assessment. We think that MPV can be used practically in nutritional risk scoring in geriatric patients hospitalized in the intensive care unit, but it would be beneficial to bring different studies to the literature with prospective and multicenter studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Keçiören Training and Research Hospital Clinical Researchs Ethics Committee (Date: 11.05.2021, Decision No: 2012-KEAK-15/2306).

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 of 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.

REFERENCES

1. Yenibertiz D, Cirik MO. The comparison of GNRI and other nutritional indexes on short-term survival in geriatric patients treated for respiratory failure. Aging Clin Exp Res 2021; 33: 611-7.
2. Javid Mishamandani Z, Norouzy A, Hashemian SM, et al. Nutritional status of patients hospitalized in the intensive care unit: A comprehensive report from Iranian hospitals. J Crit Care 2019; 54: 151-8.
3. Machado Dos Reis A, Marchetti J, Forte Dos Santos A, Franzosi OS, Steemburgo T. Nutric score: isolated and combined use with the NRS-2002 to predict hospital mortality in critically Ill patients. JPEN J Parenter Enteral Nutr 2020; 44: 1250-6.
4. Lew CCH, Yandell R, Fraser RJL, Chua AP, Chong MFF, Miller M. Association between malnutrition and clinical outcomes in the intensive care unit: a systematic review. J Parenter Enteral Nutr 2017; 41: 744-58.
5. Lin YM, Wang M, Sun NX, Liu YY, Yin TF, Chen C. Screening and application of nutritional support in elderly hospitalized patients of a tertiary care hospital in China. PLoS One 2019; 14: e0213076.
6. Bouillanne O, Morineau G, Dupont C, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr 2005; 82: 777-83.
7. Álvarez-Hernández J, Planas Vila M, León-Sanz M, et al. Prevalence and costs of malnutrition in hospitalized patients. Nutr Hosp 2012; 27: 1049-59.
8. Agarwal E, Miller M, Yaxley A, Isenring E. Malnutrition in the elderly: a narrative review. Maturitas 2013; 76: 296-302.

9. Kaya T, Açıkgöz SB, Yıldırım M, Nalbant A, Altaş AE, Cinemre H. Association between neutrophil-to-lymphocyte ratio and nutritional status in geriatric patients. J Clin Lab Anal 2019; 33: e22636.
10. Yıldırım Ö, Bayram M, Özmen RS, et al. Evaluation of hematological indices in terms of COVID-19 related mortality and ICU admission. J Health Sci Med 2021; 4: 666-70.
11. Lee JS, Kim NY, Na SH, Youn YH, Shin CS. Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea. Medicine (Baltimore) 2018; 97: e11138.
12. de Vries MC, Koekkoek WK, Opdam MH, van Blokland D, van Zanten AR. Nutritional assessment of critically ill patients: validation of the modified Nutric score. Eur J Clin Nutr 2018; 72: 428-35.
13. Tang S, Xie H, Kuang J, Gao F, Gan J, Ou H. The value of geriatric nutritional risk index in evaluating postoperative complication risk and long-term prognosis in elderly colorectal cancer patients. Cancer Manag Res 2020; 12: 165-75.
14. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). J Parenter Enteral Nutr 2016; 40: 159-211.
15. de Vries MC, Koekkoek WK, Opdam MH, van Blokland D, van Zanten AR. Nutritional assessment of critically ill patients: validation of the modified Nutric score. Eur J Clin Nutr 2018; 72: 428-35.
16. Zengin M, Alagoz A. Comparison of thoracic epidural analgesia and thoracic paravertebral block applications in the treatment of acute pain after thoracotomy in geriatric patients. Cureus 2021; 22: 18982.
17. Cavalieri TA. Managing pain in geriatric patients. J Osteopath Med 2007; 107: 10-6.
18. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J 2020; 55: 2000524.
19. Tekyol D, Hökenek NM. Comparison of the ability of the shock index, modified shock index and age shock index to predict mortality in geriatric patients with COVID-19 pneumonia. J Health Sci Med 2021; 4: 634-8.
20. Aydın N. COVID-19 ve palyatif bakım. J Med Palliat Care 2021; 2: 54-57.
21. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care 2011; 15: 268.
22. Al-Kalaldeh M, Suleiman K, Al-Kalaldeh O. Prognostic performance of nutric score in quantifying malnutrition risk in the critically Ill in congruence with the bioelectrical impedance analysis. Nutr Clin Pract 2020; 35: 559-66.
23. Cereda E, Klersy C, Pedrolli C, et al. The Geriatric Nutritional Risk Index predicts hospital length of stay and in-hospital weight loss in elderly patients. Clin Nutr 2015; 34: 74-8.
24. Miyake H, Tei H, Fujisawa M. Geriatric nutrition risk index is an important predictor of cancer-specific survival, but not recurrence-free survival, in patients undergoing surgical resection for non-metastatic renal cell carcinoma. Curr Urol 2017; 10: 26-31.
25. Yamana I, Takeno S, Shimaoka H, et al. Geriatric Nutritional Risk Index as a prognostic factor in patients with esophageal squamous cell carcinoma -retrospective cohort study. Int J Surg 2018; 56: 44-8.
26. Shoji F, Matsubara T, Kozuma Y, et al. Preoperative Geriatric Nutritional Risk Index: A predictive and prognostic factor in patients with pathological stage I non-small cell lung cancer. Surg Oncol 2017; 26: 483-8.
27. Güngörer B. Baseline demographic, clinical and laboratory risk factors for predicting admission to intensive care unit in patients diagnosed with COVID-19 in the emergency department. Anatolian Curr Med J 2021; 3: 279-83.
28. Leandro-Merhi VA, Bráz VN, Aquino JL. Is total lymphocyte count related to nutritional markers in hospitalized older adults? Arq Gastroenterol 2017; 54: 79-82.
29. Kuzuya M, Kanda S, Koike T, Suzuki Y, Iguchi A. Lack of correlation between total lymphocyte count and nutritional status in the elderly. Clin Nutr 2005; 24: 427-32.
30. Ak R, Doğanay F. Relationship between mean platelet volume and intensive care unit requirement in COVID-19 patients. J Health Sci Med 2021; 4: 353-7.
31. Sit M, Aktas G, Ozer B, et al. Mean platelet volume: an overlooked herald of malıgnant thyroid nodules. Acta Clin Croat 2019; 58: 417-20.
32. Bilgin S, Aktas G, Kahveci G, Atak BM, Kurtkulagi O, Duman TT. Does mean platelet volume/lymphocyte count ratio associate with frailty in type 2 diabetes mellitus? Bratisl Lek Listy 2021; 122: 116-9.
33. Sincer I, Gunes Y, Mansiroglu AK, Cosgun M, Aktas G. Association of mean platelet volume and red blood cell distribution width with coronary collateral development in stable coronary artery disease. Postepy Kardiol Interwencyjnej 2018; 14: 263-9.
34. Önder S, Ozturk M. How does omalizumab affect the immunoinflammatory response in patients with chronic spontaneous urticaria? Cutan Ocul Toxicol 2020; 39: 31-5.
35. Kridin K, Shihade W, Zelber-Sagi S. Mean platelet volume in pemphigus vulgaris. Angiology 2018; 69: 303-7.
36. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean platelet volume (MPV): new perspectives for an old marker in the course and prognosis of inflammatory conditions. Mediators Inflamm 2019; 2019: 9213074.
37. Şatıroğlu Ö, Durakoğlugil ME, Uydu HA, et al. The relationship between mean platelet volume and in-hospital mortality in geriatric patients with ST segment elevation myocardial infarction who underwent primary percutaneous coronary intervention. Cardiovascular Innovations and Applications 2019; 4: 135-41.

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Frequency of troponin elevations in patients with COVID-19 and clinical course in these patients

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ABSTRACT

Aim: We aimed to determine the frequency of troponin elevations in COVID-19 patients and to investigate the role of troponin in demonstrating the prognosis of COVID-19 by examining the clinical course of theese patients.

Material and Method: Patients diagnosed with COVID-19 disease were included in the study. Patient files were analyzed retrospectively through the hospital information management system.Patients with high troponin levels were identified and comparisons were made with patients with normal troponin levels.

Results: 1468 patients were included in the study.Troponin level was found to be high in 6.7% of the patients.The presence of pneumonia on thorax CT rate,hospitalization rate,ICU admission rate,intubation rate was significantly higher in patients with high troponin levels.The mortality rate was 2.1% in the whole group.The mortality rate was significantly higher in the patients with high troponin levels.Total length of hospital and ICU stay were significantly higher in patients with high troponin levels. There was a significant positive correlation between the troponin levels of the patients at admission and the total length of hospital stay and length of ICU stay. 49.5% of COVID-19 patients had another comorbid disease.Hypertension was the most common comorbid disease. The rate of troponin elevation and troponin levels were significantly higher in patients with other comorbid diseases.

Conclusion: It has been found that high troponin levels in COVID-19 patients may be associated with a poor clinical prognosis. Troponin can be used as a predictor of prognosis with more comprehensive studies and long-term follw-up results in the future.

Keywords: COVID-19, SARS-CoV-2, troponin, cardiac biomarkers, prognosis

INTRODUCTION

Cardiac troponins are highly sensitive and specific biomarkers of myocardial diseases. In acute coronary syndrome, elevated troponin levels are important in terms of both prognosis and treatment guidance. For this reason, troponin level measurements are frequently used in the diagnosis of acute coronary syndrome in emergency departments and intensive care units. After acute myocardial injury, blood levels increase within 2-4 hours, reach a peak in 24 hours, and then blood troponin levels remain high for about 2-3 weeks. In the guidelines, the increase in cardiac troponins is accepted as the basic diagnostic criterion in the definition of acute myocardial infarction (1,2).

Although troponin elevation is an important indicator of coronary ischemia, it should not be forgotten that it may increase in other clinical conditions and should not always be interpreted in favor of coronary ischemia. It is known that troponin levels can be measured high in patients who are admitted to hospital for any reason (3,4). Renal failure, myocarditis, pulmonary embolism, arrhythmia, cerebrovascular events, malignancy, trauma, severe infection, toxicity etc in such cases, high troponin levels can be detected without acute coronary syndrome.

The causative agent of coronavirus disease 2019 (COVID-19) is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (5,6). SARS-CoV-2 is an enveloped RNA virus (4). COVID-19 has similar signs, symptoms and effects as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). The agents of SARS, MERS and COVID-19 belong to the Coronaviridae family and the Coronavirinae subfamily (7,8). COVID-19 was first diagnosed in Wuhan, China, in December 2019, but then spread all over the world.

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COVID-19 has been declared a pandemic by the World Health Organization as of March 11, 2020. In humans, the main route of transmission of SARS CoV-2 is virus-carrying respiratory droplets (9). Generally, COVID-19 patients develop symptoms 5-7 days after exposure. Common symptoms are fever, sore throat, cough, myalgia, headache, dyspnea, nausea, diarrhea.

SARS-CoV-2 enters the cell by attaching to the angiotensin converting enzyme 2 (ACE2) receptor. The infection process begins with the binding of the viral envelope S protein of SARS CoV-2 to the ACE2 receptor in the cell membrane. The ACE2 receptor is found especially in the lungs, endothelium, heart, kidneys, brain and intestines (10,11). Therefore, all these organs can be the target of the virus and complications may occur in these organs.

As the ACE2 receptor is also expressed in cardiac myocytes and endothelium, they are potential targets of SARS-CoV-2. SARS CoV-2 can infect myocytes and endothelial cells directly, or damage these organs by causing thrombotic processes. Likewise, cytokine storms and activation of coagulation cascades caused by SARS Cov-2 triggering inflammatory processes are also likely to cause pathological effects on the heart and endothelium. Pathological events such as hypoxia, systemic inflammation, sepsis, thromboembolic events, systemic adrenergic hyperstimulation that may occur in COVID-19 disease can also cause non-ischemic myocardial events and endothelial pathologies.While much is unclear about Sars-Cov-2, it is likely that involvement similar to past viral outbreaks will occur. Previous viral epidemics, including MERS-CoV and SARS, have also been associated with myocardial damage and troponin elevation by the same mechanisms (12,13).

In COVID-19 disease, new markers are needed to show the prognosis of the disease. In this context, scientific studies are needed. Today, we do not have a proven marker that will enable us to take positive steps on clinical course and mortality by determining the risk of developing ischemic or non-ischemic cardiovascular events in COVID-19 disease. In this study, we planned to determine the frequency of troponin elevation in COVID-19 patients and to investigate the role of troponin test in demonstrating the prognosis of COVID-19 disease by examining the clinical course of the patient group with high troponin test.

MATERIAL AND METHOD

For this study, approval was obtained from Istanbul Sancaktepe Sehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Decision No: 2021/84, (Date: 29/01/2021). All human studies have been performed under the rules of 1964 Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Patients diagnosed with COVID-19 between 01/04/2020 and 31/07/2020 were included in the study. Patients over 18 years old, with positive COVID-19 PCR test results, and patients with thorax computerised tomography (Thorax CT) and troponin test on admission were included in the study. Patients diagnosed with acute coronary syndrome or acute cerebrovascular disease as a result of consultations due to high troponin levels were excluded from the study. Patients younger than 18 years old, had pregnancy, diagnosed with malignancy or renal failure were excluded from the study. Patient files were analyzed retrospectively through the hospital information management system. The demographic characteristics, medical history, COVID-19 PCR test results, blood test results, thorax ct reports, hospitalization status, intensive care admission status, length of hospitalization stay, intubation status and treatment results of the patients were examined. Troponin I test was performed on the patients at admission. The reference range was given as 0-28.9 pg/ml for males and 0-13.8 pg/ml for females. Patients with high troponin levels were identified and comparisons were made with patients with normal troponin levels.

Statistical Analysis

Statistical analysis was made with the data obtained. IBM Corporation SPSS (Statistical Package for Social Sciences), version 23.0, New York, US was used for statistical analyses. While evaluating the study data, the suitability of the parameters to the normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro Wilks tests. Descriptive statistical methods including percentage and mean±standard deviation (± SD) or median (interquartile range [IQR] were used to provide the basic features of the data, according to the evaluation of distribution for normality. An independent sample t-test was used to analyze quantitative data. Differences in the values of the variables between the groups were evaluated by the Mann–Whitney U test. Chi-square test was used to analyze qualitative data. A value of $P<0.05$ was considered to be statistically significant. Spearman Correlation test was performed to evaluate the relationship between troponin levels and length of hospitalization stay in hospitalized patients. Receiver Operating Characteristic (ROC) curve analysis was performed to determine the significant troponin level in prognosis in patients admitted to the intensive care unit and patients who died. As a result of the ROC curve analysis, the cut-off value of the troponin test and the sensitivity and specificity of this value were determined. The area under the ROC curve (AUC) value was calculated with a 95% confidence interval.

RESULTS

A total of 1468 patients, 708 females (48.2%), 760 males (51.8%), were included in the study. The median age of the patients was found to be 50 [IQR: 38 - 60] years (**Table 1**). 77% of females and 79.7% of males were hospitalized. 47.4% of the hospitalized patients were female and 52.6% were male. There was no significant difference in hospitalization rate according to gender (**Table 1**). The median age of the patients treated in the hospital was 54 [IQR: 43 - 63] years, and the median age of the patients treated at home was 38 [iIQR: 28-48] years. Median age was significantly higher in hospitalized patients (p<0.001) (**Table 1**). Troponin level was found to be high in 6.7% of the patients. The average age of patients with high troponin levels was found to be 68.22±14.23 years. Patients with high troponin levels were significantly older than patients with normal troponin levels (p<0.001) (**Table 2**). The troponin level was high in 8.2% of the females. In female patients, the rate of troponin elevation was found to be significantly higher than males (p <0.033) (**Table 2**). 96% of the patients with high troponin levels were treated in hospital. Troponin elevation was detected in 8.3% of the inpatients. Troponin elevation was detected in 4 of the patients treated at home. Hospitalization was significantly higher in patients with high troponin levels (p <0.001) (**Table 1**). The troponin levels of hospitalized patients were significantly higher than patients treated at home (p<0.001) (**Table 1**).

Table 1. Comparison of hospitalized patients and patients treated at home

	All (n=1468)	Treated at home (n=317)	Hospitalized (n=1151)	p
Age (year)	50 [38-60]†	38 [28-48]†	54 [43-63]†	<0.001[a]
Gender				0.199[b]
Male	760 (51.8%)	154 (20.3%)	606 (79.7%)	
Female	708 (48.2%)	163 (23%)	545 (77%)	
Patients with high troponin level	99 (6.7%)	4 (4%)	95 (96%)	<0.001[b]
Troponin Level (pg/ml)	2.70 [1.50-5.20]†	1.60 [0.90-2.70]†	3.00 [1.70-6.20]†	<0.001[a]

[a] Mann-Whitney test, [b] Chi-Square Test, † Data are presented as median (interquartile range [IQR])

Pneumonia due to COVID-19 was found on thorax CT of 72.5% of all patients. 87.9% of the patients with elevated troponin level had pneumonia on thorax CT. The presence of pneumonia on thorax CT was found to be significantly higher in patients with elevated troponin levels (p<0.001) (**Table 2**).

Table 2. Comparison of patients with high and normal troponin levels

		All patients (n=1468)	Patients with normal troponin level (n=1369)	Patients with high troponin level (n=99)	p
Age (year)		50 [38-60]†	49 [37-58]†	68.22±14.23*	<0.001[a]
Gender	Male Female	760 (51.8%) 708 (48.2%)	719 (94.6%) 650 (91.8%)	41 (5.4%) 58 (8.2%)	<0.033[b]
Comorbid disease	Yes No	727 (49.5%) 741 (50.5%)	643 (88.4%) 726 (98%)	84 (11.6%) 15 (2%)	<0.001[b]
Hypertension	Yes No	410 (27.9%) 1058 (72.1%)	351 (85.6%) 1018 (96.2%)	59 (14.4%) 40 (3.8%)	<0.001[b]
Type 2 Diabetes	Yes No	286 (19.5%) 1182 (80.5%)	252 (88.1%) 1117 (94.5%)	34 (11.9%) 65 (5.5%)	<0.001[b]
Hyperlipidemia	Yes No	141 (9.6%) 1327 (90.4%)	118 (83.7%) 1251 (94.3%)	23 (16.3%) 76 (5.7%)	<0.001[b]
Asthma	Yes No	81 (5.5%) 1387 (94.5%)	77 (95.1%) 1292 (93.2%)	4 (4.9%) 95 (6.8%)	0.505[b]
Coronary artery disease	Yes No	75 (5.1%) 1393 (94.9%)	56 (74.7%) 1313 (94.3%)	19 (25.3%) 80 (5.7%)	<0.001[b]
Hospitalisation	Yes No	317 (21.6%) 1151 (78.4%)	313 (98.7%) 1056 (91.7%)	4 (1.3%) 95 (8.3%)	<0.001[b]
Pneominoa on thorax ct	Yes No	1064 (72.5%) 404 (27.5%)	977 (91.8%) 392 (97%)	87 (8.2%) 12 (3%)	<0.001[b]
Admitted to	Ward ICU	1082 (73.7%) 69 (4.7%)	1012 (93.5%) 44 (63.8%)	70 (6.5%) 25 (36.2%)	<0.001[b]
Intubation	Non-intubated Intubated	29 (2%) 40 (2.7%)	22 (75.9%) 22 (55%)	7 (24.1%) 18 (45%)	0.075[b]
Cliinical outcome	Healed Ex	1437 (97.9%) 31 (2.1%)	1355 (94.3%) 14 (45.2%)	82 (5.7%) 17 (54.8%)	<0.001[b]
Length of stay in hospital (day)		7 [6-10]†	7 [6-9]†	11 [7-17]†	<0.001[a]
Length of stay iin ward (day)		7 [5-9]†	7 [5-8]†	7 [6-11]†	0.013[a]
Length of stay in ICU (day)		12 [7.50-17]†	10.50 [6.25-16]†	14 [9-22.50]†	0.037[a]

a Mann-Whitney test, b Chi-Square Test, * Data are presented as mean±Standard deviation (SD), † Data are presented as median (interquartile range [IQR])

The mean age of the patients admitted to the ICU was 62.07±16.21 years (**Table 2**). Patients who were admitted to the ICU were significantly older (p<0.001) (**Table 3**). 29% of the patients were females and 71% were males admitted to the ICU (**Table 3**). The ICU admission rate was 8.1% in males and %3.7 in females. The ICU admission rate was significantly higher in males (p=0.002) (**Table 3**). 26.3% of the patients with troponin elevation were admitted to the ICU. The ICU admission rate was significantly higher in patients with elevated troponin levels (p<0.001) (**Table 3**). Troponin levels of patients admitted to the ICU were found to be significantly higher (p<0.001) (**Table 3**). 36.2% of the patients admitted to ICU had high elevated levels.

Table 3. Comparison of patients admitted to ICU and infectious diseases ward

	All hospitalized patients (n=1151)	In Ward (n=1082)	In ICU (n=69)	p
Age (year)	54 [43-63]†	53 [42-62]†	62.07±16.21*	<0.001[a]
Gender				0.002[b]
Male	606 (52.6%)	557 (91.9%)	49 (8.1%)	
Female	545 (47.4%)	525 (96.3%)	20 (3.7%)	
Patients with high troponin level	95 (8.3%)	70 (73.7%)	25 (26.3%)	<0.001[b]
Troponin Level (pg/ml)	3.00 [1.70-6.20]†	2.90 [1.70-5.60]†	13.30 [6.50-48.45]†	<0.001[a]

a Mann-Whitney test, b Chi-Square Test, † Data are presented as median (interquartile range [IQR]), *Data are presented as mean±Standard deviation (SD)

While the rate of females was 55% in intubated patients, the rate of males was 59.2%. No statistically significant difference was found between the ages and genders of the intubated and non-intubated patients (**Table 4**). 72% of the patients with elevated troponin levels admitted to ICU were intubated. According to the troponin levels, no statistically significant difference was found in intubation rates (**Table 4**). The troponin levels of the intubated patients were significantly higher than patients who were not intubated (p=0.0018) (**Table 4**).

Table 4. Comparison of intubated and non-intubated patients

	In ICU (All) (v=69)	Non-intubated (n=29)	Intubated (n=40)	p
Age (year)	62.07±16.21*	58.62±14.12*	64.58±17.31*	0.133[a]
Gender				0.749[b]
Male	49 (71%)	20 (40.8%)	29 (59.2%)	
Female	20 (29%)	9 (45%)	11 (55%)	
Patients with high troponin level	25 (36.2%)	7 (28%)	18 (72%)	0.075[b]
Troponin Level (pg/ml)	13.30 [6.50-48.45]†	9.00 [4.35-17.50]†	16.45 [8.22-81.12]†	0.018[c]

a Independent sample t test, b Chi-Square Test, c Mann-Whitney test, * Data are presented as mean±Standard deviation (SD), † Data are presented as median (interquartile range [IQR])

The mortality rate in the whole patient group was found to be 2.1%. Troponin levels was high in 54.8% of the patients who died. Mortality development was significantly higher in the patient group with elevated troponin levels (p<0.001) (**Table 2**).

The median length of hospital stay in the group with elevated troponin levels was 11 [IQR: 7 - 17] days, and the medianlength of ICU stay was 14 [IQR: 9 - 22.50] days. In the group with normal troponin levels, the median length of hospital stay was 7 [IQR: 5 - 9] days, and the median length of ICU stay was 12 [IQR: 7.50 - 17] days. Total length of hospital stay and ICU stay were significantly higher in patients with elevated troponin levels (p<0.001, p=0.037) (**Table 2**). In the correlation analysis performed between troponin levels and the length of hospital stay, there was a significant positive correlation between the troponin levels of the patients at admission and the total length of hospital stay and length of ICU stay. The total length of hospital stay and length of ICU stay was significantly increased in patients with elevated troponin levels. It was determined that as the troponin levels of the patients at admission increased, the total length of hospital stay and the length of ICU stay increased (**Table 5**). The ROC curve was drawn to determine the effect level and cut off value of the troponin variable in COVID-19 patients admitted to ICU, the area under the curve was 0.821, and the standard error was found to be 0.028. The area under the ROC curve was found to be statistically significant (p<0.001). The cut off value for troponin was found to be 6.85, and the sensitivity of this value is 75.4% and the specificity is 80% **(Figure 1**) (**Table 6**).

Table 5. Correlation analysis between troponin levels and length of hospital stay

	Correlation coefficient	P
Spearman's Rho		
Length of stay in hospital	0,228	<0,001
Length of stay iin ward	0,165	<0,001
Length of stay in ICU	0,440	0,003

Table 6. ROC curve for the troponin variable of COVID-19 patients admitted to the ICU

AUC (%95 confidence interval)	Cutt-off	P	Sensitivity (%)	Specificity (%)
0,821 (0,766-0,876)	6,85	<0,001	75,4	80

In the ROC curve drawn for the troponin variable of the COVID-19 patients who died, the area under the curve is 0.896 and its standard error is 0.031. The area under the ROC curve was found to be statistically significant (p<0.001). The cut off value for troponin was found to be 7.55. The sensitivity of this value is 84.6%, and the specificity is 83.9% (**Table 7**) (**Figure 2**).

Table 7. ROC curve analysis for troponin variable in COVID-19 patients who died

AUC (%95 confidence interval)	Cutt-Off	P	Sensitivity (%)	Specificity (%)
0,896 (0,835-0,957)	7.55	<0.001	84.6	83.9

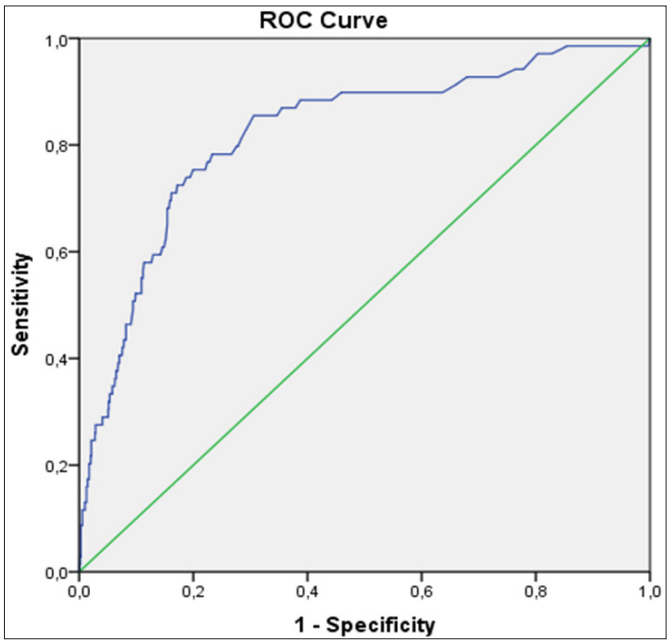

Figure 1. ROC curve for the troponin variable of the patients in ICU

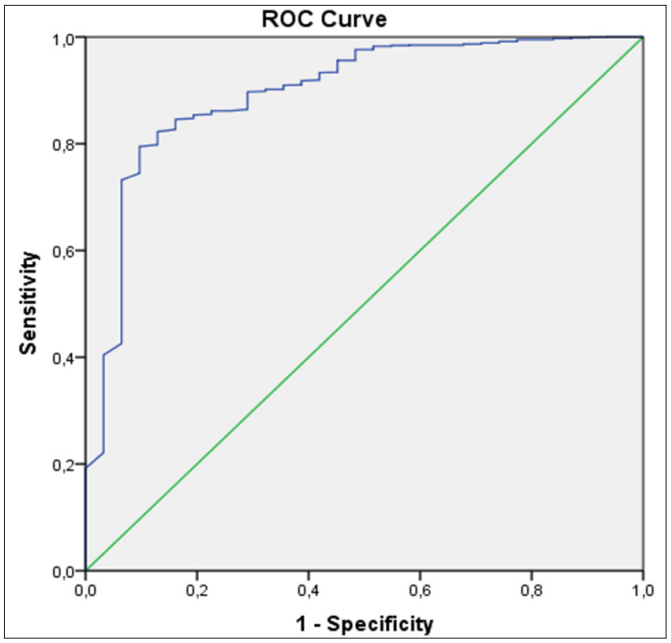

Figure 2. ROC curve for troponin variable in COVID-19 patients who died

727 patients (49.5%) had comorbid diseases accompanying COVID-19. Hypertension was the most common comorbid disease. 27.9% of the patients were diagnosed with hypertension. 19.5% of the patient had type 2 diabetes, 9.6% had hyperlipidemia, 5.5% had asthma, 5.1% had coronary artery disease (**Table 2**) (**Figure 3**).

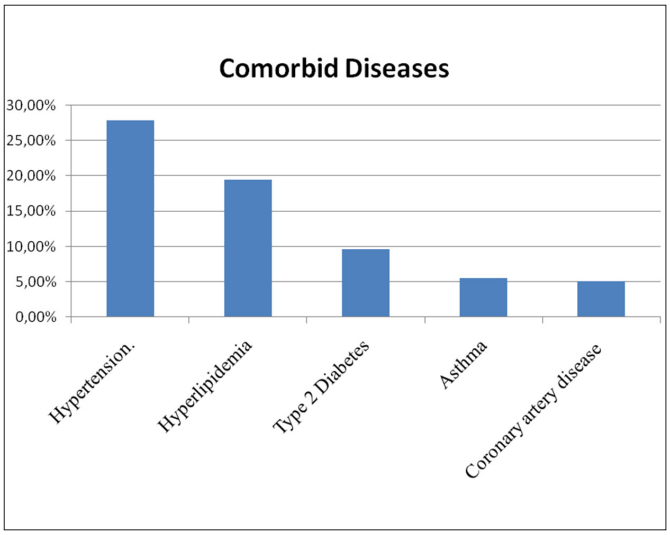

Figure 3. The most common comorbid diseases accompanying COVID-19 disease in all group

Patients with comorbid diseases accompanying COVID-19 disease had a significantly higher rate of troponin elevation (p <0.001) (**Table 2**). The rate of troponin elevation was found to be significantly higher in patients with hypertension, diabetes, hyperlipidemia and coronary artery disease (p<0.001, p <0.001, p<0.001, p<0.001). (**Table 2**) No significant difference was found with troponin elevation in patients with asthma (**Table 2**). Troponin levels in patients with comorbid diseases accompanying COVID-19 disease were found to be significantly higher than patients without comorbid diseases (p<0.001) (**Table 8**). Also troponin levels were found to be significantly higher in the patient groups with hypertension, diabetes, hyperlipidemia and coronary artery disease (p<0.001, p<0.001, p<0.001, p<0.001) (**Table 8**). Median troponin levels were the highest in patients with coronary artery disease (**Figure 4**).

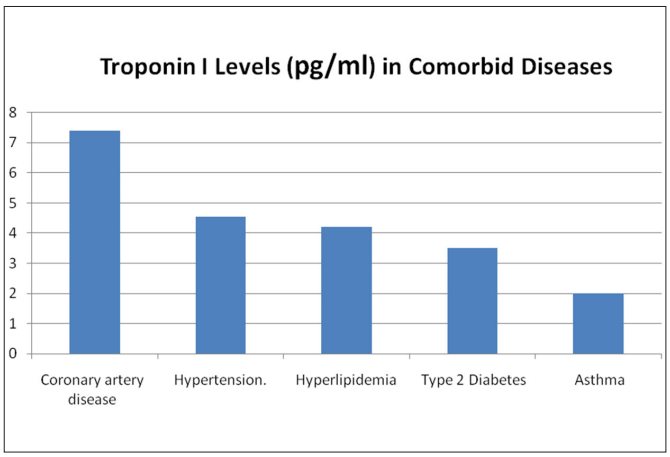

Figure 4. Median troponin levels in COVID-19 patients with comorbid disease.

Tablo 8, Comparison of the groups according to troponin levels

All patients (n=1468)	Troponin Level	p
Gender		<0,001[a]
Male (n=760, 51.8%)	2.90 [1.80-6.00][†]	
Femalen (n=708, 48.2%)	2.20 [1.20-4.70][†]	
Comorbid disease		<0.001[a]
Yes (n=727, 49.5%)	3.50 [1.90-8.40][†]	
No (n=741, 50.5%)	2.10 [1.20-3.50][†]	
Hypertension		<0.001[a]
Yes (n=410, 27.9%)	4.55 [2.50-9.47][†]	
No (n=1058, 72.1%)	2.10 [1.30-3.82][†]	
Type 2 Diabetes		<0.001[a]
Yes (n=286, 19.5%)	3.50 [1.90-8.82][†]	
No (n=1182, 80.5%)	2.40 [1.40-4.70][†]	
Hyperlipidemia		<0.001[a]
Yes (n=141, 9.6%)	4.20 [2.15-10.30][†]	
No (=1327, 90.4%)	2.50 [1.40-4.70][†]	
Asthma		0.005[a]
Yes (n=81, 5.5%)	2.00 [1.00-3.50][†]	
No (n=1387, 94.5%)	2.70 [1.50-5.30][†]	
Coronary artery disease		<0.001[a]
Yes (n=75, 5.1%)	7.40 [3.40-19.20][†]	
No (n=1393, 94.9%)	2.50 [1.40-4.75][†]	
Hospitalisation		<0.001[a]
Yes (n=317, 21.6%)	1.60 [0.90-2.70][†]	
No (n=1151, 78.4%)	3.00 [1.70-6.20][†]	
Pneominoa on thorax ct		<0.001[a]
Yes (n=1064, 72.5%)	2.80 [1.70-5.90][†]	
No (n=404, 27.5%)	2.00 [1.10-3.70][†]	
Admitted to		<0.001[a]
Ward (n=1082, 73.7%)	2.90 [1.70-5.60][†]	
ICU (n=69, 4.7%)	13.30 [6.50-48.45][†]	
Intubation		0.018[a]
Non-intubated (n=29, 2%)	9.00 [4.35-17.50][†]	
Intubated (n=40, 2.7%)	16.45 [8.22-81.12][†]	
Clinical outcome		<0.001[a]
Healed (n=1437, 97.9%)	2.50 [1.50-4.80][†]	
Ex (n=31, 2.1%)	37.00 [8.60-100.50][†]	

a Mann-Whitney test, [†] Data are presented as median (interquartile range [IQR])

DISCUSSION

Troponin elevation is a common finding in COVID-19 patients. However, the mechanism of troponin elevation in COVID-19 patients and its effect on the prognosis of the disease are not clearly known. As with other viral infections, it is possible that SARS-CoV-2 directly causes myocardial damage, but no evidence has yet been found for this. The underlying pathophysiology suggests an inflammatory response, as many COVID-19 patients have concomitant elevations in acute phase reactants such as c-reactive protein (crp) and ferritin. It may also be due to immune mechanisms as a result of cytokine increases. COVID-19 disease most frequently affects the lungs and causes pneumonia and respiratory failure. Hypoxia, hemodynamic disturbances, cardiac adrenergic overstimulation in these patients may also cause troponin elevation. It is known that thrombotic processes are activated in COVID-19 disease. The cases such as pulmonary embolism or microthrombotic disease which occurs as a result of activation of prothrombotic mechanisms can cause troponin elevation in COVID-19 patients.

In our study, we aimed to determine the frequency of troponin elevation in COVID-19 patients and to investigate the the clinical course of the patients with high troponin levels. We found the troponin level to be high in 6.7% of all COVID-19 patients. This rate was found to be higher (%12-28) in some studies with a smaller sample size.(9,14,15) Troponin elevation is seen in a considerable portion of COVID-19 patients, but its rate may vary depending on the number of patients in the study groups, the age of the patients, comorbid diseases, etc. Compared with patients with normal troponin levels, those with elevated troponin levels were older. Similar result were found in many studies.(14-16) This might be due to the accompanying comorbid conditions and the fact that the heart and endothelial structure are more vulnerable with advanced age.

In present study, troponin levels were found to be higher in patients with COVID-19-associated pneumonia on thorax CT and requiring hospitalization.We found higher troponin levels in patients who required intensive care unit due to severe COVID-19. Similar results were found in some studies. In the studies of Shi S et al. (16) and Piccioni A et al. (17), troponin levels were found to be higher in patients with severe COVID-19. The mortality rate was 2.1% in the whole patient group. This rate was similar to that of the same period of the Republic of Turkey Ministry of Health data. The mortality rate was higher in the patient group with elevated troponin levels. While the mortality rate was 1% in patients with normal troponin level, the mortality rate was 17% in patients with elevated troponin level. In many studies elevated troponin levels were associated with higher mortality and the mortality rate in COVID-19 patients with elevated troponin levels has been found between 13% and 33%.(14-16). We found that these parameters showing the prognosis in patients with COVID-19 were worse in patients with elevated troponin level. Elevated troponin level may be an indicator of myocardial damage, immunological and thrombotic reactions resulting from pathologies caused by severe infection such as respiratory failure, hypoxia, hemodynamic disturbances, cardiac adrenergic overstimulation and cytokine storm, etc. For these reasons, cardiac troponin level may be a helpful biomarker in predicting poor prognosis in patients with COVID-19.

We found that 49.5% of the patients had an associated comorbid disease. Hypertension was the most common comorbid disease. Troponin elevation rate and troponin levels were significantly higher in COVID-19 patients with comorbids when compared with COVID-19 patients witout comorbid disease. Median troponin levels were found to be the highest in patients with coronary artery disease among comorbid diseases. Similarly, in the study of Guo et al.(14), troponin levels were found to be higher in patients with cardiovascular disease and hypertension.This might be due to the fact that the heart and endothelium are more susceptible to inflammatory and prothrombotic mechanisms in these patients.

Based on the results of our study, troponin elevation can be considered as a marker showing poor prognosis in COVID-19 patients. We found a significant association between troponin test and conditions associated with the severity of COVID-19 disease, such as the requirement for hospital and intensive care unit admission, the presence of COVID-19-related pneumonia on thorax CT, and mortality rate. However, at present, we do not have the information to fully explain the mechanism of this. More comprehensive studies are needed on this subject.

Study Limitations

The limitations of our study are the small number of patients and the fact that it is a single center study. Multicenter and comprehensive studies involving more patients and long-term follow-up data are required.

CONCLUSION

The prognosis is worse in COVID-19 patients with high troponin test. The higher the troponin level, the worse the clinical course is. In the presence of other comorbid diseases, the troponin elevation rate and troponin level increase further. We found that troponin level has a prognostic significance in COVID-19 patients. Troponin test can be used as a predictor of prognosis as a result of evaluating the importance of troponin elevation in long-term follow-up results with more comprehensive studies in the future.

ETHICAL DECLARATION

Ethics Committee Approval: Approval was obtained from İstanbul Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date: 29/01/2021, Decision No: 2021/84).

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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REFERENCES

1. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of the Joint European ociety of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. J Am Coll Cardiol 2000; 36: 959-69
2. Roffi M, Patrono C, Collet J-P, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267–315
3. Alcalai R, Planer D, Culhaoglu A, Osman A, Pollak A, Lotan C. Acute coronary syndrome vs nonspecific troponin elevation: clinical predictors and survival analysis. Arch Intern Med 2007; 167: 276-81
4. Wong JA, Goodman SG, Yan RT, et al. Canadian Acute Coronary Syndromes I and II, and Canadian Global Registry of Acute Coronary Events (GRACE/GRACE) Investigators. Temporal management patterns and outcomes of non-ST elevation acute coronary syndromes in patients with kidney dysfunction. Eur Heart J 2009; 30: 549–57
5. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020; 109: 102433
6. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020; 55: 105924.
7. Poutanen SM. Etiologic agents of infectious diseases. In: Long SS, editor. Principles and practice of paediatric infectious diseases. 4th ed. 2012. p. 1547–712.
8. Pal M, Berhanu G, Desalegn C, Kandi V. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): an update. Cureus 2020; 12: e7423.
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506.
10. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020; 46: 586–90 .
11. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004; 203: 631-7.
12. Alhogbani T. Acute myocarditis associated with novel Middle East respiratory syndrome coronavirus. Ann. Saudi Med 2016; 36: 78–80.
13. Oudit GY, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur. J. Clin. Investig 2009; 39: 618–25.

14. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA cardiol 2020; 5: 811–8.
15. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England) 2020; 395: 1054–62.
16. Shi S, Qin M, Shen, B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardio 2020; e200950.
17. Piccioni A, Brigida M, Loria V, et al. Role of troponin in COVID-19 pandemic: a review of literature. Eur Rev Med Pharmacol Sci 2020; 24: 10293-300.

Original Article

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The risk of bleeding complications on percutaneous biliary drainage in patients with abnormal hemostasis

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ABSTRACT

Aim: To determine whether the risk of bleeding complications in percutaneous biliary drainage is higher in adults whose hemostasis cannot be corrected before the procedure than in those whose hemostasis is corrected.

Material and Method: 62 patients who underwent percutaneous biliary drainage were included in the study. Patients with abnormal hemostasis were divided into those with corrected hemostasis (group I) and uncorrected hemostasis (group II). The groups were evaluated for the presence of bleeding complications by ultrasonography, computed tomography and laboratory findings. The groups were compared in terms of age, gender, side, drainage type, and bleeding complications.

Results: Of the 62 patients included in the study, 52% (n:32) were female and 48% (n:30) were male, with a mean age of 67.6±9.6 (48-90). Age and female sex ratio were higher in Group II, which was statistically significant (p<0.001, p:0.014). There was no statistically significant difference between the groups in terms of side. Internal drainage was applied to patients in group II at a higher rate than group I. There was a statistically significant difference between the groups in terms of drainage type (p:0.002). There were bleeding complications in 19.3% (n:12) of the patients. Bleeding rate was higher in group II (31.8%) compared to group I (12.5%), and there was no statistically significant difference between the groups (p:0.094). None of the patients required surgical treatment due to bleeding and mortality did not occur.

Conclusion: In patients with abnormal hemostasis requiring percutaneous biliary drainage, the rate of bleeding complications was higher in patients whose hemostasis was not corrected than in those with corrected hemostasis.

Keywords: Percutaneous biliary drainage, hemobilia, bleeding complications, hemostasis

INTRODUCTION

Primary or palliative treatment of many biliary diseases demonstrated by cholangiography can be effectively performed with percutaneous biliary drainage (PBD) (1).

PBD can be performed due to benign obstructions such as cholelithiasis, congenital stenosis, cystic dilatations, surgical lesions of the biliary tract, acute cholangitis, or malignant obstructions such as cholangiocellular cancer, pancreatic cancer, gastric cancer. However, most of the patients have malignant disease (2,3).

PBD is a therapeutic procedure that includes imaging-guided wire and catheter manipulation after percutaneous puncture with a right or left-sided approach. The procedure is completed by placing a drainage catheter or stent (1).

PBD is evaluated in the literature in the group of procedures with a serious bleeding risk and difficult to detect or control (4).

Bleeding has been defined as one of several complications reported in the literature. The rate of bleeding complications can vary between 3% and 26% (5,2). Bleeding may be asymptomatic or may be seen as major bleeding that causes morbidity and/or mortality. Bleeding may occur as hematomas, hemobilia, hemoperitoneum, arteriovenous fistulas, bilioportal fistulas, and hemothorax (6-8).

Patients with biliary obstruction often have coagulation disorders and therefore an increased risk of bleeding. Hemostasis parameters should be followed in these patients (9).

Coagulopathy is a relative contraindication for PBD (1). In patients with abnormal hemostasis, the bleeding risk of the procedure, the urgency of the procedure, the type and severity of the hemostatic abnormality determine the appropriate management. According to these

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variables, there may be more than one option to correct the coagulation defect. Before the procedure, hemostasis can be corrected or improved with platelet suspension, fresh frozen plasma (ffp), and/or vitamin K (10).

However, in patients with persistent abnormal hemostasis, PBD may still be indicated if it is associated with a lower expected morbidity rate than alternative diagnostic or treatment modalities (1,4).

In studies on the risk of bleeding complications after PBD, patients with normal hemostasis were generally evaluated (11-13). A limited number of studies have compared those with corrected abnormal hemostasis with those with normal hemostasis (14). However, although there are comparative studies on patients whose hemostasis cannot be corrected in some image-guided procedures, there is no study on PBD (15-17).

The aim of this study is to compare adult patients whose hemostasis can be corrected before PBD with medical treatment (ffp, vitamin K, platelet transfusion) and patients who cannot be corrected in terms of bleeding complications.

MATERIAL AND METHOD

The study was approved by the Non-interventional Clinical Research Ethics Committee of Recep Tayyip Erdoğan University Faculty of Medicine (Date: 23.12.2021, Decision no: 2021/216). All procedures were carried out in accordance with ethical rules and the principles of the Declaration of Helsinki.

Patients over 18 years of age with abnormal hemostasis undergoing PBD for any possible indication were included in the study. Patients without abnormal hemostasis and patients with abnormal hemostasis who underwent bilateral (right and left) PBD were not included in the study.

Before the procedure, the patients were evaluated for surgical risk, routine tests (blood count, blood glucose, uremia, coagulogram) and pre-anesthesia. Platelet transfusion, fresh frozen plasma and/or vitamin K were administered to all patients due to inappropriate hemostasis. The patients were processed after signing informed consent.

Technique

The choice of right or left side before the procedure was decided according to the patient's magnetic resonance, computed tomography, ultrasonography findings and the experience of the operator.

After entering the bile duct with a 21 G Chiba needle under ultrasound and fluoroscopy guidance, a bile sample was taken for culture. 0.018 guide wire was passed through the needle. After insertion of the introducer (AccuStick, Boston Scientific) over the guidewire, cholangiography was obtained. In patients with stenosis, stenosis was passed with a 4 Fr angiographic catheter and 0.035 hydrophilic wire. Then, a multi-purpose 8Fr biliary drainage catheter was placed over a 0.038 stiff guide wire, and the procedure was terminated by fixing the catheter to the skin.

The presence of bleeding complications in the intraoperative and postoperative period was evaluated with vital signs, laboratory findings, ultrasonography or computed tomography. The patients were followed up until discharge (min-max: 2-20 days).

The patients whose hemodynamic stability did not deteriorate were followed up conservatively. Patients with worsening were first switched to a higher caliber catheter. Despite this, arteriographic embolization was planned for the patients who did not improve. Laparoscopy or laparotomy was considered in patients whose stability could not be achieved despite embolization.

According to the SIR guideline (1), the patients were divided into two groups as corrected hemostasis (group I; platelet count >50,000, INR <1.5) and uncorrected (group II; platelet count <50,000, INR >1.5). Age, gender, reason for drainage, side, type of drainage (external or internal) and presence of bleeding were recorded. The two groups were compared in terms of bleeding risk.

Statistical Analysis

Data were entered into a database (Microsoft Excel 2010) and analyzed using the SPSS version 20 program (SPSS, Chicago, IL, USA). Frequency distribution and/or percentages were created for all variables according to total cases. For ordinal scale or higher measures, the number of cases, minimum value, maximum value, arithmetic mean, typical deviation, and standard error were defined. Categorical data of both groups were given as frequencies and percentages (n, %) within the groups. Student Test, Mann Whitney-U and Chi-square tests were used as significance tests. The limit of significance was accepted as $p < 0.05$.

RESULTS

Of the 62 patients included in the study, 52% (n:32) were female and 48% (n:30) were male, with a mean age of 67.6±9.6 (48-90).

A statistically significant difference was found between groups I and II in terms of gender, and the rate of female gender was higher in group II (p:0.014) (**Table 1**).

The mean age of the patients in group I was 64.5±9.4, in group II 73.3±6.9 years, and the patients in group II were statistically significantly older (p<0.001).

FFP was given to 95% (n:59) of the patients, vitamin K was given to 56% (n:35) and platelet transfusion was given to 16% (n:10). While no statistically significant difference was found between Group I and II in terms of FFP and platelet transfusion administration, statistically significantly more vitamin K was administered to the patients in group II (**Table 1**).

Table 1. Demographic and main clinical findings of the study groups

	Group 1		Group 2		p value
	N	%	N	%	
Sex					0.014
Female	16	50%	16	50%	
Male	24	80%	6	20%	
Side					0.677
Left	24	66.7%	12	33.3%	
Right	16	61.5%	10	38.5%	
Fresh frozen plasma					0.546
No	3	100%	0	0%	
Yes	37	62.7%	22	37.3%	
Vitamin K					0.003
No	23	85.2%	4	14.8%	
Yes	17	48.6%	18	51.4%	
Platelet transfusion					0.733
No	34	65.4%	18	34.6%	
Yes	6	60%	4	40%	
Bleeding complication					0.094
No	35	70%	15	30%	
Yes	5	41.7%	7	58.3%	
Drainage type					0.002
Internal	29	80.6%	7	19.4%	
External	11	42.3%	15	57.7%	

PBD was applied to 22.6% (n:14) of the patients for pancreatic cancer, 17.7% (n: 11) for gastric cancer, 11.3% (n: 7) for cholangiocellular cancer (**Table 2**).

Table 2. Percutaneous biliary drainage indications

	n	%
Pancreas cancer	14	22.6
Gastric cancer	11	17.7
Colon cancer	8	12.9
Cholangiocellular ca	7	11.3
Lymphoma	4	6.5
Rectum cancer	4	6.5
Breast cancer	2	1.6
Choledocholithiasis	2	6.5
Lung cancer	2	6.5
Hepaticojejunostomy stenosis	2	3.2
Ampulla tumor	1	1.6
Primary sclerozan cholangitis	1	1.6
Unknown	4	6.5
Total	62	100.0

While the mean INR value was 1.62±0.1 in group II, it was 1.25±0.7 in group I. In addition, the median INR value was 1.56 (1.22-1.76) in patients with bleeding and 1.28 (1.09-1.98) in patients without bleeding, and there was a statistical difference between them (p:0.005).

PBD was applied to 41.9% (n:26) of the patients from the right side and 58.1% (n:36) of them from the left side. There was no significant difference between groups I and II in terms of sides (p:0.677). There was no difference between the right and left sides in terms of bleeding complications (**Table 3**).

Table 3. Comparison of puncture side and bleeding complication

Bleeding complication	Right	Left	
Yes	5 (19.2%)	7 (19.4%)	p:0.983
No	21 (80.8%)	29 (80.6%)	p:0.983

External drainage was applied to 41.9% (n:26) of the patients and internal drainage was applied to 58.1% (n:36) patients. Internal drainage was performed at a higher rate in group I than in group II. There was a statistically significant difference between the groups in terms of drainage type (p:0.002).

Although bleeding complication was proportionally higher in those who had external drainage, no statistically significant difference was found (p:0,200).

There was bleeding complication in 19.3% (n:12) of the patients, and bleeding was detected in 12.5% (n:5) of the patients in group I and 31.8% (n:7) in group II. The bleeding rate was higher in group II compared to group I, and there was no statistically significant difference between the groups (p:0.094).

Hemobilia was present in 9 patients with bleeding. We detected 3 patients with hematoma on ultrasound and all were asymptomatic. In 2 patients, improvement was achieved by replacing the bleeding with a higher caliber (10 or 12 french) catheter to control bleeding. No additional arterial embolization or surgical treatment was required in patients with bleeding.

No procedure-related mortality occurred in any of the patients in the intraoperative and/or perioperative period.

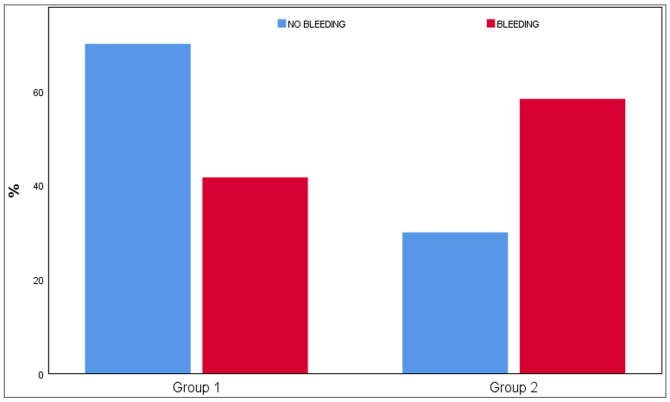

Figure 1. Distribution of patients in groups I and II in terms of bleeding complication

DISCUSSION

PBD is a safe and widely practiced interventional radiology procedure for biliary obstructions (14,18).

Bleeding is one of the important complications (5). In the literature, the incidence is in a wide range, from 3% to 26%, since some authors have defined bleeding complications only when they are symptomatic or cause a decrease in hemoglobin levels, while some authors describe it even if it is asymptomatic (1,19).

Patients undergoing percutaneous intervention often have abnormal hemostasis due to existing disease or pharmacotherapy (10).

In thrombocytopenic patients undergoing percutaneous interventions, the SIR consensus guidelines for hemostasis in a given procedure recommend platelet transfusion for all patients with a platelet count of less than 50,000/mL (20,21). In addition, the SIR consensus guidelines recommend correcting the INR based on the risk of procedural bleeding. The recommended correction threshold for the INR value for intermediate and high-risk procedures is above 1.5 (22).

In patients with a high INR value, this value can be corrected with various therapeutic options (9). However, in some patients, this value cannot be made suitable for the procedure. In these patients, if the benefit of the procedure is higher than the alternative diagnosis or treatment methods and the expected morbidity rate is low, PBD can still be applied (1,4).

There is also a relative lack of evidence of acceptable INRs for image-guided procedures. Some studies have found little association between abnormal hemostasis and hemorrhagic complications (16,17,23).

Studies on PBD have generally evaluated bleeding complications in patients with normal hemostasis, and studies on patients with abnormal hemostasis are limited (5,7,9,13,14). To the best of our knowledge, our study is the first study to group and evaluate patients with abnormal hemostasis.

In the study in which patients with abnormal hemostasis were included; Vital, laboratory and radiological follow-ups were performed. All asymptomatic or symptomatic bleeding complications were recorded.

Nenstiel et al. (19) reported the rate of bleeding complications as 13% in their study in patients with normal hemostasis, and as 15.8% in the study of Hougton et al. (14) including patients with abnormal hemostasis with corrected hemostasis. In our study, this rate was 19.3%, and we think that this is related to the patient population. L'Hermine et al. (13) reported that 6% of bleedings were severe, and 2-8% of them were caused by arterial lesions. We did not detect arterial bleeding in our study.

In our study, the rate of bleeding in patients whose abnormal hemostasis could not be corrected was higher than those whose hemostasis was corrected. Hougtan et al. reported a lower rate of bleeding complications in patients with corrected hemostasis than those with normal hemostasis, and did not analyze correction of hemostasis as a possible risk factor (14). This difference is due to the small number of patients whose hemostasis was corrected in the study of Hougtan et al.

Choi et al. (5) in a retrospective study in which they analyzed the risk factors for the development of bleeding complications in the PBD procedure; reported that platelet count of 50000/mm3 or less and INR of 1.5 or more were risk factors, but it was not statistically significant in multivariate analysis. Similarly, in our study, the percentage of bleeding in patients with an INR value above 1.5 was higher than in patients with an INR value below it, but it was not statistically significant.

Rivera-Sanfeliz et al. (7) reported that there was proportionally more bleeding in the left approach. Choi et al. (5) stated that left-access PBD was the only independent risk factor for arterial damage. Hougtan et al.(9) in their study comparing the right and left approaches; reported that the bleeding rate was low in the left approach. In this study, bleeding rates were similar in the right and left approaches.

In the study of Hougtan et al. including patients with corrected hemostasis, they found more patients with corrected hemostasis in the left approach and reported that this may be a factor reducing the risk in the left approach group (14). Similarly, in our study, a proportionally more left-sided approach was used in the group whose hemostasis was corrected. We think that this point needs analysis with studies conducted with more patients.

Rivera-Sanfeliz et al. (7) reported that there was no relationship between drainage type and bleeding, while Hougtan et al. (14) reported that there was proportionally more bleeding in those who had external drainage. We found proportionally more bleeding in patients who underwent external drainage, similar to Hougtan et al.

PBD indications are generally of malignant origin, and in the study of Uberoi et al. (3) the most common cause was pancreatic cancer, and Choi et al. (5) defined cholangiocellular carcinoma. The most common cause in this study was pancreatic cancer.

The main limitations of our study are that it was single-centered, the number of patients was small, and abnormal hemostasis parameters were not evaluated separately.

CONCLUSION

In patients with abnormal hemostasis requiring percutaneous biliary drainage, bleeding complications were more common in patients with uncorrected hemostasis than in those with corrected hemostasis, but did not reach statistical significance. Also, bleeding-related mortality did not occur.

ETHICAL DECLARATION

Ethics Committee Approval: The study was approved by the Non-interventional Clinical Research Ethics Committee of Recep Tayyip Erdogan University Faculty of Medicine (Date: 23.12.2021, Decision no: 2021/216).

Informed Consent: All patients signed the free 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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Author Contributions: All of 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.

REFERENCES

1. Saad WE, Wallace MJ, Wojak JC, Kundu S, Cardella JF. Quality improvement guidelines for percutaneous transhepatic cholangiography, biliary drainage, and percutaneous cholecystostomy. J Vasc Interv Radiol 2010; 21: 789–95.
2. Kühn JP, Busemann A, Lerch MM, et al. Percutaneous biliary drainage in patients with nondilated intrahepatic bile ducts compared with patients with dilated intrahepatic bile ducts. AJR Am J Roentgenol 2010; 195: 851-7.
3. Uberoi R, Das N, Moss J, Robertson I. British Society of Interventional Radiology: Biliary Drainage and Stenting Registry (BDSR). Cardiovasc Intervent Radiol 2012; 35: 127–38.
4. Patel, IJ, Davidson JC, Nikolic B, et al. consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. J Vasc Intervent Radiol 2012; 23: 727 -36.
5. Choi SH, Gwon DI, Ko GY, et al. Hepatic arterial injuries in 3110 patients following percutaneous transhepatic biliary drainage. Radiology 2011; 261: 969-75.
6. Tapping CR, Byass OR, Cast JE. Percutaneous transhepatic biliary drainage (PTBD) with or without stenting—complications, re-stent rate and a new risk stratification score. Eur Radiol 2011; 21: 1948–55.
7. Rivera-Sanfeliz GM, Assar OS, LaBerge JM, et al. Incidence of important hemobilia following transhepatic biliary drainage left sided versus right sided approaches. Cardiovasc Intervent Radiol 2004; 27: 137-9.
8. Özdemir A, Şahan MH. Ultrasonografi rehberliğinde perkütan kesici karaciğer biyopsisi (parankim ve lezyon): klinik deneyimimiz. Kırıkkale Üniversitesi Tıp Fakültesi Derg 2019; 21: 325-31.
9. Houghton EJ, Zeledón M, Acquafresca P, Finger C, Palermo M, Giménez ME. Prospective comparison of bleeding complications between right and left approaches in percutaneous biliary drainage. Surg Laparosc Endosc Percutan Tech 2019; 29: 7–12.
10. Wiltrout C, Kondo K. Correction of coagulopathy for percutaneous interventions. Semin Intervent Radiol 2010; 27: 338–47.
11. Donkol RH, Latif NA, Moghazy K. Percutaneous imaging-guided interventions for acute biliary disorders in high surgical risk patients. World J Radiol 2010; 28: 358-67.
12. Garcarek J, Kurcz J, Guziński M, et al. Ten years single center experience in percutaneous transhepatic decompression of biliary tree in patients with malignant obstructive jaundice. Adv Clin Exp Med 2012; 2: 621-32.
13. L'Hermine C, Ernst O, Delemazure O, et al. Arterial complications of percutaneous transhepatic biliary drainage. Cardiovasc Intervent Radiol 1996; 19: 160–4.
14. Houghton EJ, Invernizzi E, Acquafresca P, Palermo M, Giménez ME. Risk of bleeding complications in percutaneous biliary drainage: the paradox of the normal hemostasis. Arq Bras Cir Dig 2019; 21:e1454.
15. Navin PJ, White ML, Nichols FC, et al. Periprocedural major bleeding risk of image-guided percutaneous chest tube placement in patients with an elevated international normalized ratio. J Vasc Interv Radiol 2019; 30: 1765-8.
16. Martin JH, Rosser CJ, Linebach RF, McCullough DL, Assimos DG. Are coagulation studies necessary before percutaneous nephrostomy? Tech Urol 2000; 6: 205–7.
17. Fisher NC, Mutimer DJ. Central venous cannulation in patients with liver disease and coagulopathy—a prospective audit. Intens Care Med 1999; 25: 481–5.
18. Quencer K, Tadros A, Marashi K, et al. Bleeding after percutaneous transhepatic biliary drainage: incidence, causes and treatments. J Clin Med 2018; 7: 94.
19. Nennstiel S, Weber A, Frick G, et al. Drainage-related complications in percutaneous transhepatic biliary drainage an analysis over 10 years. J Clin Gastroenterol 2015; 49: 764-70.
20. Haas B, Trerotola S, Itkin M, et al. Tunneled central venous catheter insertion in patients with coagulopathy and thrombocytopenia. J Vasc Interv Radiol 2009; 20: 35–6.
21. Haas B, Chittams JL, Trerotola SO. Large-bore tunneled central venous catheter insertion in patients with coagulopathy. J Vasc Interv Radiol 2010; 21: 212–7.
22. Malloy PC, Grassi CJ, Kundu S, et al. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. J Vasc Interv Radiol 2009;20: 240–9.
23. Stecker MS, Johnson MS, Ying J, et al. Time to hemostasis after traction removal of tunneled cuffed central venous catheters. J Vasc Interv Radiol 2007; 18: 1232–9.

Original Article

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Is laparoscopic ventral rectopexy a good treatment option for rectal prolapse?

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ABSTRACT

Aim: Laparoscopic ventral rectopexy (LVR) is one of the most commonly performed procedures in the treatment of rectal prolapse (RP). This study aimed to evaluate postoperative changes in the incontinence status and short-term functional outcomes of patients with RP who underwent LVR.

Material and Method: This study included 15 patients who underwent LRV with the diagnosis of RP between January 2017 and June 2021 at Health Sciences University Ankara Numune Training and Research Hospital and Ankara City Hospital. Data were obtained by retrospectively examining the electronic records of the patients. The Wexner incontinence score (WIS) was calculated preoperatively and postoperatively by contacting the patients by phone at six months after the operation. In addition, the constipation status of the patients and whether they had recurrence of RP were questioned.

Results: The mean age of the 15 patients included in the study was 55 (range, 30-81) years. Twelve (80%) patients were female and three (20%) were male. When the preoperative and postoperative WISs of the patients were compared, the latter was statistically significantly lower than the former (p=0.002). Among the 10 (66.7%) patients who had constipation in the preoperative period, this complaint was resolved in four (40%), but new-onset constipation was detected in two (40%) of the five (33.3%) patients without preoperative constipation. The recurrence of RP was observed in only one (6.7%) patient in the postoperative follow-up.

Conclusion: Considering the short-term outcomes in the patients who underwent LRV for RP, it can be concluded that LVR is a good option in this patient group, with a low recurrence rate and satisfactory improvement in incontinence.

Keywords: Rectal prolapsus, laparoscopic ventral rectopexy, incontinence, constipation

INTRODUCTION

Rectal prolapse (RP) or anal procidentia is a debilitating disease that greatly affects the quality of life and characterized by the intussusception of the rectal mucosa (mucosal prolapse) or all the layers of the rectum (complete rectal prolapse) along the anal canal (1,2). When the prolapsed segment of the rectum is limited within the anal canal, it is called internal RP or rectal intussusception, and if it protrudes outside the anal orifice, it is referred to as external prolapse (3). In complete RP, where the rectal folds are seen outside the anal canal as concentric circles, the rectum and all its layers protrude outside the anal canal, while partial RP presents with the protrusion of only the rectal mucosa (4).

The etiology of RP, which is mostly seen in women and peaks in the seventh decade, has not yet been clearly elucidated, but redundant sigmoid colon, deep cul-de-sac, and diastasis of the levator ani muscle are the most common associated pathologies (5). While patients usually complain of fecal incontinence, which is considered to be the result of the chronic stretching of the anal sphincter and sustained stimulation of the rectoanal inhibitory reflex by the prolapsed tissue, other symptoms such as constipation, pain, and bloody mucus in stool can also be observed (5).

In the literature, many methods have been described for the treatment of RP, with the main treatment method being surgery which can be applied through perineal and abdominal (open or minimally invasive) routes, and the method to be used in the treatment is determined based on the patient's age, bowel function (constipation

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or incontinence) and comorbidities, as well as the experience and preference of the surgeon (6). To date, there has been no convincing evidence of the superiority of one procedure over another in terms of recurrence, functional improvement, or quality of life (7). An ideal surgical treatment for external and/or internal RP should correct anatomical abnormalities and relieve associated symptoms ranging from obstructive defecation to fecal incontinence (8). Ventral rectopexy (VR), first described by D'Hoore et al. in 2004, soon gained popularity as a treatment of choice for patients with RP (3).

VR is mostly performed with the laparoscopic method, in which Denonvillier's fascia is dissected without posterior rectal mobilization, and anterior rectal mobilization is provided before the synthetic mesh is fixed between the distal rectum and the sacrum (2). Laparoscopic VR (LVR) is increasingly acknowledged as an effective surgical treatment for posterior pelvic floor dysfunctions, such as external full-thickness RP, internal rectal intussusception, enteroceles, and complex rectoceles (9).

It has been shown that LVR provides 70-90% improvement in fecal incontinence complaints and 60-80% improvement in obstructive defecation complaints in patients with RP, and in addition to improvement in quality of life and incontinence, it results in 40% to 50% improvement in constipation scores (9, 10).

The aim of this retrospective study was to evaluate postoperative changes in the incontinence status and short-term functional outcomes of patients who underwent LVR with the diagnosis of a rectocele and RP.

MATERIAL AND METHOD

The study was started after receiving approval from the No 1 Clinical Research Ethics Committee of Ankara City Hospital (Date: 03.11.2021, Decision No: E1-21-2123). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Data

This study was conducted by retrospectively examining the electronic records of the demographic data of patients who underwent LRV with the diagnosis of RP in Health Sciences University Ankara Numune Training and Research Hospital and Ankara City Hospital between January 2017 and June 2021. In order to evaluate the patients' continence status and lifestyle alteration, their preoperative and postoperative Wexner incontinence scores (WISs) were calculated and recorded by contacting them by phone at six months after the operation. In the calculation of WIS, each of the parameters of solid, liquid and gas incontinence, requirement of pad use, and lifestyle alteration was rated from 0 to 4, and an evaluation was made over a total of 0 to 20 points (0=best score, 20=worst score) (**Table 1**) (11). Patients with complete RP confirmed by physical examination findings were included in the study. Difficult, unsatisfactory, or infrequent defecation (fewer than 3 bowel movements per week) was evaluated as constipation. Patients with inflammatory bowel disease, history of major abdominal surgery, diverticular disease, connective tissue disease, morbid obesity and comorbidities such as severe heart and kidney disease were not included in the study.

Table 1. Wexner incontinence scoring

Type of incontinence	Never	Frequency			Always
		Rarely	Sometimes	Usually	
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Pad requirement	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4

0, Perfect; 20, Complete incontinence; Never, 0; Rarely, <1/month; Sometimes, <1/week, ≥1/month; Usually, <1/day, ≥1/week; Always, ≥1/day

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) (version 17.0, SPSS Inc., Chicago, IL, USA). Data for continuous variables were expressed as mean±standard deviation. Nominal values were analyzed using the Wilcoxon signed-rank test and Fisher's exact test and expressed as %. A p value of <0.05 was considered statistically significant.

RESULTS

The mean age of the 15 patients included in the study was 55 (range, 30-81) years. Twelve (80%) patients were female and three (20%) were male. While there was no systemic disease in nine patients, two patients had only hypertension (HT), one had HT and diabetes mellitus (DM), one had HT, DM and asthma, one had HT and asthma, and one had only asthma. The preoperative WIS of the patients was 0 in three (20%) patients, 3 in two (13.3%), 4 in one (6.7%), 5 in one (6.7%), 8 in three (20%), 9 in one (6.7%), 11 in one (6.7%), 15 in one (6.7%), 18 in one (6.7%), and 19 in one (6.7%). The postoperative WIS was 0 in 10 (66.6%) patients, 2 in one (6.7%), 3 in two (13.3%), and 4 in two (13.3%). The demographic data and preoperative and postoperative WISs of the patients are summarized in **Table 2**. When the preoperative and postoperative WISs were compared, it was seen that the latter was statistically significantly lower than the former (p=0.002) (**Table 3**). Constipation was present in 10 (66.6%) patients preoperatively and eight (53.3%) patients postoperatively, indicating no statistically significant change (p>0.05). Postoperative

constipation was resolved in four (40%) of the 10 patients with constipation in the preoperative period, but new-onset constipation was detected in two (40%) of the five patients without preoperative constipation. The recurrence of RP developed in only one (6.7%) patient in the postoperative follow-up.

Table 2. Demographic data of the patients and distribution of WIS (n=15)

Age [Mean (min-max)]	55 (30-81)	
Gender (%)		
Male	3 (20)	
Female	12 (80)	
WIS (%)	**Preoperative n**	**Postoperative n**
0	3 (20)	10 (66.6)
1	-	-
2	-	1 (6.7)
3	2 (13.3)	2 (13.3)
4	1 (6.7)	2 (13.3)
5	1 (6.7)	-
6	-	-
7	-	-
8	3 (20)	-
9	1 (6.7)	-
10	-	-
11	1 (6.7)	-
12	-	-
13	-	-
14	-	-
15	1 (6.7)	-
16	-	-
17	-	-
18	1 (6.7)	-
19	1 (6.7)	-
20	-	-

Min, Minimum; Max, Maximum; WIS, Wexner Incontinence Score

Table 3. Comparison of the preoperative and postoperative WIS and constipation status

	Preoperative	Postoperative	p
WIS (n=15)(median±SD)	7.4±6.22	1.7±1.62	0.002*
Constipation (%)	10 (66.7)	8 (53.3)	>0.05

WIS, Wexner Incontinence Score; SD, Standard deviation, *p<0.05

DISCUSSION

Abdominal (open/laparoscopic) and perineal surgical methods have been defined in the surgical treatment of RP, and the surgical treatment procedure to be applied is selected based on the patient's age, comorbidities, type of RP, and patient preference. The aim of surgical treatment is not only to correct the anatomical problem but also to resolve anorectal functional problems. Contrary to abdominal operations, anatomical restoration may not be achieved in perineal procedures due to the inability to achieve adequate exposure for the pelvic part of the rectum and other pelvic organs; however, pelvic approaches continue to be an appropriate surgical option in high-risk elderly patients (12). With the introduction of minimally invasive surgical procedures, abdominal procedures have been increasingly performed, but the type of abdominal procedure associated with improved postoperative functional outcomes remains unclear (13).

Today, LVR is performed by many pelvic floor surgeons in the treatment of symptomatic rectoceles, as well as that of internal and external RP (10). In a prospective randomized study, it was reported that this minimally invasive surgery had certain advantages over the open approach, such as less postoperative pain, shorter hospital stay, faster recovery, and most importantly a lower postoperative complication rate (14). The safe and satisfactory results of LVR have contributed to its popularity and preference among colorectal surgeons across the world, but there are still concerns pertaining to mesh-related complications, its suitability in some patient groups such as male patients, and recurrence of RP in the long term (3).

Although abdominal operations appear to have a lower recurrence rate compared to perineal operations, a Cochrane database review including 15 randomized controlled trials comparing 1,007 patients reported no significant difference in recurrence between the two approaches (15). However, in an original article, the recurrence rate was reported as 4% (0-6%) in abdominal rectopexy and 18% (4-38%) in perineal approaches (14). Recurrence rates after LVR are generally low, being reported as 0%-15% in a systematic review (10). Low recurrence rates after rectopexy have been generally observed in studies with short follow-up periods, and studies with a follow-up period exceeding 15 years are rare. Nevertheless, many publications suggest that recurrence increases over time (16). Although studies on the optimal approach to recurrent rectal prolapse repair are conflicting, abdominal approaches are also frequently used to repair rectal prolapse recurrence (4). Steele et al. reported that patients who underwent an abdominal approach for recurrent rectal prolapse had significantly fewer re-recurrences than those who had a perineal procedure (15% versus 37%)(17). In our study, recurrence developed in only one (6.7%) patient according to the short-term (six-months) results. This is consistent with the literature. The patient was opereted with a perineal approach for recurrence.

Approximately 25%-50% of patients with RP have constipation complaints (15). Abdominal procedures are associated with higher postoperative morbidity and may have adverse side effects, such as postoperative constipation (14). LVR using the anterior approach with limited rectal mobilization without lateral dissection,

as defined by D'Hoore and Penninck in 2004, reduces the incidence of postoperative constipation when compared with posterior rectopexy (18). Posterior and lateral rectum dissection is not performed in LVR, and therefore its greatest advantage can be considered as the prevention of autonomic denervation and postoperative constipation (1). In a meta-analysis, improvement rates in constipation complaints after LVR were reported to vary between 33% and 100% in eight studies (3). In our study, constipation was present in 10 (66.7%) patients preoperatively and eight (53.3%) patients postoperatively ($p>0.05$). Postoperative constipation complaints disappeared in four (40%) patients with preoperative constipation, whereas new-onset constipation developed in two (40%) patients without preoperative constipation. Despite the low number of our patients, it can be stated that an effective treatment method is still controversial considering the high rate of constipation and the wide variety of surgical treatment options in these patients.

Incontinence associated with complete rectal prolapse has been attributed not only to the intermittent activation of the rectoanal reflex due to RP but also to sphincter dilation due to pudendal nerve neuropathy caused by prolapse, and fecal incontinence complaints are reported to decrease by up to 90% after LVR (19). Jonkers et al. reported that the rate of fecal incontinence, which was 59% in the preoperative period, decreased by 14% in the postoperative period (20). In a systematic review of VR, it was reported that improvement in the fecal incontinence score ranged from 45% to 95% in the short-term follow-up after LVR (2). In the current study, WIS was used to evaluate the incontinence status of the patients. When the preoperative and postoperative WISs were compared, a statistically significant difference was found in terms of incontinence after LVR ($p=0.002$), which is in agreement with the literature.

The important limitations of this study are the small number of patients in the sample and the short postoperative follow-up period.

CONCLUSION

Considering the short-term results of the patients who underwent LRV for RP, LVR presents as a good option in this patient group, with a low recurrence rate and satisfactory improvement in incontinence.

ETHICAL DECLARATION

Ethics Committee Approval: The study was started after receiving approval from the No 1 Clinical Research Ethics Committee of Ankara City Hospital (Date: 03.11.2021, Decision No: E1-21-2123).

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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REFERENCES

1. Soare C, Lasithiotakis K, Dearden H, Singh S, McNaught C. The surgical management of rectal prolapse. Indian J Surg 2020: 1-7.
2. Samaranayake C, Luo C, Plank A, Merrie A, Plank L, Bissett I. Systematic review on ventral rectopexy for rectal prolapse and intussusception. Colorectal Dis 2010; 12: 504-12.
3. Emile SH, Elfeki H, Shalaby M, Sakr A, Sileri P, Wexner SD. Outcome of laparoscopic ventral mesh rectopexy for full-thickness external rectal prolapse: a systematic review, meta-analysis, and meta-regression analysis of the predictors for recurrence. Surg Endosc 2019; 33: 2444-55.
4. Nacion AJD, Park YY, Kim HS, Yang SY, Kim NK. Surgical treatment of rectal prolapse: a 10-year experience at a single institution. J Minim Invasive Surg 2019; 22: 164-70
5. Leventoglu S, Mentes B, Balci B, Yildiz A. Surgical techniques for rectal prolapse. Gastroenterol Insights 2021; 12: 310-8.
6. Bordeianou L, Paquette I, Johnson E, et al. Clinical practice guidelines for the treatment of rectal prolapse. Dis Colon Rectum 2017; 60: 1121-31.
7. Loh KC, Umanskiy K. Ventral Rectopexy. Clin Colon Rectal Surg 2021; 34: 62-8.
8. Tsunoda A, Takahashi T, Matsuda S, Oka N, Kusanagi H. Midterm functional outcome after laparoscopic ventral rectopexy for external rectal prolapse. Asian J Endoscopic Surg 2020; 13: 25-32.
9. Mäkelä-Kaikkonen J, Rautio T, Kairaluoma M, et al. Does ventral rectopexy improve pelvic floor function in the long term? Dis Colon Rectum 2018; 61: 230-8.
10. Fu CW, Stevenson AR. Risk factors for recurrence after laparoscopic ventral rectopexy. Dis Colon Rectum 2017; 60: 178-86.
11. Jorge JMN, Wexner SD. Etiology and management of fecal incontinence. Dis Colon Rectum 1993; 36: 77-97.
12. Ahmad NZ, Stefan S, Adukia V, Naqvi SAH, Khan J. Laparoscopic ventral mesh rectopexy: functional outcomes after surgery. Surg J 2018; 4: e205-e11.
13. Lundby L, Iversen LH, Buntzen S, Wara P, Høyer K, Laurberg S. Bowel function after laparoscopic posterior sutured rectopexy versus ventral mesh rectopexy for rectal prolapse: a double-blind, randomised single-centre study. Lancet Gastroenterol Hepatol 2016; 1: 291-7.
14. Maggiori L, Bretagnol F, Ferron M, Panis Y. Laparoscopic ventral rectopexy: a prospective long-term evaluation of functional results and quality of life. Tech Coloproctol 2013; 17: 431-6.
15. Tsunoda A. Surgical treatment of rectal prolapse in the laparoscopic era; a review of the literature. J Anus Rectum Colon 2020; 4: 89-99.

16. Gleditsch D, Wexels WA, Nesbakken A. Surgical options and trends in treating rectal prolapse: long-term results in a 19-year follow-up study. Langenbeck's Arch Surg 2018; 403: 991-8.
17. Steele SR, Goetz LH, Minami S, Madoff RD, Mellgren AF, Parker SC. Management of recurrent rectal prolapse: surgical approach influences outcome. Dis Colon Rectum 2006; 49: 440-5.
18. Tsunoda A, Takahashi T, Ohta T, Fujii W, Kusanagi H. New-onset rectoanal intussusception may not result in symptomatic improvement after laparoscopic ventral rectopexy for external rectal prolapse. Tech Coloproctol 2016; 20: 101-7.
19. Madbouly KM, Youssef M. Laparoscopic ventral rectopexy versus laparoscopic wells rectopexy for complete rectal prolapse: long-term results. J Laparoendosc Adv Surg Tech 2018; 28: 1-6.
20. Jonkers HF, Maya A, Draaisma W, Bemelman W, Broeders I, Consten E, et al. Laparoscopic resection rectopexy versus laparoscopic ventral rectopexy for complete rectal prolapse. Tech Coloproctol 2014; 18: 641-6.

Original Article

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Evaluation of the serum visfatin eotaxin and fetuin-A levels of patients with type 2 diabetes mellitus

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ABSTRACT

Objective: The aim of this study was to determine the serum visfatin, eotaxin and fetuin-A levels in patients with normal BMI and overweight type 2 diabetes mellitus (T2DM).

Material and Method: This study perform in 30 T2DM patients and in 20 healthy subjects. Test subjects were divided into four groups as two diabetics and two controls. Diabetics with a body mass index (BMI) of 26.2-29.9 kg/m² were included in the overweight diabetic group (OD), and those with a body mass index of 20.9-24.9 kg/m² were included in the normal BMI diabetic group (ND). The volunteers in the control group were also divided into two groups as overweight (OC) and normal BMI (NC). Smoking and alcohol users were not included in the study. In addition, patients with significant diabetic complications such as retinopathy, hypertension, neuropathy, renal failure, and cardiovascular disease were excluded from the study. The serum visfatin eotaxin and fetuin-A levels were measured using the ELISA method. The Mann-Whitney U test was used to compare the data of the groups, while Spearman's analysis was applied for the correlations.

Results: The visfatin levels of the OD and ND were significantly higher compared to those of their control groups ($p<0.05$ and $p<0.05$ respectively). In addition, the eotaxin levels of the diabetic patients both OD and ND were significantly higher than those of their control group ($p<0.001$ and $p<0.05$, respectively). Serum fetuin-A level was not different between groups.

Conclusion: Serum visfatin and eotaxin levels are high in patients with T2DM, and this elevation is dependent on BMI. In addition, visfatin level is high in overweight non-diabetic subjects.

Keywords: Visfatin, eotaxin, fetuin-A, type 2 diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is accepted as one of the most prominent metabolic diseases of the 21st century (1). The main reason for this disease is insulin resistance, increased liver glucose production, and deficiency in insulin secretion against glucose stimulation (2,3). Although the pathogenesis of T2DM is not completely known, it is thought to be due to the interactions of genetic, environmental, and behavioral risk factors (4). Economic developments, urbanization, longevity, physical inactivity, unhealthy diet, smoking, drinking alcohol, and obesity all contribute to the development of T2DM (5). A significant number of patients with T2DM are obese and the incidence of diabetes is closely related to the increase in obesity prevalence (6). Obesity to the development of the disease in approximately 55% of patients with T2DM (7).

A parallel relation is thought to exist between the pancreas and adipose tissue, and the majority of patients with T2DM are obese individuals with visceral fat. Overweight and obesity causes an increase in adipose tissue stores and irregular adipokine secretion. Adipokines secreted from macrophages that infiltrate fat cells and adipose tissue are believed to cause a low-grade chronic inflammatory condition, which in turn, leads to the insulin resistance in tissues such as liver and skeletal muscle, and subsequently to T2DM (8).

Visfatin, which is a new member of the adipocytokine family, was first described by Fukuhara et al. (9) in 2005. The most interesting feature of visfatin is its insulin-mimetic feature, which has only recently been put forward. It has been reported that visfatin mimics the effects of insulin such as inhibiting hepatic glucose

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release, increasing glucose uptake in fat and muscle cells, and increasing triglyceride synthesis. It has been found that visfatin activates the phosphorylation and signal transmission of insulin receptors by binding to a place that is different to the place where insulin binds and using a different pathway to insulin (9).

It is known that chronic inflammation plays a part in the pathogenesis of T2DM and that various cytokines play a critical role in the onset and progress of the disease. Eotaxin is a fundamental cytokine in the pathogenesis of allergic respiratory diseases, inflammatory bowel disease and gastrointestinal allergic hypersensitivity (10). It has been reported that eotaxin is a secretory product of adipose tissue and its plasma level increased in obese patients and is believed to be associated with the pathogenesis of diabetes (11).

It has been determined that protein structured fetuin-A synthesized in the liver significantly increases with obesity. Moreover, it has been suggested that there is a significant link between obesity and fetuin-A and insulin resistance in humans (12,13). Recent researches have reported that fetuin-A can play a part in the glucose metabolism and induce insulin resistance in target tissues by inhibiting insulin receptor activity in the liver, muscles and adipose tissue (14,15). Within this context, in this study determined the visfatin, eotaxin and fetuin-A levels of normal and overweight patients with T2DM and investigated their relationship with fasting blood glucose (FBG), insulin resistance, fasting insulin level, BMI, and the relationship between these molecules.

MATERIAL AND METHOD

The study was approved by the Non-interventional Studies Ethics Committee of Dicle University Faculty of Medicine (Date: 15.04.2015, Decision No: 195). Consent was acquired from all of the participants, who were also informed about what to do, also the study was carried out in accordance with the Declaration of Helsinki.

Subjects

The study was comprised of 30 patients who had applied to the Endocrinology and Metabolic Diseases Outpatient Clinic of Dicle University Hospital, had been diagnosed with T2DM in accordance with the American Diabetes Association (ADA) criteria, had received oral antidiabetic treatment and were between the ages of 47-63 years and 20 healthy participants between the same ages. The patients and healthy participants included in the study were selected from people who did not smoke or drink alcohol. In addition, patients with significant diabetic complications such as retinopathy, hypertension, neuropathy, renal failure, and cardiovascular disease were excluded from the experiment. The BMI of the participants was calculated when they were first admitted. The 30 patients with T2DM and healty participants were divided into two groups according to their BMI. Those with a BMI of 26.2-29.9 kg/m² were included in the overweight diabetic group, while those with a BMI between 20.9-24.9 kg/m² were included in the normalweight diabetic group. The volunteer subjects in the control group were also divided into two groups in the same way. All patients were using metformin at a dose of 2000 mg/day for more than 1 year.

Blood Sampling and Measurements

The biochemical measurements of the participants were carried out at the Central Laboratory of Dicle University Hospital. In venous blood samples were obtained from the participants after at least 8-12 hours of fasting to determine their glucose measurement. These measurements were carried out with Abbott Diagnostics original kits and in accordance with the spectrophotometrical method. The glycated hemoglobin (HbA1c) levels of the participants were also measured on the same day according to the liquid chromatography (HPLC) method and the fasting insulin levels were determined by using Roche Diagnostics original kits and the Cobas e601 module (Roche Diagnostics, Mannheim, Germany) in accordance with the electrochemiluminescence measurement method. An extra tube of blood was taken from the participants and centrifuged at 4000 rpm for ten minutes then the serum samples were taken into another eppendorf tube. The visfatin, eotaxin and fetuin-A levels in the serum samples stored at -80°C were measured in accordance with the ELISA method using human ELISA kits (visfatin catalog number: 201-12-0026; SunRed Biotechnology, Shanghai, China, eotaxin (catalog number: CK-E90892; Hangzhou Eastbiopharm Co., Ltd., Zhejiang, China, and fetuin-A catalog number: 201-12-1387; SunRed Biotechnology, Shanghai, China). The insulin resistance of the patient and control groups were calculated according to the HOMA-IR index (16).

Statistical Analysis

Microsoft Excel was used to record the data collected from the all participants, and the statistical analyses were carried out using SPSS software (version 18.0). Kolmogorov-Smirnov test was used for checking normality of the obtained data. Since the data were not normally distributed, The Mann Whitney U test was used for the analysis of the data. Moreover, to investigate the correlation of visfatin, eotaxin and fetuin-A with FBG, HbA1c, fasting insulin, Insulin resistance, and BMI Spearman's correlation analysis was applied. The results were stated as median values. Furthermore, p values less than 5% ($p<0.05$) were considered significant, while those greater than 5% ($p>0.05$) were considered insignificant.

RESULTS

The principal characteristics of all groups are presented in **Table 1**. The patient groups and their control groups were found to be similar in terms of age, height, weight, and BMI.

The FBG level of the OD was measured as 137 mg/dl, while the level of the ND was found as 140 mg/dl. Even though both patient groups were using oral antidiabetic medicines their FBG levels were found to be significantly higher than those of their control groups (OD: p<0.001 and ND: p<0.05). The fasting insulin level of the OD was found to be significantly higher than the ND (p<0.05). The HbA1c values were significantly higher in the OD and ND compared to their control groups (P<0.001). Insulin resistance was significantly higher in the OD compared to the ND (p<0.05).

The visfatin level of the OD was found to be 16.65 ng/ml, while those of the OC was 10.60 ng/ml, those of the ND was 14 ng/ml and those of the NC was 3.50 ng/ml. The visfatin levels of the OD and ND were significantly higher than those in the control groups as shown in **Figure 1** (p<0.05). Similarly, the eotaxin levels were found to be significantly higher in the OD and ND compared to the control groups as shown in **Figure 2** (p<0.001 and p<0.05). No significant difference was determined between the fetuin-A levels of OD and ND and those of the controls (**Figure 3**).

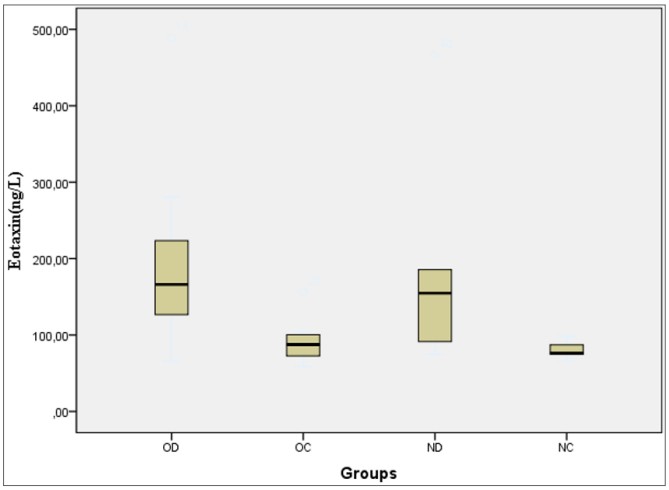

Figure 2. A Boxplot illustration of serum eotaxin concentrations in subjects of overweight and normalweight diabetic patients and their healty controls. OD: overweight diabetic, OC: overweight control, ND: normalweight diabetic, NC: normalweight control

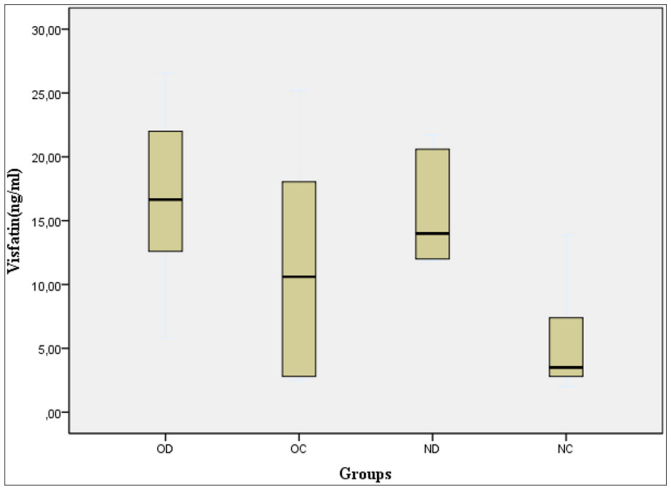

Figure 1. A Boxplot illustration of serum visfatin concentrations in subjects of overweight and normalweight diabetic patients and their healty controls. OD: overweight diabetic, OC: overweight control, ND: normalweight diabetic, NC: normalweight control

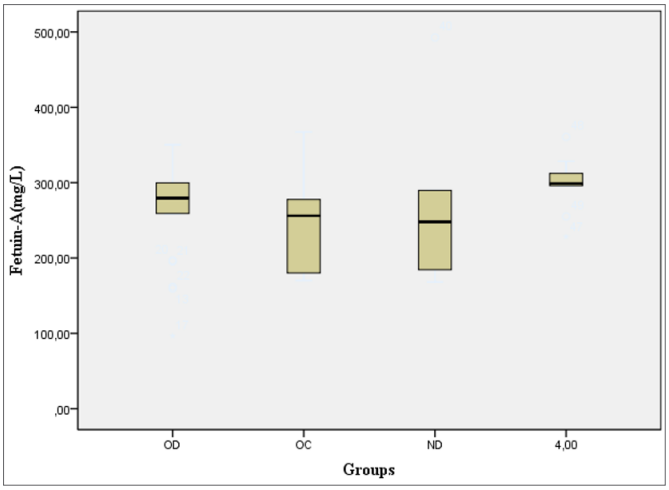

Figure 3. A Boxplot illustration of serum fetuin-A concentrations in subjects of overweight and normalweight diabetic patients and their healty controls. OD: overweight diabetic, OC: overweight control, ND: normalweight diabetic, NC: normalweight control

Table 1. Demographic and laboratory datas of overweight and normalweight diabetic patients and their controls.

	OD (n=23)		OC (n=11)		ND (n=7)		NC (n=9)	
	Median	Min-Max	Median	Min-Max	Median	Min-Max	Median	Min-Max
Age (years)	61	54-67	59	53-64	55	53-62	58	51-65
Height (cm)	163	150-188	170	159-193	166	150-172	165	158-182
Weight (kg)	81.5b	75.4-111	78	76-116.5	62.4	47.7-66	65	50.8-71.3
BMI (kg/m²)	28.91b	26.15-29.33	27.96	26.10-29.93	22.57	20.89-23.57	23.67	21.03-24.98
FBG (mg/dl)	137**	117-162	98	88-110	140*	101-164	91	82-101
Fasting insülin (µU/ml)	12.65a	8.56-17.40	12.20	9.20-14.50	6.05*	4.40-7.52	10.20	7.40-12.38
HOMA-IR	5.15a	4.36-6.81	4.01	3.21-4.28	2.12	2.07-3.13	2.18	1.62-3.58
HbA1c (%)	6.75**	5.30-8.15	5.30	4.20-6.00	6.51**	5.83-7.60	5.20	4.40-5.67

BMI: body mass index; HbA1c: hemoglobin A1c; HOMA-IR: homeostatic model assessment of insülin resistance, Data represents median and min-max. *P<0.05, **P<0.001 compared to controls. aP<0.05, bP<0.01 compared to normalweight diabetic participants.

Table 2. Correlation coefficients of studied variables with visfatin, eotaxin and fetuin-A in each group.

	OD (n=23)			OC (n=11)			ND (n= 7)			NC (n=9)		
	Visfatin	Eotaxin	Fetuin-A	Visfatin	Eotaxin	Fetuin-A	Visfatin	Eotaxin	Fetuin-A	Visfatin	Eotaxin	Fetuin-A
Visfatin (ng/ml)	-	0.003	-0.284	-	0.700*	0.291	-	0.714	0.657	-	-0.377	0.226
Eotaxin (ng/L)	0.003	-	0.315	0.700*	-	0.291	0.714	-	0.714	-0.377	-	0.183
Fetuin-A (mg/L)	-0.284	0.315	-	0.291	0.291	-	0.657	0.714	-	0.226	0.183	-
BMI (kg/m²)	0.474*	0.038	-0.292	0.782**	0.518	.000	0.257	0.429	-0.086	-0.695*	0.283	-0.133
FBG (mg/dl)	0.179	-0.336	-0.394	0.609*	0.455	0.255	-0.771	-0.943**	-0.771	-0.017	-0.360	-0.184
Fasting insulin (µU/ml)	0.192	0.293	0.364	0.709*	0.445	0.345	-0.029	-0.200	-0.029	0.544	-0.067	0.817**
HbA1c (%)	0.231	0.017	-0.234	-0.148	-0.491	-0.343	-0.696	-0.899*	-0.696	-0.658	0.281	0.026
HOMA-IR	0,252	0,220	0,241	0,691*	0,391	0,309	-0,058	-0,319	-0,145	0,703*	-0,233	0,667*

BMI: body mass index; HbA1c: hemoglobin A1c; HOMA-IR: homeostatic model assessment of insülin resistance, *P<0.05, **P<0.01

As shown in **Table 2**. A positive correlation was found between the visfatin level and BMI in OD and OC (p<0.05 and p<0.01), while a negative correlation was found in NC. A linear correlation was determined between visfatin level and eotaxin, FBG, fasting insulin level, and HOMA-IR in OC (p<0.05). A positive correlation was determined between visfatin level and HOMA-IR in the NC (p<0.05). A negative correlation was observed between the eotaxin levels and FBG and HbA1c levels in the ND (p<0.05 and p<0.01), while a positive correlation was determined between the fetuin-A levels and fasting insulin levels and insulin resistance in the NC (p<0.01 and p<0.05).

DISCUSSION

Owerweight and/or obesity is a major risk factor of T2DM, is closely related to irregular adipokine release, macrophage infiltration into adipose tissue and inflammation processes. Very little is known about the potential role of these processes in the development of T2DM. This study examined the serum visfatin, eotaxin and fetuin-A levels in normal and owerweight patients with T2DM with the purpose of contributing to closing the gap regarding this issue.

Individuals with T2DM may be exposed to various complications despite receiving medical treatment. In cases where medical treatment fails to satisfy, hyperglycemia, increased HbA1c and increased insulin resistance can be observed. In the present study, FBG levels and HbA1c concentrations were significantly higher in the normal and overweight patients with T2DM who received oral antidiabetic treatment. The fasting insulin level and insulin resistance of the OD were higher than the ND. Similarly, these parameters were determined to be higher in the OC compared to the NC. In general, insulin resistance is high in patients with T2DM and is more exacerbated in the presence of obesity (17). The acquired data were in support of the literature indicating that there were relationships between fasting insulin level, insulin resistance and BMI (4,5,18,19). Despite there being unsurprising and expected results, it was observed that the participants of the present study were not fully biochemically controlled with the antidiabetic treatment they were receiving. This may be due to them not using their medication regularly, not paying attention to their diet and periodic health checks, and their sedentary lifestyle habits.

Adipose tissue, which was known only as an energy store until approximately 10-15 years ago, is now known as the largest endocrine organ in the human body. As an active tissue, the adipose tissue, secretes important proteins called adipokine that have metabolic activity. Some of the adipokines secreted from this tissue may be protective against T2DM. One of these is visfatin, which acts like insulin in muscles, adipose tissue, and liver and increases insulin sensitivity (9). The antidiabetic effects of visfatin, insulin resistance and its relationship with T2DM have been investigated in many studies. However, contradictory results have been obtained in similar studies conducted on this subject. Some researchers have reported that there is no relationship between plasma visfatin level and diabetes or vice versa. Takebayashi et al. (20) determined that there was no significant relationship between visfatin level and T2DM. Gündüz et al. (21) found that the visfatin levels of the control group and patients with T2DM were similar. Toruner et al. (22) reported that plasma visfatin levels were significantly lower in T2DM patients. Moreover, they determined that there was a negative relationship between visfatin and HbA1c levels. Contrary to the findings of previous studies, the present study found that visfatin levels of the patients with T2DM were higher compared to those of the control group. Similarly, in a study conducted with a large number of patients it was found that visfatin concentrations were significantly higher in T2DM patients compared to the control group (23). Lopez et al. (24) determined that plasma visfatin levels were positively related with insulin resistance and that visfatin may be significant in the pathogenesis of diabetes. Habib et al. (25) found the serum visfatin levels of patients with T2DM to be 7.01±3.79 ng/ml and those of healthy subjects to be 4.02±2.74 ng/ml (p=0.046).

Researchers have found that patients with T2DM have high visfatin levels and higher visfatin levels with poor glycemic control and increased body adiposity indices. Haider et al. (26) determined that when blood glucose increased plasma visfatin levels also increased in healthy participants who underwent glucose infusion tests. In addition, they reported that when the glucose level increased in fat cell cultures, the expression of visfatin also increased. With this regard, the results of the present study agreed with these results and those of various other studies in the literature (27,28,29). When the findings of the present study and previous studies are considered, it was considered that this increase in visfatin levels in the T2DM patients was likely to be due to the impairment of the visfatin signal in target tissues, the development of visfatin resistance or an increase in biosynthesis due to hyperglycemia, hyperinsulinemia, or the reaction to adipokines, and was accepted as a protective physiological mechanism (29).

In this study, a positive correlation was determined between visfatin levels and BMI. Similarly, in the relevant studies conducted in the literature a significant positive correlation was also reported between visfatin levels and BMI (27, 30-32). Choi et al. (33) determined that visfatin levels of non-obese patients were lower than obese patients. Moreover, they found that the plasma visfatin levels could be decreased when body weight was reduced by means of an exercise program. Kara et al. (32) compared obese and non-obese patients with T2DM with healthy control groups and determined that the serum visfatin levels of obese patients with T2DM were higher compared to those of the control groups.

In brief, the association between serum visfatin levels and diabetes has not been fully explained with the studies conducted thus far. According to the results of this study, the visfatin levels were significantly higher in the OD and ND. However, visfatin levels were also determined to be high in the OC. The findings of this study proved that there was a notable association between visfatin and obesity and/or visfatin and diabetes. However, the role of visfatin in the pathophysiology of diabetes is still controversial. Although it is believed that visfatin may be a compensatory mechanism in this process, the role of visfatin in insulin resistance related disorders is not fully known.

It has become increasingly clear that diabetes is a low-grade inflammatory disease, and that inflammation is closely related to insulin resistance (34). In the presence of T2DM, changes can be observed in the serum levels of inflammatory markers. Determining inflammatory markers in diabetes can be important in gaining insight into the processes underlying the onset and progression of the disease. A clearer understanding of the inflammatory basis of T2DM may also be significant in putting forward new approaches to currently used pharmacological/ non-pharmacological interventions (35). Studies on biomarkers associated with the chronic inflammatory condition underlying T2DM and their interactions with one another are ongoing (36-39).

Eotaxin, which is an important pro-inflammatory cytokine is synthesized in various cells of the immune system. It has also been determined that it is secretory product of adipose tissue and that plasma levels are increased in obese individuals (11). Vasudevan et al. (11) determined that serum eotaxin level in obese individuals were high. However, in the present study, it was determined that the serum eotaxin levels of obese and non-obese participants were similar. As eotaxin is a pro-inflammatory agent and has previously been reported to have a possible role in the development of obesity-related disorders such as T2DM, its associated with T2DM was determined. In the literature review, only one study was found to have directly examined the relationship between T2DM and eotaxin. In this study, conducted by Herder et al. (40) no changes were determined in the serum eotaxin levels of patients with T2DM. However, in the present study, it was observed that serum eotaxin levels were higher in OD and ND compared to their control groups. These results suggest that eotaxin may play a part in glucose metabolism and the pathogenesis of T2DM.

Fetuin-A is a multifunctional molecule that is secreted from the liver. According to the results of previous studies, fetuin-A is a biomarker of the risk of T2DM (14,41). Ix et al. (14) reported that among the healthy individuals they followed up for 6 years the serum fetuin-A levels of 135 patients who developed diabetes were higher than those of the healthy individuals who did not develop diabetes. Furthermore, they determined that there was a relationship between serum fetuin-A levels and insulin resistance. Song et al. (42) determined that middle-aged subjects with T2DM showed high fetuin-A levels and that there was a positive correlation between the fetuin-A level and insulin resistance. However, some researchers have reported no significant difference between fetuin-A levels between patients with T2DM and healthy individuals, and no relationship between fetuin-A levels and insulin resistance (12,21). Yılmaz et al. (43) determined that fetuin-A levels were significantly lower in T2DM patients. In the present study, no significant difference was observed in serum fetuin-A levels between the OD and ND patients with T2DM and their control groups. However, we determined a positive relationship between the serum fetuin-A and fasting insulin levels and insulin resistance in the NC. These findings are consistent with the results of various

similar studies (12,21), while they contradict the results of others (41,44). The differences between the results may be due to the subjects being of different ethnic origins and gender, having different lifestyles, and dietary habits and receiving different medication.

Our study has certain limitations; firstly the metabolic parameters of the T2DM patients included in the study were not under control. Second, the small number of patients in the study. Third, It can be listed as the fact that the compliance of patients with drug therapy was not evaluated.

CONCLUSION

Serum visfatin and eotaxin levels are high in patients with T2DM, and this elevation is dependent of BMI. In addition, visfatin level is high in overweight non-diabetic subjects.

ETHICAL DECLARATION

Ethics Committee Approval: The study was approved by the Non-interventional Studies Ethics Committee of Dicle University Faculty of Medicine (Date: 15.04.2015, Decision No: 195).

Informed Consent: All patients signed the free 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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Author Contributions: All of 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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REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes-2015. Diabetes Care 2015; 38: S1–S2.
2. Mitrakou A, Kelley D, Mokan M, et al. Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. N Engl J Med 1992; 326: 22-9.
3. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-607.
4. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus: present and future perspectives. Nat Rev Endocrinol 2011; 8; 8: 228-36.
5. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care 2011; 34: 1249-57.
6. Opara E. Nutrition and diabetes. Pathophysiology and management. Taylor and Francis Group 2006.
7. Centers for Disease Control and Prevention (CDC). Prevalence of overweight and obesity among adults with diagnosed diabetes--United States, 1988-1994 and 1999-2002. Morb Mortal Wkly Rep. (MMWR) 2004; 19; 53: 1066-8.
8. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J. Clin. Invest 2003; 112: 1821-30.
9. Fukuhara A, Matsuda M, Nishizawa M, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science 2005 Jan 21; 307: 426-30.
10. Jean-Baptiste S, O'Toole EA, Chen M, Guitart J, Paller A, Chan LS. Expression of eotaxin, an eosinophil-selective chemokine, parallels eosinophil accumulation in the vesiculobullous stage of incontinentia pigmenti. Clin Exp Immunol 2002; 127: 470-8.
11. Vasudevan AR, Wu H, Xydakis AM, et al. Eotaxin and obesity. J Clin Endocrinol Metab 2006; 91: 256-61.
12. Mori K, Emoto M, Yokoyama H, et al. Association of serum fetuin-A with insulin resistance in type 2 diabetic and nondiabetic subjects. Diabetes Care 2006; 29: 468.
13. Ix JH, Shlipak MG, Brandenburg VM, Ali S, Ketteler M, Whooley MA. Association between human fetuin-A and the metabolic syndrome: data from the Heart and Soul Study. Circulation 2006; 113: 1760-7.
14. Ix JH, Wassel CL, Kanaya AM, et al. Fetuin-A and incident diabetes mellitus in older persons. JAMA 2008; 300: 182-8.
15. Mathews ST, Rakhade S, Zhou X, Parker GC, Coscina DV, Grunberger G. Fetuin-null mice are protected against obesity and insulin resistance associated with aging. Biochem Biophys Res Commun 2006; 350: 437-43.
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-9.
17. Kelley DE, Williams KV, Price JC, McKolanis TM, Goodpaster BH, Thaete FL. Plasma fatty acids, adiposity, and variance of skeletal muscle insulin resistance in type 2 diabetes mellitus. J Clin Endocrinol Metab 2001; 86: 5412-9.
18. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. Diabetes 1998; 47: 699-713.
19. Huxley R, James WP, Barzi F, et al. Ethnic comparisons of the cross-sectional relationships between measures of body size with diabetes and hypertension. Obes Rev 2008 Mar; 9: 53-61.
20. Takebayashi K, Suetsugu M, Wakabayashi S, Aso Y, Inukai T. Association between plasma visfatin and vascular endothelial function in patients with type 2 diabetes mellitus. Metabolism 2007; 56: 451-8.
21. Gunduz FO, Yildirmak ST, Temizel M, et al. Serum visfatin and fetuin-a levels and glycemic control in patients with obese type 2 diabetes mellitus. Diabetes Metab J 2011; 35: 523-8.
22. Toruner F, Altinova AE, Bukan N, et al. Plasma visfatin concentrations in subjects with type 1 diabetes mellitus. Horm Res 2009; 72: 33-7.
23. Sandeep S, Velmurugan K, Deepa R, Mohan V. Serum visfatin in relation to visceral fat, obesity, and type 2 diabetes mellitus in Asian Indians. Metabolism 2007; 56: 565-70.
24. López-Bermejo A, Chico-Julià B, Fernàndez-Balsells M, et al. Serum visfatin increases with progressive beta-cell deterioration. Diabetes 2006; 55: 2871-5.
25. Habib SS, Bashir S, Habib SH. Serum visfatin relationship with glycemic control and adiposity indices in patients with type 2 diabetes mellitus. Khyber Med Univ J 2020; 12: 263-7.

26. Haider DG, Schaller G, Kapiotis S, Maier C, Luger A, Wolzt M. The release of the adipocytokine visfatin is regulated by glucose and insulin. Diabetologia 2006; 49: 1909-14.
27. El-Shaer OS, Belal KM, Issa HA, El-Adl T. Increased serum visfatin levels in patients with type 2 diabetic patients. Life Sci. J 2012; 9: 114-20.
28. Dogru T, Sonmez A, Tasci I, et al. Plasma visfatin levels in patients with newly diagnosed and untreated type 2 diabetes mellitus and impaired glucose tolerance. Diabetes Res Clin Pract 2007; 76: 24-9.
29. Chen MP, Chung FM, Chang DM, et al. Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2006; 91: 295-9.
30. Varma V, Yao-Borengasser A, Rasouli N, et al. Human visfatin expression: relationship to insulin sensitivity, intramyocellular lipids, and inflammation. J Clin Endocrinol Metab 2007; 92: 666-72.
31. Berndt J, Klöting N, Kralisch S, et al. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes 2005; 54: 2911-6.
32. Kara M, Uslu S, Kebapçı N, Özçelik E, Bal C. Evaluation of the serum visfatin and adiponectin levels in patients with type 2 diabetes mellitus. Turkish J. Biochem 2014; 39: 181–7.
33. Choi KM, Kim JH, Cho GJ, Baik SH, Park HS, Kim SM. Effect of exercise training on plasma visfatin and eotaxin levels. Eur J Endocrinol 2007; 157: 437-42.
34. Esposito K, Giugliano D. The metabolic syndrome and inflammation: association or causation? Nutr Metab Cardiovasc Dis 2004; 14: 228-32.
35. King GL. The role of inflammatory cytokines in diabetes and its complications. J Periodontol 2008; 79: 1527-34.
36. Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004; 27: 813-23.
37. Lukic L, Lalic NM, Rajkovic N, et al. Hypertension in obese type 2 diabetes patients is associated with increases in insulin resistance and IL-6 cytokine levels: potential targets for an efficient preventive intervention. Int J Environ Res Public Health 2014; 11: 3586-98.
38. Kashiwagi R, Yamada Y, Ito Y, et al. Increase in adiponectin level prevents the development of type 2 diabetes in japanese men with low adiponectin levels. J Endocr Soc 2018; 2: 753-64.
39. Zheng M, Wang X, Guo H, et al. The cytokine profiles and ımmune response are ıncreased in covıd-19 patients with type 2 diabetes mellitus. J Diabetes Res 2021; 2021: 9526701.
40. Herder C, Haastert B, Müller-Scholze S, et al. Association of systemic chemokine concentrations with impaired glucose tolerance and type 2 diabetes: results from the Cooperative Health Research in the Region of Augsburg Survey S4 (KORA S4). Diabetes 2005; 54: S11-7.
41. Sun Q, Cornelis MC, Manson JE, Hu FB. Plasma levels of fetuin-A and hepatic enzymes and risk of type 2 diabetes in women in the U.S. Diabetes 2013; 62: 49-55.
42. Song A, Xu M, Bi Y, et al. Serum fetuin-A associates with type 2 diabetes and insulin resistance in Chinese adults. PLoS One 2011; 6: e19228.
43. Yilmaz MI, Saglam M, Qureshi AR, et al. Endothelial dysfunction in type-2 diabetics with early diabetic nephropathy is associated with low circulating adiponectin. Nephrol Dial Transplant 2008; 23: 1621-7.
44. Dutta D, Mondal SA, Kumar M, et al. Serum fetuin-A concentration predicts glycaemic outcomes in people with prediabetes: a prospective study from eastern India. Diabet Med 2014 Dec; 31: 1594-9

Case Report

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A large intra-abdominal leiomyoma with unusual urinary symptom: case report

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ABSTRACT

Abdominal or intra-abdominal masses are defined as any enlargement or swelling localized in the abdominal area. Intra-abdominal masses can be diagnosed from abdominal symptoms or through physical examination, as well as can incidentally be detected from radiological imaging performed for other reasons. In this study, the diagnosis and treatment of intra-abdominal mass in a 27-year-old nulliparous female patient with unusual urinary symptom is presented. Preoperative magnetic resonance (MRI) images showed an intra-abdominal solid mass. The mass excision was performed, and surgical recovery was achieved. Pathological results revealed that the mass was a large leiomyoma of 15 cm×14 cm×11 cm size with extrauterine localization, which is quite rare in the literature. Post-operative results showed that the patient's existing urinary complaint had completely disappeared.

Keywords: Intra-abdominal mass, leiomyoma, urinary symptom

INTRODUCTION

Abdominal or intra-abdominal mass is any enlargement or swelling in the abdomen. Abdominal masses may be caused by hepatomegaly, splenomegaly, a retroperitoneal mass, a pancreatic mass, or omental metastasis (1). Abdominal pain, weight loss, notice of abdominal mass, fever, hematuria, dysuria, and intestinal complaints can be considered as various symptoms of the abdominal masses. In some cases, especially those deeply retroperitonal or pelvic localized may go unnoticed by the patient. Abdominal masses may have different pathological features in solid or cystic, benign, or malignant properties. It may also vary depending on age, gender, localization, and the source of tissue. Leiomyomas are the most common benign tumors in the female reproductive system, observed in 20-30% of women of reproductive age. Extrauterine leiomyomas, on the other hand, are quite rare, usually benign and can occur in any area of the body. Unusual growth patterns of such leiomyomas can even mimic malignancy and cause a clinical dilemma (2,3). In this study, a large case of intra-abdominal mass, which was diagnosed as leiomyoma in pathology, and which unusually causes urinary symptom, is presented.

CASE

A 27-year-old nulliparous female patient was admitted to our hospital with a history of two years of frequent urination complaint. She was diagnosed with intra-abdominal mass, which causes urinary symptom by pressing onto the urethra. Pre-operation Magnetic Resonance (MRI) images showed that the size of the solid mass was 17.7 cm×17.3 cm×7.8 cm, and it was localized in the superior of the bladder and anterior of the uterus and showed an extension to the umbilicus superior (**Figure 1**). It has also been reported that the mass was in contact with the right ovary and histopathological evaluation is recommended.

Intra-abdominal mass excision was performed, surgical recovery was achieved, and the treatment was completed. Images of the mass excised from the patient are shown in **Figure 2**.

According to pathological results, a large leiomyoma with dimensions of 15 cm×14 cm×11 cm was diagnosed. In the post-operative follow-up, the pre-operation urinary complaints of the patient disappeared completely.

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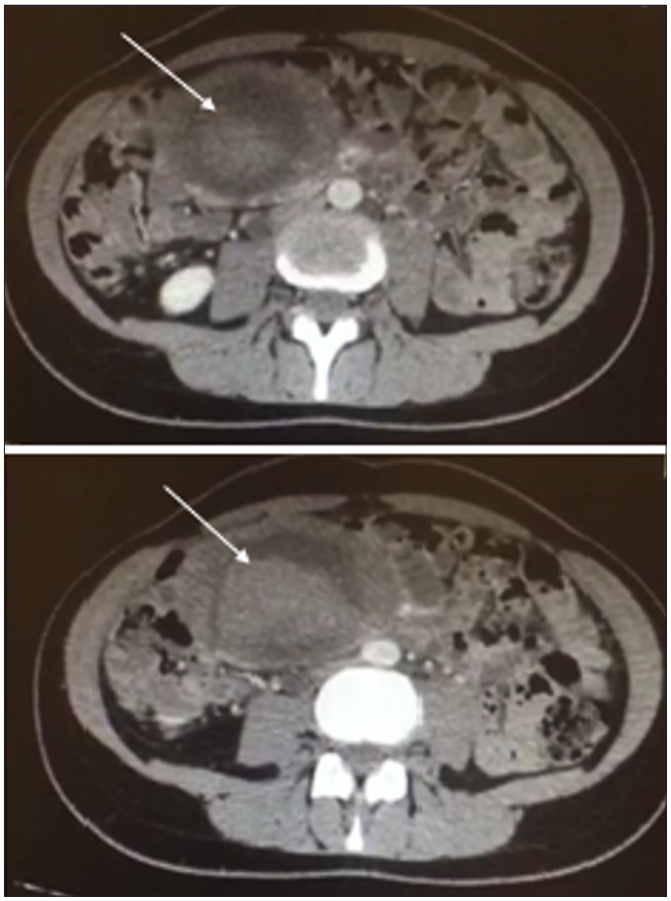

Figure 1. Magnetic Resonance (MR) images of the mass

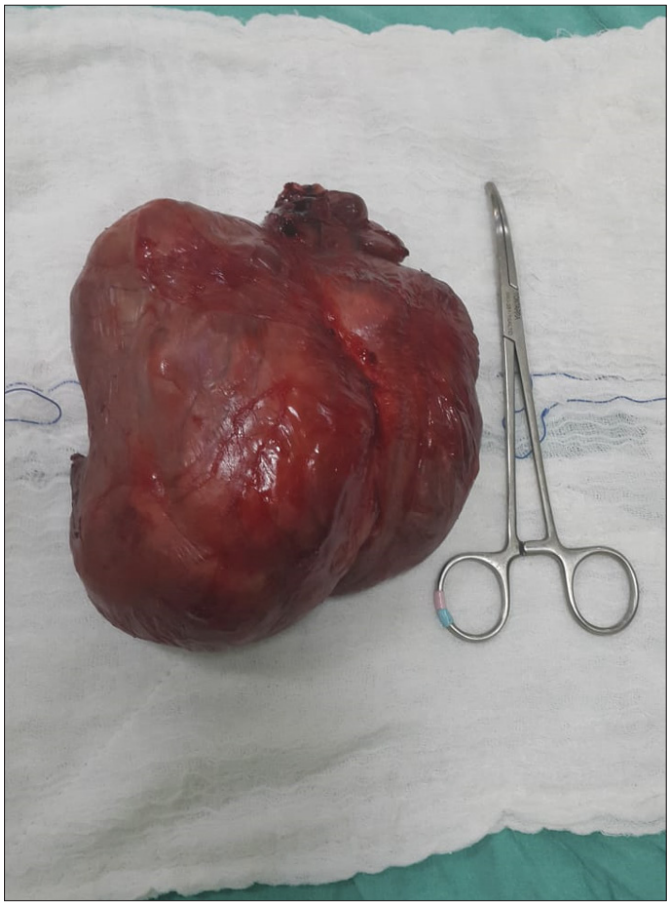

Figure 2. Image of intra-abdominal leiomyoma (15 cm×14 cm×11 cm) excised from the patient

DISCUSSION

Intra-abdominal masses can be evaluated with knowledge of abdominal anatomy. In the basic approach, there are nine regions of the abdomen: umbilical, epigastric, suprapubic, right and left hypochondrium, right and left lumbar, right and left inguinal regions. In the clinical practice of surgeons, the regions of the abdomen are evaluated as right and left upper and lower quadrants, epigastric and hypogastric regions (4). Detection of intra-abdominal masses can be performed by physical examination findings due to symptoms or incidentally during radiological imaging for different reasons. For investigation of abdominal masses, several radiological imaging can be used such as X-ray radiography, abdominal ultrasonography (USG), magnetic resonance imaging (MRI), and computed tomography (CT) method (5). MRI is useful for imaging of the abdomen in cases with pancreatic, retroperitoneal masses, patients with renal insufficiency, or in patients for whom the use of contrast agents containing iodine is a contraindication (6). The diagnosis of an intra-abdominal mass consists of two stages which are a detailed anamnesis: an assessment of the patient's history and a physical examination. Evaluation of the patient's history includes the symptoms and the time since the onset of symptoms, past illnesses, family history, and, if any, the patient's previous surgeries (7). Some abdominal masses that are not very large in size may remain asymptomatic or cause abdominal pain in some cases. In some cases, it may be difficult for the patient to notice the masses, especially in those that are located deep retroperitoneal or pelvic (8). Leiomyomas are benign tumors that occur in the female reproductive system. In leiomyomas, surgery is the main treatment approach and is curative. Extrauterine leiomyomas have been reported quite rarely in the literature (9).

CONCLUSION

The case presented in this study is a large leiomyoma with an extrauterine location detected in the intra-abdominal region and causing unusual urinary symptom, which is quite rare in the literature. The postoperative results of the patient showed that all urinary symptoms had disappeared, and surgery was curative in the treatment. Consequently, urinary complaint should be considered in the differential diagnosis of intra-abdominal leiomyomas.

ETHICAL DECLARATIONS

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.

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

Author Contributions: All of 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.

REFERENCES

1. Das S. Examination of abdominal lump: A manual on clinical surgery. 11th ed. Calcutta: S.D. Publications; 2015.
2. Fasih N, Prasad Shanbhogue AK, Macdonald DB, et al. Leiomyomas beyond the uterus: unusual locations, rare manifestations. Radiographics 2008; 28: 1931-48.
3. Midya, M, Dewanda, NK. Primary anterior abdominal wall leiomyoma-a diagnostic enigma. J Clin Diag Res 2014; 8: NJ01-2.
4. Swartz, MH. Textbook of physical diagnosis: History and examination. 5th ed. Philadelphia: Saunders Elsevier; 2006.
5. Bhagat S, Gauba N, Singh S, Singh A, Mahal GBS. Assessment and comparison of abdominal masses by sonography and computed tomography. J Evol Med Dent Sci 2014; 3: 84-94.
6. Gascin CM, Helms CA. Lipomas, lipoma variants, and well differentiated liposarcomas (atypical lipomas): results of MRI evaluations of 126 consecutive fatty masses. Am J Roentgenol 2004; 182: 733-9.
7. Brady MS, Gaynor JJ, Brennan MF. Radiation associated sarcoma of bone and soft tissue. Arch Surg 1992; 127: 1379-85.
8. Akkoca, M, Tokgöz, S, Yılmaz, KB, Akıncı, M, Yılmazer, D. Diagnosis and treatment approaches for intraabdominal masses in adults. Ankara Üniv Tıp Fak Mec 2017; 70: 201-5.
9. Nasta A, Nandy K, Bansod Y. An unusual case of abdominal leiomyoma presenting as a free lying intraperitoneal mass in an elderly gentleman. Case Rep in Surg 2016; 1714958.

Case Report

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Rupture of a pseudoaneurysm in brachial artery after hemodialysis therapy: rare but serious complication

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ABSTRACT

Pseudoaneurysm (PSA) is a common complication that may occur on the AV fistula line. However, the 5 development of the PSA on a wrong cannulated brachial artery is a rarely seen and catastrophic 6 complication as occured in this case. Rupture is one of the serious complication of PSA. In our case 64 years old male with left snuff-box arteriovenous fistula (AVF) refer to emergency service with pain, swelling, tension on left arm after hemodialysis session. Doppler ultrasound confirmed brachial artery ruptured PSA active bleeding in to the approximately 4 cm diameter hematoma. The patient was transferred to the operating room and underwent to surgery for ruptured PSA repair. Four weeks after surgery, the arteriovenous fistula was used as an access for hemodialysis. Left hand 1st and 2nd digits distal phalanx flexion was limited Clinical suspicion, physical examination, and Doppler ultrasound are essential for early diagnosis and for optimal treatment. Doppler ultrasound can detect the lesion accurately. In patients with arteriovenous fistula during hemodialysis it should be considered pseudoaneurysm, rupture and neuropathy may occur. These are rare but serious complications so suspicion, clinical examination and doppler ultrasound are very important for early diagnosis and treatment.

Keywords: Hemodialysis, brachial artery pseudoaneurysm, pseudoaneurysm rupture

INTRODUCTION

Pseudoaneurysms or false aneurysms are pulsatil masses which is encircled by a fibrous capsule and which has anomalous connection between a ruptured vessel and the soft tissue (1). Causes of PSAs are Ehler Danlos Syndrome, Kawasaki's disease, mycotic aneurysm, trauma and iatrogenic (2). Iatrogenic PSAs rate has increased due to increasing endovascular arterial interventions such as endovascular diagnostic and therapeutic procedures and in advertent puncture of vascular access in hemodialysis patients (3). Peripheric artery PSA are rare in upper extremity than lower extremity (4). Brachial artery PSA early diagnosis and surgical treatment are very important they can cause severe complications as upper extremity and finger loss (5). PSA can lead rupture and hemorrhage, neurologic deficit, local infection or ischemia (6).

We report a case of a patient with ruptured PSA of the brachial artery due to unsuccessful venous cannulation after a hemodialysis session.

CASE REPORT

A 64-year-old male patient was admitted to the emergency department with pain, swelling, and tension on left arm. His medical history was hypertension, coronary bypass surgery 4 years ago, and snuffbox AVF in the left arm had been under hemodialysis for 4 years. After hemodialysis session, the patient had tension, pain in the left arm. Left brachial artery, radial and ulnar artery pulses were palpated and the snuffbox AVF thrill was positive. Left hand 1st and 2nd digits distal phalanx flexion was limited. Doppler ultrasound confirmed active bleeding approximately 4 cm diameter hematoma which was originated from the brachial artery in left arm. Patient was taken urgently to the operating room. The surgery was performed under general anesthesia. Left brachial artery was surgically exposed. After dissection fibrous capsule and active bleeding was seen in the puncture site of brachial artery. Hemostasis was achieved by 6.0 proline stitch. Postoperative temporary internal jugular vein dialysis catheter was inserted.

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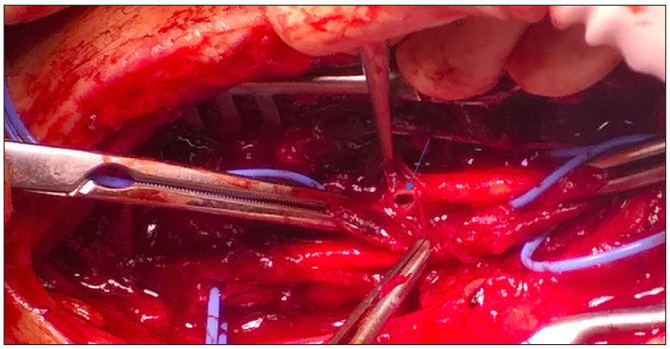

Figure 1. Perioperative ruptured brachial artery PSA neck

Postoperative there were no additional circulatory problems and AVF thrill was positive. The 1st and 2nd digits distal phalanx flexion was limited. Patient had an uneventful recovery and he discharged postoperative 5th day without any deficit in the left arm.

After operation patient received hemodialysis from his temporary hemodialysis catheter and after 4 weeks AVF was used again. Postoperative control ultrasonography confirmed the integrity of the brachial artery.

DISCUSSION

Upper extremity PSAs are rarer than lower extremity. The etiology of PSAs are congenital diseases such as Ehlers-Danlos syndrome, polyarteritis nodosa, Behçet disease, Kawasaki disease, osteochondromas or to iatrogenic complications such as diagnostic, therapeutic and accidental punctures or drug abuse (2,6).

Brachial artery PSAs are mainly due to traumas, cannulations and blood gas samplings (3,7).

Patients with arteriovenous fistula has high risk for developing iatrogenic PSAs due to repeated cannulation and heparinization. After traumatic penetration of the vessel hemorrhage and extravasation can occur. The brachial artery PSA usually develops slowly. It tooks days to months even years to be detected clinically. Brachial PSA usually presents with erythema, induration and expanding painful pulsatile mass. Sometimes it can be with cyanosis, loss of pulsation, paresthesia, nerve compression (8). There are many reported brachial artery PSA due to hemodialysis venous puncture but there is few cases with ruptured PSA with arteriovenous fistula. In the presence of a vascular complication early diagnosis is very essential for adequate treatment. For early diagnosis, clinical suspicion and being aware of pulsatile mass is important. For diagnosis, many imaging modalities can be used as arterial Doppler sltrasonography, conventional angiography, computed tomography (CT) angiography and magnetic resonance imaging (MRI). Angiography is the gold Standard diagnostic method (9). Doppler ultrasonography is faster, cost-effective and easy accessible imaging method (10). Complications are infection, hemorrhage, distal vascular insufficiency and rupture of the PSA (3,7,12,13).

Treatment of brachial PSAs depends on the location, size and the pathogenesis of the PSAs (11). Surgical methods like ligation, resection and reanastomosis or vein graft interpositioning can be performed. Endovascular methods such as endovascular stent-graft implantations and embolization of sac can be used. US-guided external compression and percutaneous thrombin injection can be used for treatment. US-guided compression can also applied in brachial artery PSA treatment (14). In patients whom taking anticoagulation, long procedural time and patient discomfort are limitations for US-guided compression.

Surgical indications are rapidly expanding PSA, distal ischemia, neuropathy or ischemic soft tissues and skin caused by local pressure, infected PSA, failure of percutaneous treatment (15). Surgical excision and arterial reconstruction is the Standard treatment. Arterial continuity is provided with end-to-end anastomosis or a venous interposition graft (16,17).

When there is infection, limb ischemia, skin ischemia, coexisting large hematomas with compartment syndrome like our case US-guided compression therapy is contraindicated (15).

After hemodialysis session PSA was not suspected at first because there was only small hematoma that we thought the origin was cephalic vein. PSA generally present weeks to months after blunt or penetrating trauma (3,12). In our patient 12 hours after he referred to emergency service with pain, tension and compartment syndrome. Patient with snuff-box AV fistula, brachial artery puncture is unexpectable. It may be related with unexperienced dialysis technician and nurses. Early diagnosis is very essential for planning adequate treatment. We have observed rupture of the brachial artery PSA and neuropathy due to pressure on an adjacent nerve. Despite the successful surgical treatment in the 1th and 2nd digits distal phalanx flexion was limited. Third month after the surgery, neuropathy recovered. Forth weeks after the surgery, AV fistulas gets used.

CONCLUSION

Rupture of brachial artery PSA is very rare after hemodialysis therapy in a patient with AV fistula. Incidence of brachial artery PSA is increasing due to endovascular techniques and arterial cannulations. These complications should be considered by emergency physicians, cardiovascular surgeons, nephrologists and hemodialysis nurses to avoid delayed diagnosis and treatment. Emergent surgical repair is essential for good

results. Surgery is especially indicated in compartment syndrome with large hematoma.

ETHICAL DECLARATIONS

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

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REFERENCES

1. Esteban MP, Otálora SB, Landeras RM, et al. Posttraumatic pseudoaneurysm of the brachial artery and postsurgical retraction of median nerve: description of a case and ultrasonography findings. Emerg Radiol 2007; 13: 269-72.
2. Lee JY, Kim H, Kwon H, Jung S-N. Delayed rupture of a pseudoaneurysm in the brachial artery of a burn reconstruction patient. World J Emerg Surg 2013; 8.
3. Cına G, Rosa MG, Viola G, Tazza L. Arteriel injuries following diagnostic,therapeutic and accidental arterial cannulation in hemodialysis patients. Nephrol Dial Transplant 1997; 12: 1448-52.
4. Wielenberg A, Borge MA, Demos TC, Lomasney L, Marra G. Traumatic pseudoaneurysm of the brachial artery. Orthopedics 2000; 23: 1250-1322–4.
5. Nugud OO, Hedges AR. Axillary artery pseudoaneurysm. Int J ClinPract2001; 55: 494–9.
6. Kemp K, Radwan R, Shingler G, Davies C. Brachial artery pseudoaneurysm. BMJ Case Rep 2014; pii: bcr2014203924.
7. Lapus TP, Trerotola SO, Savader SJ. Radial artery pseudoaneurysm complicating a brecia-cimino dialysis fistula. Nephron 1996; 72: 673-5.
8. Habermann ET, Cabot WD: Median nerve compression secondary to false aneurysm of the brachial artery. Bull Hosp Joint Dis 1974; 35: 158-61.
9. Ho PK, Weiland AJ, McClinton MA, Wilgis EF: Aneurysms of the upper extremity. J Hand Surg 1987;12: 39–46.
10. Pelaz Esteban M, Beltran de Otalora S, Landeras RM, Gallardo E, Fernandez Echevarria MA, Perez Aguilar D. Posttraumatic pseudoaneurysm of the brachial artery and postsurgical retraction of median nerve: description of a case and ultrasonography findings. Emerg Radiol 2007; 13: 269–72
11. Yetkin U, Gurbuz A. Post-traumatic pseudoaneurysm of the brachial artery and its surgical treatment. Texas Heart Institute journal/from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital 2003, 30: 293–7.
12. Demırcin M, Peker O, Tok M, Özen H. False aneurysm of the brachial artery in an infant following attemtedvenipuncture. Turkish J Pediatr 1996; 38: 389-91.
13. Popovsky MA, McCarty S, Hawkins RE. Pseudoaneurysm of the brachial artery: a rare complication of blood donation. Transfusion 1994;34: 253-4.
14. Kehoe ME. US-guided compression repair of a pseudoaneurysm in the brachial artery. Radiology 1992; 182: 896.
15. Morgan R, Belli AM: Current treatment methods for postcatheterization pseudoaneurysms. J Vasc Intervent Radiol JVIR 2003; 14: 697-710.
16. Siu WT, Yau KK, Cheung HY, et al. Management of brachial artery pseudoaneurysms secondary to drug abuse. Ann Vasc Surg 2005, 19: 657-61.
17. Pages ON, Alicchio F, Keren B, et al. Management of brachial artery aneurisms in infants. Pediatr SurgInt 2008; 24: 509–13.

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