MIDDLE BLACK SEA JOURNAL OF

HEALTH SCIENCE

(MBSJHS)

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Middle Black Sea Journal of Health Science is an international journal that publishes original clinical and scientific research. Middle Black Sea Journal of Health Science, published by Ordu University, publishes basic innovations in health education, case reports, reviews, letters to the editor, case reports and research articles.

The aim of the journal is to contribute to the international literature with clinical and experimental research articles, case reports, reviews and letters to the editor in the field of health sciences.

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Middle Black Sea Journal of Health Science

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Key words

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Methods

Results

Discussion

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References (most 40)

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Introduction

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Discussion

Conclusion

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d) Review articles

Structure

Title

Abstract (average 200-400 word)

Key words

Introduction

The compilation text also including appropriate sub-headings,

Conclusion

Acknowledgements

References (most 50)

Whole text should not exceed 6550 words except for resources and English summary.

CONTENTS

EDITORIAL

Our New İssue…

In this issue of our journal, we are happy to present to you the rich articles in which many valuable academicians and scientists convey their observations and experiences. While we are trying to bring our journal to a better level in the international scientific community with each new issue we publish, I would like to extend my sincere thanks to all our authors who stood by us during this process and to everyone who worked with us during the intensive preparation process until the journal took its final form.

Hope to meet you in new issues...

PhD, Assoc. Prof. Ülkü KARAMAN

Editor

Rapid Antigen Tests for COVID-19: Are Their Specificity, Sensivity and Accuracy Sufficient?

Hulya Sinan[1](ID), Emel Uzunoglu[2](ID), Mediha Cerrah Ugur[2](ID), Esin Avci[3](ID), Cihangir Akdemir[2](ID), Sahin Direkel[2](ID)

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Abstract

Objective: The aim of our study was to determine the sensitivity and specificity of rapid antigen and Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) tests which are widely used today in patients presenting with Covid-19 complaints and to evaluate these tests' routine usability.

Methods: Two samples were taken from oropharyngeal and nasopharyngeal from 100 patients (50 women, 50 men) who applied to the Covid-19 outpatient clinic of our hospital between April and May 2022. The patients attended to the study were volunteers between the ages of 18-90. One of the samples was studied with the BNG SARS-CoV-2 Antigen Rapid Test (Saliva) and evaluated with the naked eye after 15 minutes according to the company's recommendations. The other sample was studied with RT-PCR on BIO-RAD CFX Real Time System with DSCoronex Covid-19 QPCR Test Kit. The epidemiological data and clinical conditions of the patients were determined by questionnaires. The age, gender, symptoms (fever, cough, headache, diarrhea, sore throat, shortness of breath, loss of taste and smell, myalgia) of the patient and the day of the symptoms were noted down.

Results: It is known that technically rapid antigen tests generally have lower sensitivity and higher specificity than RT-PCR. In our study, the sensitivity was 71% and the specificity was 100%. The Accuracy (Diagnostic Value) rate of the rapid antigen test was determined as 90%. Our results suggest that rapid antigen tests are inexpensive and practical tests to reduce transmission, especially in epidemics however they should be selected carefully by the health care authorities.

Conclusion: The prevalence of self-reported FA based on web-based survey in Eastern Black Sea residents is relatively high and specific to the region.

Key words: Covid-19, PCR, Rapid antigen test

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INTRODUCTION

Policies regarding SARS-CoV-2 testing approaches and services vary from country to country, including rapid antigen testing for the current ongoing Covid-19 infection. RT-PCR is recommended as the gold standard test in the diagnosis of Covid-19 infection all over the world, including Turkey. However, molecular tests are expensive, require experienced personnel and equipped laboratories. Rapid antigen tests are suitable tests for several advantageous such as short lead times, user-friendliness, being able to be used anytime, anywhere, requiring minimum equipment, no preparation step, low cost and reduced personnel load. Antigen tests investigate proteins of the infectious agents and have lower specificity and sensitivity for technical reasons than nucleic acid amplification methods, depending on the infectious agent, the course of the disease and the sample type. Since the onset of the Covid-19 pandemic antigen tests have gained momentum and they have been approved for use by the World Health Organization, Centers for Disease Control and Prevention (CDC), US. Food and Drug Administration (FDA), European Center for Disease Control and Prevention (ECDC) (1-4).

Commonly used parameters to evaluate diagnostic tests are sensitivity and specificity. The Sensitivity rate is the ability of a test accurately identifying individuals with the disease, while the Specificity ratio is the test's accurately identification ability of patients without the disease. The Accuracy (Diagnostic Value) ratio indicates how confidently the results of the test can be used for diagnostic purposes. (1,3). The tests that will be used for diagnostic or screening purposes should be compared with the reference test in terms of sensitivity and specificity, The prevalence/incidence data of the population in which the test will be applied should be known in order to create the algorithms of the countries. The sensitivity of SARS-CoV-2 antigen tests is highest within the first 5 days after the onset of symptoms. The sensitivity of the test decreases especially in upper respiratory tract samples after the 5th day in symptomatic patients. (4).

Rapid antigen tests can be replaced by molecular tests when urgent decision is required in clinical patients, but symptomatic cases with negative test results and contact with a COVID-19 case should be confirmed with PCR (Polymerase Chain Reaction) or new antigen tests within 48 hours (5,2,3).

Apart from diagnostic purposes, rapid antigen tests can also be used for screening the disease. ECDC states that these tests can be used for screening purposes by repeating them at 3-day intervals in public areas. However, WHO says that nucleic acid amplification tests should be the first choice when there are sporadic cases in a country, if there is risky

patients who will undergo surgery and at the airports (4,1).

In our study, it was aimed to evaluate the routine usability of rapid antigen tests by studying simultaneous rapid antigen and PCR tests in patients who applied to the outpatient clinic with complaints suggestive of Covid-19.

METHODS

Our study was carried out with the approval of Local Ethics Committee, dated 23.02.2022 and numbered 2022/1 and with the permission of the Ministry of Health of the Turkish Republic. Informed consent form was obtained from each participant before starting the study. Our study was single blinded. Since the rates of male and female patients who applied to our hospital's Covid-19 outpatient clinic were equal, between April and May 2022, 100 patients aged between 18-90 years and who filled out the patient consent form were randomly selected, and 50 male and 50 female patients were included in the study. With the questionnaires made, the patients were questioned for age, gender, symptoms (fever, cough, headache, diarrhea, sore throat, shortness of breath, loss of taste and smell, myalgia) and the day of the symptoms.

Simultaneously, two different oropharyngeal and nasopharyngeal samples were taken for Covid-19 rapid antigen and RT-PCR test. While one of the samples was studied and evaluated with the BNG SARS-CoV-2 (saliva) rapid antigen test at the bedside, the other sample was studied with the DS Coronex Covid-19 QPCR Test Kit and the BIO-RAD CFX Real Time System. Negativity status and Ct values were noted.

Statistical Analysis

Statistical analyses were conducted with SPSS for Windows version 26.0. The sensitivity and specificity of two diagnostic tests in the same patient group were compared using the McNemar test. An independent two-sample t-test was performed to compare the Ct values of these two groups because it was assumed that each group had a normal distribution (p>0.05). The Spearman's rho correlation coefficient used to determine a relationship between the Ct levels and the day that symptoms first appeared. The specificity, sensitivity, and accuracy (diagnostic value) rate (diagnostic test evaluation calculator) was used to compare a rapid antigen test to a PCR test.

RESULTS

The median age of 100 patients participating in the study was 41.5 (Min-Max: 19;85). The distribution of cases by gender was equal (50%).

Sore throat was present in 23%, cough in 13%, and fever in 8% of the patients. It was observed that the patients intensified on the 2nd, 3rd and 1st days of their symptomatic phase, respectively (Figure 1).

Distribution by time from symptom onset
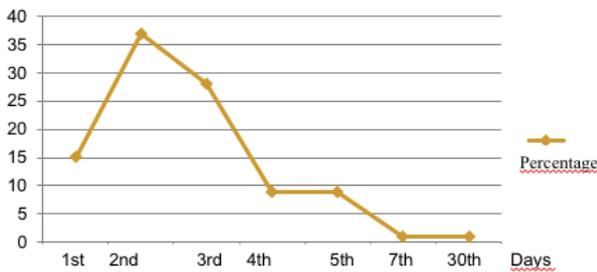
Figure 1. Distribution of patients according to the time from the onset of symptoms

As a result of PCR test, 66 (66%) of the patients were negative and 34 (34%) were positive. All of the patients who were found to be negative with the rapid antigen test were also found to be negative with the PCR test. Only 24 of the 34 PCR positive patients were also positive with the antigen test (Table 1).

Table 1. Distribution of test results

		PCR		**McNemar p-value**
		Negative	Positive	
Antigen	Negative	66	10	0.002*
	Positive	0	24	

* p ≤ 0.05 was considered as statistically significant

The Specificity rate of the test was 100%. According to the PCR test results, 24 of the 34 patients who were positive were also positive with the rapid antigen test, and 10 were negative. Therefore, the Sensitivity rate of the test was 71%. The Accuracy (Diagnostic Value) rate, which shows how confidently the results of the rapid antigen test can be used for diagnosis, was determined as 90%.

When the Ct values obtained by PCR test and rapid antigen test results of the patients were compared, no significant difference was

found between them (p>0.05). The results are given in Table 2.

Table 2. Independent two-sample t-test results

	Group	Patient Number (n)	Average	Standard Deviation	t test (p-value)
CT	Antigen negative	10	26,8000	4,15799	1.817 (0.079)
	Antigen positive	24	24,2083	3,63532	

* p ≤ 0.05 was considered statistically significant

In our study, Ct values for both groups were compared with the onset days of symptoms, but no significant relationship was found between the two groups (p>0.05) (Table 3)

Table 3. Relationship between Ct values and day of onset of symptoms

		Spearman's rho	p-value
Antigen negative	CT- Day of onset of symptoms	0.034	0.926
Antigen positive	CT- Day of onset of symptoms	0.227	0.287

* p ≤ 0.05 was considered statistically significant

DISCUSSION

According to the detailed statistical analysis results; The rapid antigen test of our study was able to detect the diagnosis of SARS-CoV19 virus infection with 100% specificity, 71% sensitivity and 90% accuracy. Our results were in line with some publications in the literature, however the rapid antigen test we used could not meet the specificity and sensitivity criteria of WHO and ECDC for SARS-CoV-2 (1,4).

The Covid-19 pandemic has once again reminded us of the importance of fast and accurate diagnosis in the treatment of patients.

Rapid antigen tests provides many advantages with their short delivery times, ability to be used anytime, anywhere, no need for extra equipment, low cost and laboratory workers especially for the diagnosis of symptomatic patients who are in the first 5 days of the disease with high viral load (6). However rapid antigen tests' sensitivity and specificity need to be determined in order to be used more widely (7).

While the specificity of antigen tests has been found to be quite high in many studies, the sensitivity rates are variable. In a study of Scohy et al., the sensitivity of the rapid antigen test was 30.2%, the specificity was 100%, while the sensitivity was determined as 94% in the study of Porte et al., the specificity was determined as 100%. In another study with a sample size of 1186, the sensitivity was found to be 86.7% and the specificity as 100% with the rapid antigen test (8-10). The specificity rate of the test we used in our study was 100% and the sensitivity was determined as 71%. The sensitivity and specificity criteria suggested by WHO and ECDC for the antigen tests are ≥80% sensitivity, ≥97% specificity and ≥90% sensitivity, ≥97% specificity, respectively (1,4). Our test was far from these sensitivity criterias. This might be due to the the limitations of our study such as low sample number or the patients who applied to our outpatient clinic after the symptomatic period.

In our study, no significant relationship was found between antigen positivity and the time elapsed since the onset of symptoms. However positive cases were seen to be intensified especially in the first days of their disease. Consistent with our study, in the study of Porte et al., 93.7% of the positive samples were concentrated in the first week after symptom onset. In a study by Ristic et al., they said that the sensitivity of rapid antigen tests changed according to the day of the symptoms of the patients, and therefore the sensitivity of the test they used could vary from 67.7% to 100% (8,11).

Although there was no statistically significant relationship between Ct values and antigen test results in our study, it was observed that the Ct values of the samples with positive antigen test were lower. This might be again due to the inadequacy of the sample size, which was the limitation of our study. In the study performed by Mak et al., it was observed that the sensitivity of antigen test results of 160 respiratory tract samples with positive PCR test was higher in samples with a Ct value of less than 18.7 (12) In a study of Ford et al., RT-PCR positive samples with higher Ct values were found to have lower antigen positivity, while the antigen test was found to be >90% positive in samples with Ct values <29. (13).

CONCLUSION

As a result, when we look at the findings obtained from our research and literature, in order to reduce the workload of health professionals working in emergency services,

hospitals, cargo companies, nursing homes, schools, prisons and etc. rapid antigen tests can be used to for both diagnosis and screening. However, the performance of the selected kits must be officially approved by independent institutions, how the performances of the tests are determined must be clearly written in the kit content and each country must create its own algorithm. For these reasons, more studies with larger samples and different antigen test kits are needed to evaluate the specificity and sensitivity of these tests.

Ethical Approval: Ethics committee approval was received for this study from Scientific Research and Publication Ethics Committee of Gumushane University and Ministry of Health of the Republic of Turkey.

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Evaluation of Infections Associated with Central Venous Catheters in ICU

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Abstract

Objective: Central venous catheter-related infections lead to an increase in widespread antibiotic use, prolonged hospital stays, increased costs, as well as morbidity and mortality. In this study, we aimed to evaluate the infections associated with central venous catheters used in our intensive care unit (ICU) and identify the possible contributing factors.

Methods: The hospital records of patients aged 18 and above who were admitted to ICU and had central venous catheters (femoral, jugular, and subclavian catheters) were retrospectively evaluated. Patients' demographic data and also reason for admission, APACHE II score, duration of ICU stay, and 28-day mortality were recorded. Additionally, data on the time of catheter insertion, catheter site, catheter type, administration of blood and total parenteral nutrition (TPN) through the catheter, presence of catheter-related infection, identified pathogens, time of infection development after catheter insertion, and concurrent blood culture results were recorded.

Results: A total of 169 patients were included in the study, of whom 99 (58.6%) were male and 70 (41.4%) were female. The catheters were located in the femoral region in 56 (33.1%) cases, jugular region in 99 (58.6%) cases, and subclavian region in 14 (8.3%) cases. There was no significant difference in the development of catheter infection based on the site of application (p=0.929). The rates of infection were significantly higher in catheters used for TPN and blood transfusion (p=0.002 and p=0.005, respectively). The average duration of intensive care stay was significantly higher in patients who developed catheter infections.

Conclusion: Catheter-related bacteremia is an important risk factor for morbidity and mortality, especially in critically ill patients. In our study, no significant differences were found in the rates of catheter-related infection based on the application sites. We observed that the use of TPN, blood transfusion, and longer catheter duration posed risks for infection.

Key words: Catheter-Related Bacteremia, Central Venous Catheter, İntensive Care Unit

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INTRODUCTION

The use of central venous catheters is a commonly preferred practice in ICU for monitoring patients. It is often chosen for purposes such as fluid therapy, medication administration, blood transfusions, total parenteral nutrition (TPN) delivery, and monitoring of hemodynamic status, particularly in critically ill patients. However, central venous catheterization can lead to complications such as hemorrhage, infection, and thrombosis. The increasing frequency of catheter use in ICU also contributes to the higher rates of nosocomial infections and catheter-related sepsis (1-3). Central venous catheter-associated infections not only result in widespread antibiotic use, prolonged hospital stays, increased costs, but also lead to increased morbidity and mortality. Catheter-related bloodstream infections occur in approximately 1-13% of central catheters, and the incidence of bloodstream infections has been reported as 2-4.5 per 1000 catheter-days in studies. The choice of catheterization site, including femoral, jugular, and subclavian catheterization, varies depending on clinical preferences, although the literature yields different results regarding the risk of infection development associated with each site. Catheter material, site of insertion, paying attention to sterile precautions during insertion, and host defense are important for catheter infections. Furthermore, it has been suggested that the administration of blood and TPN infusions through the catheter may also contribute to the development of infections (3-5). In this study, we aimed to evaluate infections associated with central venous catheters used in our ICU and review the underlying reasons in accordance with the literature.

METHODS

After obtaining ethical committee approval and institutional permissions, our study was conducted by retrospectively evaluation of the medical records. We included the patients aged 18 and above who had central venous catheterization during ICU stay at between January 1, 2022, and December 31, 2022. We excluded the patients who were discharged or died within 48 hours after ICU admission, those with a diagnosis of malignancy, and those with immunodeficiency. Patient data including age, gender, comorbidities, reason for ICU admission, APACHE II score, duration of ICU stay, and 28-day mortality were recorded. Additionally, information regarding the timing of central venous catheter insertion, catheter site, catheter type, administration of blood and TPN through the catheter, presence of catheter infection, causative agents, time of infection development after catheter insertion, and

simultaneous blood culture results were recorded.

Statistical Analysis

We used Statistical Analysis IBM SPSS Statistics 20.0 (IBM SPSS, Chicago) software for statistical analysis of the data obtained in the study. Categorical variables were presented as frequencies and percentages, while continuous variables were presented as median (minimum-maximum). The normal distribution of variables was evaluated with the Kolmogorov-Smirnov test. Non-parametric Mann-Whitney U test was performed for comparisons between groups. We used the chi-square test while evaluating the categorical data. A p-value lower than 0.05 was considered statistically significant.

RESULTS

A total of 169 patients were included in the study, with 99 (58.6%) being male and 70 (41.4%) female. Table 1 presents the demographic data of the patients.

The average age of the patients was 68.83±19.28, with males having an average age of 66.90±18.31 and females 71.55±20.40. Among the patients, 18.9% had no comorbidities, while 81.1% had at least one diagnosed comorbidity. Common comorbidities included hypertension (51.47%), respiratory conditions such as asthma and chronic obstructive pulmonary disease (23.07%), diabetes mellitus (22.48%), neurological conditions such as Alzheimer's

and cerebrovascular disease (21.30%), and cardiac diseases such as coronary artery disease and heart failure (18.34%). The main reasons for ICU admission were respiratory failure (34.3%), COVID-19 (20.7%), and multitrauma (17.2%). The 28-day mortality rate of the patients was 53.8%, with 54.5% in males and 52.9% in females. Central venous catheters were inserted on average 4.17±3.99 days after admission to the ICU. Among the inserted catheters, 56 (33.1%) were femoral, 99 (58.6%) were jugular, and 14 (8.3%) were subclavian. Of the catheters, 91.1% were central venous catheters, while 8.9% were hemodialysis catheters. The evaluation of infection development according to the sites of catheter application is presented in Table 2.

Table 1. Demographic data of the patients

Age (Mean±SD)		
	Male (n=99)	66,90±18,31
	Female (n=70)	71,55±20,40
Length of stay (day)		30,65±27,73
APACHE-II score		17,05±9,31
28 days-mortality		
	Male, n (%)	54 (% 54,5)
	Female, n (%)	37 (% 52,9)
Reason for admission, n (%)		
	Respiratory failure	58 (% 34,3)
	Covid-19	35 (% 20,7)
	Multitrauma	29 (% 17,2)
	Others	47 (% 27,8)
Co-morbidities		
	Hypertension	87 (% 51,47)
	Respiratory disease	39 (% 23,07)
	Diabetes mellitus	38 (% 22,48)
	Neurological diseases	36 (% 21,30)
	Cardiac	31 (% 18,34)
	Others	33 (% 19,52)
	None	32 (% 18,93)

There was no significant difference in the incidence of catheter-related infections based on the sites of application. The average time for infection development after catheter insertion

was 16.00±11.39 days, but it was not significantly different between the catheter sites. Simultaneous blood culture results indicated significant growth of bacteria. However, we couldn't find any significant difference in the comparison of blood culture results based on the catheter sites (Table 3). Furthermore, there was a significantly higher rate of infection development in catheters used for total parenteral nutrition and blood transfusions (Table 3). Regarding the causative agents of catheter infections, Gram-positive cocci (Coagulase-Negative Staphylococci and Staphylococcus spp.) were found in 53.9% of cases, Gram-negative bacilli (Acinetobacter spp., Klebsiella spp., Enterobacter spp., Pseudomonas spp., Proteus mirabilis, E. coli) in

41.2%, and Candida spp. in 0.4%. The causative agents in simultaneous blood cultures were Gram-negative bacilli (51.2%), Gram-positive cocci (43.5%), and Candida spp. (5.1%) (Table 4). The distribution of catheter infection causative agents according to the sites of application is shown in Table 5. Gram-positive cocci (Staphylococcus spp.) were found in 54.5% of femoral catheters, 55.5% of jugular catheters, and 40% of subclavian catheters. In our study, 42.9% of patients who developed catheter infections died within 28 days. Additionally, there was a significantly longer average length of ICU stay among patients who developed catheter infections (Table 3).

Table 2. Comparison of infection development according to the application sites of the catheters

Catheter site	n (%)	Age		Catheter infection			Time of catheter infection		Growth in the blood culture		
		ort±ss	p değeri	Yes (n/%)	No (n/%)	P value	Day (Mean±SD)	p value	Yes (n/%)	No (n/%)	P value
Femoral	56 (%33,1)	72,80 ± 19,89		22 (%39,3)	34 (%60,7)		17,38 ± 11,42		10 (%45,5)	12 (%54,5)	
Jugular	99 (%58,6)	66,83 ± 18,75	0,047*	36 (%36,4)	63 (%63,6)	0,929	15,65 ± 11,83	0,656	25 (%69,4)	11 (%30,6)	0,130
Subclaavian	14 (% 8,3)	67,07 ± 19,45		5 (%35,7)	9 (%64,3)		12,60 ± 8,93		4 (%80,0)	1 (%20,0)	

*p<0,05 statistically significant

Table 3. Evaluation of the relationship between catheter infections and usage patterns

		Catheter infection		
		Yes (n=63)	No (n=106)	P value
TPN	Yes	33 (%52,4)	30 (%47,6)	0,002*
	No	30 (%28,3)	76 (%71,7)	
Hemodialysis	Yes	10 (%15,9)	21 (%19,8)	0,522
	No	53 (%84,1)	85 (%80,2)	
Blood transfusion	Yes	53 (%84,1)	68 (%64,2)	0,005*
	No	10 (%15,9)	38 (%35,8)	
Growth in blood culture	Yes	39 (%61,9)	10 (% 9,4)	0,000*
	No	24 (%38,1)	96 (%90,6)	
Catheter type	Central venous catheter	60 (%95,2)	94 (%88,7)	0,147
	Hemodialysis catheter	3 (%4,8)	12 (%11,3)	
Co-morbidities	No	12 (%19,0)	20 (%18,9)	0,977
	Yes	51 (%81,0)	86 (%81,1)	
Length of stay in ICU		45,03±33,74)	22,11±19,00	0,000*

*p<0,05 statistically significant

Table 4. Microorganisms grown from the catheter culture and the blood culture taken simultaneously

Microorganism	Catheter culture(n/%)	Blood culture (n/%)
Gr (-) bacillus	26 (%41,2)	20 (%51,2)
Klebsiella spp.	9	8
Acinetobacter spp.	7	6
Enterobacter spp.	6	4
Pseudomonas spp.	2	1
Proteus mirabilis	1	1
E.coli	1	
Gr (+) cocci	34 (%53,9)	17 (%43,5)
Stafilokok spp.	23	13
Koagülaz Negatif Stafilakok	11	4
Candida spp.	3 (%0,4)	2 (%5,1)

Table 5. Microorganisms grown in culture according to catheter sites

Microorganisms	Femoral (n/%)	Jugular (n/%)	Subclavian (n/%)
Gr (-) bacillus	9 (%40,9)	15 (%41,6)	2 (%40,0)
Klebsiella spp.	3	5	1
Acinetobacter spp.	3	3	1
Enterobacter spp.	2	4	-
Pseudomonas spp.	-	2	-
Proteus mirabilis	-	1	-
E.coli	1	-	-
Gr (+) cocci	12 (%54,5)	20 (%55,5)	2 (%40,0)
Stafilokok spp.	7	14	2
Koagülaz Negatif Stafilakok	5	6	-
Candida spp.	1 (%4,5)	1(%2,7)	1(%10,0)

DISCUSSION

Catheter-related infections play a significant role among the complications associated with the use of central venous catheters. Central venous catheters are commonly used in the patients who were hospitalized for intensive care/palliative care. In these units, the length of stay for patients is often prolonged. Factors such as not changing the catheter at appropriate intervals, failure to be careful for asepsis-antisepsis precaution during catheter insertion, prolonged duration of catheterization, and ineffective catheter care pose a significant risk for infection (6,7). In a study conducted in the United States, it was stated that approximately 150 million central venous catheters are used each year, and 800,000 catheter-related bloodstream infections are observed. Furthermore, the study found that the attributed mortality rate for these infections ranges from 0-35% (8). In Europe, it has been reported that the rate of bloodstream infections in ICU is 3.7% (1.9/1000 patients), and 43.6% of these cases are attributed to intravenous catheters (5). In a study conducted in Turkey with the participation of 24 centers, catheter-related

bloodstream infection was found to be the most common healthcare-associated infection, with a 30-day mortality rate of around 27% (9). The development of catheter-related infections leads to prolonged hospital stays, increased mortality and morbidity rates and so health costs. In our study, it was observed that the rate of catheter-related infection was 37.2%, and the 28-day mortality rate in those with infection was 42.9%. Furthermore, the length of ICU stay was significantly higher in patients who developed catheter infections compared to those who did not. When looking at the literature, it is evident that our study results are similar to the results in developing countries, indicating that catheter-related infections increase ICU stay and mortality rates. When evaluating catheter-related infections based on the site of insertion, studies have reported varying results, but it is generally stated that the rates are higher in femoral regions (10,11). It has also been found that infections are less common in subclavian catheters compared to jugular and femoral catheters (2,12). In our study, when comparing infection rates based on the application sites, they were similar. The higher likelihood of infection in femoral catheters is often attributed to the flora and contamination of the region in previous studies (10-12). However, the lack of difference, as found in our study, could be attributed to the use of chlorhexidine-impregnated catheter dressings routinely used in our clinic.

The microorganisms isolated in catheter-related infections may vary depending on factors such as the patient's condition, the ICU where they are located, the site of catheter application, and the type of catheter. Studies have generally shown that Gram-positive cocci commonly found in the normal flora at the site of colonization, such as Staphylococcus aureus, Streptococcus spp., Staphylococcus epidermidis, Enterococcus spp., Corynebacterium spp., and Candida spp., are among the causative agents of infection (13,14).

However, recent studies have indicated an increasing frequency of Gram-negative bacteria such as Acinetobacter spp., Klebsiella spp., Pseudomonas spp., and E. coli (15,16). In our study, the most common pathogens were Gram-positive cocci, especially Staph spp. and Coagulase-negative Staphylococci, followed by Gram-negative bacteria, with Acinetobacter spp., Klebsiella spp., and Pseudomonas spp. being prominent within this group. This result suggests that the flora at the site of catheter insertion may contribute to catheter infections, similar with findings in the literature.

Additional risk factors such as the use of total parenteral nutrition (TPN) and duration of catheterization have been mentioned in studies regarding the development of catheter-related infections (2,17). It has been observed that the risk of infection increases by 4-fold for catheter durations between 7-14 days and by up to 5-fold

for durations exceeding 14 days. The same study found an association between the use of TPN and an increased risk of catheter-related infections (17). Similarly, studies have shown that the administration of blood transfusions also increases the incidence of catheter infections (18). In our study, significant increases in infection rates were observed in catheters with TPN infusion and blood transfusion. Additionally, infections occurred on average around the 16th day of catheter insertion, but there was no significant difference in infection development time based on catheter sites.

We can count some limitations for this study. Firstly, we designed the study as a retrospective research. Also, the narrow time interval for data collection and the inability to access all patient data from the hospital information management system are another limiting factors.

CONCLUSION

In conclusion, catheter-related bacteremia is a significant risk factor that increases mortality and morbidity, particularly in critically ill patients. Therefore, paying attention to aseptic-antiseptic conditions during the insertion of central venous catheters in both ICU and palliative care units, effective catheter care, and the use of barrier covers with antibacterial properties will help reduce catheter-related infections. Decreasing the incidence of catheter-related infections

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Investigation of Postgraduate Theses on Using of Web-Based Education in Nursing Education

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Abstract

Objective: This study was conducted to examine the master's and doctoral dissertations investigating the effects of web-based education in the courses conducted in the nursing undergraduate programs of universities in Turkey.

Methods: In this study, the database of the Council of Higher Education (CoHE) National Thesis Center was searched using the keywords "nursing and web" regardless of the year interval. As a result of the screening, 16 postgraduate theses meeting the inclusion criteria were included in the study.

Results: It was determined that the first thesis was published in 2007, and the number of theses increased in 2017 and 2019. It was determined that 37.2% of the theses were at the master's level, 62.5% at the doctoral level and 93.75% of them were experimental/semi-experimental research designs. It was determined that 50% of the theses were published in the field of nursing principles. It has been found that the use of web-based teaching methods in the education of nursing students positively affects students' gaining knowledge and skills.

Conclusion: Although there has been an increase in the number of theses using web-based education in nursing education in recent years, it is recommended that more randomized controlled studies be conducted and that the use of face-to-face education should be supported with web-based education.

Keywords: Education, nursing, graduate, student, technology, thesis, web.

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INTRODUCTION

Nursing education in our country has been continuing its development and change with undergraduate education since 1955 and postgraduate education since 1968 (1). Nursing education requires the use of an education system based on theoretical knowledge and clinical practice, supporting students' cognitive, sensory and psychomotor skills. For this reason, it aims to gain and develop clinical skills and theoretical knowledge in nursing education. Clinical practice training enables the student to integrate theoretical knowledge and practice in healthcare settings and to learn by experience. During the clinical practice education process, the student develops skills in subjects such as professional competence, professionalism, teamwork, communication, critical thinking, and critical decision-making (2).

Nursing education is affected by technological changes in the world, new-generation student profiles, and orientation differences (1). Today, graduates of nursing departments of universities are expected to have many technological competencies. The use of technologies, including computers, phones and tablets, digital communication, professional documents, data processing, and computer software necessary to create multimedia presentations, is in the field of duty of nurses today (3). There are many problems in the nursing education process in our country, such as the excess number of students, the inadequacy of the number of teaching staff per student, the lack of classrooms and equipment, and the inadequacy of laboratory facilities (4). To develop solutions to these problems, different education systems have been started to be used in nursing education by making use of the developments in the field of instructional technologies (2).

One of the most important technologies used in education is web-based education (5). Web-based education is learning supported by multimedia applications such as text, motion pictures, graphics, sound, animation, and video, where educator-student-lesson interaction is ensured by using computer networks, individuals in the same or different environments are connected to each other by computer networks and share information and documents environments (6). Web-based education meets the educational needs of individuals whose ages, education levels, working conditions, interests, and abilities are very different and who have educational disabilities due to geographical conditions. In addition, since this education is based on self-learning, it supports the development of decision-making and problem-solving skills of individuals, who leave the responsibility of learning to the individual (5). However, the lack of physical interaction with the instructor, the inability to receive immediate feedback from

the teacher, the lack of motivation, and social isolation are important disadvantages (7).

The basic competencies of nursing students are cognitive (knowledge), affective (attitudes and behaviors), and psychomotor (skills) learning areas (8). Studies have reported positive effects of web-based education on cognitive (9-11) and psychomotor learning in nursing education (12-14). Problem-based learning sessions can be carried out on cases by using technological methods in nursing education. It is also used to develop skills such as critical thinking and clinical decision-making. Such applications allow the student to repeat as much as they want, help them learn the skill permanently, and enable them to see the result of their action thanks to computer software (3).

There are many new applications for web-based education such as virtual reality technology, virtual classrooms, integrated E-learning systems, distance mobile education, three-dimensional virtual campus application, distance education with Internet Protocol Television (IPTV) technology, and cloud computing Technologies (15). CliniSpace, Digital Clinical Experience, vSim for Nursing are among the web-based systems used in nursing training (3). In the design of web-based educational environments, knowing the student's learning styles and ensuring the consistency of the environments with their learning styles are important in terms of

ensuring the permanence of learning and increasing academic success (5).

In our country, no study has been found in which postgraduate theses are made by using web-based education approaches in nursing programs that provide education at the undergraduate level. This study was conducted to examine the postgraduate theses made using web-based education in undergraduate nursing programs in Turkey.

METHODS

This study was conducted as a retrospective descriptive study. In the research, postgraduate theses made without year intervals were scanned using the National Thesis Center database of the CoHE. The keywords "nursing and web" were used while scanning. As a result of the scanning, 121 doctorate and master's theses made between 2007-2022 were reached. As a result of examining the theses in chronological order, 94 theses that were made in the field of nursing but whose participants were not nursing undergraduate program students and 11 theses that were not from the field of nursing were excluded from the study. Then, in the Nursing Departments/Programs, a total of 16 theses, including master's and doctoral theses, related to web-based education applied to nursing undergraduate program students, were included in the scope of the study.

The data were summarized in a form developed by the researchers as the author of

the thesis, publication year, study type, purpose, sample size, and results. The literature review was carried out between August and September 2022.

The inclusion criteria for the study are;

• Access in full text,

• In the field of nursing, it has been done to nursing students,

• Using web-based-supported education as a method.

Data Analysis

Analysis of data was used descriptive statistics including frequency and percentage.

RESULTS

16 postgraduate theses that met the inclusion criteria were included in this study. It was determined that there were a total of 1,412 participants in the theses included in the research, 6 of them were master's theses and 10 of them were doctoral theses (Table 1).

Table 1. Distribution of thesis types (n=16)

Thesis Type	n	%
Master's thesis	6	37.5
Doctoral thesis	10	62.5

It was determined that the first thesis on web-based education was published in 2007, and the most published years were 2017 (n=4) and 2019 (n=4), (Table 2).

It was determined that the theses were descriptive and methodological (n=1), experimental/semi-experimental (n=15) according to the research method (Table 3).

Table 2. Distribution of Theses According to Publication Years (n=16)

Publication Year	n	%
2007	1	6.25
2011	1	6.25
2013	2	12.5
2017	4	25.0
2018	1	6.25
2019	4	25.0
2021	1	6.25
2022	2	12.5

Table 3. Distribution of Theses according to Research Method (n=16)

Research Method	n	%
Descriptive and methodological	1	6.25
Experimental/Semi-experimental	15	93.75

When the departments/programs in which the theses were made were examined, it was determined that half of the theses (n=8) were made in the nursing principles department (Table 4).

Table 4. Distribution of Theses by Department/Programc(n=16)

Department/Program	n	%
Nursing Education	1	6.25
Fundamentals of Nursing	8	50.00
Pediatric Nursing	4	25.00
Surgical Nursing	2	12.50
Obstetric and Women's Diseases Nursing	1	6.25

The author, publication year, purpose, type, sample size and results of the theses included in the study are given in Table 5.

When the results of the theses are examined; The aim of the descriptive and methodological study conducted with the participation of 167 students was the preparation/development and implementation of the "Patient Education" course in nursing education in line with the

"Mixed Design Model" with the web-based distance education method and its evaluation in line with the student's opinions. In the study, students' opinions about the patient education course prepared with the web-based method were generally positive. It was found that the difference between the students' self-study habit and their total point average from the Information Form II was highly significant and this difference was in favor of the students who could study by themselves (16).

In the quasi-experimental doctoral thesis conducted by Akdemir with the participation of 60 nursing students, it was determined that the web-based education applied in addition to the demonstration method had a positive effect on the skill education of nursing students (17).

In the experimental type doctoral thesis conducted to evaluate the effect of web-assisted teaching on the learning of bladder catheterization by nursing students, it was found that the knowledge and skill averages of the experimental group students were higher than the average points of the control group students (18).

Karabağ Aydın found that the use of a web-based teaching method increased students' ability to calculate drug doses in a pretest-posttest comparative thesis study (19).

In the experimental designed doctoral thesis, which aimed to determine the effect of web-based education and nursing approach education in multimodal analgesia on the knowledge and practice skills of the students, it was found that the web-based teaching method, which was applied in addition to the in-class face-to-face education, was effective in helping students gain nursing skills for pain (20).

In the quasi-experimental type doctoral thesis conducted to examine the effect of web-based education given to pediatric nursing interns on the self-confidence and anxiety of pediatric nursing interns in their clinical decision-making skills, it was found that the application of the web-based education program was effective in increasing the self-confidence and lowering the anxiety levels in the clinical decision-making of the nursing students (21).

In the master's thesis conducted by Öztürk using the pretest-posttest control group design, it was found that web-assisted teaching is a more effective method for the drug dose calculation skills of nursing students compared to the traditional narrative (22).

In the master's thesis made by Erol, support was provided by using web-based training videos in addition to the classical classroom training and demonstration application in the education of students. The use of this method increased the students' ability to administer intramuscular injections. In addition, the satisfaction level of the students who applied the web-assisted education method was higher (23).

It was determined that the hypermedia method in nursing education has a positive effect on nutrition education through a nasogastric tube in the randomized controlled type doctoral thesis made by Turac (24).

It was found that web-based nursing process teaching affected students' ability to prepare a patient care plan with the nursing process approach in the quasi-experimental designed doctoral thesis conducted by Basit (25).

In the quasi-experimental designed master's thesis comparing the effects of web-supported education and peer education on the knowledge and skills of nursing students regarding stoma care, it was observed that the knowledge test mean scores of both groups increased significantly at the end of the training. The increase in knowledge scores was similar in the two groups. There was no statistically significant difference between the skill point averages of the groups (26).

It was found that web-based pain management education in children was effective in increasing the knowledge scores of nursing students in the pretest-posttest quasi-experimental design doctoral thesis conducted by Aydın (27).

It aimed to examine the effects of the education method based on the web-based video model method on the skill practices of Gynecology and Diseases Nursing, the satisfaction and the anxiety levels of the students before and after the skill practice in the quasi-experimental doctoral thesis made by Kirlek (28). It was determined that the education method based on the web-based video model method positively affected the nursing students' learning and practice of clinical skills in the pregnant and puerperal women examination.

It was aimed to eliminate the lack of knowledge of student nurses on the prevention of infection in pediatric clinics and to evaluate the effectiveness of the web-based infection prevention education program in the quasi-experimental type of master's thesis made by Dernek (29). It was found that the infection prevention education given to nursing students increased their knowledge level of the students.

It was found that web-based simulation had a limited effect on the development of nursing students' clinical decision-making, while it had a significant effect on the development of triage practices in the quasi-experimental master's thesis conducted by Demir (30).

In the master's thesis conducted by Yıldırım, using a prospective randomized controlled pre-test-post-test control group design, the effect of web-assisted instruction on pediatric drug dose calculation on the knowledge level of nursing students was examined. In the study, only traditional teaching was applied to the students in the control group, and web-supported teaching was applied to the students in the intervention group in addition to the traditional teaching. It was found that the post-test scores

of the students in the intervention group increased twice, but there was no significant increase in the control group. In addition, there was a statistically significant difference between the number of students access to web-supported teaching and their post-test mean scores (31).

DISCUSSION

In this study, 16 postgraduate thesis studies on the use of web-based education in undergraduate nursing students of universities in Turkey were examined. It is seen that the first thesis study was done in 2007 and most of the theses (62.5%) were doctoral theses, and the number of theses increased in 2017 and 2019. Web-based education requires the educator and student to have up-to-date information on technology use and to provide adequate infrastructure and technical equipment for students' access. Web-based education should be integrated into student education, and course content and course materials should be created. In addition to these, it is thought that the number of theses made in this field is limited due to the thought that nursing education requires intensive clinical practice, the use of technology in education has not yet become widespread enough, it has not been adopted, and due to economic inadequacies. Due to the COVID-19 pandemic, there have been significant changes in the field of education, as in many other fields. To control the spread of the coronavirus, many educational institutions

have entered the process of ensuring the continuity of education with the distance education method (32). As a necessity of this process, educators and students have experienced web-based education. Thanks to this experience, it is predicted that the method will be adopted more easily by the users, its use will become widespread and the studies in this field will increase.

When the thesis studies were evaluated according to their types, it was seen that only one of the theses was descriptive and methodological, while the other theses were experimental/semi-experimental. In three of the experimental/semi-experimental studies, web-based education was applied to a single group. While thesis studies in the field of nursing are mostly descriptive at the master's level, they are mostly experimental/semi-experimental at the doctoral level. The fact that rate of studies using experimental/semi-experimental methods is important in terms of evaluating the effectiveness of web-based education by making comparisons.

It was determined that half of the theses were made in the department of nursing principles when the departments/programs in which the theses are made are examined. It is seen that web-based education, which has a supportive and complementary role in nursing education, is suitable for application by other departments/programs. However, it is thought that studies could not be carried out in other

departments/programs due to the lack of information about technology use, infrastructure, and economic inadequacies.

In the results of the theses, it is seen that the use of web-based teaching methods in the education of nursing students has a positive effect on the students' gaining knowledge and skills. It is reported that the use of web-based learning in nursing undergraduate programs by integrating it into education creates a potential for students to better develop their clinical skills, pose less risk to patients, and provide a better quality of care (14). In the literature, studies are reporting the positive effects of web-based education (11, 14, 33, 34) as well as studies reporting negative opinions of students (35, 36). Jang et al. prepared a website for students to gain the ability to interpret electrocardiography on their own, and students had the opportunity to access the prepared course content from anywhere they wanted and to repeat the course content. As a result of the research, it was determined that there was an increase in the learning motivation and satisfaction of the students (33). Virtual and traditional teaching methods were applied in the training for nursing students to interpret cardiac arrhythmia, and the groups were compared. In the study, it was found that there was no difference between the groups before the training, and there were significant differences between the groups after the training (11). It has been found that the web-based learning applied to nursing students on insertion of a urinary catheter, insertion of a nasogastric tube, taking a blood sample, and the insertion of a peripheral intravenous line effectively supports the clinical learning process of the students by providing virtual visual support, thanks to its ease of use and unlimited access. (14). It was determined that the clinical virtual simulation used in the education of Portuguese nursing students improved the retention of knowledge and the initial clinical reasoning over time (2 months) without affecting the overall perception of efficiency and improved student satisfaction with learning (34). In another study, students' opinions about the web-based patient education course given to nursing students were investigated. It was determined that the students had positive opinions about the design, method, and achievements of the course. In addition, students stated that it is appropriate to give web-based theoretical courses without application (6). In another study investigating student views on a web-based course, it was determined that students predominantly had a converging and assimilating learning style. In addition, it was determined that the students generally had positive opinions about the layout, visuals, typography, color, moving images, navigation and orientation, content, and functionality dimensions of the course design (5).

In another study, contrary to these findings, it was found that there was no difference in a

study comparing face-to-face education and web-based education in nursing students in terms of self-learning ability, clinical reasoning ability, and satisfaction (35). The feedback of nursing students on web-based distance education applied during the COVID-19 process was evaluated. It was determined that 84.4% of the students stated that web-based distance education was not as effective as face-to-face education, 49.9% of them could not communicate easily with the instructors, and 60.7% of them stated that web-based education allowed them to learn at their own pace (36). In another study in which medical and nursing students participated in India, it was determined that the majority of students had negative opinions about the lack of interaction and focus, practical learning, teaching content, and technological infrastructure regarding distance preclinical and clinical teaching applied during the COVID-19 process (7). In the pandemic situation, distance education practice is seen as the best way to be applied in education, but it does not seem possible to conduct the entire education on a web basis due to its limited effectiveness in teaching nursing courses that require clinical/field practice. However, it is thought that effective results will be obtained with the use of web-based education as a supportive and complementary method to face-to-face education.

Limitations

Limitations of this study that are the theses in the database of the National Thesis Center of the CoHE and made in the nursing department were included in the study.

CONCLUSION

In this study, postgraduate theses on the use of web-based-supported education in the nursing undergraduate programs of universities were examined in the nursing education process. As a result, it has been determined that most of the theses are doctoral theses and the studies have increased significantly in recent years. It was determined that the majority of theses were made in the experimental/semi-experimental type, and half of the theses were in the field of nursing principles. In all of the theses included in the study, it was determined that the support of face-to-face education with web-based education had a positive effect on the development of nursing knowledge and skills of students.

An important part of nursing education consists of clinical practices. It is not possible to carry out such a training program entirely with distance education. It is predicted that supporting some courses, which are carried out in the form of direct transfer of theoretical knowledge in the classroom, especially in classrooms with a large number of students, with web-based education will contribute positively to the acquisition of knowledge and skills by students.

These results suggest that the thesis studies on the use of web-based education in nursing undergraduate programs should be carried out in all nursing departments, and in-class education should be supported with web-based education, considering the individual differences and learning styles of the students. In addition, it is recommended to encourage nursing educators to use this method and to conduct more experimental research using web-based education.

Table 5. Characteristics of the Methods Used in Graduate Theses

Authors (Year)	Type	Aim	Method	Number of Samples	Conclusion
Senyuva, (16)	Doctoral thesis	Preparation, development, implementation, and evaluation of the "Patient Education" course in nursing education as an example based on the web-based distance education method in line with the "Mixed Design Model", evaluation in line with the student's opinions and creating a resource for related researches.	A descriptive and methodological study	Sample of the study: 167	It was determined that the student's opinions about the Patient Education course prepared with the web-based method were generally positive. It was found that the difference between the students' self-study habit and their total point average from Information Form II was highly significant and this difference was in favor of the students who could study by themselves.
Akdemir, (17)	Doctoral thesis	To examine the effect of web-based learning applied to nursing students in addition to the demonstration method of basic nursing skills on the student's basic nursing skill level	Semi-experimental study	Sample of the study: 60	It has been found that the web-based education applied in addition to the demonstration method has a positive effect on the skill training of nursing students.
Ozturk, (18)	Doctoral thesis	To evaluate the effect of web-based instruction on nursing students' learning about bladder catheterization	Experimental study	Total: 111 Experimental group: 59 Control group: 52	It was found that the knowledge and skill averages of the experimental group students were higher than the averages of the control group students with the web-based teaching application.
Karabag Aydin, (19)	Doctoral thesis	To examine the effects of web-based instruction on nursing students' arithmetic and drug dose calculation skills	Pre-test – post-test comparative study	Sample group: 63	It was determined that the use of web-based teaching methods increased students' arithmetic and drug dose calculation skills.
Yılmaz Senyuz, (20)	Doctoral thesis	To determine the effect of nursing approach training in multimodal analgesia given with web-based education on students' knowledge and practice skills	Experimental study	Total: 69 Experimental group:34 Control group 35	It has been found that the web-based teaching method applied in addition to in-class face-to-face education is effective in helping students gain nursing skills for pain.
Bektas, (21)	Doctoral thesis	To examine the effects of web-based instruction on the self-confidence and anxiety levels of pediatric nursing interns in clinical decision-making.	Semi-experimental study	Total: 61 Intervention group:31 Control group: 30	It was found that the application of the web-supported education program was effective in increasing the self-confidence level and reducing the anxiety levels of nursing students in clinical decision-making.
Ozturk, (22)	Master's thesis	To examine the effect of web-supported instruction on nursing students' drug dose calculation skills	Pretest-post-test with the control group study	Total: 95 Experimental group:50 Control group: 45	It has been found that web-assisted teaching is a more effective method for nursing students' drug dose calculation skills compared to the traditional narrative.
Erol, (23)	Master's thesis	To examine the effect of the web-supported instruction applied on the intramuscular injection application of nursing students on the students' learning of intramuscular injection.	Semi-experimental study	Total: 66 Experimental group:33 Control group: 33	In addition to the classical classroom training and demonstration practice, it was found that the student's ability to administer intramuscular injections increased as a result of the support of the students via the web using educational videos. Also, it was determined that the students who applied the web-assisted education method had higher satisfaction levels from the teaching method.

Table 5. Characteristics of the Methods Used in Graduate Theses **(Continued)**

Authors (Year)	Type	Aim	Method	Number of Samples	Conclusion
Turac, (24)	Doctoral thesis	To determine the effect of the education given with the hypermedia method on the students' learning of the nutrition application through the nasogastric tube	Randomized controlled	Total: 60 Experimental group:30 Control group: 30	It has been determined that the hypermedia method used in nursing education has a positive effect on the teaching of nasogastric tube feeding practice.
Basit, (25)	Doctoral thesis	To examine the effect of web-based nursing process teaching on senior nursing students' ability to prepare a care plan	Semi-experimental study	Total: 131 Intervention group:64 Control group: 67	It has been found that web-based nursing process teaching has an effect on the ability of students to prepare a patient care plan with the nursing process approach.
Kaplan, (26)	Master's thesis	To compare the effects of web-based instruction and peer education on the knowledge and skills of nursing students regarding stoma care	Semi-experimental study	Total: 67 Web-based education group:33 Peer education group:34	At the end of the training, it was observed that the knowledge test mean scores of both groups increased significantly. It was determined that this increase in knowledge scores was similar in the two groups. It was determined that there was no statistically significant difference between the skill point averages of the groups.
Aydin, (27)	Doctoral thesis	To evaluate the effectiveness of the web-based children's pain management training program given to nursing students	Pretest-posttest quasi-experimental design	Total: 94 Intervention group:45 Control group: 39	It has been determined that web-based children's pain management education is effective in increasing the knowledge scores of nursing students.
Kirlek, (28)	Doctoral thesis	To examine the effects of the web-based video model method on Gynecology Nursing skills practices, students' satisfaction levels, and students' anxiety levels before and after skill practice.	Semi-experimental design	Total: 80 Intervention group:40 Control group: 40	It has been determined that the web-based video model training method has a positive effect on the learning and practice of nursing students' clinical skills in pregnant women and puerperal examination.
Dernek, (29)	Master's thesis	To eliminate the lack of knowledge of student nurses on the prevention of infection in pediatric clinics and to evaluate the effectiveness of the web-based infection prevention education program	The pretest-posttest semi-experimental	Total: 35 Intervention group:19 Control group: 16	It was found that the web-based education given to nursing students increased the knowledge level of students on the prevention of infection.
Demir, (30)	Master's thesis	To examine the effect of web-based simulation on the development of triage practice and decision-making skills of nursing students	Semi-experimental design	Total 169 Intervention group:89 Control group: 80	It has been determined found that web-based simulation has a limited effect on the development of nursing students' clinical decision-making, while it has a significant effect on the development of triage practices.
Yildirim, (31)	Master's thesis	To examine the effect of web-assisted teaching given to nursing students on the level of knowledge about pediatric drug dose calculation.	A prospective randomized controlled design with the pretest-posttest control group	Total: 84 Intervention group:42 Control group: 42	It was determined that web-based instruction doubled the post-test scores of the students in the intervention group, but there was no significant increase in the control group. In addition, it was found that there was a statistically significant difference between the number of students entering web-assisted teaching and their post-test mean scores.

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Investigation of the Effectiveness of Cl-Amidine on Wound Healing: an in Vitro Study

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Abstract

Objective: Peptidylarginine deiminases (PADs) are enzymes converting the arginine to citrulline. They play a role in embryogenesis and cell signaling activities. But excessive or dysregulated PAD levels were determined to be associated with disorders and to increase in many diseases. It has been shown that Chloramidine (Cl-amidine) used as a PAD inhibitor suppresses increased PAD activity and shows anti-cancer, anti-inflammatory and antioxidant activities. Anti-inflammatory and antioxidant properties play an important role in wound healing. In this study, the possible efficacy of Cl-amidine on wound healing in the keratinocyte cell line was investigated by considering these parameters.

Methods: Cell proliferation evaluations of Cl-amidine concentrations (500, 125, 31.25 and 7.81 µM) determined according to the results of MTT method on HaCaT keratinocyte cells were performed using Real-Time Cell Analysis System (RTCA DP). COL1A1 mRNA expression levels were analyzed by RT (Real Time)-PCR (Polymerase Chain Reaction) method at the concentrations where proliferation was achieved (125, 31.25 µM). Migration effects of Cl-amidine on cells were evaluated by performing scratch analysis. MTT results were statistically analyzed with one-way ANOVA and Tukey test, and $p < 0.05$ was accepted as significant. RTCA DP and RT-PCR results were evaluated using device software programs.

Results: In the study, it was found that certain concentrations of Cl-amidine had a proliferative effect on HaCaT keratinocyte cells. It was determined that Cl-amidine increased the amount of type 1 collagen, which is an important parameter for wound healing, by RT-PCR method. In addition, according to scratch analysis, it was detected that it positively affected cell migration in relation to wound closure.

Conclusion: This research shows that Cl-amidine may have a significant potential for wound healing.

Key words: Peptidyl arginine deiminase (PAD), Cl-amidine, wound healing, HaCat keratinocyte cell line

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INTRODUCTION

Peptidyl (protein) arginine deaminases (PADs) provide the conversion of peptidyl arginine to peptidyl citrulline in the presence of calcium with posttranslational modification (1). Increased PAD activity has been observed in many diseases, including rheumatoid arthritis, multiple sclerosis, ulcerative colitis, lupus, Alzheimer's, Parkinson's, and many cancers (2-5). There are five identified types of PAD in other mammals, including humans: PAD1, PAD2, PAD3, PAD4, and PAD6 (6-8). In animal experimental models of diseases with high PAD values, it has been shown that PAD inhibitor agents reduce the severity of disease symptoms. Cl-amidine (Chlor-amidine), which is a PAD inhibitory substance, suppresses all PAD activities (9).

It has been shown that PAD1, PAD 2 and PAD3 are expressed in epidermis cells. Although PAD1 is found in all keratinocyte layers of the epidermis, it increases from the basal to the granular layer. PAD2 is expressed in all keratinocytes, least in basal cells and most in granular layer cells. PAD3 is specifically expressed by granular keratinocytes. Cl-amidine treatment in human primary keratinocyte cell culture causes a dose-dependent reduction in the total amount of deiminated proteins (10).

Wound is a term that refers to the deterioration of skin epithelial integrity due to surgical procedure or trauma (11). Wound healing requires the formation of four sequential stages to restore the histological and functional properties of the skin: hemostasis, inflammation, proliferation and remodeling. The healthy functioning of these stages is essential for optimal wound healing. Among these, re-epithelialization and fibroblast activity play an important role in the proliferation stage, where cellular activity is dominant (12,13).

In our study, it was aimed to investigate the wound healing activity of Cl-amidine, a PAD inhibitor, in human HaCaT keratinocyte cells.

METHODS

Cell Culture and Treatment

HaCaT cells, human skin keratinocytes, were supplied by Professor Dr. Arzu Onay Besikci, Ankara University. HaCaT cells were grown in DMEM medium supplemented with 10 % fetal bovine serum (FBS) and 1 % penicillin/streptomycin at 37ºC in a humidified incubator with a 5 % CO_2 atmosphere. Cl-amidine was dissolved in dimethyl sulfoxide (DMSO) as a stock solution.

Determination of Cytotoxicity by MTT Method

MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) is a tetrazolium salt that specifically binds to the succinate-dehydrogenase enzyme in the mitochondria of living cells and converts to water-insoluble formazan salts. The amount of formazan formed directly indicates metabolically active (live) cells in culture (14).

HaCat cells were seeded in 96-well plates at 10,000 cells per well. Different concentrations of Cl-amidine (3.90, 7.81, 15.625, 31.25, 62.5, 125, 250 and 500 µM) were applied to HaCat cells. At the end of 48-hour incubation period, it was incubated with 100 µl MTT for 3 hours. At the end of the incubation, absorbances were read at a wavelength of 540 nm in an ELISA reader device, with 8 wells in each group. Experiments were performed as 3 independent repetitions. The results were calculated according to the viability formula and determined as % viability.

Determination of HaCaT Cell Proliferation in Real-Time Cell Analysis System (RTCA DP)

RTCA DP detects cell viability by measuring electrical impedance and creates real-time data by continuing this measurement at desired intervals. The values received by the system from the E-plate are calculated as the unitless 'cell index (CI)' value accepted in the literature. This value increases in parallel with the electrical response as the cells cover the bottom of the E-plate and multiply (15). Cl-amidine concentrations (7.81, 31.25, 125 and 500 µM)

applied to HaCat cells in Real-Time Cell Analysis System (RTCA DP) were determined according to MTT method. HaCat cells were seeded into each well of E-plate as 10,000 cells in 100 µl of medium. After 24 hours, concentrations of Cl-amidine were applied to E-plate wells in 100 µl of medium. The results were analyzed using RTCA DP Software 1.2.1 program and IC_{50} values were determined in the same program.

Wound healing with scratch assay

In order to determine the effects of Cl-amidine on wound healing, HaCaT keratinocyte cells were seeded in 6-well plates as $1x10^6$ cells and waited for 24 hours for adhesion. Then, for creating an *in vitro* wound model with HaCaT keratinocyte cells reaching approximately 90% density, a linear opening of approximately 1 mm was created using a 200 ml sterile pipette tip and the wells were washed with PBS. This opening was accepted at 0 hour and photographed. Cl-amidine concentrations (31.25 and 125 µM), which provided proliferation more than the control group according to RTCA DP proliferation results, were applied to determine cell migration by scratch wound healing method. After 48 hours of incubation, the effects of Cl-amidine concentrations on the amount of closure of the wounds were visualized under an inverted light microscope (Leica DM 300 invert microscope) (16).

Determination of COL1A1 mRNA Expression Levels by Real-time Polymerase Chain Reaction Method

RNA was isolated from HaCaT cells treated with Cl-amidine concentrations (31.25 ve 125 µM). Total RNA isolation was performed on MagNA Pure LC 2.0 system (Roche, Germany). From each RNA population, 500 ng total RNA was used for cDNA synthesis (Transcriptor High Fidelity cDNA Synthesis Kit).

Quantitative real time polymerase chain reaction (qRT-PCR) was used to assess mRNA levels of collagen type I alpha 1 chain (*COL1A1*, Assay ID;100861, Roche) gene in relation to wound healing. As an internal positive control, glucose-6-phosphate dehydrogenase (G6PD) mRNA levels were used. Results were analysed by advanced relative quantification with LightCycler® 480 System's software (version 1.5.0.39).

Statistical Analysis

Using GraphPad Prism 6.0 analysis program, % cell viability graphs of the groups compared to the control were drawn and statistical analyzes were realized. The obtained data were analyzed by applying one-way ANOVA and post-hoc Tukey tests. Statistical significance values were evaluated as; $p > 0.05$ no difference, $p < 0.5*$, $p < 0.01**$, $p < 0.001***$ and $p < 0.0001****$.

RESULTS

Evaluation of Cytotoxic Effects of Cl-amidine in HaCaT Keratinocyte Cells by MTT Method

The cytotoxic effects of Cl-amidine in HaCaT cells determined by MTT method using 3.90, 7.81, 15.625, 31.25, 62.5, 125, 250 and 500 µM concentrations are shown in **Figure 1**. When MTT results were evaluated, it was determined that Cl-amidine decreased cell viability in 250 and 500 µM concentrations in HaCaT cells compared to the control group.
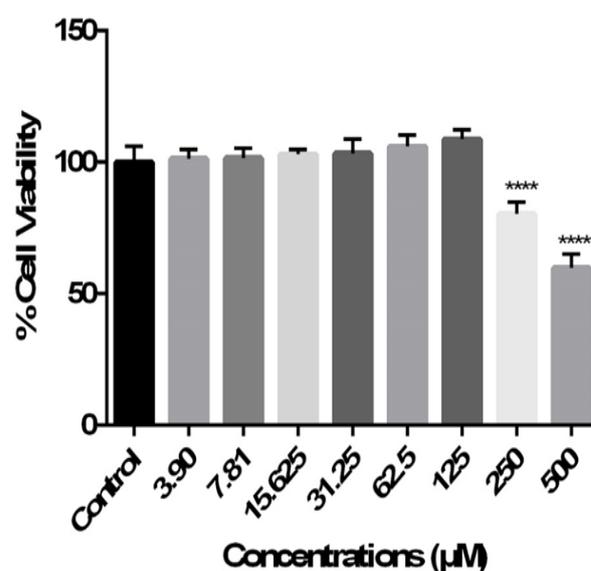
Figure 1. Viability (%) values of Cl-amidine concentrations calculated according to MTT Method in HaCat cells at 48 hours and statistical evaluation (Mean±SD, solvent control: % 0.1 DMSO, n=8)

Evaluation of Cell Proliferation Using Real Time Cell Analysis System (RTCA DP)

Proliferation and IC50 concentration determination studies in HaCaT cells at 7.81, 31.25, 125 and 500 µM concentrations of Cl-amidine (determined according to MTT method) were performed in Real-Time Cell Analysis System (RTCA-DP). According to the results, it was determined that 31.25 and 125 µM concentrations of Cl-amidine had an increasing effect on HaCat cell proliferation compared to

the control group (Figure 2). In addition, IC50 concentration of Cl-amidine in HaCaT cells at 48 hours was determined and calculated as 432 µM using the RTCA DP system (Figure 3).
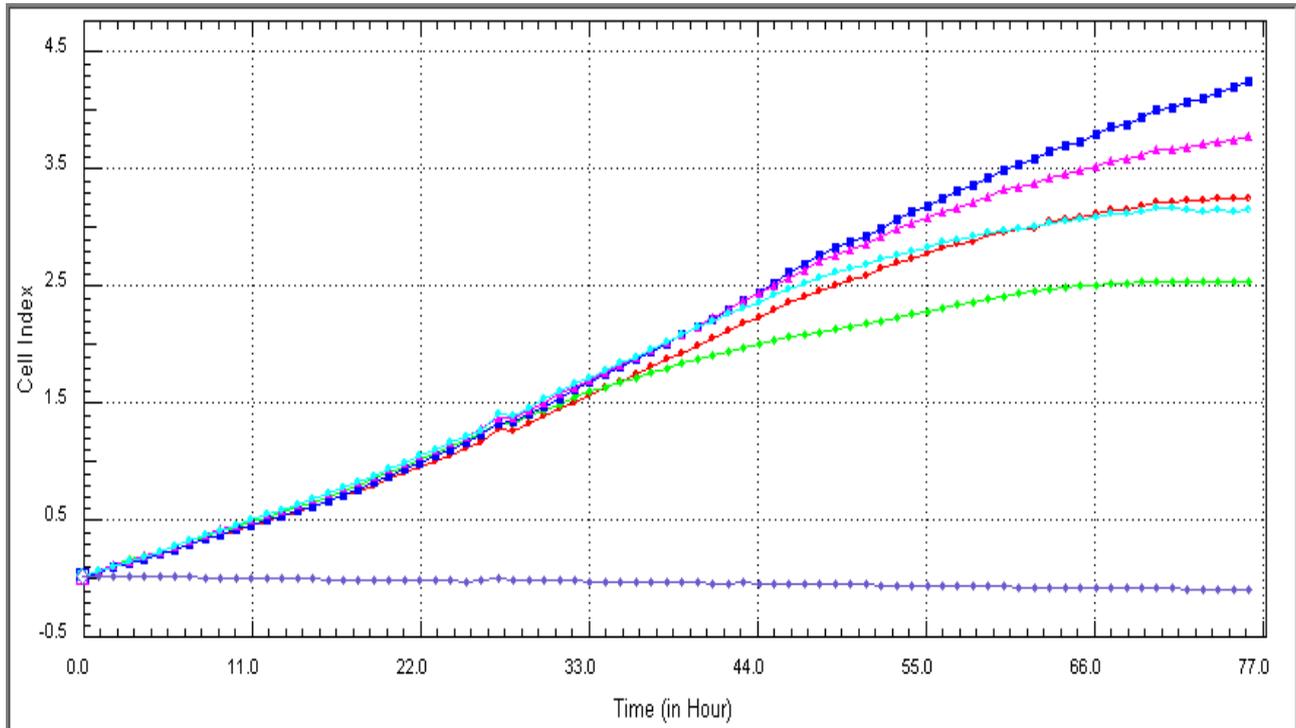
Figure 2. 48-hour proliferative effects of Cl-amidine in HaCaT cells and slope graph in RTCA-DP system (n=6, mean± standard deviation).
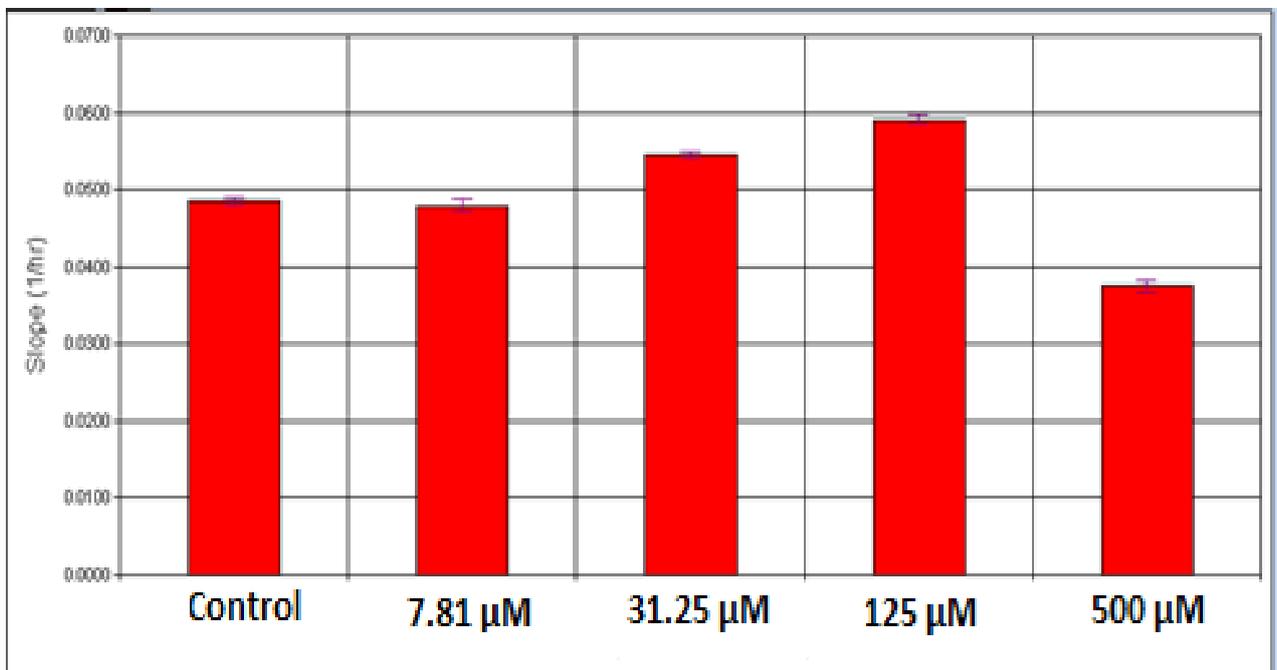
Figure 3. IC50 value of Cl-amidine on HaCaT keratinocyte cell line at 48 hours in Real-Time Cell Analysis System (IC50: 432 µM).

Assessment of Wound Healing

The growth and migration effects of Cl-amidine on HaCaT cells were investigated using the strach wound healing method.

The ability of cells to migrate in the wound area is another important parameter for wound healing. According to the results of the scratch wound healing method performed in vitro for this purpose, it was determined that Cl-amidine increased HaCaT cell migration at both 31.25 and 125 µM concentrations. It was determined that this effect was higher especially at the concentration of 31.25 µM (Figure 4).
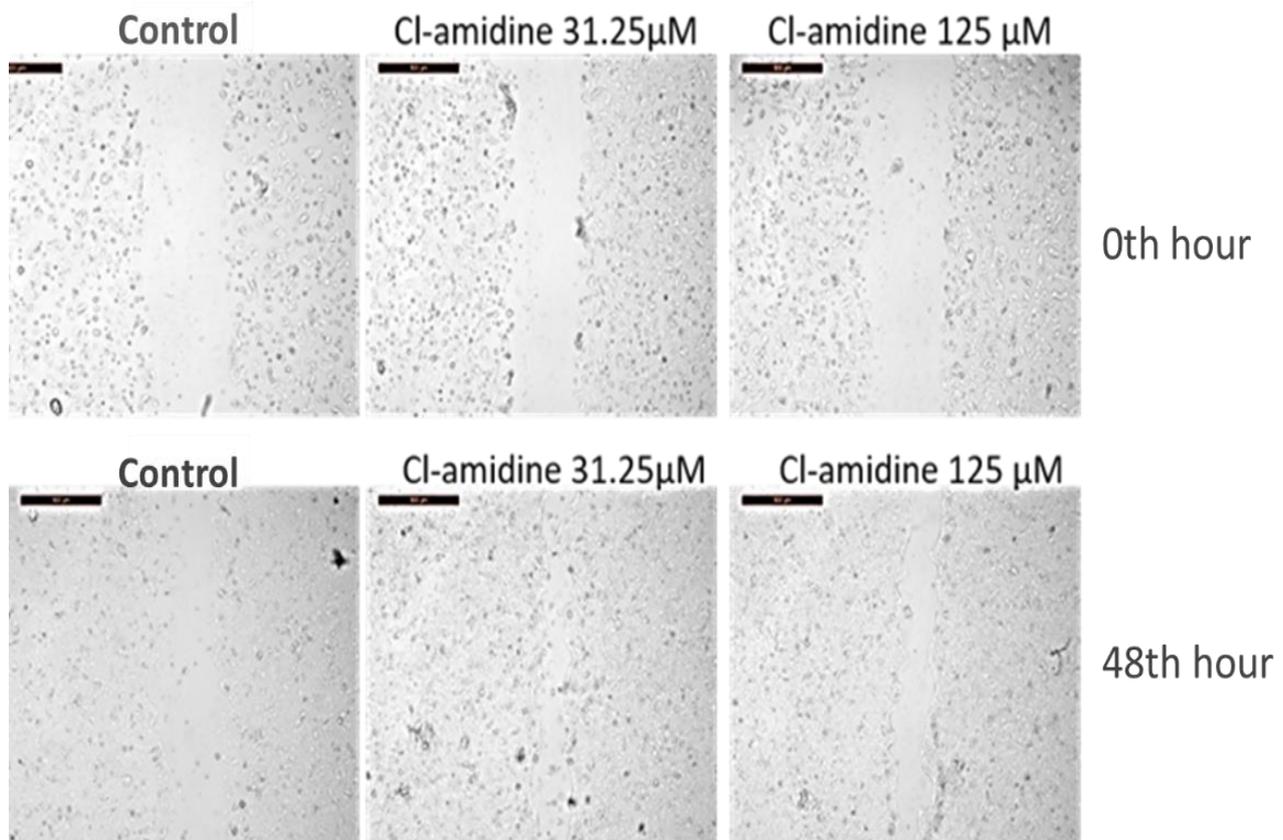
Figure 4. Light microscope images of HaCAT cell migration determined by scratch wound healing method (10X)

Evaluation of *COL1A1* mRNA Expression Levels by RT-PCR Analysis

The effects of different concentrations of Cl-amidine (31.25 and 125 µM) on *COL1A1* mRNA expression levels in HaCaT cells were determined by RT-PCR method. According to these results, it was determined that *COL1A1* mRNA level, which is an important marker in wound healing, was approximately twice (1.74) higher than the control, especially at 31.25 µM concentration (**Table 1** and **Figure 5**).

Table 1. Target/reference ratios and normalized values of *COL1A1* gene in HaCaT cells incubated for 48 hours with Cl-amidine concentrations

Sample Name	Target Name		Tgt Cp	Ref Cp	Ratios	
	Target	Reference	Mean	Mean	Tgt/Ref	Norm
Control	*COL1A1*	G6PD	32.05	30.61	0.3688	**1.000**
Cl-amidine 125 μM	*COL1A1*	G6PD	31.74	29.71	0.2449	0.6642
Cl-amidine 31 μM	*COL1A1*	G6PD	31.26	30.62	0.6432	**1.744**
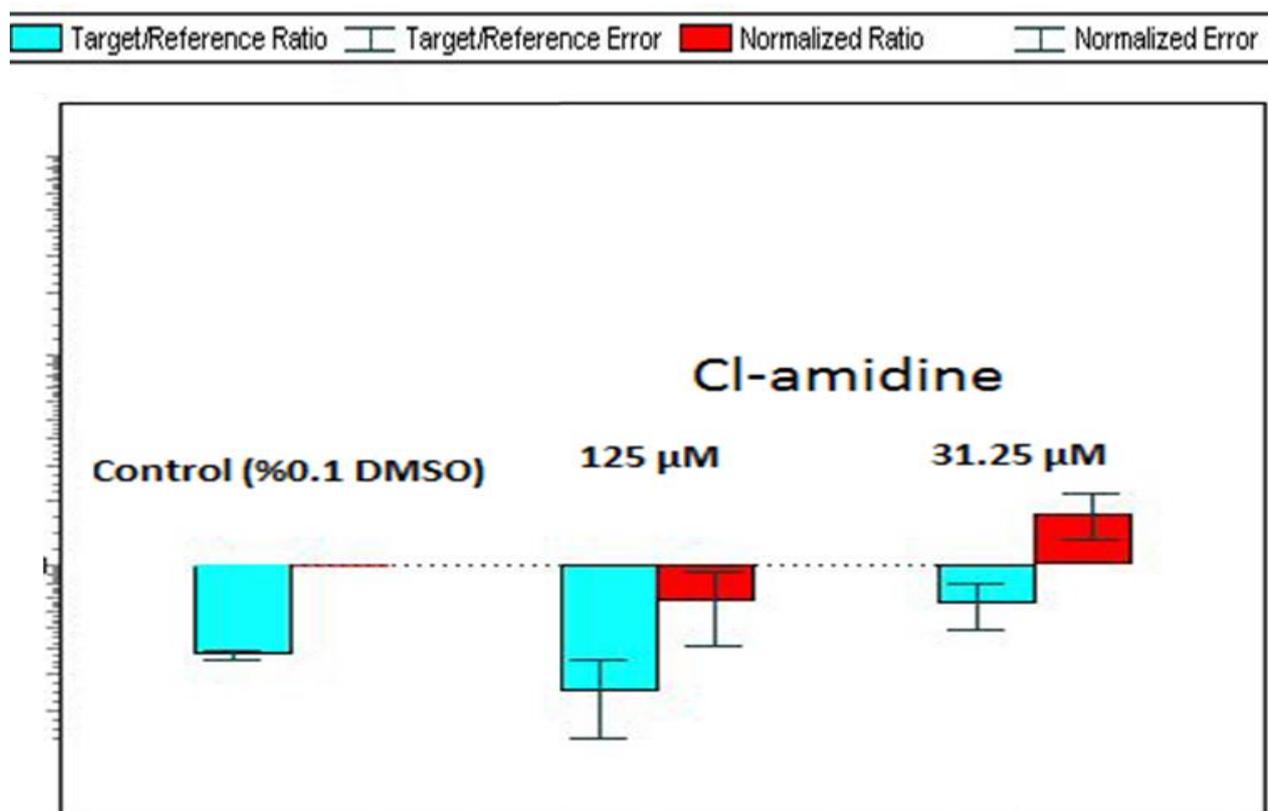
Figure 5. Normalized value graph of *COL1A1* gene mRNA levels in HaCaT Cells.

DISCUSSION

Peptidyl arginine deiminases (PADs) are enzymes that convert arginine to citrulline (1). They play a role in embryogenesis and cell signal transduction activities. However, it has been determined that excessive or dysregulated PAD levels increase in many diseases and may be associated with diseases (2-5). It has been reported that Cl-amidine, which is used as a PAD inhibitor substance, suppresses increased PAD activity and exhibits anti-cancer, anti-inflammatory and antioxidant activities. Anti-inflammatory and antioxidant properties play an important role in wound healing (2, 4-8).

Re-epithelialization is an important step in the wound healing process in order to restore the barrier function of the skin (17). Following

injury, keratinocytes migrate from each other and break their connections in the basal lamina. Then, the basement membrane is reconstructed by the proliferation of keratinocytes that come to the environment to carry out the formation of the epidermis. Basal layer keratinocytes at the wound margin show excessive proliferation in the days following wound formation (18). Some phenotypic changes occur in proliferating keratinocytes to migrate; cell shapes change, intracellular tonofilaments shorten, intercellular desmosomes dissolve, and the connection between epidermis and dermis is broken. Keratinocytes migrate to the wound area by ameboid movements. In addition to the division activity, the cells synthesize the basement membrane components, type 4 collagen and heparin sulfate, gradually repair the basement membrane, return to their normal shapes and connect to each other and to the basement membrane. Keratinocytes divide and differentiate to form layers of the epidermis and connect the newly formed epidermis with the basement membrane and dermis (12, 19).

HaCaT cell line has a similar migration index to primary human keratinocytes and mimics many features of normal keratinocytes (20, 21). For this reason, HaCaT cell line was used as an in vitro wound healing experiment model in our study.

In our study, the concentrations of Cl-amidine increasing HaCaT cell proliferation at 48 hours were determined as 31.25 and 125 μM

by Real-Time Cell Analysis System. Then, these determined concentrations were evaluated with the strach wound healing model, which is a model used to investigate cell migration in wound healing, and it was determined that Cl-amidine was effective at both 31.25 and 125 μM concentrations. Especially, the most significant increase in HaCaT cell migration was observed at 31.25 μM concentration at 48th hour. When we look at the results of COL1A1 mRNA expression levels, which support these results, it was determined that the highest gene expression increase was at 31.25 μM Cl-amidine concentration (approximately 2 times) compared to the control, and our experimental results show parallelism.

CONCLUSION

In the study, it was found that Cl-amidine, which is a PAD inhibitor, has a proliferative effect on HaCat keratinocyte cells. The effects of Cl-amidine on type 1 collagen, which is an important marker for wound healing, were determined by the increase in COL1A1 mRNA gene expression levels by RT-PCR method. In addition, according to scratch analysis, it was determined that it positively affected cell migration in relation to wound closure. This study shows that Cl-amidine may have significant potential in wound healing.

Ethical Approval: Ethics committee approval is not required in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: PNO Design: PNO Literature search: PNO Data Collection and Processing: SEO, MD Analysis or Interpretation: SEO, MD, PNO Writing: PNO

Conflict of Interest: No conflict of interest was declared by the authors.

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Determination of Factors Affecting Severity of *Helicobacter pylori* for Gastric Biopsy Samples by CART Decision Tree Algorithm

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Abstract

Objective: *H. pylori* wich is one of the important gastric pathogens and is a motile, non-sporeless, encapsulated, microaerophilic, gram-negative bacterium. The aim of this study was to determine the factors affecting disease severity in patients with a positive pathologic diagnosis of Helicobacter pylori after gastric biopsy by data mining. It was aimed to utilize the more descriptive structure of data mining algorithms compared to traditional classification and regression approaches.

Methods: The study data were obtained from gastric biopsy samples of 1247 patients, 40.5% male and 59.5% female, who were sent to the pathology laboratory between 2014 and 2018. A total of 6 factors including age, gender, inflammation, metaplasia, atrophy and activation, which are thought to have an effect on gastric *H. pylori* severity, were examined. Querying the effects of factors was done with the CART (Classification and Regression Trees) decision tree algorithm, one of the data mining algorithms.

Results: The factors ranking as their effect on the severity of gastric h. pylori, as follows; activation > inflammation > metaplasia > atrophy > age > gender in a percentage of normalized importance at 100.00%, 88.6%, 51.4%, 38.1%, 12.8%, 3.3% respectively.

Conclusion: As a result, levels of activation, inflammation, and metaplasia emerged as the most important factors affecting gastric *H. pylori* severity.

Key words: Data mining, Decision Tree, CART Algorithm, *H. pylori* stomach

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INTRODUCTION

H. pylori is one of the important gastric pathogens and is a motile, non-sporeless, encapsulated, microaerophilic, gram-negative bacterium. This bacterium settles in theantrumpart of the stomach and can generally be spiral andcurved (Dağdartan, 2011). *H. pylori* is a bacteriumthat causes important upper gastrointestinal diseases such as gastroduodenal ulcer, gastritis, adenocarcinoma, gastricmucosa-associated lymphoid tissue lymphoma. While more than 50% of the world's population is infected with H. pylori, this rate is 70-90% in developing countries, while it may be lower in developedcountries (Kanadalı et al, 2004, Kuslers et al, 2006).

Some different noninvasive and invasive methods are used in thediagnosis of *H. pylori* infection. Among these methods, non-invasive methods that do not require endoscopy, such as urea-breath test, serological methods, stool culture, antigen/nucleic acid search in stool are used. Many invasive methods that require endoscopy are gastric biopsy culture sample, histopathological examination, rapid urease test, and molecular methods (Hirschi et al, 2007, Uyanık et al, 2007). Although many invasive and noninvasive tests are used in thediagnosis of H. pylori, culture and histological examinations are accepted as the gold standard in the diagnosis of this infection. In the diagnosis of H. pylori, it is important to take, transport and store the gastric biopsy sample in appropriate ways. At least two biopsy samples should be takenfromtheantrumregionandthepatient'scimetidineintakeshould be discontinued 5-7 days before the procedure. In the diagnosis, successful results can be obtained by staining and examining the smears prepared by crushing on a slide from biopsy samples by gram stainingmethod (Erdem, 1999).

A decision tree is a model that shows classification outcomes and decision rules in a data structure that resembles a tree. As an inductive learning method, its goal is to turn the ostensibly disorganized and disorganized known cases into a tree model that, by technological means, can predict unknown instances (Greff et al., 2016).

In this study, the decision tree model was used to take advantage of the more descriptive nature of this method compared to the traditional Classification and Regression approaches. For this purpose, CART (Classification and Regression Trees) Decision Tree Algorithm was preferred.

Our aim in the study is to determine the factors affecting the severity of the disease in patients who applied to Ordu University Training and Research Hospital with dyspeptic complaints in May-Grünwald & Giemsa and Hematoxylin & eosin and *H. pylori* retrospectively found positive gastric antrum biopsy samples by data mining. It is aimed to benefit from the more descriptive structure of data mining algorithms compared to

traditional classification and regression approaches.

METHODS

Data of the study

The study data were obtained retrospectivelyfrom gastric biopsy samples of 1247 patients, who were sent to the pathology laboratory and diagnosed as *H. pylori* positive between 2014 and 2018 in Ordu University Research and Training Hospital.The patients were included into the study by considering the Sydney criteria in accordance with *H. pylori* severity degrees in 3 groups; mild (n=538), moderate (n=445) and severe (n=264).

Statistical Analysis

In this study, the decision tree model was used to take advantage of the more descriptive structure of this method compared to traditional Classification and Regression approaches. For this purpose, CART (Classification and Regression Trees) Decision Tree Algorithm was preferred.

The classification appears to be one of the most crucial approaches and strategies utilized in machine learning or data mining among the many others (Rutkowski et al., 2014).

With a maximum tree depth of 5, all minimum cases in the parent node were 100, and the minimum cases in the child node were 50, the CART method was used. The Gini index was used to calculate the homogeneity of the nodes. IBM SPSS v28 (IBM, Armonk, NY, USA) statistical software was used to calculatethe

algorithmand to calculate descriptive statistics of the dataset.

The frequencies and percentages were given as descriptive statistics for categorical variables, whereas the mean+standard deviation (SD) and minimum-maximum values were given for continuous variables.

CART Algorithm

To handle categorization and prediction issues, data miners utilize decision trees, a visual technique that is simple to grasp and interpret. Breiman et al. (1984) initially created Classification and Regression Trees (CART), one of the decision tree methods, which uses both categorical and continuous data to solve classification and regression issues. Regression Trees-RT are used when the dependent variable is continuous, while technique classification trees (CT) are used when the dependent variable is categorical (Chang and Wang, 2006).

CART may be used serially and is based on Hunt's algorithm. When choosing the dividing attribute, it makes use of the Gini index splitting measure. Because it uses regression analysis with the aid of regression trees, CART differs from previous Hunt's-based algorithms (Kumar and Vijayalakshmi, 2011; Priyama et al. 2013).

RESULTS

The sample of the study consisted of a total of 1247 gastric biopsy samples, 40.5% male and 59.5% female, sent to the pathology laboratory and diagnosed as *H. pylori* positive between 2014 and 2018. The samples' frequency

distributions of gender,levels of the severityof *H. pylori*, inflammation, metaplasia, atrophy, and activation (increased neutrophil count) were given in Table 1.Descriptive statistics of the samples' according to the severity of *H. pylori*were given in Table 2.The mean age of mild, moderate and severe groups, which are *H. pylori* severity levels, were 50.17±15.10(17-84),47.67±15.15(17-83) and 47.58±14.31(20-86) years, respectively.

Table 1: Frequency distributions of gender,levels of the severityof H. pylori, inflammation, metaplasia, atrophy, and activation

Variables		n	%
Gender	Female	742	59.5
	Male	505	40.5
H. pylori severity	Mild	538	43.1
	Moderate	445	35.7
	Severe	264	21.2
Inflammation	Negative	19	1.5
	Mild	395	31.7
	Moderate	449	36.0
	Severe	384	30.8
Metaplasia	Negative	813	65.2
	Type 1	294	23.6
	Type 2	112	9.0
	Type 3	28	2.2
Atrophy	Negative	612	49.1
	Mild	500	40.1
	Moderate	115	9.2
	Severe	20	1.6
Activation	Negative	209	16.8
	Mild	459	36.8
	Moderate	417	33.4
	Severe	162	13.0

Table2: Descriptive statistics of the samples according to the severity of *H. pylori*

H. pylori Severity	Female		Male		Total		Age	
	n	%	n	%	*n*	*%*	Mean±SD	Min.-Max.
Mild	342	63.6	196	36.4	*538*	*43.1*	50.17±15.10	17-84
Moderate	260	58.4	185	41.6	*445*	*35.7*	47.67±15.15	17-83
Severe	140	53.0	124	47.0	*264*	*21.2*	47.58±14.31	20-86

The tree was designed in the root (node 0), branch (nodes: 1, 2, 4, 5, 8, 9 and 12) and leaf (nodes: 3, 6, 7, 10, 11, 13, 14, 15 and 16) nodes (Figure 1).

In the study, theseverity of *H. pylori* was found to be 43.1%, 35.7% and 21.2%, respectively, in the mild, moderate and severe groups (Node 0). Potential factors that caused this variation in the severity of *H. pylori* were ranked according to their estimation importance with the CART Decision Tree Algorithm.With the CART, the most effective factor on the severity of H. pyloriwas estimated as activation level (p=0.048). Therefore, the root node was first divided into two branches negative-mild (53.6%) and moderate-severe (46.4%) according to activation levelwhile the rate of H. pylorimildwashigh (59.7%) in those with negative-mild activation (Node 1), the rate of those with moderate *H. pylori* severity (43.4%) washigher in thosewithmoderate-severe activation (Node 2). Those with negative-mild activation were dividedinto two childnodes as

moderate-severe (Node3) and negative-mild (Node4) according to the level of inflammation (p=0.010). In both groups, the rate of those with mild *H. pylori* severity was high (47.9 and 69.6%, respectively), but the rate of those with severe *H. pylori* severity was approximately 2 times higher in the moderate-severe group (14.9% versus 8.2%).

Those with negative-mild inflammation level were dividedinto two childnodes as ≤ 39.5 (Node7) and >39.5 (Node8) according to age (p=0.002). The rate of thosewith severe *H. pylori* severity was higher in those whose age was ≤39.5 (15.2% versus 5.9%). In those with age>39.5, two childnodeswereseparated as negative (Node 11) and type1-type-2 (Node 12) according to metaplasia level (p=0.001). Compared to type1-type 2 in terms of metaplasia, in negativeones; The rate of those with mild *H. pylori* severity was lower, whereas the rate of those with moderate and severe levels was higher (67.2% versus 77.3%; 26.1% versus 17.5%; 6.7% versus 5.2%). While there was no other factor affecting theseverity of H. pyloriin patient saged>39.5 years with metaplasia negative, those with metaplasia type1-type2 were divided into two age groups as ≤60.5 (Node 15) and >60.5 (Node 16) (p=0.001). Compared to those aged >60.5, those aged ≤60.5; The rate of those with mild *H. pylori* severity was lower, where as the rate of those with moderate and severe levels was

higher (70.0% versus 87.5%; 22.2% versus 10.9%; 7.8% versus 1.6%).

Those with moderate-severe activation levels were divided into two childnodes, which see the metaplasial level in themselves, as negative-type 1 (Node5) and type2-type3 (Node4) (p=0.003). In the metaplasia negative-type 1 group, the proportion of those with moderate *H. pylori* severity was high (44.0%) in themetaplasia type2-type3 group. The rate of those with severe pylori severity was high (45.0%) *H. pylori* severity was not affected by any other factor.

However, Metaplasia negative-type 1 group was divided into two childnodes, severe (Node 9) and negative-mild-moderate (Node 10) in terms of inflammation level (p=0.001). Those with severe inflammation had a higher rate of *H. pylori* (34.3% versus 24.3%). Those with severe inflammation showed branching according to the level of activation (p=0.001). When the two groups showing moderate level activation (Node 13) and severe level activation (Node 14) were compared in terms of *H. pylori* severity; The rate of mild was moderate in the moderate activation group (28.8% versus 16.1%), and the rate of severe was higher in the severe activation group (43.7% versus 40.4%; 40.2% versus 30.8%). The rate of thosewith severe *H. pylori* inflammation was approximately 2 times higher (14.9% versus 8.2%) in the moderate-severe group. Those with negative-mild inflammation level were

dividedinto two childnodes as ≤ 39.5 (Node7) and >39.5 (Node8) according to age (p=0.002). The rate of those with severe *H. pylori* severity was higher in those whose age was ≤39.5 (15.2% versus 5.9%). In those with age>39.5, two childnodeswereseparated as Negative (Node 11) and type1-type-2 (Node 12) according to metaplasia level (p=0.001). Compared to type1-type 2 in terms of metaplasia, in negative ones; The rate of those with mild *H. pylori* severity was lower, whereas the rate of those with moderate and severe levels was higher (67.2% versus 77.3%; 26.1% versus 17.5%; 6.7% versus 5.2%).

While there was no other factor affecting the severity of *H. pylori* in patients aged > 39.5 years with metaplasia negative, those with metaplasia type1-type2 were divided into two age groups as ≤60.5 (Node 15) and >60.5 (Node 16) (p=0.001). Compared to those aged >60.5, those aged ≤ 60.5; The rate of those with mild H. pyloriseveritywaslower, whereas the rate of those with moderate and severe levels was higher (70.0% versus 87.5%; 22.2% versus 10.9%; 7.8% versus 1.6%).

DISCUSSION

H. pylori is an aerophilic bacteria species that can be the cause of many diseases such as chronic gastritis, gastritis malt lymphoma, aseptic carriage colonized in the gastric mucosa, usually in the antrumand corpus, and gastric cancer in humans (Mirza, 2011). It has been reported that *H. pylori* can generally settle in the antrum and cause chronic active gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and gastric cancer (Topal et al, 2004). Most of the samples examined in the study were takenfromtheantrumregionandthe condition of the patients was evaluated in terms of intestinal metaplasia, atrophy, inflammationand activation.

In the study, inflammation was found in 98% of *H. pylori* positive patients, intestinal metaplasia in 34.6% and atrophy in 50.7%. Activation was positive in 82.9%. In studies on intestinal metaplasia; Kesici (2018) found a significant relationship between *H. pylori* positivity and intestinal metaplasia. They also found a significant relationship between intestinal metaplasma positivity and *H. pylori* density. Kurtulus et al. (2017) could not detect a significant relationship between *H. pylori* positivity and intestinal metaplasia. Sasa et al. (2002) found an increase of 50.7% in intestinal metaplasia and atrophy frequency and in *H. pylori* positivity.

Güner andTuncer (2019) found that H. pylori positivity was effective on duodenal ulcer, atrophic gastritis, intestinal metaplasia. A significant correlation was found between the colonization status of the bacteria and inflammation in patients with H. pylori positivity (p<0.01) Sipponen et al. (1997) reported a positive correlation between H. pylori inflammation and colonization.
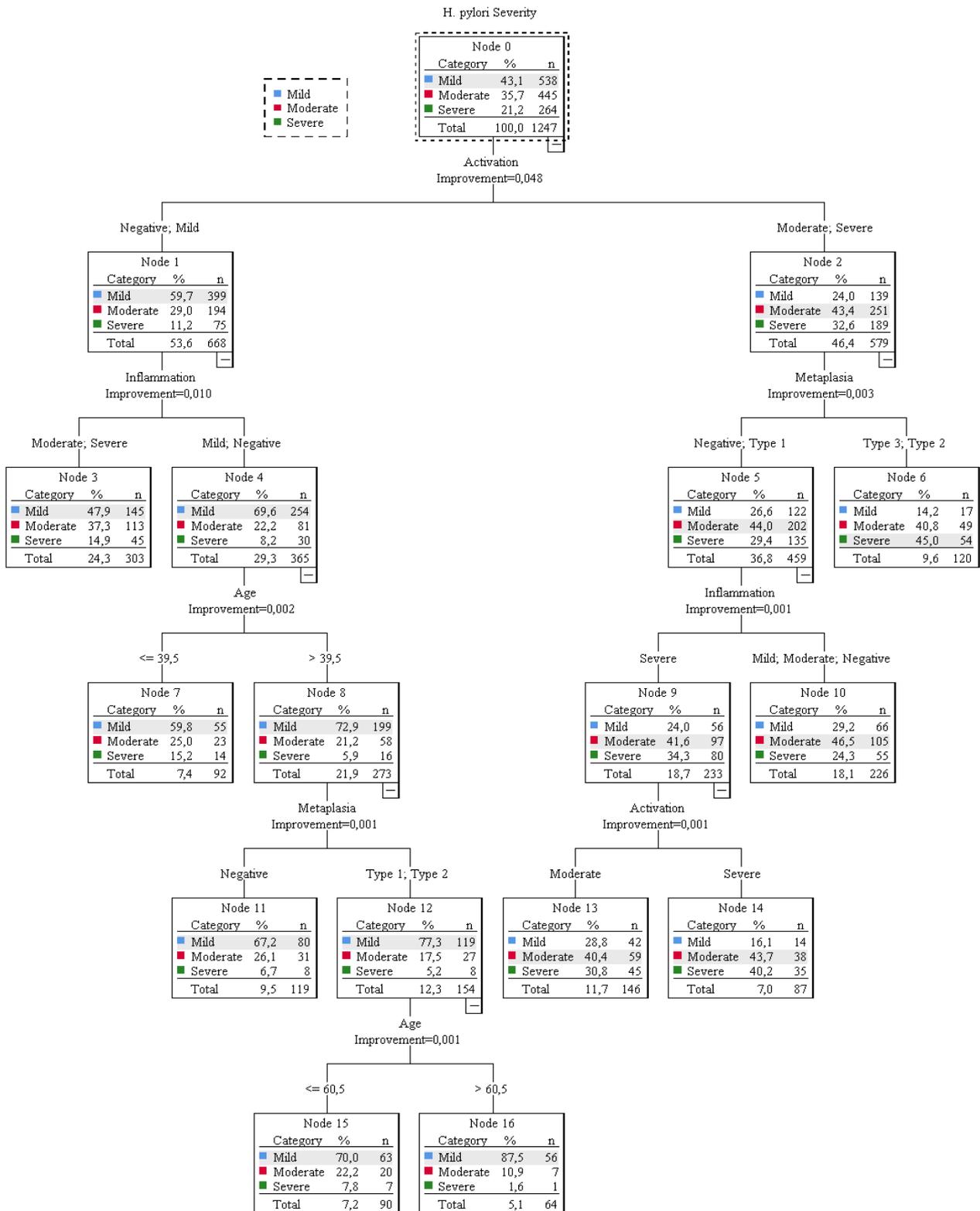
Figure 1. Decision treediagram obtained by CART algorithm for the severity of gastric *H. pylori* The importance levels of the factors (independent variables) based on CART predictive algorithm for the severity of gastric *H. pylori* was presented in Figure 2.
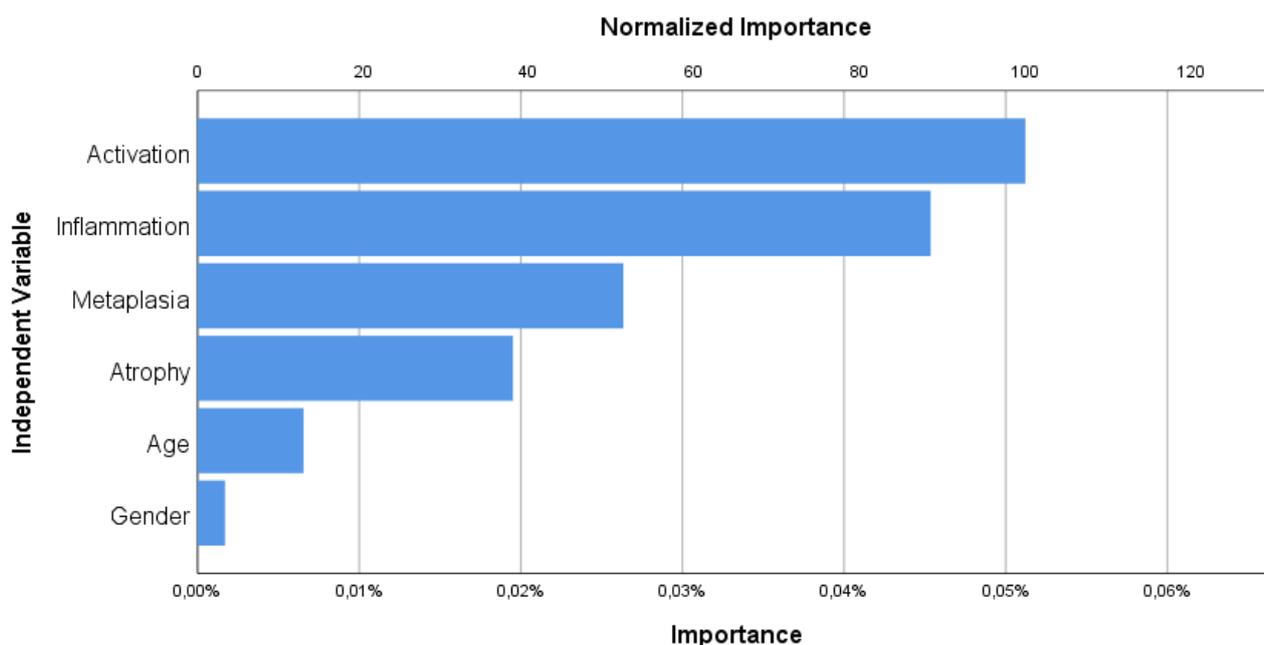
Figure 2. Normalized importance levels of the factors,sorted by decreasing importance

They reported that there is a positive correlation between H. pylori severity and activation. A significant correlation was found between *H. pylori* severity and activation positivity (p<0.001). The increase in the severity of *H. pylori* increased the rate of activation positivity. The rate of patients with mild and moderate *H. pylori* positivity was found to be higher than those without atrophy, and the rate of those with atrophy (56.4%) in severe H. pylori-positive patients was higher than the rate (43.6%) in patientswith severe *H. pylori* positivity. Asaka et al. (2001) also reported that atrophic gastritis increased in *H. pylori* positivity. Kurtulus et al. (2017) found a significant relationship between atrophy and *H. pylori* positivity.

In the study of *Karaman*, inflammation was found in 98% of *H. pylori* positive patients, intestinal metaplasia in 34.6% and atrophy in 50.7%. Activation was positive in 82.9 of the patients. It has been determined that there is a significant relationship between the colonization status of the bacteria and inflammation in patients with *H. pylori* positive. The relationship between positivity of intestinal metaplasia and *H. pylori* density was found to be statistically significant. Intestinal metaplasia and an increase of 50.7% were detected in bacterial positivity. The increase in *H. pylori* severity increased the incidence of activation positivity. While the rate of patients with mild and moderate *H. pylori* positivity was higher than those without atrophy, the rate of patients with severe *H. pylori* positivity

(56.4%) was higher than the rate of patients without atrophy (43.6%) (Karaman, 2020). Similar results were obtained with data mining in the study. *H. pylori* activation > inflammation > metaplasia > atrophy > age > sex gives normalized significance percentages of 100%, 88.6%, 51.4%, 38.1%, 12.8%, and 3.3%, respectively. Activation and inflammation with a given normalized significance greater than 50% indicated that themarkers of metaplasiaweresignificant.

CONCLUSION

In this study activation showed the highest percentage of normalized importance due to the severity of gastric *H. pylori* because therefore, the presence of activation is important in the follow-up of the treatment of the bacteria. Inflammation showed 88.6% of importance where it conveys high effect although it was not the highest because Inflammation was also found to increase in the presence of bacteria.In this the study as a result, activation, inflammation and metaplasia were determined as the most important factors affecting the severity of gastric *H. pylori* .

Ethical Approval: Ethical approval for this study was not required as data mining was used.
Peer-review: Externally peer-reviewed.
Author Contributions:
Concept: TMY, ÜK, YKA, Design: TMY, ÜK, YKA, Supervision: TMY, ÜK, YKA, Data Collection and/or Processing: TMY, ÜK, YKA,

Analysis and/or Interpretation: TMY, ÜK, YKA, Writing: HS, EU, MCU, EA, CA, SD
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Machine Learning Approach for Thyroid Cancer Diagnosis Using Clinical Data

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Abstract

Objective: With an early diagnosis of thyroid cancer, one of the world's most significant health issues, it is feasible to treat the nodules before the spread of malignant thyroid gland cells. It has become crucial to develop models for predicting thyroid cancer. In light of this, the purpose of this study is to develop a clinical decision support model using the Bagged CART model, a machine learning (ML) model for the prediction of thyroid cancer.

Methods: Between 2010 and 2012, 724 patients who applied to China Median University Shengjing Hospital comprised the study's data set. The dataset comprises information on nodule malignancies, demographic characteristics, ultrasound characteristics, and blood test results for all patients who underwent thyroidectomy. Using this open-access data set, the Bagged CART modeling technique was applied. Negative predictive value (NPV), specificity (Spe), balanced accuracy (BACC), positive predictive value (PPV), accuracy (ACC), sensitivity (Sen), and F1-score performance metrics were used to evaluate the model's predictive performance. In addition, a 10-fold cross-validation method was used to determine the validity of the model. In addition, variable importance was established, which reveals how much the input variables impact the output variable.

Results: ACC, BACC, Sen, Spe, PPV, NPV, and F1-score obtained from the model performance metrics were calculated to 99.1%, 98.7%, 99.7%, 97.7%, 99.1%, 99.2%, and 99.4%, respectively, as a result of modeling. According to the variable importance values that were acquired for the input variables in the dataset that was investigated in this study, the seven variable that hold the greatest significance are as follows: size, TSH, blood flow: size, TSH, blood flow: enriched, multilateral: yes, FT4, site: isthmus, and age, in that order.

Conclusion: As a result, the Bagged CART model was found to be effective at predicting thyroid cancer based on the findings of this study. In addition, in this study, risk factors for thyroid cancer were evaluated and their importance values were given. With these results, the decision-making process about the disease will be able to accelerate and thus, it will be able to effective in preventive medicine practices.

Key words: Bagged CART, machine learning, thyroid cancer, risk factors, classification.

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INTRODUCTION

Thyroid cancer is caused by the abnormal growth of malignant tumor cells in thyroid gland tissue. The development of thyroid cancer occurs when cells within a malignant tumor change or adapt their cellular structure. The frequency of thyroid cancer has gradually climbed during the previous three decades (1). The American Cancer Society estimates that there were around 43.800 newly diagnosed cases of thyroid cancer in 2022, with roughly 2.230 people losing their lives to the disease. Cancer of the thyroid is a solid tumor that most often manifests in the thyroid gland as a nodule or mass at the front base of the neck (2). Thyroid cancer is the most common type of cancer in teens and young adults, and it is the ninth most common type of cancer in women overall (3). The death rate for thyroid cancer is quite low; nevertheless, the sickness recurrence rate is rather high, which is directly correlated to a greater level of incurability, morbidity, and mortality among patients (4). Even though there are several different varieties of thyroid cancer, the two types that are most common account for around 95% of all occurrences of thyroid cancer.

The two types of thyroid cancer are papillary and follicular thyroid cancer (5).

Early detection of malignant thyroid nodules can lead to efficient therapy and minimal harm if the nodules are treated before the cancerous cells in the thyroid gland spread (6). In addition, having a pre-surgical diagnosis that determines whether thyroid nodules are benign or malignant helps the procedure go more smoothly and lowers the chance of recurrence following surgery. Thyroid cancer screening is a process that enables the early identification of malignant thyroid nodules (7). Neck palpation during a physical examination and ultrasonography, which may identify both nonpalpable and palpable nodules, particularly those with a diameter of less than 1 cm, are the two main approaches for detecting thyroid cancer (8). Ultrasonography (US), as the primary diagnostic tool, is used to detect the features of thyroid nodules. These discovered traits assist in the classification of nodules as benign or malignant (9). Until date, the bulk of malignant nodule diagnoses are based on surgeons' and radiologists' clinical experience (10). Human judgment is slow and prone to mistakes in many circumstances. To enhance medical decisions and minimize labor effort, accurate and comprehensible prediction models are desperately needed (11).

As a novel technology, computer-aided diagnosis (CAD) has been used to diagnose

thyroid nodules in recent decades. The use of artificial intelligence into CAD tools makes them more intelligent and enhances the quality and consistency of ultrasound feature interpretation, resulting in fewer needless biopsies. The basic methodologies of artificial intelligence-based CAD systems that have a significant influence on the medical field are ML (12).

In the medicine, like in all other sectors of human knowledge, novel approaches based on ML and collaborative reasoning are utilized in an attempt to succeed where traditional predicting methods have failed (13). ML algorithms uncover more complex associations among existing data than traditional regression models. A ML system is one that studies the design and operation of data-learning and prediction-capable algorithms. Based on input samples, these algorithms create a model to make and anticipate decisions (14).

CART is a continually improving nonparametric ML tool for regression and classification problems. CART recursively partitions data based on the binary partitioning technique to investigate the link between response variables and predictors (15). Bagged CART is an advancement on the CART algorithm that combines CART with bagging techniques in order to improve predictive model performance and reduce overfitting. Bagged CART was developed to improve the CART algorithm. (16). Each classifier in this approach generates and saves its model by categorizing a

piece of the data. Eventually, based on vote intention among these categories, the class with the highest votes is chosen as the final classifier (17).

By employing the ML method of Bagged CART on an open access dataset consisting of open access with benign and malignant nodules patients, the purpose of this investigation is to classify thyroid cancer and identify the factors associated with it.

METHODS

Dataset and Variables

The data for this investigation were obtained from 724 patients admitted between 2010 and 2012 to the Shengjing Hospital of China Median University. The datasets comprise information on each patient's nodule malignancy, demographics, ultrasound characteristics, and blood test results. Each patient had a single or multiple nodules in three distinct areas: the right lobe, the left lobe, and the isthmus. If a patient had multiple nodules in a single region, only the largest one was included in the dataset. The "Thyroid" open-access dataset used in this study is available at https://zenodo.org/record/6465436#.Y06MQ3Z BxZ.In this dataset, there are a total of 724 patients, 204(28.2%) of whom are benign nodules patients and 520(71.8%) are malignant nodules patients. Table 1 shows the variables included in the dataset.

Table 1: The variables contained inside the dataset.

Variables	Variable Types	Variable Roles
Age: The Age of the Patient	Quantitative	Predictor
Gender: 0: Male, 1: Female	Qualitative	Predictor
FT3: Triiodothyronine Test Result	Quantitative	Predictor
FT4: Thyroxine Test Result	Quantitative	Predictor
TSH: Thyroid-Stimulating Hormone Test Result	Quantitative	Predictor
TPO: Thyroid Peroxidase Antibody Test Result	Quantitative	Predictor
TGAb: Thyroglobulin Antibodies Test Result	Quantitative	Predictor
Site: The Nodule Location, 0: Right, 1: Left, 2: Isthmus	Qualitative	Predictor
Echo Pattern: Thyroid Echogenicity, 0: Even, 1: Uneven	Qualitative	Predictor
Multifocality: If Multiple Nodules Exist in One Location, 0: No, 1: Yes	Qualitative	Predictor
Size: The Nodule Size in Cm	Quantitative	Predictor
Shape: The Nodule Shape, 0: Regular, 1: Irregular	Qualitative	Predictor
Margin: The Clarity of Nodule Margin, 0: Clear; 1: Unclear	Qualitative	Predictor
Calcification: The Nodule Calcification, 0: Absent, 1: Present	Qualitative	Predictor
Echo Strength: The Nodule Echogenicity, 0: None, 1: Isoechoic, 2: Medium-Echogenic, 3: Hyperechogenic, 4: Hypoechogenic	Qualitative	Predictor
Blood Flow: The Nodule Blood Flow, 0: Normal, 1: Enriched	Qualitative	Predictor
Composition: The Nodule Composition, 0: Cystic, 1: Mixed, 2: Solid	Qualitative	Predictor
Multilateral: If Nodules Occur in More Than One Location, 0: No, 1: Yes	Qualitative	Predictor
Mal: The Nodule Malignancy, 0: Benign, 1: Malignant	Qualitative	Output

Bagged Classification and Regression Trees (Bagged CART)

The non-parametric decision tree logging method known as CART has become quite popular. Breiman et al. devised this technique (1984) (18). Binary trees serve as the foundation for this strategy. This tree serves as the foundation for more complicated algorithms such as Random Forest, in addition to other trees. The CART decision tree method first divides the input into binary components before moving on to the construction of the decision tree. In order to identify which variables should be provided additional information on classification, the CART tree makes use of the Gini index. When classifying, variables that have lower Gini indices are given a larger amount of weight. The CART algorithm uses trial and error to figure out the best possible value for the separator point in each dimension or variable, which leads to a lower Gini index in the end (19).

The bagging approach has the potential to significantly enhance the accuracy of the CART, which is well recognized as an unstable model (20). The bagged CART improves classification performance, eliminates overfitting, and considerably reduces prediction variation. The CART algorithm begins by performing a

recursive split on the training sample units using a predetermined number of variables. The method then assesses each of the predictive elements in order to ascertain which binary division of a predictive variable is most likely to diverge from the variable that was anticipated as the result of the analysis. In order to construct homogenous end nodes in a hierarchical tree, the method is frequently repeated for each of the initial split outcomes. CART prunes the trees to minimize overfitting when the results of cross validation give the lowest error rate (15, 21).

Biostatistical analysis

Qualitative data from the variables included in the study were summarized with number (percentage). The Kolmogorov-Smirnov test was utilized in order to investigate whether or not the quantitative data adhered to a normal distribution. Data that did not show normal distribution were summarized with the median (minimum-maximum). Normally distributed ones were summarized as mean±standard deviation. In the statistical analyses, the Pearson chi-square test, the Continuity Correction test, and the Mann-Whitney U test were utilized, depending on the circumstances, to determine whether or not there is a statistically significant difference between the target variable and the input variables. In the statistical analyses that were carried out, a value of p less than 0.05 (p<0.05) was regarded as statistically significant. All of the analyses were carried out with the help of IBM SPSS Statistics 26.0 for Windows (New York; USA).

Machine Learning Modeling and Performance Evaluation

During the modeling phase of the investigation pertaining to the aforementioned data set, the Bagged CART technique was employed. For modeling, the entire data set was utilized. For the analysis, the technique of n-fold cross validation was utilized. n-fold cross-validation divides the data into n segments and applies the model to n of them. One of the n components is utilized for testing, while the remaining n-minus-one components are used to educate the model. The study employed a 10-fold cross-validation method to increas the model's validity. As criteria for performance evaluation, the BACC, ACC, Spe, Sen, NPV, PPV, and F1-score were utilized. In addition, variable importance was determined, which represents the extent to which the input variables influence the target variable. Modeling was accomplished using R Studio 4.2.1. (22).

RESULTS

The study's data set contains 724 individuals, 204 (28.2%) of whom had benign nodules and 520 (71.8%) have malignant nodules. The patients' mean age was 45.59±12.609 years. The median age of patients with benign nodules was 48 (15-79) years, whereas the median age of patients with malignant nodules was 44 years (13-82 years). The study included 121 (16.7%) men and 603 (83.3%) women.

In addition, of the male patients, 27(22.3%) have benign nodules and 94 (77.7%) have malignant nodules. While 177(29.4%) of the female patients have benign nodules, 426(%70.6) have malignant nodules.

Table 2 displays the results of statistical analyses of the independent variables in terms of the dependent variable.

Table 2. The results of the statistical analyses between the target variable and independent variables

Variables		The Nodule Malignancy		p
		Benign	**Malignant**	
Gender n(%)	**Male**	27 (13.24)	94 (18.08)	0.116**
	Female	177 (86.76)	426 (81.92)	
Site n(%)	**Right**	80 (39.22)	275 (52.88)	<0.001**
	Left	82 (40.20)	230 (44.23)	
	Isthmus	42 (20.59)	15 (2.88)	
Echo Pattern n(%)	**Even**	187 (91.67)	449 (86.35)	0.065***
	Uneven	17 (8.33)	71 (13.65)	
Multifocality n(%)	**No**	117 (57.35)	310 (59.62)	0.578**
	Yes	87 (42.65)	210 (40.38)	
Shape n(%)	**Regular**	194 (95.10)	363 (69.81)	<0.001***
	Irregular	10 (4.90)	157 (30.19)	
Margin n(%)	**Clear**	93 (45.59)	131 (25.19)	<0.001**
	Unclear	111 (54.41)	389 (74.81)	
Calcification n(%)	**Absent**	178 (87.25)	229 (44.04)	<0.001**
	Present	26 (12.75)	291 (55.96)	
Echo Strength n(%)	**None**	5 (2.45)	3 (0.58)	0.002**
	Isoechoic	5 (2.45)	7 (1.35)	
	Medium-echogenic	31 (15.20)	46 (8.85)	
	Hyperechogenic	3 (1.47)	1 (0.19)	
	Hypoechogenic	160 (78.43)	463 (89.04)	
Blood Flow n(%)	**Normal**	173 (84.80)	250 (48.08)	<0.001**
	Enriched	31 (15.20)	270 (51.92)	
Composition n(%)	**Cystic**	10 (4.90)	8 (1.54)	0.012**
	Mixed	19 (9.31)	34 (6.54)	
	Solid	175 (85.78)	478 (91.92)	
Multilateral n(%)	**No**	20 (9.80)	0 (0.00)	<0.001***
	Yes	184 (90.20)	520 (100.00)	
		Median(Min-Max)	**Median(Min-Max)**	
Age		48 (15-79)	44 (13-82)	0.002*
FT3		4.44 (2.63-22.9)	4.32 (2.47-15.43)	0.196*
FT4		14.595 (6.65-59.08)	14.43 (5-28.76)	0.388*
TSH		1.327 (0.002-56.254)	1.561 (0-101)	0.018*
TPO		0.595 (0-1001)	0.64 (0-1001)	0.950*
TGAb		2.695 (0-1001)	2.825 (0-1001)	0.980*
Size		0.9 (0.05-5.4)	1.6 (0-9)	<0.001*

*: Mann Whitney U test, **:Pearson chi-square test, ***: Continuity Correction test, Min: Minimum, Max: Maximum

ACC, BACC, Sen, Spe, PPV, NPV, and F1-score obtained from the Bagged CART model as a result of the modeling were 99.1%, 98.7%, 99.7%, 97.7%, 99.1%, 99.2%, and 99.4%, respectively.

In Figure 1, values of performance metrics obtained from Bagged CART model are shown.

Table 3: Performance metric values calculated from Bagged CART model.

Performance Metrics	Value (%)
ACC	99.1
BACC	98.7
Sen	99.7
Spe	97.7
PPV	99.1
NPV	99.2
F1-score	99.4
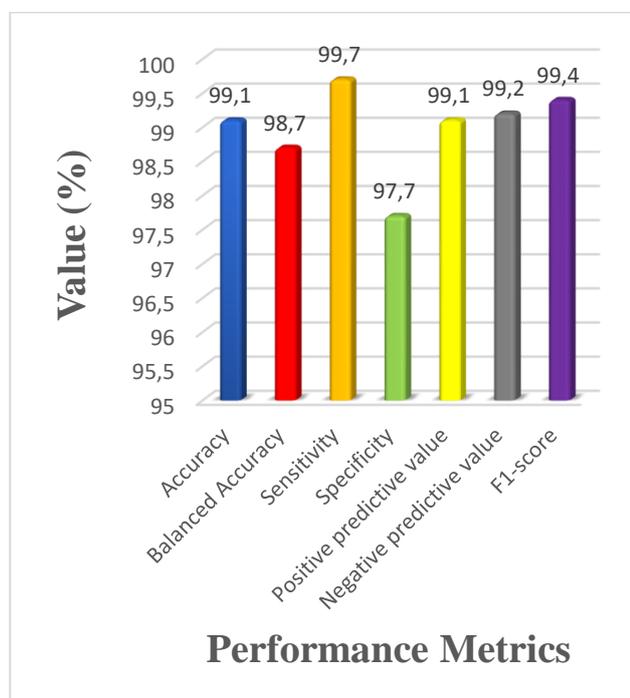
Figure 1: Performance metric values acquired from Bagged CART model.

Table 4 is a table of the variable importance values computed as a consequence of the Bagged CART model.

Figure 2 depicts a graph of the variable importance values obtained as consequence of the Bagged CART model. The seven most important variables related to multiple sclerosis

were found as size, TSH, blood flow: enriched, multilateral: yes, FT4, site: isthmus, age.

Table 4: The variable importance values obtained as a result of the Bagged CART model

Variables	Importance Values
Size	100
TSH	63.292
Blood Flow: Enriched	59.741
Multilateral: Yes	59.293
FT4	56.479
Site: Isthmus	54.789
Age	53.434
FT3	53.179
Calcification: Present	50.695
TGAb	48.839
TPO	48.814
Shape: Irregular	33.286
Margin: Unclear	19.02
Multifocality: Yes	11.994
Site: Left	8.716
Echo Strength: Hypoechogenic	7.711
Echo Strength: Medium-Echogenic	6.201
Composition: Solid	5.554
Gender: Female	4.592
Echo Pattern: Uneven	4.573
Echo Strength: Isoechoic	2.882
Composition: Mixed	2.627

Figure 2 depicts a graph of the variable importance values obtained as consequence of the Bagged CART model. The seven most important variables related to multiple sclerosis were found as size, TSH, blood flow: enriched, multilateral: yes, FT4, site: isthmus, age.
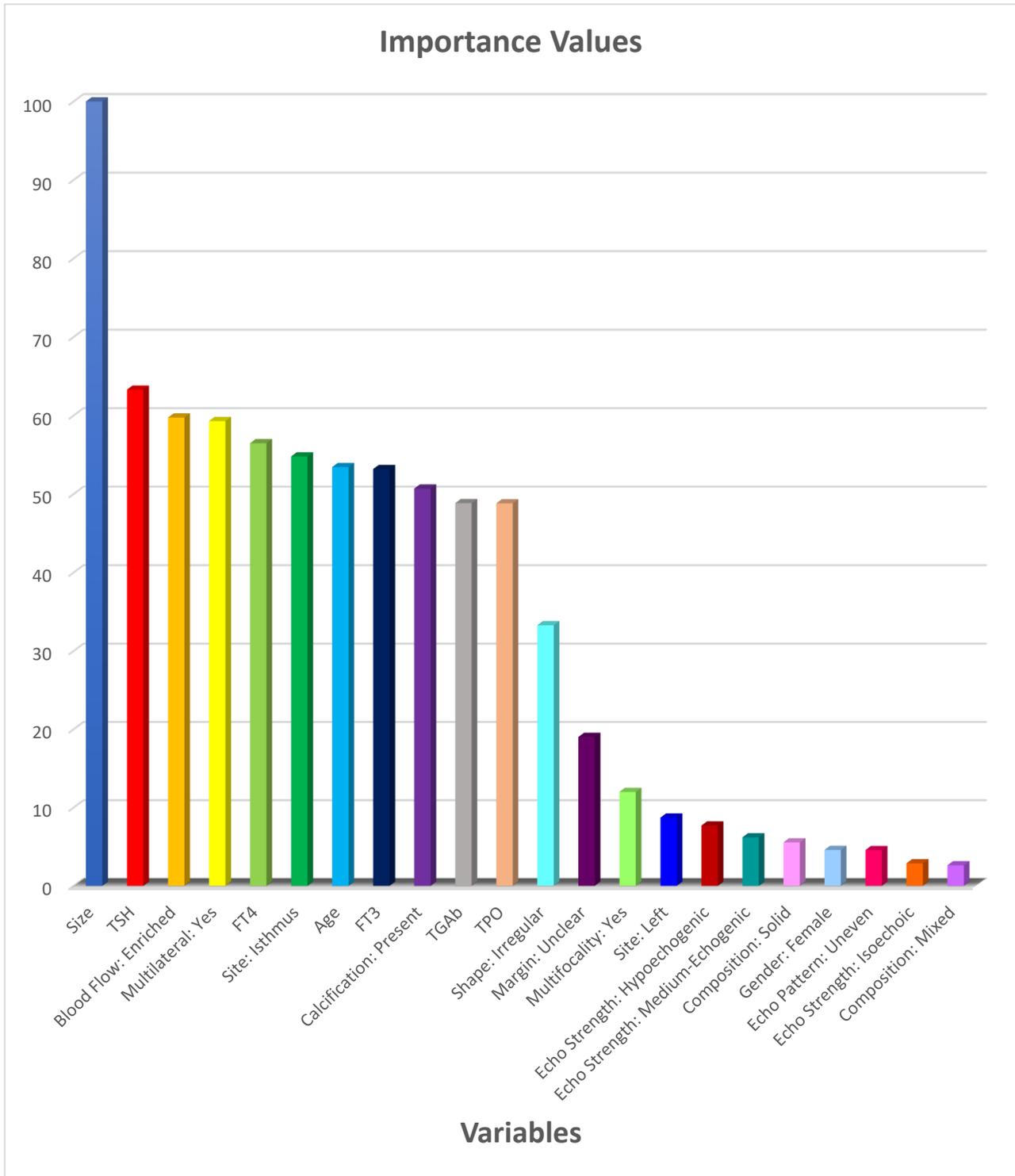
Importance Values

Figure 2: The variables' importance values as a consequence of the Bagged CART mode

DISCUSSION

As a crucial component of the human body, the thyroid generates a variety of hormones that perform several vital functions in the human body. Thyroid illness therefore endangers the human body in all physiological systems, including the endocrine, circulatory, neurological, respiratory, digestive, muscular,

and reproductive systems (23). Thyroid diseases and disorders are widespread hormonal conditions that affect the overwhelming majority of the global population. Diseases and conditions affecting the thyroid include thyroiditis, thyroid nodules, and thyroid carcinoma. The prevalence of thyroid nodules and thyroid cancer is rising globally, predominantly owing to improved diagnostic procedures. The widespread use of US has exponentially increased thyroid nodule detection to approximately 20–67% (24).

It is essential to distinguish between benign and malignant thyroid nodules in order to prevent performing unneeded fine-needle aspiration biopsies and overtreating the condition, such as through surgery (25). The intricate nature of the nodules leads in complicated ultrasound pictures and perhaps mixed signals between benign and malignant nodules. As a result, the US cannot distinguish between cancerous and benign nodules. Early detection and classification of benign and malignant thyroid nodules is critical for directing clinical therapy and choosing surgical methods (26).

It has been demonstrated that machine-learning algorithms produce much more accurate predictions than human experts. ML models are becoming more popular and widely employed in a variety of fields. These models' main aim is to determine the effective factors and their relationships, and they may also be used to forecast. These models are a branch of artificial intelligence that may be utilized as a study and application area in a variety of fields. Additionally, ML techniques are frequently employed and applied in medical science for illness detection (27-29). For this reason, in the study, the classification of thyroid cancer using the Bagged CART model, which is an ML approach, and the predictive features related with the diagnosis of the disease were revealed with variable importance values.

The performance criteria obtained from the Bagged CART method result, accuracy, balanced ACC, BACC, Sen, Spe, PPV, NPV, and F1-score were obtained as 99.1%, 98.7%, 99.7%, 97.7%, 99.1%, 99.2%, and 99.4%, respectively. Successful findings were achieved for the diagnosis of thyroid cancer, and according to the variable importance produced as a consequence of the model, the seven variables most related with the diagnosis were size, TSH, blood flow: enriched, multilateral: yes, FT4, site: isthmus, and age, respectively.

Numerous investigations on various thyroid datasets have been conducted to date. Parikh et al. (2015), describe the two prediction models they built to address their multiclass classification challenge. They employed artificial neural networks and support vector machines, and the ANN obtained an accuracy of 97.17% (30). Ionita et al. (2016), investigated hybrid medical datasets and outlined a variety of applications of Naive

Bayes, Decision trees, MLP, and RBF networks. For classification accuracy, all classifiers classify and provide separate outcomes; however, a decision tree obtained 97.35% accuracy (31). Chaurasia et al. (2018), used a number of machine learning methods to examine data. Using Naive Bayes, they achieved 97.37% accuracy (32). Talasila et al. (2020), exhibited and evaluated numerous ways before determining that LightGBM gave more accurate predictions than other methods available (33). Kumar et al. (2020), used SVM to diagnose thyroid stage with an accuracy of 83.37%. Other classification techniques have been shown to be less efficient than Multiclass SVM. Furthermore, the model accurately differentiates between the four thyroid states (34). Aversano et al. used a range of machine learning methods to examine data. They specifically compared the output of 10 different classifiers. The other algorithms' performance is encouraging, notably the Extra-TreeClassifier, which obtains an accuracy of 84%. They also used a catboost classifier and attained a precision of 71% (35).

In addition, the machine learning method used is a tree-based method and includes some arrangements to increase model performance. Therefore, it gives better results than known basic machine learning methods. Thus, the model performance from this study demonstrates that clinically, it can reliably distinguish benign from malignant nodules.

As a result; early detection of malignant nodules is essential for effective disease management and reducing mortality rates. In the past ten years, the development of CAD systems utilizing artificial intelligence for the early detection of thyroid cancer has been extremely rapid. Thanks to these technologies, thyroid nodule treatment will develop. This article provides an review of the use of ML in the diagnosis of thyroid nodules. The overall result of this study showed that it will significantly benefit thyroid tumor classification with the latest advances in ML approaches and high specificity, sensitivity, accuracy and other performance metrics.

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RESEARCH ARTICLE

What Impact does a Pandemic have on Emergency Department Visits? COVID-19 Pandemic and Coronaphobia

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Abstract

Objective: During the COVID-19 pandemic, emergency department visits decreased all around the world. This has been linked to reduced access to health care services associated with the pandemic, changes in social life, and individuals avoiding health care facilities to avoid disease contamination. Lack of access to emergency department services for health problems requiring urgent care can lead to complications and outcomes resulting in mortality and disability. The purpose of this study was to examine the postponement of emergency department visits during the pandemic and to explore the reasons for these delays.

Methods: A cross-sectional study was conducted in the emergency department of a university hospital in the Black Sea region of Turkey. The study population consisted of patients 18 years of age and older. Patients who met the inclusion criteria were given a questionnaire that included a COVID-19 Phobia Scale. The data collection forms were administered by ED physicians through face-to-face interviews.

Results: The research was completed with 352 patients. 27.0% of the participants stated delays in their emergency department visits due to COVID-19 pandemic. The most common reasons for postponing emergency department visits were reluctance to visit a hospital because of the pandemic (46.3%), lack of an individual to accompany the patient (28.4%), and difficulty in finding proper transportation (18.9%). ED visit delays were significantly higher among single patients than married ones and were significantly lower in patients aged 31-55 compared to other patients (p<0.05). No statistically significant difference was found in terms of COVID-19 Phobia Scale scores between patients postponing emergency department visits and those not postponing them (p>0.05).

Conclusion: Around one in three patients postponed their visits to the emergency department (ED) due to the COVID-19 pandemic. This delay can be attributed to the "fear of exposure to the disease," which is a direct effect of the pandemic. However, there are also indirect effects, such as concerns over finding transportation and an individual to accompany the patient.

Key words: Positive birth experience, birth satisfaction, labor, delivery, midwife.

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INTRODUCTION

The pneumonia cases of unknown cause began being seen in the city of Wuhan in the Chinese province of Hubei after 31st of December 2019. The agent causing these cases was identified on 7th of January 2020, as a new Coronavirus Disease (COVID-19) that had not been previously detected in humans. The first case outside of China was observed in Thailand on 13th of January 2020, after which the virus spread rapidly across the world (1). The number of confirmed cases of COVID-19 infections as of 30th of October 2020, was 44,888,869 worldwide, with 1,178,475 individuals dying in association with the infection (2).

No pharmaceutical methods for treating the disease or preventive measures was developed, at the time of data collection. Therefore, the basic strategy aimed at controlling case numbers in the pandemic and decreasing the burden on the health system had relied on community-based non-pharmaceutical interventions (14). These interventions included case-based isolation aimed at reducing transmission from person to person to the lowest level possible, personal protective measures such as mask-wearing, social distancing, and compliance with hygiene rules, the protection of vulnerable groups, school closures, the banning of mass participation activities, lockdowns, and quarantine apart from under exceptional circumstances (21). Health service provision had also been significantly affected during this time. Postponement of elective care and the prioritization of emergency health problems were adopted to prevent the spread of the disease in health institutions (3).

The changes in social life and health service provision caused by the COVID-19 pandemic, and the fear of contracting the disease had also resulted in a significant decrease in ED visits, while the prevalence of the Coronaphobia also increased among health care workers as well (8). ED visits decreased 42% in the USA (6), 30% in the UK (11), and 34.9% in Germany (7). A reduction in non-urgent visits had formed a significant portion of this decrease (20). 10-60% reduction in ED visits was reported which involved emergency health problems with significant risks of mortality and disability,

such as myocardial infarction, stroke, and hyperglycemic crisis (3, 12, 13).

The decreases in ED visits involving urgent health problems have been linked to a reluctance to visit health care providers out of concerns regarding the COVID-19 pandemic (4, 7). Delayed visits of critical patients, whose clinical conditions require immediate attention, can have severe consequences, such as increased complication rates, limited therapeutic options, and mortality (15, 17, 18, 19). The present study investigated whether patients going to the emergency department of a university hospital in Turkey, which served as a regional reference hospital during the COVID-19 pandemic, delayed their visit to the emergency department.

METHODS

Type of research

A cross-sectional study.

Research location

The research was conducted over one-week period at the xxx Health Application and Research Center emergency department. This is a tertiary university hospital with a 780-bed capacity. The hospital emergency department contains 38 beds in a trauma, yellow, red, and green zones specially designed for the provision of treatment and observation services. The emergency department receives approximately 250 visits a day, and serves as an emergency care center receiving patients referred for treatment and care from other provinces in its region.

The research population and sample selection

Patients aged 18 and over going to the emergency department during the study period constituted the research population. The following criteria were applied during sample selection:

- Inclusion criteria: Patients aged 18 or over visiting the xxx Hospital Emergency Department between the dates specified. To agree to participate in the study.

- Exclusion criteria: Patients aged under 18, or who were unconscious or disoriented and unable to cooperate were excluded. Not agreeing to participate in the study.

Data collection

A questionnaire developed by authors who serve as physicians in the study hospital, and the COVID-19 Phobia Scale was applied to patients meeting the inclusion criteria. Data collection is performed by ED physicians via face-to-face interviews following examination and treatment of patients. All participants were informed about the study before the questionnaire was administered, the ethics committee approval document was submitted, and they were verbally asked if they wished to participate in the questionnaire. Those who declined were not interviewed and continued their usual care in the emergency department.

The questionnaire consisted of seven questions concerning demographic characteristics (sex, education, marital status, smoking, alcohol consumption, presence of chronic disease, and other people in the household), five questions concerning ED visit (level of urgency, postponement of presentations and reasons therefore, time of onset of symptoms, whether any measures had been taken to resolve health symptoms before presentation, and attendance at any other health institution), eleven questions concerning personal protective measures against COVID-19 disease (wearing masks, carrying hand sanitizers, social distancing, changing clothing after returning home, hand-washing, accepting invitations, paying visits to others, receiving visitors at home, use of mass transportation, and changes in shopping frequency and frequency of smoking and/or alcohol consumption), and three questions intended to elicit patients' anxiety regarding COVID-19 disease. The applicability of the questionnaire was evaluated by an emergency medicine physician working in the Emergency Medicine Department, and public health specialist from the Public Health Department, and a psychiatrist from the Psychiatric Department.

The COVID-19 Phobia Scale was used to determine the effect of Coronaphobia on patients' postponement of emergency department visits. This five-point Likert-type scale developed by Arpacı et al. (2020) consists of 20 items in four sub-dimensions – psychological (six items), somatic (five items), social (five items) and economic (four items). Possible scores range between 20 and 100, with higher scores indicating greater coronaphobia. Validity and reliability study of the scale showed that the sub-dimensions exhibit adequate internal consistency ($0.853 < \alpha < 0.897$), with a Cronbach alpha value for the entire scale of 0.926 (16). The Cronbach alpha value of the COVID-19 Phobia Scale in the present study was 0.920.

Ethical committee approval

Ethical committee (No 2020-196 dated 13.07.2020) for the study was obtained from the Regional Clinical Research Ethical Committee, together with institution approval from the hospital where it was performed, and verbal consent from the participants.

Statistical analysis

The study data were analyzed on IBM Statistical Package for Social Sciences software (IBM SPSS; Armonk, NY, USA). Descriptive data were presented as raw numbers and percentages. The chi-square test was applied to analyze qualitative data. Normality of distribution was evaluated using the Kolmogorov-Smirnov test. Normally distributed data were compared between two groups using Student's t-test, or using ANOVA for comparisons between more than two groups. Non-normally distributed data were analyzed using the Mann Whitney-U test for

comparisons between two groups, and the Kruskal Wallis test for three or more groups. p values <0.05 were regarded as statistically significant.

RESULTS

379 patients participated in the research who visited to the emergency department during the data collection period. Out of this number, 27 patients were excluded because of incomplete responses to the questions on the data collection form. The research analyses were thus conducted with data from 352 patients.

The sociodemographic characteristics of the patients in the study are given in Table 1. The median age of the participants was 46 (min=17, max=98), 63.4% were men, 73.6% were married, and 41.9% were educated at the middle or high school level. A chronic disease was present in 47.6% of the participants (Table 1).

Twenty-seven percent (n=95) of the patients reported delaying their visits after the onset of symptoms due to the COVID-19 pandemic. The most common reasons for postponing emergency department visits were reluctance to go to hospital because of the pandemic (46.8%), the lack of an individual to accompany the patient at that time (28.7%), and difficulty in finding transportation (19.1%). In addition, 15.4% of patients reported visiting the ED at least three days after the onset of symptoms, and 56.5% of patients took no measures to overcome their health problems prior to visiting the emergency department (Table 2).

One hundred and forty patients (39.8%) were reluctant to present to hospitals during the COVID-19 pandemic, 70.7% of whom attributed this to a fear of exposure to the virus. Other reasons reported by patients included clinics being closed (12.9%), anxiety over inability to find a doctor (9.3%), and inability to make an appointment (7.1%).

Analysis of postponement of emergency department visits during the COVID-19 pandemic in terms of sociodemographic characteristics revealed significant variation between patient groups established on the basis of age (p=0.023). Two-way comparisons between the groups revealed a significantly lower prevalence of delaying emergency department visits in patients aged 31-55 (19.3%) compared to those aged 30 or under (35.0%) and those aged over 55 (30.3%) (p=0.035 and p=0.015, respectively). The rate of emergency department visit delays was also higher among single patients (38.0%) than among married patients (23.3%) (p=0.007). Comparisons based on other sociodemographic characteristics and levels of urgency revealed no significant differences between patients in terms of delaying emergency department visits (p>0.05). No significant difference was found in this study between delayed and non-delayed visits in terms of level of urgency or time of onset of symptoms (p>0.05) (Table 3).

In this study, 54.3% of patients postponing emergency department visits always wore masks outside the home, 57.4% always complied with social distancing, and 50.9% always changed their clothes after returning home. In addition, 34.7% of the patients significantly increased the frequency of handwashing during the coronavirus pandemic, 73.5% significantly reduced their attendance of social activities such as communal fast-breaking dinners, and 67.3% significantly reduced their frequency of visiting friends and family in their houses (Table 4).

Examination of anxiety and concerns due to COVID-19 pandemic revealed that 81.5% of the participants had never experienced symptoms such as chest pain, respiratory difficulty, palpitations, syncope, or weakness due to fear of coronavirus. 40.3% of participants felt no anxiety because of the pandemic becoming a social disaster or causing economic problems (Table 5).

The mean COVID-19 Phobia Scale score of patients visiting emergency department was 48.3±14.9. Analysis revealed that patients delaying their visits had a higher median score on all subscales than those not delaying their visits. However, this difference between the patient groups was not statistically significant (p>0.05) (Table 5).

Patients' COVID-19 Phobia Sale scores according to sociodemographic and presentation-related characteristics are shown in Table 6. Our analysis showed that women had significantly higher mean scale scores (50.4±13.97) than men (47.0±15.34), and that individuals who applied some method intended to overcome health problems prior to presenting to the emergency department also had higher mean scores (50.1± 14.67) than those not employing such methods (p=0.040 and p=0.044, respectively). Patients' scores did not differ significantly in terms of other variables (p>0.05).

DISCUSSION

Approximately one in three patients visiting the emergency department delayed their visits. The most common reason for postponements was reluctance to visit hospital due to the COVID-19 pandemic, followed by absence of an accompanying relative, and difficulty in finding transportation. No significant difference was determined between patients postponing and not postponing visits to the emergency department in terms of mean COVID-19 Phobia Scale scores and subscale scores. Analysis of compliance with personal protective measures against the COVID-19 pandemic among the patients revealed that more than half of them always applied personal protective measures. The rate of postponement of ED visits was also higher among single patients than married individuals.

Twenty-seven percent of patients going to the emergency department in the present study delayed their visits after the onset of symptoms

due to fear of contracting COVID-19. Similarly, research from the United States reported that 12.0% of adults avoided the ED visits due to anxieties over the COVID-19 pandemic (4). A significant global decrease in ED visits was observed due to reluctance to visit (5,6). However, a noteworthy increase was recorded in deaths due to complications other than COVID-19 during the pandemic (7). Avoidance of emergency department visits not requiring urgent care has led to a decreased workload in these departments during the pandemic and has contributed to the prevention of the spread of COVID-19 in the community. However, inability to intervene promptly in emergency conditions can result in the exacerbation of health problems and increased mortality, and it is therefore important for the public to be appropriately informed on this subject.

The study results show that the COVID-19 pandemic leads directly to avoidance of emergency department presentations by causing fear of transmission of the disease, and that it also plays an indirect role in decreased presentations to health institutions due to its impacts on social and daily life.

Marital status and age found to be correlated with postponement of visits. ED visit delays was higher among participants age 30 or below and 55 or above, and among singles. The lower rate of postponement of visits in the 31-55 age group may be due to individuals in that age

group having fewer difficulties related to finding transportation or someone to accompany them than individuals aged over 55 or under 30.

Table 1. Sociodemographic characteristics of patients included in the study.

	n	%
Age (n=347)		
<35 years	98	29.3
35-49	97	27.6
50-64	66	18.8
≥65	86	24.4
Gender (n=352)		
Female	129	36.6
Male	223	63.4
Education (n=351)		
Illiterate or elementary school	138	39.3
Middle and high school	147	41.9
University and postgraduate	66	18.8
Marital status (n=349)		
Single	92	26.4
Married	257	73.6
Place of residence (n=343)		
Village	89	25.9
City	254	74.1
Smoking status (n=352)		
Smoker	121	34.4
Non-smoker	231	65.6
Alcohol consumption (n=348)		
Yes	23	6.6
No	325	93.4
Chronic disease (n=351)		
Yes	167	47.6
No	184	52.4
Individuals in the household (n=350)		
Family	324	92.6
Friend	10	2.9
Living alone	16	4.6

The higher rate of visit postponement among unmarried individuals may be associated with the fact that most single participants were aged under 30. Results in Czeisler et al. (2020) showed that being in the younger age group (18-24) was linked to avoidance of requesting emergency health services during the COVID-19 pandemic is compatible with our own finding

Table 2. ED visits characteristics, reasons for postponements, and measures adopted before presentation.

Urgency level. (n=351)	n	%
High (USI 1-3)	213	60.7
Low (USI 4-5)	138	39.3
Time of inset of symptoms (n=338)		
≤3 hours	116	34.3
>3-24 hours	63	18.6
1-3 hours	107	31.7
>3 days	52	15.4
Emergency department postponement status (n=352)		
Postponed	95	27.0
Not postponed	257	73.0
Reasons for postponement of emergency department presentations (n=94)		
I waited because I was reluctant to go to hospital because of the pandemic	44	46.8
I waited so relatives could accompany me	27	28.7
I waited to find transportation	18	19.1
I waited because of lockdown	4	4.3
I waited because my relative was reluctant to take me to hospital because of the pandemic	1	1.1
Measures taken to resolve the health problem before presentation ** (n=352)		
No measures taken	199	56.5
Medical treatment decided by the patient	47	13.4
Herbal therapy	4	1.1
Massage	2	0.6
Telephone consultation with health officials	12	3.4
Presentation to family physicians	11	3.1
Presentation to public hospital	69	19.6
Presentation to university hospital	20	5.7
Presentation to private hospital	4	1.1

*USI: Urgency Severity Index, **Participants were able to select more than one option

Table 3. Characteristics of emergency department presentations depending on reasons for postponement

Sociodemographic characteristics	Delayed ED presentations		Non-delayed ED presentations		
	n	%	n	%	p value
Age (n=347)					
<30	28	30.1	52	20.5	
31-55	27	29.0	113	44.5	**0.023**
≥55	38	40.9	89	35.0	
Sex (n=352)					
Female	40	42.1	89	34.6	0.196
Male	55	57.9	168	65.4	
Education (n=351)					
Illiterate or primary school	40	42.1	98	38.3	
Middle and high school	32	33.7	115	44.9	0.112
University and postgraduate	23	24.2	43	16.8	
Marital status (n=349)					
Single	35	36.8	57	22.2	**0.007**
Married	60	63.2	197	77.6	
Place of residence (n=343)					
Village	27	29.3	62	24.7	0.465
City	65	70.7	189	75.3	
Chronic disease (n=351)					
Yes	43	45.3	124	48.7	0.597
No	52	54.7	132	51.6	
Presentation-related characteristics					
Urgency level (n=351)					
High (USI 1-3)	53	55.8	160	62.5	0.253
Low (USI 4-5)	42	44.2	96	37.5	
Time of onset of symptoms (n=338)					
≤3 hours	24	26.7	92	37.1	
>3-24 hours	20	22.2	43	17.3	0.129
1-3 days	27	30.0	80	32.3	
>3 days	19	21.1	33	13.3	

*: Emergency Department

Table 4. Patients' compliance with personal precautions during the COVID-19 pandemic (N=352)

Personal precautions. N (%)	Never	Rarely	Sometimes	Often	Always
Social distancing	-	12 (3.4)	31 (8.8)	107 (30.4)	202 (57.4)
Wearing masks outside the home	12 (3.4)	20 (5.7)	37 (10.5)	92 (26.1)	191 (54.3)
Changing clothes after returning home	8 (2.3)	21 (6.0)	43 (12.2)	101 (28.7)	179 (50.9)
Carrying hand disinfectant	39 (11.1)	52 (14.8)	59 (16.8)	90 (25.6)	112 (31.8)
	Decreased significantly	Decreased	Unchanged	Increased	Increased significantly
Handwashing	4 (1.1)	1 (0.3)	71 (20.2)	154 (43.8)	122 (34.7)
*Accepting invitations to communal activities	258 (73.5)	76 (21.7)	13 (3.7)	3 (0.9)	1 (0.3)
Visiting others' homes	237 (67.3)	97 (27.6)	11 (3.1)	6 (1.7)	1 (0.3)
Receiving visitors in the home	215 (61.1)	117 (33.2)	12 (3.4)	6 (1.7)	2 (0.6)
Using mass transportation	177 (50.3)	94 (26.7)	66 (18.8)	8 (2.3)	7 (2.0)
* Going shopping	195 (55.6)	109 (31.1)	38 (10.8)	6 (1.7)	3 (0.9)
**Frequency of smoking/alcohol use	86 (33.1)	42 (16.2)	124 (47.7)	8 (3.1)	-

*Answered by 351 participants y, ** Answered by 260 participants

Table 5: Patients' anxiety status regarding infectious COVID-19 disease (N=352)

Anxiety regarding the pandemic. n (%)	Never	Rarely	Sometimes	Often	Always
Physical findings associated with fear of the pandemic (palpitations. weakness. etc.)	287 (81.5)	36 (10.2)	16 (4.5)	8 (2.3)	5 (1.4)
*Concern that the pandemic may result in a social disaster	142 (40.3)	72 (20.5)	82 (23.3)	38 (10.8)	18 (5.1)
*Economic anxieties concerning the pandemic	142 (40.3)	71 (20.2)	83 (23.6)	38 (10.8)	18 (5.1)

*Answered by 351 participants.

Table 6: COVID-19 Phobia Scale scores of patients presenting to the emergency department (N=352)

	Not postponing ED presentations*		Postponing ED presentations		
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	p value
Psychological subscale	14.6±5.34	14 (6-28)	15.0 ± 4.56	15 (6-24)	0.378
Somatic subscale	12.5±4.07	13 (5-24)	13.2 ± 3.57	14 (5-21)	0.092
Social subscale	10.9±4.04	11 (5-23)	11.5 ± 3.27	12 (5-18)	0.081
Economic subscale	9.4±3.33	9 (4-19)	9.6 ± 3.08	10 (4-16)	0.410
Total score	47.8±15.50	48 (20-92)	49.5 ± 13.23	50 (20-77)	0.215

ED*: Emergency Department

Table 7: Distribution of COVID-19 Phobia Scale scores by sociodemographic and presentation-related characteristics

Sociodemographic characteristics	COVID-19 Phobia Scale scores			
	n	Mean	SD	p value
Age (n=347)				
<30	80	50.8	13.80	
31-55	140	49.0	15.07	0.070
≥55	127	46.1	15.11	
Sex (n=352)				
Female	129	50.4	13.97	**0.040**
Male	223	47.0	15.34	
Education (n=351)				
Illiterate or primary school	138	47.3	15.12	
Middle and high school	147	49.6	14.62	0.334
University and postgraduate	66	47.1	15.20	
Marital status (n=349)				
Single	92	50.1	13.88	0.180
Married	257	47.6	15.32	
Place of residence (n=343)				
Village	89	46.7	15.63	0.294
City	254	48.6	14.58	
Chronic disease (n=351)				
Yes	167	46.9	15.12	0.122
No	184	49.4	14.58	
Presentation-related characteristics				
Urgency level (n=351)				
High (USI 1-3)	213	47.6	15.37	0.323
Low (USI 4-5)	138	49.3	14.27	
Presentation to another health institution before the ED (n=352)				
Yes	98	48.1	15.03	0.876
No	254	48.4	14.91	
Use of measures to resolve the health problem before presentation to the ED (n=352)				
Yes	153	50.1	14.67	**0.044**
No	199	46.9	15.00	

ED*: Emergency Department

No significant relationship was found between visit delays for reasons associated with the COVID-19 pandemic and other visits in terms of level of urgency. Reports from across the world have reported significant exacerbation of health problems because of delayed emergency department visits during the COVID-19 pandemic, together with an increase in numbers of critical visits (10).

The study has some limitations. The absence of any relationship between visits delayed for reasons associated with the COVID-19 pandemic and others in terms of level of urgency may be associated with the absence of any difference among visits in terms of time

since the onset of symptoms. Further multicenter studies with larger sample numbers are now needed for a better understanding of reasons for postponement of emergency department visits during the pandemic.

The median COVID-19 Phobia Scale score of individuals postponing visits to the emergency department due to anxieties concerning the COVID-19 pandemic (median= 50) was slightly higher than that of patients who did not delay their visits (median= 48), although the difference was not statistically significant. Our review of the literature revealed no previous study investigating the effect of corona-phobia on the postponement of emergency department presentations, at the time of this study. However, the findings of the present study show no significant relationship between COVID-19 Phobia Scale scores and visit delay. Due to the confusion caused by the rapid spread of the disease and unconfirmed information about treatment, and rising mortality rates, the COVID-19 can result in panic and anxiety disorders, in addition to fear (9). We think that further studies evaluating the fear due to the pandemic and other psychological consequences and considering changes in social life can provide useful information in elucidating the association between the pandemic and postponement of emergency department visits.

At least half of patients visiting the emergency department reported 'always complying with precautionary measures' against COVID-19 disease. Compliance with personal protection measures is regarded as the most effective means of individual and mass protection against COVID-19 disease. From that perspective, social information and awareness activities are particularly important in terms of raising compliance with such measures.

CONCLUSION

As many as approximately one in three patients visiting the ED during the pandemic delayed their visits after the onset of symptoms due to anxiety over contracting COVID-19 disease and reasons associated with the pandemic. The mortality and disability rates resulting from such delays are still unknown. Considering that the pandemic could persist for a long time, it is even more important for the society to be properly informed about the importance of timely use of emergency care services. Therefore, we believe that communication and collaboration between public health specialists, health service managers, and emergency health service providers need to be established for the society to be accurately informed on this subject. (1–14)

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RESEARCH ARTICLE

Determination of Satisfaction Levels and Related Factors Regarding Women's Positive Birth Experience: A Sectional Study

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Abstract

Objective: The aim of this study was to determine the satisfaction levels and related factors related to the positive birth experience of women.

Methods: This study, using a quantitative approach, is a descriptive and cross-sectional study based on the general survey model. The sample of the study consisted of 276 women who gave normal birth in the gynecology and obstetrics services 24 hours after giving birth in a training and research hospital in a province in the south of Turkey between 17.05.2022 and 29.12.2022. The study included postpartum women who were over 37 weeks of gestation, had a healthy fetus, had no complications during pregnancy-birth-postpartum period, were healthy, could speak, understand and write Turkish, had no communication barriers and volunteered to participate in the study. The data were collected face-to-face with a questionnaire prepared using the literature. A series of chi-square analyzes were conducted to examine whether overall satisfaction with the birth experience differed depending on the characteristics of childbirth care.

Results: The ages of the women ranged from 19 to 42 (mean: 28.67±5.25). 54.3% of the participants are under the age of 30, 46% are secondary school graduates and 47.8% are working. 52.2% stated that they were generally satisfied with the birth experience. It is observed that there are significant differences between the groups in all cases except when women are given the freedom to eat and drink during the contraction period and the baby is given to the lap as soon as the baby is born (p < .001).

Conclusion: In our study, it was determined that more than half of the women were generally satisfied with the birth experience. The characteristics of the room where the mothers spent in labor, accompanying the birth of a person they want, receiving one-to-one midwife support, exposure of the personnel to negative behavior, being involved in the decision-making process at birth, receiving understandable information from the health personnel, respecting the privacy of being allowed to move in labor, ensuring the safety of the baby's life It was determined that providing breastfeeding in the first hour affected the satisfaction of the mothers. It is recommended to conduct large-scale, comprehensive studies evaluating the effect of positive birth experience on maternal satisfaction.

Key words: Positive birth experience, birth satisfaction, labor, delivery, midwife.

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INTRODUCTION

Birth is the most important life experience in the transition to motherhood (1). Birth is a process that is expected in excitement and happiness; it is an event where physical and psychological changes are experienced and different meanings are attributed with different social values, traditions and beliefs (2). Concluding the birth with a positive experience; it can enable the development of positive behavioral patterns such as the mother's return to her normal activity in a short time, the easy establishment of the mother-infant bond and the breastfeeding of the baby in a short time (3).

The World Health Organization's (WHO, 2018d) intrapartum care guide includes definitions and recommendations for a positive birth experience. Care is defined that protects the privacy, property and privacy of all women, is free from harm and ill-treatment, guarantees freedom in their choices, includes information, and includes continuous support during labor and delivery. Evidence-based practice recommendations are given on respectful care and good communication between women and health personnel, pain management in labor, and labor and delivery positions. It is also recommended that women be supported by a person of their choice during the entire birth (4). In recent years, the importance given to birth service quality, women's perceptions of their birth experiences and their satisfaction at birth has been increasing. For this reason, in obstetric practices, health care services have directed women to provide a safe birth, effective birth support, and a high level of satisfaction in birth experience (5).

Birth satisfaction can be defined as psychologically affecting different aspects of birth positively. It is emphasized that the positive birth experience contributes to women's self-confidence, such as increasing their self-confidence, less intervention in childbirth, facilitating postpartum adjustment, stronger mother-infant bonding, positive approach to their next birth (6, 7). As for the negative birth experience; It is associated with inadequacy in breastfeeding and maternal attachment, postpartum depression, difficulty in providing care to the baby, sexual reluctance, and fear of next birth (8, 9). Birth satisfaction, which is a multidimensional concept; many factors affect women's socio-demographic and obstetric characteristics, personal expectations,

care and support characteristics during the birth process (6, 10). As having a positive birth experience is an outcome that is increasingly valued, the characteristics of the woman, the mode of delivery, etc. no matter what, the primary approach of health professionals in labor should be to achieve a high level of satisfaction (11, 12). Therefore, evaluating whether experiencing a positive birth affects the mother's satisfaction with the birth may be important to make the mother's birth experiences positive. There are few studies in the literature evaluating positive birth experiences and mothers' satisfaction with birth. With this study, it was aimed to determine the satisfaction levels and related factors related to the positive birth experience of women.

METHODS

Research design

This study, using a quantitative approach, is a descriptive and cross-sectional study based on the general survey model.

Participants

The population of the study consisted of 426 women who gave birth in a training and research hospital in a province in the south of Turkey between 17.05.2022 and 29.12.2022. The result of the power analysis made with the help of the Gpower 3.1 software program; it was determined that 262 women should be included in the sample with 80% power, 5% margin of error and medium effect size. The sample of the study consisted of a total of 276

women who had a normal delivery in the obstetrics and gynecology services 24 hours after delivery. The study included postpartum women who were over 37 weeks of gestation, had a healthy fetus, had no complications during pregnancy-birth-postpartum period, were healthy, could speak, understand and write Turkish, had no communication barriers (hearing, visual impairment, etc.) and volunteered to participate in the study.

Measure

In the research, a questionnaire form prepared by making use of the literature suitable for the purpose of the study was used as a data collection tool (1-7, 10-12). Survey form; personal information 6 questions (age, education status, employment status, etc.), information about pregnancy 7 questions (number of pregnancies, number of births, pregnancy planning status, type of delivery requested at the beginning of pregnancy, number of antenatal follow-ups, institution and satisfaction status, etc.), birth 13 questions (type of birth, receiving birth support, negative behavior from healthcare professionals, participating in the process, providing information about the process, having freedom of movement and eating and drinking, protecting privacy, providing skin contact and early breastfeeding), birth It consists of a total of 3 sections and 26 questions, 1 question questioning the general satisfaction with the

experience (from hospital admission to discharge).

Procedure

In order to evaluate the comprehensibility and operability of the questionnaire, a preliminary application was made with a total of 30 women who met the sample selection criteria and agreed to participate in the research. Since no changes were made in the questions in the form after the pre-application, the women who took part in the pre-application were included in the sample of the study. The process of collecting the research data was applied to women who met the sample selection criteria in the obstetrics and gynecology services, approximately 24 hours after delivery. The data were filled in by the woman herself in her room. The questionnaires were filled in approximately within 10 minutes.

Ethical aspect

The study was conducted under the ethical principles of the Declaration of Helsinki for medical research involving human subjects. Ethics committee approval of the research; it was obtained from the Non-Interventional Clinical Research Ethics Committee of a state university (Approval Date: 08.04.2022 and Decision No: 121/71). Institutional permission was obtained to carry out the study (Approval Date: 16.05.2022 and Decision No: 050.06.04). In addition, before the interview to the participants, necessary explanations were made and written informed consent was obtained from the volunteers.

Statistical analysis

The data obtained from the research were evaluated by the researcher using the Statistical Program for Social Sciences (SPSS) for Windows 24 program. In the analysis of descriptive data; number, percentage, minimum and maximum values, mean and standard deviation values were used. Continuity correction according to expected value levels and Pearson-$\chi2$ test statistics were used to examine the relationships between two qualitative variables. The statistical significance level was accepted as $p<0.05$ in all statistical analyzes.

RESULTS

The sample of this study consists of 276 participants aged between 19 and 42 (mean = 28.67±5.25). One hundred and fifty participants (54.3%) are under 30 years old and 126 (45.7%) are 30 years old and over. 76 (27.5%) participants are primary school graduates, 127 (46%) participants are secondary education graduates and 73 (26.4%) participants are higher education graduates. One hundred thirty two (47.8%) participants are working and 247 (89.5%) of them have social security. One hundred forty nine (54%) participants live in the province and the vast majority (67.8%) stated that their income is less than their expenses. Information on the socio-

demographic characteristics of the participants is presented in Table 1.

Hundred and two (37%) participants were primar and 174 (63%) were multipara. The last pregnancy of 169 (61.2%) was planned. Pregnancy follow-ups of the majority of the participants were carried out in the state hospital (77.9%), and 159 (57.6%) stated that they were satisfied with the care in the pregnancy follow-ups, while 144 (52.2%) stated that they were generally satisfied with the birth experience. The characteristics of the participants regarding the birth experience are presented in Table 2.

One hundred thirty six of the participants (49.3%) had labor pains in a single room, and 140 (50.7%) in a ward type room. A relative of 99 (35.8%) participants was accompanied at birth. One hundred sixty four (59.4%) participants received adequate one-to-one midwife support at birth. However, 117 (42.4%) participants reported that they were exposed to the negative behavior of the staff at birth. One hundred thirty six (49.3%) participants stated that health personnel provided participation in decisions about birth, 134 (48.6%) participants stated that they

provided understandable information from health personnel at birth. While 127 (46%) participants were allowed to move during the contraction period, 19 (6.9%) participants were given the freedom to eat and drink during the contraction period. One hundred thirty six (49.3%) participants stated that they paid attention to privacy during birth. None of the participants were allowed to give birth in the desired position. Two hundred sixty eight (97.1%) babies were given to the lap after they were cared for. Finally, 150 (54.3%) of the infants were breastfed in the first hours of their lives. Features related to birth process care are presented in Table 3.

A series of chi-square analyzes were conducted to examine whether overall satisfaction with the birth experience differed depending on the characteristics of childbirth care. When the results obtained are examined, it is seen that there are significant differences between the groups in all cases except when the freedom to eat and drink is given during the contraction period and the baby is given to the lap as soon as it is born (p < .001). The findings are presented in Table 4.

Table 1 Socio-demographic characteristics of the participants

Variables	n	%
Age		
<30	150	54.3
≥30	126	45.7
Education level		
Primary education	76	27.5
Secondary education	127	46.0
High education	73	26.4
Working status		
Yes	132	47.8
No	144	52.2
Social insurance		
Yes	247	89.5
No	29	10.5
Place of residence		
Province	149	54.0
County	94	34.1
Village	33	12.0
Income rate		
Income less than expenses	187	67.8
Income less than expenses	79	28.6
Income more than expenses	10	3.6

Table 2 Characteristics of the participants regarding the birth experience

Variables	n	%
Total number of births		
Primiparous	102	37.0
Multiparous	174	63.0
Is the last pregnancy planned?		
Yes	169	61.2
No	107	38.8
Institution that carries out pregnancy follow-up		
Public hospital	215	77.9
Private hospital	9	3.3
Both of them	52	18.8
Satisfaction with care in pregnancy follow-ups		
Pleased	159	57.6
Not glad	117	42.4
General satisfaction with your birth experience		
Pleased	144	52.2
Not glad	132	47.8

Table 3 Features related to childbirth care

Variables	n	%
The feature of the room where labor pains were experienced		
Single	136	49.3
Ward	140	50.7
Accompanying a preferred relative at birth		
Yes	99	35.8
No	177	64.2
Availability of adequate one-to-one midwife support at birth		
Yes	164	59.4
No	112	40.6
Exposure of staff to negative behavior at birth		
Yes	117	42.4
No	159	57.6
The state of ensuring participation of health personnel in decisions about birth		
Yes	136	49.3
No	140	50.7
Providing comprehensible information from healthcare professionals at birth		
Yes	134	48.6
No	142	51.4
No movement allowed during the contraction period		
Yes	127	46.0

No	149	54.0
Giving the freedom to eat and drink during the contraction period		
Yes	19	6.9
No	257	93.1
Paying attention to the protection of privacy at birth		
Yes	136	49.3
No	140	50.7
Giving birth in the desired position		
No	276	100.0
Don't cuddle immediately after the baby is born		
Yes, given at birth	8	2.9
Given after baby's care	268	97.1
Breastfeeding in the first hour of a baby's life		
Yes	150	54.3
No	126	45.7

Table 4 Comparison of general satisfaction rates with birth experience according to characteristics related to childbirth care

Variables		General satisfaction with the birthing experience			χ^2	p
		Glad	**Not glad**	**Total**		
The feature of the room where labor pains were experienced	Single	104 (72.2)	32 (24.2)	136 (49.3)	**63.430**	**.000**
	Ward	40 (27.8)	100 (75.8)	140 (50.7)		
Accompanying a preferred relative at birth	Yes	90 (62.5)	9 (6.8)	99 (35.8)	**36.803**	**.000**
	No	54 (37.5)	123 (93.2)	177 (64.2)		
Availability of adequate one-to-one midwife support at birth	Yes	107 (74.3)	57 (43.2)	164 (59.4)	**27.667**	**.000**
	No	37 (25.7)	75 (56.8)	112 (40.6)		
Exposure of staff to negative behavior at birth	Yes	30 (20.8)	87 (65.9)	117 (42.4)	**57.299**	**.000**
	No	114 (79.2)	45 (34.1)	159 (57.6)		
The state of ensuring participation of health personnel in decisions about birth	Yes	99 (68.8)	37 (28)	136 (49.3)	**45.686**	**.000**
	No	45 (31.3)	95 (72)	140 (50.7)		
Providing comprehensible information from healthcare professionals at birth	Yes	91 (63.2)	43 (32.6)	134 (48.6)	**25.848**	**.000**
	No	53 (36.8)	89 (67.4)	142 (51.4)		
No movement allowed during the contraction period	Yes	83 (57.6)	44 (33.3)	127 (46)	**16.378**	**.000**
	No	61 (42.4)	88 (66.7)	149 (54)		
Giving the freedom to eat and drink during the contraction period	Yes	13 (9)	6 (4.5)	19 (6.9)	2.159	.142
	No	131 (91)	126 (95.5)	257 (93.1)		
Paying attention to the protection of privacy at birth	Yes	86 (59.7)	50 (37.9)	136 (49.3)	**13.147**	**.000**
	No	58 (40.3)	82 (62.1)	140 (50.7)		
Don't cuddle immediately after the baby is born	Yes, given at birth	5 (3.5)	3 (2.3)	8 (2.9)	.352	.553
	Given after baby's care	139 (96.5)	129 (97.7)	268 (97.1)		
Breastfeeding in the first hour of a baby's life	Yes	95 (66)	55 (41.7)	150 (54.3)	**16.398**	**.000**
	No	49 (34)	77 (58.3)	126 (45.7)		

DISCUSSION

With this study, it was aimed to determine the satisfaction levels and related factors related to the positive birth experience of women. In our study, more than half of the women stated that they were generally satisfied with the birth experience (Table 2). Satisfaction with birth and birth, which is a very important experience in women's lives, is extremely important in ensuring the health of the mother and newborn and the continuity of a positive family atmosphere (15).

In this study, about half of the women; it was determined that she stayed in a single room, received adequate one-to-one midwife support during birth, health personnel participated in the decisions about birth, provided understandable information from health personnel during birth, attention was paid to the protection of privacy, and most women were accompanied by a relative at birth, that is, they experienced positive birth. In addition, it was determined that no woman was allowed to give birth in the position she wanted. Few women breastfed their babies within the first hour (Table 3). For this reason, it will play a key role in ensuring that couples receive quality care during pregnancy, childbirth and postpartum period, especially with the support of health personnel, and being supportive in deciding the appropriate and correct delivery method, in order for couples, especially women, to have a

positive birth experience and to be satisfied with the birth method. (10, 16).

Women mostly give birth in the position preferred by health professionals, not in the birth position they prefer (17). Miselle and Eustace (2020) stated in their study that the decision about which position women should take when giving birth is commonly made by obstetricians or midwives/nurses based on their knowledge and experience (18). Similar results were obtained in our study (Table 4). However, joint decision making with the mother will provide positive experiences for both the mothers who gave birth and the health workers and will increase the satisfaction of the mothers from the birth process (19).

Many factors related to women's positive birth experience and midwifery care have been associated with birth satisfaction (20, 21). In the present study, it was determined that women who were satisfied with the birth experience mostly stayed in a single room, were accompanied by their preferred relatives during the birth, and attention was paid to the protection of privacy. It is of great importance for the birth comfort that the woman spends the birth process in a single room and stays in the same room during the birth (19). Similar to our study, not staying in a single room, having another patient with her, and not having a private room for her during labor were defined as a violation of privacy by women, and it was seen that this process affected the positive

experience they received from birth (22, 23). For a positive birth experience, it is recommended that all women be accompanied by someone (spouse, friend, relative) during labor and delivery (24). It is stated that it is important to respect the wishes of all women and that cultural sensitivities should be taken care of (17). If there are no separate rooms in the institution providing care services, that is, if there is a ward system with more than one bed, curtains, screens, etc. It is emphasized that the privacy and confidentiality of all women with separatists should be protected (25).

It is stated that respectful and supportive approaches of healthcare professionals during the birth process have a very important effect on experiencing positive birth, one-to-one midwife support increases positive birth perception and birth satisfaction, on the other hand, negative and non-empathetic approach causes traumatic birth (16, 26). In this study, it was determined that women who were satisfied with their birth experience were mostly not exposed to negative behavior from the health worker and obtained comprehensible information (Table 4). Garthus-Niegel et al. (2013) stated that if the woman feels safe and well cared for during the birth process, the overall experience is positive despite serious complications, Nilsson et al. (2013) the factors that increase a woman's chance of having a positive birth experience; she reported that she was a supportive and competent midwife and

doctor, meeting with a midwife who helped in prenatal delivery, constant information about the progress of labor, opportunity to participate in decisions during birth (27, 28). The present study findings support the literature. A positive birth experience is an experience that includes giving birth to a healthy baby in a clinically and psychologically safe environment for healthy mothers and healthy babies, and is an important goal of obstetric care (19).

It is stated that as long as there is no problem that prevents the woman from walking or standing during childbirth, freedom of movement and walking should be given to the woman at birth (29). In this study, it was determined that mothers who were allowed to move during the contraction period had a higher overall satisfaction with the birth experience than mothers who were not allowed to move (Table 4). In the current study, less than half of the mothers were allowed to move during the contraction period (Table 3). Similar to these results, Akyıldız et al. (2021), movement restriction is widely used in the first stage of labor, Dasikan et al. (2020) stated that most of the women remained immobile during childbirth (30, 31). It is stated that freedom of movement at birth shortens the time of birth, provides effective birth contraction, reduces the need for painkillers, and also increases birth comfort, satisfaction and enables them to have a positive birth experience (29).

In this study, it was determined that the overall satisfaction with the birth experience of mothers who breastfed their baby in the first hour of life was higher than mothers who could not breastfeed (Table 4).

Offering women the opportunity to have skin-to-skin contact with their babies soon after birth and providing early breastfeeding assistance are best practices to encourage bonding, breastfeeding and birth satisfaction (15). A woman's satisfaction with her birth experience is also important to the well-being of the baby. A mother's positive birth experience has been associated with positive feelings towards her baby and adjustment to the maternal role. Conversely, traumatic births affected women's ability to breastfeed and bond with their children, leading to child neglect and abuse (10, 32).

Birth can be a special and wonderful experience as well as a traumatic experience (6). Having a positive birth experience, recovering in the early postpartum period and achieving physical comfort are the most basic expectations of women after birth (33).

The limitations of the study are that the study is limited to the number of samples in which the study was conducted, and that the results can be generalized only within the group in which the study was conducted.

CONCLUSION

In our study, it was determined that more than half of the women were generally satisfied with the birth experience. It was determined that the characteristics of the room where the mothers gave birth, accompanying the birth of the person they wanted and receiving one-to-one midwife support affected the satisfaction of the mothers. In addition, the negative behaviors of the personnel, being involved in the decision-making process at birth, receiving clear information from the health personnel, freedom of movement and respect for their privacy during birth were other factors affecting the satisfaction of the mothers. In addition, it was determined that ensuring the safety of the baby and providing breastfeeding in the first hour affected the satisfaction of the mothers.

It is recommended to conduct large-scale, comprehensive studies evaluating the effect of positive birth experience on maternal satisfaction. More research is needed to understand the factors that influence birth satisfaction and outcomes from both positive and negative birth.

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The Impact of Carbon Monoxide Intoxication on Thiol/Disulfide Hemostasis

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Abstract

Objective: Carbon monoxide (CO) poisoning is an oxidative stress factor. The aim of the study is to evaluate impact of CO intoxication on thiol/disulfide homeostasis (TDH), an important antioxidative system of the body.

Methods: This is a prospective study included 84 participants in each group. Blood samples were taken two time in study group (CO intoxication group), before and at the end of the 3rd hour of normobaric oxygen therapy and once in the control group. TDH parameters were studied with an automated assay developed by Erel et al. Statistical analysis done with SPSS program.

Results: Among thiol/disulfide homeostasis parameters, in study group native (sh) and total thiol (tt) levels in samples taken at the beginning of the oxygen treatment were significantly higher than sh and tt levels of the control group [Study group sh: 399.70 µmoll−1 (354.50-423.65), tt: 439.1 µmoll−1 (390.9-467.3) and control group sh: 362.95 µmoll−1 (321.95-401.25), tt: 396.1 µmoll−1 (358.5-435), p=0.01 and p<0.001 respectively]. There was no difference between the groups in term of other TDH parameters. TDH parameters were measured after 3-hour normobaric oxygen treatment, and it was shown sh and tt levels were significantly reduced after treatment.

Conclusion: Our study demonstrated that among TDH parameters native and total thiol levels were increasing in patients with CO poisoning and those levels were decreasing in time during normobaric oxygen treatment.

Key words: Carbon monoxide intoxication; Thiol/disulfide homeostasis; oxidative stress; antioxidant systems

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INTRODUCTION

Carbon monoxide (CO) which is also known as "silent killer" is an odorless, colorless, nonirritant gas that is produced by incomplete combustion of carbon-containing components (1). Main mechanism of action is the binding of CO to hemoglobin with a higher affinity, that results with decreased oxygen presentation to tissues. CO also, directly effects electron transport systems in mitochondria and causes an oxidative stress (2). Those oxidative stress triggers many metabolic reactions in platelets, leukocytes, and endothelium and finally, CO intoxication results with production of free radicals, apoptosis, endothelial dysfunction, and lipid peroxidation (3).

Free oxygen radicals are removed by antioxidative systems in the body (4, 5). Thiol/disulfide hemostasis (TDH) is one of the important components of these antioxidative systems. Thiol which is an organic component that contains sulfhydryl group (-SH), exists in proteins such as albumin, cysteine, methionine (6). In case of oxidative stress, thiol groups oxidized and turn into reversible disulfide bridge, that reduced back to thiol groups again. Dynamic TDH is crucial for cellular signal mechanisms, antioxidant defense, detoxification, apoptosis, inflammation, and immune response (3).

The aim of this study is to evaluate changes in thiol/disulfide homeostasis during an important oxidative stress factor, CO poisoning.

METHODS

This is a prospective study, conducted in a training and research hospital with approval of the local ethics committee during six months period. Study included 84 patients diagnosed as carbon monoxide poisoning during their ED visit and 84 healthy volunteers as control group.

Study process

Diagnosis of CO intoxication done with measurement of carboxyhemoglobin (COHb) levels in venous blood samples of patients who had suspicious complaints for CO intoxication like headache, dizziness, etc. Patients who have COHb levels greater than 10% regardless of smoking habit, diagnosed as CO intoxication. Patients younger than 18, who did not consent to participate, who had malignancies or chronic inflammatory diseases, who were pregnant and who had trauma were excluded. After initial evaluation patients in the study group treated with normobaric oxygen. Demographic variables, vital sings and laboratory findings of the participants were recorded into the study forms.

Measurement of thiol/disulfide homeostasis

In the study group blood samples were taken two times, first at the beginning of oxygen treatment and second at the end of the 3rd hour of oxygen treatment; in the control group blood samples were taken only once. The participants' blood samples were stored at −80°C after ten minutes of centrifuge at 3600 cycles. All samples were dissolved simultaneously and studied with

an automated assay developed by Erel et al. with a Roche Hitachi Cobas c501 automatic analyzer (6). By this method we measured the total thiol (tt), native thiol (sh), disulfide (ss), native thiol/total thiol % (sh/tt), disulfide/native thiol % (ss/sh) and disulfide/total thiol % (ss/tt) levels.

Statistical analyses

Statistical analyses were done with SPSS 16.0 (Chicago, IL, USA). Distribution of normality tested with Kolmogorov–Smirnov test and data did not fit normal distribution expressed as median and inter quartile range 25-75. Categorical variables were expressed as number and percentages. Comparison between independent groups were done with Mann-Whitney U test and between dependent groups with Wilcoxon singed-rank test. P value <0.05 considered statistically significant. ROC analyze was done to define cut off values. The value at which sensitivity, specificity, positive predictive and negative predictive values were all greatest, chosen as the best cut off value.

RESULTS

Results of 168 participants (84 in each group) were evaluated. Gender distribution and median age was similar between study and control groups. There was no difference in terms of vital parameters, hemogram values and biochemical parameters; despite lactate, blood urea nitrogen (BUN), glucose and aspartate aminotransferase (AST) which were significantly higher in the study group. Median level of COHb was %27.7 (18.6-32.9) in the study group. (Table 1).

As a result of PCR test, 66 (66%) of the patients were negative and 34 (34%) were positive. All of the patients who were found to be negative with the rapid antigen test were also found to be negative with the PCR test. Only 24 of the 34 PCR positive patients were also positive with the antigen test (Table 1).

Among thiol/disulfide homeostasis parameters, in study group native and total thiol levels in samples taken at the beginning of the oxygen treatment were significantly higher than the native and total thiol levels of the control group [Study group sh: 399.70 µmoll−1 (354.50-423.65), tt: 439.1 µmoll−1 (390.9-467.3) and control group sh: 362.95 µmoll−1 (321.95-401.25), tt: 396.1 µmoll−1 (358.5-435), p=0.01 and p<0.001 respectively]. There was no difference between the groups in term of other TDH parameters (ss, sh/tt, ss/sh and ss/tt ratios, p>0.05 for all circumstances). (Table 2).

In the study group TDH parameters were measured after 3 hour normobaric oxygen treatment and it was shown that native and total thiol levels were significantly reduced after treatment [At the beginning of the treatment sh: 399.7 µmoll−1 (354.5-423.6), tt: 439.1 µmoll−1 (390.9-467.3), at the end of the 3rd hour of oxygen treatment sh: 354.1 µmoll−1 (309.2-398.5), tt: 401.3 µmoll−1 (354.4-444.5), p<0.001 for both]. There was no change in other TDH parameters with treatment. (Table 2).

Table 1. Demographic characteristics, vital parameters and laboratory findings of study and control groups.

	Study group n=84	Control group n=84	P value
Demographics			
Gender: female/male	42/42	39/45	0.6
Age: median (IQR25-75)	36 (26-48)	37.5 (27-49)	0.6
Vitals			
Median (IQR25-75)	125(119-134)	130(121-138)	0.09
Systolic blood pressure	70(63-80)	73(64-80)	0.54
Diastolic blood pressure	80(72-97)	73 (64-80)	0.74
Heart rate	36.2(36-36.5)	36.1(36-36.5)	0.85
Temperature	96 (94-98)	97 (95-98)	0.09
Oxygen saturation			
Laboratory findings			
Median (IQR25-75)			
COHb (%)	27.7 (18.6-32.9)	0.1 (0-0.1)	<0.001
pH	7.41 (7,36-7,45)	7.41 (7.38-7.42)	0.9
Lactate (mmol/L)	1.9 (1.2-2.6)	1.2 (0.9-1.77)	<0.001
Hemoglobin (gr/ dl)	13.9 (12.7-15.3)	13.2 (12.1-14.8)	0.03
White blood cell (10-3/ µl)	9.07 (7.4-12.1)	8.8 (7.1-11.3)	0.5
Platelet (10-3/ µl)	233 (204-287)	256 (223-308)	0.03
Glucose (mmol/L)	106 (96-127)	100 (90-111)	0.007
AST (U/L)	20 (16-26)	17 (14-23)	0.03
ALT (U/L)	18 (13-24)	15 (11-22)	0.07
Creatinine (mg/dl)	0.78 (0.67-0.89)	0.72 (0.66-0.80)	0.16
BUN (mmol/L)	13 (11-16)	13 (10-15)	0.01
Troponin I (ng/ mL)	2.1 (0.6-5.1)	1.65 (0.8-2.6)	0.14

Table 2: Levels of thiol/disulfide parameters in control and study groups

TDH parameters Median (IQR25-75)	Control group	Study group 1st measurement	Study group 2nd measurement	p1*	p2**
Native thiol (µmoll−1)	362.95 (321.9-401.2)	399.7 (354.5-423.6)	354.1 (309.2-398.5)	0.01	<0.001
Disulfide (µmoll−1)	17.5 (10.9-23.1)	19.7 (15.7-23.02)	19.6 (15.5-24)	0.09	0.57
Total thiol (µmoll−1)	396.1 (358.5-435)	439.1 (390.9-467.3)	401.3 (354.4-444.5)	<0.001	<0.001
Native thiol/total thiol %	91.1 (87-94.3)	90.9 (89.6-92.04)	90.1 (88.1-92.3)	0.43	0.23
Disulfide/native thiol %	4.87 (3.02-7.27)	5.01 (4.33-5.78)	5.5 (4.1-6.8)	0.43	0.21
Disulfide/total thiol %	4.44 (2.83-6.48)	4.55 (3.97-5.19)	5 (3.8-6)	0.43	0.23

*p1: Comparison of thiol/disulfide parameters between control group and 1st measurement (beginning of the oxygen treatment) of the study group.

**p2: Comparison of thiol/disulfide parameters between 1st measurement (beginning of the oxygen treatment) and 2nd measurement (at the end of the 3rd hour of oxygen treatment) of the study group.

To evaluate clinical value of total and native thiol for diagnosis of CO poisoning, we made receiver-operating characteristic (ROC) analyze. Area under curve (AUC) was calculated as 0.65 for native thiol and 0.67 for total thiol. Best cut off value for native thiol was 383 µmoll−1 with 61% sensitivity and 61%specificity, 61% positive predictive value (PPV) and %61 negative predictive value (NPV); for total thiol it was 425 µmoll−1 with 62% sensitivity and 67% specificity, 65%PPV and 64% NPV. (Figure 1)

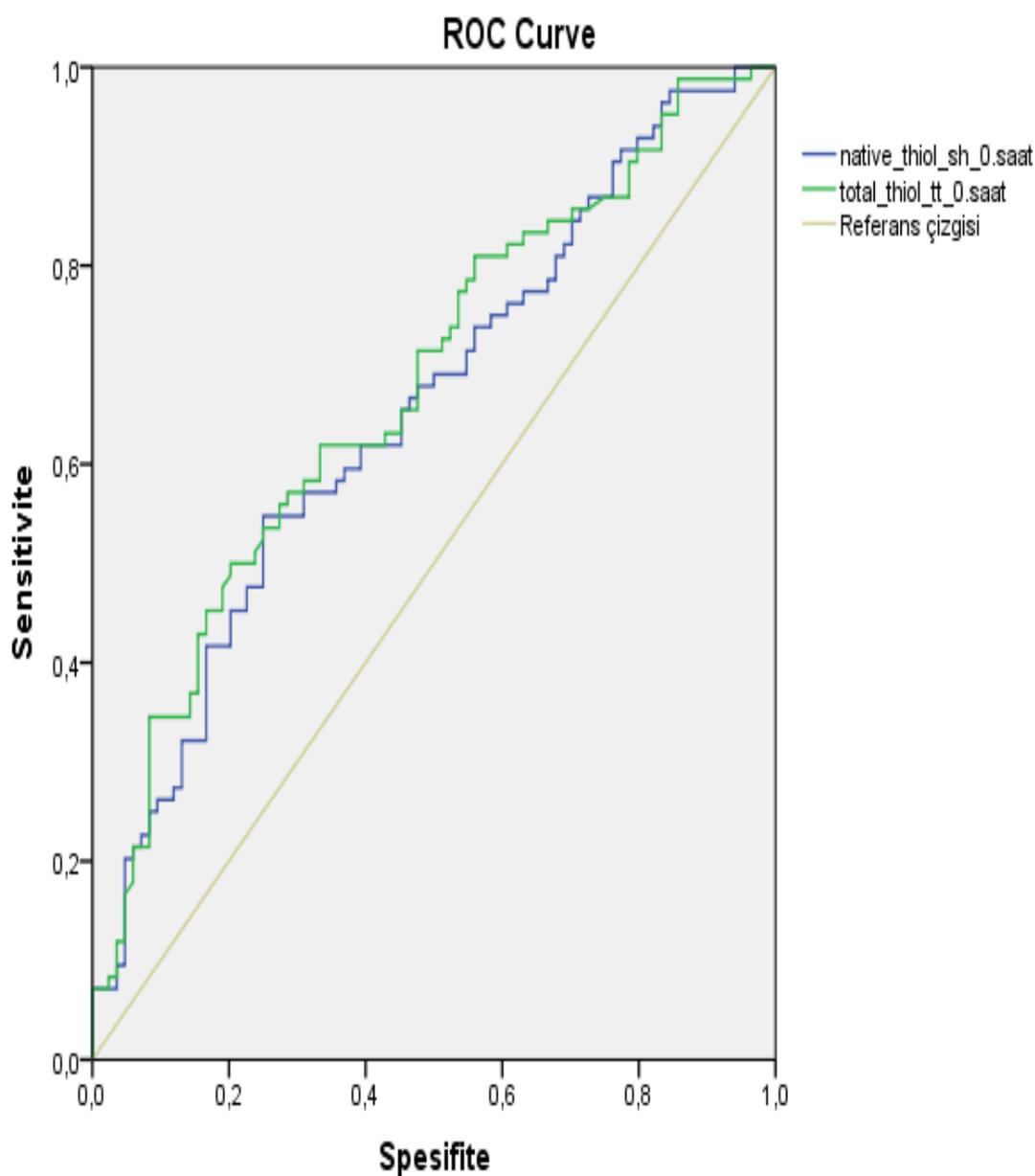**Figure 1:** ROC curve for native and total thiol levels for diagnosis of CO poisoning.

Figure 1. *AUC for native thiol, 0.65; for total thiol, 0.67. P values are 0.001 and <0.001 respectively*.

DISCUSSION

Our study, at which we analyzed the impact of CO intoxication on thiol/disulfide homeostasis, demonstrated that among TDH parameters, only native thiol and total thiol levels were changed with CO intoxication. Despite there was a statistically significant increase at native and total thiol levels during CO intoxication, ROC analyzed showed low AUC values, that means TDH parameters are not useful for differential diagnosis of CO poisoning. Our data also showed, among CO intoxicated patients, native and total thiol levels were decreasing in time during normobaric oxygen therapy.

Main mechanism of CO toxicity defined through hemoglobin, myoglobin, cytochrome oxidase, and cytochrome P450-dependent mechanisms; that higher affinity of those molecules to CO than oxygen leading to tissue hypoxia, myocardial ischemia, and disruption of cellular respiration (7). On the other hand, effect of CO on intracellular targets has not well understood yet but, reason of the cellular damage thought to be the result of oxidative stress. Studies demonstrated that, delayed encephalopathy at CO intoxicated patients is a consequence of lipid peroxidation triggered by oxidative stress (8). Kavaklı et al. studied total oxidant, total antioxidant status and oxidative stress index in their study conducted with CO intoxicated patients and showed that total oxidant status level and oxidative stress index

were significantly higher at CO poisoned group than the control group (9,10). Also, among CO poisoned group those parameters were higher at the beginning of the oxygen therapy, than the levels after the treatment.

Free radicals are produced during normal physiologic process of the body and oxidative effect of those molecules neutralized by antioxidant capacity of the cells; if oxidative stress overwhelms the antioxidative defense, cellular damage occur (11,12). One of the important antioxidant mechanisms of the body is dynamic thiol/disulfide homeostasis. Until now, TDH parameters were studied in several different pathologies, such as endocrine disorders, cardiac pathologies, neurologic diseases, gastrointestinal disorders etc., to elucidate the pathologic mechanism, as a predictor for diagnosis or as a prognostic marker (13). Also, there were studies about TDH parameters in CO intoxicated patients, but they have some conflicting results.

Ergin et al. demonstrated in their study that native thiol and total thiol levels were significantly lower and disulfide was significantly higher in CO intoxicated patients comparing to control group (shCO: 344.29 ± 62.29, shControl: 475 ± 49.01, ttCO: 385.71 ± 66.92, ttControl: 507.87 ± 50.54, ssCO: 20.7 ± 5.03, ssControl: 16.43 ± 3.97 µmol/L, p<0.001, p<0.001 and p=0.001 respectively) (3). Those results were completely different from our results, we found higher native and total thiol

levels in CO intoxicated group and no significant difference in disulfide levels between the groups. The reason of this different results might because of the small sample size and timing of sample intake at Ergin's study. Ergin et al. also studied other oxidant and antioxidant parameters in their study and showed reduced total antioxidant response, paraoxonase and arylesterase levels in CO intoxicated group, with significantly increased total oxidant status and ceruloplasmin levels.

On the other hand, İşler et al., similar with our results demonstrated that native and total thiol levels were significantly higher in CO intoxicated patients and disulfide levels were similar between the groups (shCO: 382.8 ± 106.1, shControl: 330.9 ± 101.7, ttCO: 416.1 ± 98,6, ttControl: 371.0 ± 98.0, ssCO: 16.50 ± 8.15, ssControl: 15.57 ± 7.30 μmol/L, p=0.006, p=0.006, p>0.05 respectively) (14). However, in this study differently from our results native and total thiol levels were increased more after normobaric oxygen therapy. İşler et al. also analyzed the oxidative stress parameters between the groups who received normobaric or hyperbaric oxygen treatment and there was no difference between the groups.

In another study comparing TDH parameters among CO intoxicated patients receiving normobaric or hyperbaric oxygen therapy, Bağcı et al. showed a decrease in native and total thiol levels after treatment with hyperbaric oxygen therapy; there was no difference in TDH parameters before and after the treatment with normobaric oxygen (15). In this study indication of hyperbaric oxygen was having COHb level greater than %15. In our study group median COHb level was 27.7%. Therefore, we might think similar oxidative stress levels in our study group and patients received hyperbaric therapy at that study and our TDH parameter changes were similar with Bağcı et al.'s study. So, role of thiols in antioxidant systems are very complicated and despite knowing thiol disulfide homeostasis' crucial role in redox systems, it is still not known clearly how the balance is achieved in this mechanism (16).

This study has some limitations. First, we did not analyze other oxidative stress markers and total antioxidant status of the patients, which might be helpful to interpret the oxidative status better. Second, we did not evaluate the patients who transferred for hyperbaric oxygen therapy later. It should be better to study TDH parameters before and after hyperbaric oxygen therapy to understand effects of this treatment on oxidative stress.

CONCLUSION

Our study demonstrated that among TDH parameters native and total thiol levels were increasing in patients with CO poisoning and those levels were decreasing in time during normobaric oxygen treatment. There are conflicting results in the literature and to clearly understand how the balance in TDH is

achieved, more comprehensive studies are needed.

Ethical Approval: Ethical approval for this study was obtained from Kecioren Training and Research Hospital Ethics Committee (No: 2012-aKAEK-15).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: ÖEDV, GÇI, ME, TŞ, ŞKÇ, YÇ, Design: ÖEDV, GÇI, ME, TŞ, ŞKÇ, YÇ, Supervision: ÖEDV, GÇI, ME, TŞ, ŞKÇ, YÇ, Data Collection and/or Processing: ÖEDV, GÇI, ME, TŞ, ŞKÇ, YÇ Analysis and/or Interpretation: ÖEDV, GÇI, ME, TŞ, ŞKÇ, YÇ Writing: ÖEDV, GÇI, ME, TŞ, ŞKÇ, YÇ

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Conflict of Interest: The authors declare that there is no conflict of interest.

Informed consent: Written informed consent was not necessary, the present study retrospective and no specific patient data has been included in the manuscript.

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RESEARCH ARTICLE

The Prevalence of Questionnare Based Food Allergy in Adult Population of Eastern Blacksea Region of Turkey

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Abstract

Objective: Food allergy (FA) is an important public health problem which affects children and adults, its prevelance is increasing with the change of dietary habits in recent years. FA is a life-threatening allergic reaction which can lead to anaphylaxis and is very difficult to treat. In our study, we wanted to contribute to the literature by investigating the prevalence of FA in the Eastern Black Sea Region based on a questionnaire.

Methods: This study was planned as a cross-sectional web-based survey study. The questionnaire was prepared including 12 questions related with health problems that develop following food intake. Eastern Black Sea Region of Turkey was chosen as the target group of the study population. The questionnaire was published in local online and printed media during three months and the participants were allowed to fill it out.

Results: The study included 920 people (604 female, 316 male) who completed the questionnaire and 157 (17%) of the participants noted that they had food allergies. The most common allergen foods were spices (15%), tomatoes (10.9%), and cow's milk (7.5%). The most common symptoms were urticaria (63.5%), gastrointestinal symptoms (30.2%), rhinitis (15.1%), oral allergy syndrome (OAS) symptoms (11.3%). Young age (p= 0.004), presence of atopic disease or family history of atopy (p=0.001) were found to be risk factors for the development of food allergy.

Conclusion: The prevalence of self-reported FA based on web-based survey in Eastern Black Sea residents is relatively high and specific to the region.

Key words: Adult, Epidemiology, Food Hypersensitivity, Prevalence, Questionnaire

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INTRODUCTION

FA occurs when foods are mistakenly perceived as foreign by the immune system and clinical symptoms appear that respond to it with different mechanisms. According to population-based studies conducted from various countries with different methodologies, 25% of people think that they are allergic to any food. (1). FA studies all over the world are mostly related to childhood. The data on the prevalence of FA in the adult age group are in a very wide range, such as 3-35% (2). Because, FA prevalence assessment is carried out with different methods in different countries. Double-blind placebo-controlled food challenge tests, which are accepted as the gold standard in the diagnosis of food allergy, are very laborious and are not recommended for population screening. Questionnaires prepared by considering the genetic, cultural and/or nutritional habits of the region are recommended for population screening (3). Based on the questionnaire formed in line with these recommendations, the prevalence of FA in adults was 14.7% in England, 16% in the USA and 12% in the Netherlands. In a European study, the lowest prevalence was found in Spain with 4.6% (2). In our country, the prevalence of FA was found to be 9.5%, according to a telephone survey study conducted only in the adult population of Istanbul province (4).

FA has become an increasing health problem in many countries. FA can affect multiple organ systems, cause widespread allergic reaction and anaphylaxis and has been associated with many specific clinical syndromes. Early detection and appropriate treatment of acute reactions not only saves lives, but also increases the quality of life of individuals. Data on food allergy are mostly related to childhood since it is observed more frequently in childhood and comprehensive studies evaluating FA in the adult population are not available in the world or in our country (5). In this study, it was aimed to determine the prevalence of FA in the adult population and to obtain data for the detection of food allergens specific to the Eastern Black Sea region.

METHODS

Patient Population

In the study, it was aimed to determine the prevalence of FA in the adult population in the Eastern Black Sea Region. This study was conducted as a prospective cross-sectional web-based survey between April 2014 and July 2014. Approval for this thesis was obtained from the local ethics committee. (Approval number: 2014/28, Approval date: 18.02.2014). All procedures performed in the present study were made in accordance with the ethical standards of the Helsinki Declaration (2008). In order to find out the prevalence of FA in the adult population in the Eastern Black Sea region, a questionnaire consisting of 23

questions was prepared by considering the genetic, cultural and/or nutritional habits of the region. General information about FA was put in the local online and printed media, and it was aimed to fill the questionnaire by individuals who are over the age of 18 and living in the Eastern Black Sea region. The questionnaire was filled in completely by the participants on a voluntary basis. Among the participants who filled out the questionnaire published in the local online media, the participants whose age and residence were not suitable were deemed invalid and the questionnaires of 920 individuals who met the necessary conditions were evaluated as valid.

Inclusion and Exclusion Criteria

Inclusion criteria: Individuals over the age of 18, individuals who can answer the survey questions. Exclusion criteria: individuals under the age of 18, individuals who cannot answer the survey questions.

Survey form

In the first 6 questions of our survey, patients were asked questions about their demographic characteristics such as name-surname, age, gender, smoking status, place of birth, place of residence and occupation. In order to detect the presence of additional allergic disease, the participants were asked whether they or their first-degree relatives had allergic disease. Participants who stated that they had an allergic disease were asked to state the allergic disease. Allergic rhinitis, conjunctivitis, asthma, urticaria, angioedema, eczema, drug allergy was offered as options to the participants. The "other" option was offered to those who had other allergic diseases to specify. In the tenth question of the questionnaire, the question "Have you had any health problems with any food item?" was asked to the participants. While the questionnaires of the participants who answered "no" to this question were completed, additional questions were asked to the participants who answered "yes".

Statistical Method

Data from valid questionnaires were analyzed using PASW 18 (SPSS/IBM, Chicago, IL, USA). Descriptive statistics such as frequency distribution, mean and standard deviation were used to define the data. Categorical data were analyzed with "chi-square test" or "Fisher's Exact test". Continuous variables were checked for normality by using Kolmogorov Smirnov test and due to the related variable was non-parametric, the Mann-Whitney U test was performed to compare age of patients.

RESULTS

Web-based questionnaire was answered by 920 subjects voluntarily. The mean age of the study population was 38±15 minumum 18 years and maximum 82 years. Of the participants, 316 (34.3%) were male and 604 (65.7%) were female. Among the 920 participants who filled out the questionnaire, who stated that they lived in the Eastern Black Sea Region, 19 resided in

Artvin, 44 in Trabzon and 862 in Rize. Detailed demographics are summarized in Table 1.

In order to determine the prevalence of FA in the adult population in which the Eastern Black Sea region was chosen as the target population, 158 (17%) of 920 people who filled out the questionnaire published in the local online media stated that they had food allergies. Among participants with food allergy, 104 (11.3%) of them stated that they were allergic to only one food, and 54 (5.8%) of them were allergic to more than one food.
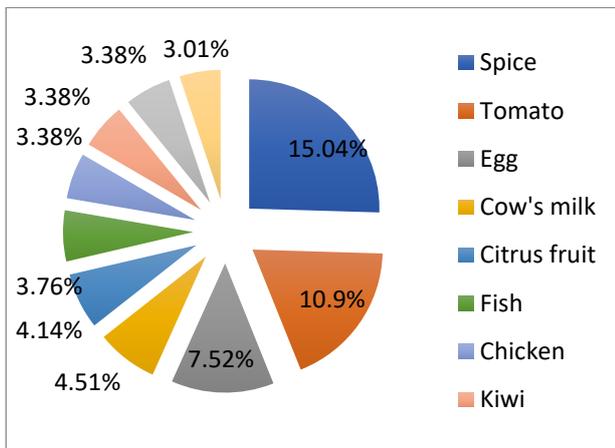

Figure 1. The most common reported foods as food hypersensitivity

Forty participants (15%) who filled out the questionnaire stated that they were allergic to spices which is the highest rate. In order of frequency, 29 participants (11%) had tomato allergy and 20 participants (7.5%) had egg allergy (Table3) (Figure 1). Allergic rhinitis was found to be the most common allergic

disease among individuals who filled out the questionnaire with 174 (18.9%). The second most common allergic disease reported by the participants was asthma and urticaria coexistence with 71 (7.71%), and the third most common allergic disease was eczema with 69 (7.5%). They are followed by asthma with 55 (6%), drug allergy with 46 (5%), and bee allergy with 28 (3%) individuals.

Of the 920 participants who filled out the questionnaire, 122 (13%) stated that they had more than one allergic disease. The most common comorbidities were stated as allergic rhinitis and conjunctivitis with 110 participants (12%). Participants were questioned that if there was an allergic disease in the first-degree relatives of the participants who filled out the questionnaire, 269 (29%) individuals stated that they had an allergic disease in their first-degree relatives.
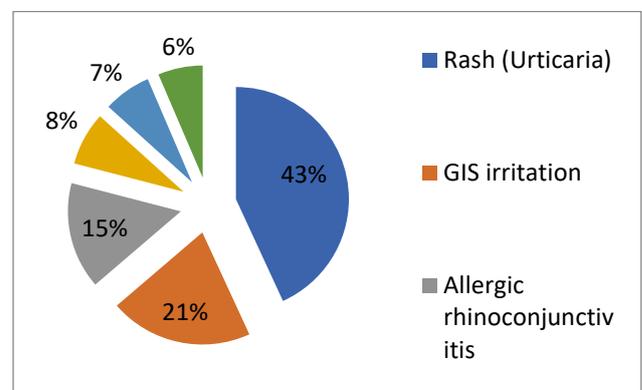
Figure 2. Self-reported symptoms and signs after food intake

The health problems experienced by the participants were, in order of frequency, skin rash, itching, redness (n=101, 63.9%), nausea-vomiting-abdominal pain-bloating (n=48,

Table 1. Demographiccharacteristics of the study population

Parameters		n	%
Gender	Female	604	65.7%
	Male	316	34.3%
City where they live	Rize	862	93.7%
	Trabzon	44	4.78%
	Artvin	19	2.06%
Occupation	Housewife	317	34.45%
	Self-employee	74	8.04%
	Student	117	8.04%
	Other	508	55.21%
Smoking history	Non-smoker	621	68%
	Ex-smoker	113	12%
	Smoker	186	20%

Table 2. Allergic diseases of the participants

Alergic disease	Number (n= 338)	%
Allergic rhinitis	174	18.9
Asthma urticaria-angioedema	71	7.71
Eczema	69	7.5
Asthma	55	5.97
Drug allergy	46	5
Bee sting allergy	28	3.04

Table 3. Top ten food items that participants state they are allergic to food that has been reported

Allergens	Number of people	%
Spice	40	15.04
Tomatoes	29	10.90
Egg	20	7.52
Cow milk	12	4.51
Tangerine-orange	11	4.14
Fish	10	3.76
Chicken meat	9	3.38
Kiwi	9	3.38
Garlic	9	3.38
Veal	8	3.01

Table 4. Young age a risk factor

Allergic status	FA (+) (n=158)	FA (-) (n=762)	All patients (n=920)	P value
Age	38.96 (18-88)	41.2 (20-90)	38 (17-90)	0.004
Gender (female)n (%)	103 (65.1)	501 (65.7)	604 (65.7)	>0.05

DISCUSSION

This study is a survey-based study that reflects the prevalence of FA in the adult age group in the Eastern Black Sea region of Turkey. The questionnaire was filled by 920 participants between the ages of 18-88. As a result of the survey, the frequency of food allergies in adults in the region where the survey was conducted was found to be 17%, and it was determined that the frequency of allergy was more common in younger ages.

The frequency of FA has been increasing in recent years, especially in industrialized societies. There are many epidemiological studies on asthma, atopic dermatitis, and allergic rhinitis, however the number of studies on FA in our country and in the world are limited (5,6). As far as we know, there is not enough data on the prevalence of FA in our country. In the regional studies conducted in our country, the prevalence of FA was observed as 6.2% (7). FA is an immune response to certain foods or food additives. 90% of these reactions are caused by certain foods, such as milk, eggs, peanuts, fish, shellfish, soy and wheat (2,8). In our study, it was determined that there was more allergy to spices. When an allergic reaction develops against these foods, various reactions can be seen around the mouth and lips, ranging from itching to death. In our study, gastrointestinal irritation reactions such as dyspepsia and bloating were found to be more common than other reactions.

In many studies, prevalence of food allergies reported frequencies were quite different. In a multicenter cohort study, McBride et al. reported that the frequency of FA was between 5-30% (9). In other studies on the frequency of FA; with the survey method, Orhan et al. reported that 5.7% of 3500 school children aged 6-9 years in the Eastern Black Sea Region; Roehr et al. reported that 31.4% of 2354 children aged 0-17 years in Germany; Osterballe et al. reported that 16.6% aged 0-22 years (5, 10, 11).

In recent studies, the prevalence of FA in adults has been reported as 12-20% (12,13). In a multicenter study conducted in Europe, FA estimates differ significantly between countries and regions (14). The estimated prevalence was reported as 9.1.% in the United States, 8.3% in Canada. The diversity, methodological differences, dermographic and cultural conditions related to dietary habits should be taken into consideration in the worldwide prevalence of food allergies (15).

Studies on the prevalence of food allergies are limited in Turkey, as in the rest of the world. The prevalence of FA was reported by Orhan et al. was 5.7% in school children aged 6-9 in the Eastern Black Sea region, and 9.4% in adults aged 18-80 in Istanbul by Gelincik et al. (4,5). As a result of our survey-based study of the prevalence of food allergies in the adult population of the Eastern Black Sea Region, 158 of 920 people who filled out the questionnaire stated that they had food allergies. One of the reasons for this may be that the Eastern Black Sea is a closed society and there is a genetic predisposition to FA due to the frequent consanguineous marriages. In some studies, especially in children, male gender was associated with an increased risk (16,17). However, no relationship was reported between gender and the risk of food allergy (18). In studies conducted in Europe, increased age was found to be a risk factor in general (4,19). In our study, the average age of the participants who stated that they had FA was younger, and it was significantly different from the average age of those who did not state food allergy.

In many studies, the presence of allergic diseases or allergic sensitivity in parents or siblings has been reported as a strong risk factor for the development of food allergy (4,20,21). In our study, one third of the participants stated that their first-degree relatives had an allergic disease.

When the symptoms were evaluated, skin findings and nasal symptoms were prominent in our study in parallel with other studies (11,22). In the study, in which we took the adult population of the Eastern Black Sea Region as the target population; spices, tomatoes and eggs were found to be the most allergenic foods. In the Eastern Black Sea Region, where seafood is consumed frequently, fish allergy ranked sixth. (23). Regional eating habits and food preparation methods play an important role in

the prevalence of food hypersensitivity. In our study, tomato is in the 2nd place, egg is in the 3rd place. No parallelism was showed with the eating habits specific to the Eastern Black Sea Region. It is known that our country is an intensive hazelnut production region, but it is an interesting finding that hazelnut allergy is rare both in our study and in the study conducted by Orhan's et al. (5). The reason for this may be that although the production is high, the consumption is not parallel with this. In the study conducted by Gelincik et al. vegetables and fruits, especially eggs, tomatoes and strawberries, were found to be the most common allergenic foods. In the same study, cocoa was identified as another frequent nutrient (4). In our study, the most common allergens were found to be spices, eggs and tomatoes. The most common allergy-causing foods partially overlap with the allergic foods stated in other studies. In many studies, it is shown that there may be up to 30-fold differences between the declaration of individuals and the actual frequency of FA (9,22). Therefore, in order to determine the frequency of FA in our region, individuals with suspected FA should be evaluated with diagnostic methods such as oral food challenge and plasebo control double-blind oral challenge test in future studies.

The limitations of our study are that the questions in the questionnaire are not standardized, different age groups are included and societies have different awareness and perceptions about diseases. Since there was no question about socioeconomic status in our questionnaire, the effect of socioeconomic status on the development of FA in the adult population of the Eastern Black Sea Region could not be evaluated. Another limitation of our study is that the diagnosis is not supported by laboratory methods. Another limitatıons are that our questıonnare is filled by people who lives in a few of cities in eastern regıon of black sea.

CONCLUSION

In our study we investigated the frequecyof food allergy based on a questionnare in our region an done out of every six people reported that they had FA. In survey studies, feedback rates can be 10 times higher than real FA rates. FA dıagnostic methods costs are quite high and their implementations are diffucult therefore making study of FA prevelance based on questionnaire and then implement diagnostic methods to induviduals who said had a food allergy seems like a rational method.

Author Contributions: Concept: HD, ABD, Design: HD, Supervision: HD, ABD, Data Collection and/or Processing: HD, ABD, Analysis and/or Interpretation: HD, ABD, Writing manuscript: HD.

Conflict of Interest: No conflicts of interest between the authors of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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RESEARCH ARTICLE

Association of Vitamin D, IL-6, TNF-α, CRP and Periodontal Health Status in the Eastern Black Sea Region

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Abstract

Objective: It is well established that vitamin D deficiency may increase risk of periodontitis, and that supplementation with vitamin D can contribute to maintain periodontal health. Since the Eastern Black Sea Region receives little sunlight due to its location, individuals living in this region don't produce enough vitamin D and these individuals generally have vitamin D deficiency. The goal of this study was to analyze that association of vitamin D and periodontal health status in a study population of the Eastern Black Sea Region.

Methods: In this study, which was planned as a case control study, it was planned to reach a total of 72 samples, with at least 24 samples in each group in the sample calculation. As a result of data collection, 29 individuals with periodontitis, 28 individuals with gingivitis and 25 periodontally healthy individuals, a total of 82 individuals were included in the study. Cytokines in inflamed periodontal tissues have a marked effect on host modulation and onset and progression of periodontal disease. Venous blood samples were collected from the individuals. Periodontal clinical parameters were measured. Serum levels of 1.25(OH)2D3, 25(OH)D, C-reactive protein (CRP), tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) were assessed.

Results: Periodontally healthy group had statistically significantly lower periodontal clinical parameter values compared to gingivitis and periodontitis group (p<0.05). The serum 1.25(OH)2D3 level was lower in the periodontitis group compared to the periodontally healthy group and gingivitis group (p<0.05). But there was no statistically significant difference in the periodontitis 10.20 (3.70-29.50) ng/mL, gingivitis 11.35 (5.60-29.50) ng/mL and periodontally healthy groups 9.10 (2.90-55.40) ng/mL in terms of serum 25(OH)D levels (p>0.05).

Conclusion: The outcomes of this study support the idea that lower serum 1.25(OH)2D3 level has a negative effect on periodontal health status. Our data suggest that vitamin D supplementation to people living in the Eastern Black Sea Region would be beneficial in reducing the risk of developing periodontal disease. Further studies are needed on this subject.

Keywords: Cytokine, gingivitis, pathogenesis of periodontal disease, periodontitis, 1.25-hydroxyvitamin D

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INTRODUCTION

Periodontal diseases are chronic infectious inflammatory diseases that lead to alveolar bone loss and destruction of periodontal tissues (1). Although the major etiologic factor is bacteria at the onset of periodontitis, many environmental factors, genetic factors and systemic disorders, such as heart disease, diabetes, obesity and metabolic syndrome, play roles in the progression and development of the disease. Periodontal diseases and interactions between these systemic conditions are associated with the inflammatory process related to the common pathophysiological mechanism (2).

Today, periodontal pathogenic microorganisms and virulence factors are known to cause a systemic inflammatory response by mixing into the blood circulation (2). Increased serum levels of acute-phase proteins such as C-reactive protein (CRP), an important indicator of systemic inflammation (3), and other cytokines associated with inflammation, support this association (2). Tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6) are important cytokines in the initiation of systemic inflammation and play a role in the progression and severity of periodontitis (2). In addition, it has been demonstrated by many studies that cytokines such as TNF-α and IL-6 are higher in individuals with periodontitis than in periodontally healthy individuals (4-8).

Vitamin D is a host-derived molecule and has a secosteroid structure that is not only taken into the body after dietary consumption (D2 and D3), but is also produced by a person's own skin after exposure to ultraviolet (UV) radiation from sunlight (D3) (9). Vitamin D2 (ergocalciferol) is the product of the UVB 290–315 mm irradiation of ergosterol. Also it can be ingested as a supplement or with fortified foods (10). Vitamin D3 (cholecalciferol) is produced after the exposure of 7-dehydrocholesterol to UVB radiation in the human epidermis.

The prevalence of vitamin D insufficiency and deficiency is affected by latitude and seasonal changes (11). The prevalence decreases in summer and increases in spring and winter (12). The production of vitamin D is the highest when the sun is at its apex and decreases when the angle narrows. The production of vitamin D in the regions above and below 33° latitude is almost non-existent (13.) The eastern Black Sea Region where our study was conducted is located 41° northern latitude. For this reason, there is almost no vitamin D production in winter in eastern Black

Sea Region and vitamin D deficiency is common.

The roles of vitamin D in regulating bone metabolism and inflammatory response, the preservation of serum phosphate and calcium levels, and bone development and continuity suggest that it also has effects on periodontal health. Dietrich et al. (14) suggest that vitamin D has positive effects on gingival inflammation, periodontal diseases and tooth loss. Therefore, sufficient serum levels of vitamin D can be significant in the therapy and prevention of periodontal diseases. The purpose of this study was to analyse that association of vitamin D and periodontal health status in a study population of the Eastern Black Sea Region.

METHODS

Study groups

Design of the clinical trial

This study was planned as a case-control study. It is planned to reach a total of 72 samples, with at least 24 samples in each group, with 95% confidence, 85% theoretical power and 0.4 effect size in the sample calculation. The sample was increased by 20% in case of missing data. As a result of data collection, it was completed with 29 samples in periodontitis, 28 samples in gingivitis and 25 samples in periodontally healthy controls. Analyzes were completed with a total of 82 samples.

This study was approved by the human subjects ethics committee of our university (meeting date: 07 April 2016; Ethics Committee Decision No. 2016/09) with regard to the Declaration of Helsinki. The aim and content of the research were clarified to the individuals included in the study, and voluntary consent forms were signed. Individuals with certain exclusion criteria were not included in the study and a total of 82 participants were included, including 29 periodontitis, 28 gingivitis, 25 periodontally healthy controls.

The volunteers were selected from among individuals who referred for periodontal examination to our faculty. Inclusion criteria for this study; being systemically healthy, not using antibiotics and immunosuppressive drugs for the past three months, not smoking, not receiving periodontal treatment in the past six months, not taking supplemental vitamin D. Individuals who had been systemic diseases, under antibiotic or immunosuppressive medication for the past three months, smokers, periodontal therapy within the past six months, supplementary or additional vitamin D were excluded.

The subjects were divided into three groups according to the 2017 classification of periodontal diseases. The groups were defined as follows: periodontitis group (group 1, n = 29), interdental clinical attachment level (CAL) ≥2 mm, probing depth (PD) ≥4 mm, history of multiple tooth loss, presence of deep

periodontal lesions extending to the apical portion of the root; gingivitis group (group 2, n=28), no CAL, PD ≤3 mm, bleeding on probing (BOP) ≥10%, no radiographic bone loss; periodontally healthy control group (group 3, n=25), no CAL, PD ≤3 mm, minimal BOP (≤10%), no radiographic bone loss. All periodontal examinations and measurements were performed in the November–March period.

Periodontal examination

In the periodontal examination of the mouth, a Williams periodontal probe was used. CAL and PD were measured on six surfaces of each teeth (buccal, mesiobuccal, distobuccal, lingual/palatal, distolingual and mesiolingual) excluding the third molars. PD was measured as distance from gingival margin to the base of pocket. CAL was recorded by measuring the distance between the cement–enamel junction and the base of the pocket. A total of 10–15 s after probing, the amount of bleeding was recorded as bleeding (+) or no bleeding (-) on the four surfaces of the teeth (buccal, palatal/lingual, mesial, distal). The gingival index (GI) and plaque index (PI) (Silness&Löe) were measured by evaluating mesial, distal, buccal and palatal/lingual gingiva of each tooth.

Laboratory analysis

Venous blood samples were collected from the individuals on the day of dental examination. Serum samples were centrifuged and then were separated into tubes, stored at -

20˚C until assays. Serum samples' analysis were exercised in accordance with manufacturer's order. TNF-α levels in serum were analyzed by the EASIA method (enzyme-amplified sensitivity immunoassay; DIAsource ImmunAssays S.A., Belgium). The sensitivity of the method was 0.7 pg/mL, and the intra- and inter-study coefficients of variation (CVs) by percentage were 6.3 and 3.3, respectively. 1.25(OH)2D3 levels in serum were analyzed using radioimmunoassay (RIA) method in a Stratec PC-RIA MAS (Germany) auto-analyser. The CRP levels were studied in an Abbott Architect c8000 (USA) auto-analyser with the immunoturbidimetric method, and 25(OH)D vitamin levels were studied in an Abbott Architect i2000 (USA) auto-analyser with the chemiluminescent microparticle immunoassay (CMIA) method. IL-6 levels were studied through an enzyme-labelled chemiluminescent immunometric assay in a Siemens Immulite 2000 Xp (Germany) auto-analyser.

Statistical analysis

Statistical analyses were exercised with SPSS 20 programme (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Shapiro–Wilk's was used to investigating the appropriateness of variables for a normal distribution. In the analysis of the differences between the groups because the variables did not comply with a normal distribution were analyzed using Mann–

Whitney U and Kruskal–Wallis H tests. When statistically significant differences occurred in the Kruskal–Wallis H test, intergroup differences were determined with using post-hoc test. The correlations were analyzed using Spearman correlation analysis.

RESULTS

Clinical characteristics of all groups were presented in Table 1. Group 3 had significantly lower BOP, PD, GI and PI values (P<0.05) compared to Group 1 and Group 2. Group 2 had significantly lower BOP, PD, GI and PI values (P<0.05) compared to Group 1.

Table 1: All groups' probing depth (PD), clinical attachment level (CAL), bleeding in probing (BOP), plaque index (PI), gingival index (GI) and age values.

	Group			H	p	Post hoc		
	Group 1	Group 2	Group 3			1–2	1–3	2–3
	Median (min–max)	Median (min–max)	Median (min–max)					
PI	2.75 (2.12–3.00)	1.69 (1.25–2.25)	0.25 (0.12–0.62)	71.3	0.001*	0.035*	0.013*	0.042*
BOP	83.33 (70–100)	70.09 (53.57–87.50)	9 (4.46–19.7)	59.4	0.001*	0.003*	0.001*	0.014*
PPD	4.13 (3.14–5.72)	2.18 (1.46–2.84)	1.14 (1.01–2.28)	70	0.001*	0.039*	0.018*	0.031*
CAL	4.42 (3.21–5.78)	0 (0–0)	0 (0–0)	76.1	0.001*	0.0001*	0.0001*	0.99
GI	2.75 (2–3)	1.75 (1.25–2.25)	0.13 (0.06–0.19)	71.2	0.001*	0.033*	0.019*	0.026
Age	44 (32-57)	35 (28-47)	34 (27-41)	22.80	0.001*	<0.001*	<0.001*	*0.271

PPD (probing pocket depth), CAL (clinical attachment level), BOP (bleeding in probing), PI (plaque index), GI (gingival index)
H, p: H and p values for Kruskal-Wallis test.
*Statistically significant at p<0.05.

Table 2: Distribution of laboratory findings according to groups.

	Group			H	p	Post hoc		
	Group 1	**Group 2**	**Group 3**			**1-2**	**1-3**	**2-3**
	Median (Min-Max)	**Median (Min-Max)**	**Median (Min-Max)**					
25(OH)D (ng/mL)	*10.20(3.70-29.50)*	11.35(5.60-29.50)	9.10(2.90-55.40)	4.07	0.131			
1,25(OH)$_3$ (pg/mL)	27(22-33)	32.5(27-38)	34(29-36)	43.5	0.001*	0.034*	0.023*	0.651
TNF-α (pg/mL)	5.24(0.61-26.18)	5.91(0.84-12.87)	6.41(0.31-13.74)	0.2	0.904			
CRP (mg/dL)	0.02(0.019-2.79)	0.02(0.019-0.65)	0.02(0.019-0.86)	0.9	0.631			
IL-6 (pg/mL)	1.9(1.9-7.47)	1.9(1.9-5.55)	1.9(1.9-10.1)	1.3	0.532			

25(OH)D (25-hydroxyvitamin D), 1.25(OH)$_2$D$_3$ (1.25-hydroxyvitamin D), TNF-α (tumour necrosis factor-α), CRP (C-reactive protein), IL-6 (interleukin-6).
H, p: H and p values for Kruskal-Wallis test.
*Statistically significant at p<0.05.

25(OH)D levels in serum were below the limits of vitamin D deficiency (< 20 ng/mL) and insufficiency (< 30 ng/mL) in all three groups. As showed in Table 2, there was no statistically significant difference in the periodontitis *10.20(3.70-29.50)* ng/mL, gingivitis 11.35(5.60-29.50) ng/mL and periodontally healthy groups 9.10(2.90-55.40) ng/mL in

terms of serum 25(OH)D levels (P>0.05). Group 1 (periodontitis group) had significantly lower mean $1.25(OH)_2D_3$ value 27(22-33) pg/mL compared to Group 2 (gingivitis group) 32.5(27-38) pg/mL and Group 3 (periodontally healthy group) 34(29-36) pg/mL (P<0.05) (Table 2).

As showed in Table 2, there was no statistically significant difference between TNF-α, IL-6, CRP levels and all three groups (P>0.05).

There was no statistically significant correlation between laboratory parameters and clinical parameters and mean 25(OH)D values (p>0.05). There was inverse association between 1.25(OH)2D3 values and PI, BOP, PD, CAL, GI and CRP (p< 0.05). While 1.25(OH)2D3 values increased, it was found that the aforementioned variables decreased (Table 3).

Table 3: Correlation of serum vitamin D levels with clinical parameters and laboratory findings.

		Age	PI	BOP	PD	CAL	GI	TNF-α (pg/mL)	CRP (mg/mL)	IL-6 (pg/mL)
25(OH)D (ng/mL)	*r*	-0.077	0.002	0.078	-0.108	-0.174	0.008	0.216	-0.008	-0.031
	p	0.492	0.983	0.489	0.333	0.117	0.945	0.051	0.942	0.780
	n	82	82	82	82	29	82	82	82	82
1.25(OH)₂D₃ (pg/mL)	*r*	-0.570	-0.626	-0.497	-0.703	-0.729	-0.603	0.042	-0.228	-0.072
	p	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**	0.707	0.039*	0.523
	n	82	82	82	82	29	82	82	82	82

PD (probing depth), CAL (clinical attachment level), BOP (bleeding in probing), PI (plaque index), GI (gingival index)
25(OH)D (25-hydroxyvitamin D), $1.25(OH)_2D_3$ (1.25-hydroxyvitamin D), TNF-α (tumour necrosis factor-α), CRP (C-reactive protein), IL-6 (interleukin-6).
*Statistically significant at $p \leq 0.05$. ** Statistically significant at $p \leq 0.001$.
r, correlation coefficient

DISCUSSION

The primary finding in present study is that there is association between periodontal health status and serum 1.25(OH)2D3 level. While 1.25(OH)2D3 level in serum was found to be lower in the group with periodontitis than group with gingivitis and periodontally healthy group. Other finding was that there is no association between periodontal health status and serum 25(OH)D level. The association observed between serum 1.25(OH)2D3 level and tissue destruction and periodontal inflammation can

be explained by the effects of vitamin D on calcium–bone metabolism and the immunomodulatory effects of vitamin D. Antonoglou et al. (15) observed a significant increase in the level of serum 1.25(OH)2D3 after the elimination of periodontal inflammation and suggested that possible favorable effects of vitamin D could be dedicated to immunomodulatory functions. Rafique et al. (16) reported that the serum 1.25(OH)2D3 level was significantly lower in the periodontitis group compared to the healthy

control group. Bhargava et al. (17) found, low serum 25(OH)D levels in individuals with chronic periodontitis. In study performed by Alzahrani et al. (18), the serum 25(OH)D level has been found to be lower in the periodontitis group than in the control group. In another study conducted by Antonoglou et al. (9), the association between periodontal health and 1.25(OH)2D3 and 25(OH)D levels in serum has been examined; while 1.25(OH)2D3 level in serum was found to be related to periodontal health status, 25(OH)D level in serum was not found to be related. Pradhan et al. (19) found, no significant association between vitamin D and periodontitis. Similarly, in the present study, the level of serum 1.25(OH)2D3 has been found to be associated to periodontal health status, while no relation has been found between periodontal health status and 25(OH)D level in serum. In the periodontitis group, the serum 1.25(OH)2D3 level was remarkably lower than in the gingivitis and periodontally healthy group. 25(OH)D level in serum was below the limits of vitamin D insufficiency (< 30 ng/mL) and vitamin D deficiency (< 20 ng/mL) in all three groups, except for only 3 subjects. The reason for this is that the eastern Black Sea region, where the study was conducted, receives too little sunlight since it is situated on the the 41st parallel North (13).

The anti-inflammatory feature of vitamin D has been supported by many studies. Bhargava et al. (17) reported that there was a statistically significant relationship between serum 25(OH)D level and GI, PD and CAL, while there was no statistically significant relationship between 25(OH)D level and PI. Isola et al. (20) found an inverse relationship between 25(OH)D level and PD, CAL, PI and BOP. Dietrich et al. (21) found in their study conducted in 2005 that there was less bleeding on probing in the group with high level of serum 25(OH)D. They suggested that this negative relation could be due to an anti-inflammatory effect when the serum 25(OH)D level is ≥ 90–100 nmol/L. Hiremath et al. (22) reported on the anti-inflammatory effects of various doses of vitamin D on gingivitis: gingivitis scores changed in proportion to the dose of vitamin D supplementation, and significant anti-inflammatory effects were observed after vitamin D supplementation. Garcia et al. (23) declared that calcium and vitamin D supplementation had a favourable effect on periodontal health status and that high doses of vitamin D could have a reducing effect on the severity of periodontal disease. Alshouibi et al. (24) researched the relationship between periodontal health and vitamin D intake and concluded that vitamin D intake can have protective effect versus the progression of periodontal disease. Contrary to some previous studies, one of the reasons why we could not find a relationship between serum 25(OH)D levels and periodontal health in our study may be the lower serum 25(OH)D levels in our

subjects. Only 3% (3 subjects) of our subjects had values above the recommended level of 30 ng/mL (25). This situation is accordance with the results of the study of Millen et al. (26), who recommended an adequate serum 25(OH)D level of 30 ng/mL, and Dietrich et al. (21), who reported that serum 25(OH)D level should be 36-40 ng/mL for anti-inflammatory effect to be observed.

Vitamin D has a significant role in calcium homeostasis, bone growth and protection. The anti-inflammatory roles of 1.25(OH)2D3 have been extensively studied, and it has been shown that they inhibit cytokine production and antigen-induced T cell proliferation, and they act as an immunomodulatory agent (27, 28). According to these findings, it may be reasonable to consider a low serum vitamin D level as an indicator of inflammatory status in periodontium.

There is no consensus on what the needed level of serum 25(OH)D should be for homeostasis, bone metabolism and adequate immunity. Dietrich et al. (21) have suggested that serum 25(OH)D level should be $\geq$ 90–100 nM/L for an anti-inflammatory impact of vitamin D on gingival inflammation. Millen et al. (26) reported that there was less bleeding on probing and shallower periodontal pockets in patients with a level of serum 25(OH)D $\geq$ 50 nM/L than in those with an inadequate level (< 50 nM/L).

The quantity of vitamin D production in the skin depends on the season, latitude and amount of sunlight coming from different angles at varied times of the day (13). Antonoglou et al. (9), in a study conducted in 2015, investigated serum 25(OH)D and 1.25(OH)2D3 values in blood samples taken in different seasons and found that serum vitamin D values vary depending on the season. Therefore, serum samples were collected in the same period (winter; November-March) from our study groups. In our study, a remarkable and inverse relationship has been found between 1.25(OH)2D3 levels and clinical parameters as well as between CRP and 1.25(OH)2D3 levels (p<0.05). This negative relationship of 1.25(OH)2D3 with tissue destruction and periodontal inflammation may be clarified by the immune modulatory effects of vitamin D and bone-associated functions.

CRP is a plasma protein that reflects the grade of the acute-phase response of inflammation and is used by many investigators for the prediction and early diagnosis of periodontal disease (3). There are several studies showing a favourable association between CRP and the severity of periodontal disease, as well as a reduction in the level of serum CRP after non-surgical periodontal therapy (29-33). Podzimek et al. (3) reported that the CRP level increases with the severity of periodontal disease in a study designed to evaluate the systemic level of CRP and

compare its relationship with periodontal clinical parameters. Also, in the research of Jayaprakash et al. (32), in which they examined the effect of periodontal therapy on the serum CRP levels in individuals with chronic periodontitis and chronic gingivitis, a higher CRP value in the patients with chronic periodontitis was detected; it has been suggested that there was a reduced in CRP values in the patients with chronic gingivitis and chronic periodontitis after three months of treatment. There was no statistically significant relationship among CRP and the groups in our study ($p > 0.05$). Unlike other studies, we think that the reason why there was no statistically significant difference in serum CRP levels between our study groups may be due to the fact that they were in stable or active periods of periodontitis. In our study, samples may have been collected during the stable period of periodontitis. In addition, there may not be a difference due to reasons such as the sample sizes selected in the studies and the differences in the evaluation methods, the sensitivity of the kits used.

In a research conducted by Andrukhov et al. (34) it was suggested that vitamin D3 may play a significant role in the regulation of periodontal inflammation through the production of cytokines by periodontal ligament cells. According to this finding, both 1.25(OH)2D3 and 25(OH)D are thought to affect the inflammatory process in periodontal disease. In the study conducted by Yousefimanesh et al. (35) in order to explain the importance of TNF-α in the destruction of periodontal tissues, saliva samples of those in the periodontally healthy control group and those with chronic periodontitis were examined; no statistically significant relationship was found between TNF-α levels and two groups ($p > 0.05$). Likewise, there was no association between groups and TNF-α values ($p > 0.05$) in our study. The reasons why we could not find a statistically significant difference in TNF-α levels between the groups may be the selection of individuals in different age groups in the studies, the number of samples, the differences in the sampling and evaluation methods.

In this study, 25(OH)D and 1.25(OH)2D3 values have been measured in a certain time interval to prevent the effect of different sun angles in different months from affecting the capacity for vitamin D production in the skin. Overall, this research promotes the idea that vitamin D deficiency has a negative effect on periodontal health status.

CONCLUSION

The Eastern Black Sea Region receives little sunlight because of its northern location. Therefore, vitamin D deficiency is often observed there. In light of this information, we hypothesise that vitamin D supplementation will be beneficial in reducing the risk of periodontal disease for people living in

geographic locations with relatively less sunlight than other locations. However, more studies need to be conducted on this issue. In addition, further studies are needed to better understand the preventive effect of vitamin D on periodontal tissue destruction, with larger sample numbers and locally evaluation of the parameters by collecting gingival crevicular fluid, saliva or tissue biopsies samples.

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Analysis of 55 Adult Cases Surgically Treated for Pontocerebellar Angle Tumors

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Abstract

Objective: Pontocerebellar angle (PCA) tumors, although typically of benign nature, are of significant clinical and pathological importance. The aim of this study is to investigate the clinical and pathological characteristics of PCA tumors, as well as surgical outcomes, which hold a significant place in clinical practice.

Methods: 55 adult patients who underwent surgery for PCA tumors at the Department of Neurosurgery, Dicle University Faculty of Medicine, between 2013 and 2023 were included in the study. The clinical and pathological records of these patients were retrospectively reviewed.

Results: The age of the patients (17 male, 38 female) ranged from 18 to 75 years. According to pathological diagnosis, 23 cases were diagnosed as meningioma, 19 as schwannoma, 6 as epidermoid tumors, 2 as metastases, 1 as hemangioblastoma, 1 as hemangioma, 1 as medulloblastoma, 1 as neuroblastoma, and 1 as small round cell tumor. Gross total resection was achieved in all cases. Overall, 47.3% of the patients had one or more postoperative complications. Postoperative permanent facial palsy developed in 6 patients. The overall mortality rate was 9%.

Conclusion: PCA tumors constitute a significant group among intracranial tumors. Surgical treatment is an important option for the management of these tumors. Primary goal of the surgery is gross total resection which is feasible in today. Though postoperative complications are common, majority of them is temporary.

Keywords: Pontocerebellar, Tumor, Neoplasm, Surgery, Complication

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INTRODUCTION

The pontocerebellar angle (PCA) is defined as the subarachnoid space between the ventral surface of the brainstem and the medial cerebellar hemisphere. It is limited laterally by the superior and inferior limbs of the cerebellopontine fissure (1).

The first successful surgery for tumors located in the PCA was performed by Charles Ballance in 1894 (2). In 1925, Dandy demonstrated the total resection of vestibular schwannomas with acceptable morbidity and mortality rates (3). With advancements in surgical microscopy and microsurgical techniques, the mortality and morbidity rates have further decreased (3, 4).

In the region of the PCA, various tumors can arise from neuroglial tissues, cranial nerve sheaths, meninges, and embryonic remnants (5). Among adults, the majority of these tumors are vestibular schwannomas, followed by meningiomas and epidermoid tumors (6, 7).

Although PCA tumors are generally benign, they present unique challenges and complications due to the involvement of cranial nerves. Possible surgical complications include facial and cochlear nerve damage, cerebrospinal fluid (CSF) leakage, ischemic or hemorrhagic vascular injuries, hydrocephalus, and headache (8).

In this study, we aimed to examine the symptoms, clinical, radiological, and pathological characteristics, as well as surgical complications related to the surgically treated PCA tumors in our department.

METHODS

This retrospective study was approved by Dicle University Medical Faculty Committee for Noninterventional Studies (Date: 17.01.2023, No: 38). The patients that were operated for PCA tumors at Dicle University Department of Neurosurgery, between January 2013 and December 2022 were included in this study.

The patients that were surgically treated for PCA tumors were identified by searching hospital patient archives and radiology database and age, gender, clinical presentation, radiological findings, extent of resection, pathological classification, and complications were recorded.

RESULTS

The mean age of the 55 patients included in this study was 45.38 ± 13.74, with a female to male ratio of 2.23 (Table 1).

The most commonly identified tumors were meningiomas (41.8%), schwannomas (34.5%), and epidermoid tumors (10.9%). In two patients

(3.6%), the tumor pathology was determined as metastasis (squamous cell carcinoma and pleomorphic breast carcinoma). All histopathological types are summarized in Table 2.

Table 1. Demographical and clinical data of 55 patients included in the study

Age (years)		
	Mean ± SD	45.38 ± 13.74
	Median (Minimum – Maximum)	45 (18 – 75)
Gender		
	Female, n (%)	38 (69.1)
	Male, n (%)	17 (30.9)
Symptoms		
	Pain, n (%)	37 (67.3)
	Vertigo, n (%)	10 (18.2)
	Hearing loss, n (%)	9 (16.4)
	Imbalance, n (%)	5 (9.1)
	Tinnitus, n (%)	5 (9.1)
	Facial asymmetry, n (%)	3 (5.5)
	Nausea vomiting, n (%)	1 (1.8)
	Double vision, n (%)	1 (1.8)
	Hoarseness, n (%)	1 (1.8)
	Dysphagia, n (%)	1 (1.8)
	Memory impairment, n (%)	1 (1.8)
	Incidental, n (%)	1 (1.8)
Signs		
	Hearing loss, n (%)	16 (29.1)
	Facial palsy, n (%)	5 (9.1)
	Diplopia, n (%)	1 (1.8)
	Hoarseness, n (%)	1 (1.8)
	Visual loss, n (%)	1 (1.8)
	Dysmetria, n (%)	1 (1.8)
	Dysdiakokinesia, n (%)	1 (1.8)
	Normal, n (%)	34 (61.8)
Side		
	Right, n (%)	29 (52.7)
	Left, n (%)	25 (45.5)
	Bilateral, n (%)	1 (1.8)
Diameter (mm)		
	Mean ± SD	33.60 ± 10.62
	Median (Minimum – Maximum)	35 (8 – 52)

SD: standard deviation

Overall, the most common presenting symptom in the population was pain (67.3%), followed by vertigo and hearing loss (18.2% and 16.4% respectively) (Table 2). When looking at specific tumor types, the most common presenting complaints in

Table 2. Surgical data of the population

Resection			
	Gross total resection, n (%)		55 (100)
Pathology			
	Meningioma, n (%)		23 (41.8)
	Schwannoma, n (%)		19 (34.5)
	Epidermoid tümor, n (%)		6 (10.9)
	Metastasis, n (%)		2 (3,6)
	Hemangioblastoma, n (%)		1 (1.8)
	Hemangioma, n (%)		1 (1.8)
	Medulloblastoma, n (%)		1 (1.8)
	Neurofibroma, n (%)		1 (1.8)
	Small round cell tumor, n (%)		1 (1.8)
Postoperative complication, n (%)			26 (47.3)
	Facial palsy, n (%)		14 (25.4)
		Temporary, n (%)	8 (14.5)
		Permanent, n (%)	6 (10.9)
	Dysphagia, n (%)		3 (5.5)
		Temporary, n (%)	3 (5.5)
		Permanent, n (%)	0 (0.0)
	CNS infection, n (%)		7 (12.7)
	CSF fistula, n (%)		5 (9.1)
	Pneumonia, n (%)		5 (9.1)
	Wound infection, n (%)		1 (1.8)
	Pulmonary embolism, n (%)		1 (1.8)
	SVT, n (%)		1 (1.8)
	DVT, n (%)		1 (1.8)
Follow up (months)			
	Mean ± SD		19.49 ± 21.61
	Median (Minimum –Maximum)		10 (0.5 – 72)
Outcome			
	Better, n (%)		8 (14.5)
	No change, n (%)		36 (65.5)
		Deficit -, n (%)	29 (52.7)
		Deficit +, n (%)	7 (12.7)
	Worse, n (%)		6 (10.9)
	Exitus, n (%)		5 (9.1)

SD: standard deviation, CNS: central nervous system, CSF: cerebrospinal fluid, SVT: sinus venous trombosis, DVT: deep vein thrombosis

Table 3. Symptoms, signs, and complications of most common PCA tumor

		Meningioma (n=23)	Schwannoma (n=19)	Epidermoid tümor (n=6)
Symptoms				
	Pain, n (%)	19 (82.6)	11 (57.9)	4 (66.7)
	Vertigo, n (%)	7 (30.4)	3 (15.8)	0 (0.0)
	Hearing loss, n (%)	1 (4.3)	7 (36.8)	0 (0.0)
	Imbalance, n (%)	1 (4.3)	1 (5.3)	1 (16.7)
	Tinnitus, n (%)	0 (0.0)	4 (21.0)	0 (0.0)
	Facial asymmetry, n (%)	1 (4.3)	1 (5.3)	1 (16.7)
	Nausea vomiting, n (%)	1 (4.3)	0 (0.0)	0 (0.0)
	Double vision, n (%)	1 (4.3)	0 (0.0)	0 (0.0)
	Hoarseness, n (%)	1 (4.3)	0 (0.0)	0 (0.0)
	Dysphagia, n (%)	0 (0.0)	0 (0.0)	1 (16.7)
	Memory impairment, n (%)	1 (4.3)	0 (0.0)	0 (0.0)
Signs				
	Hearing loss, n (%)	3 (13.0)	12 (63.1)	0 (0.0)
	Facial palsy, n (%)	2 (8.7)	2 (10.5)	1 (16.7)
	Diplopia, n (%)	1 (4.3)	0 (0.0)	0 (0.0)
	Hoarseness, n (%)	1 (4.3)	0 (0.0)	0 (0.0)
	Visual loss, n (%)	0 (0.0)	0 (0.0)	1 (16.7)
	Dysmetria, n (%)	1 (4.3)	0 (0.0)	0 (0.0)
	Dysdiakokinesia, n (%)	0 (0.0)	1 (5.3)	0 (0.0)
	Normal, n (%)	18 (78.3)	6 (31.6)	4 (66.7)
Postoperative complication, n (%)		9 (39.1)	13 (68.4)	2 (33.3)
	Facial palsy, n (%)			
	Temporary, n (%)	0 (0.0)	8 (42.1)	0 (0.0)
	Permanent, n (%)	1 (4.3)	5 (26.3)	0 (0.0)
	Dysphagia, n (%)			
	Temporary, n (%)	2 (8.7)	1 (5.3)	0 (0.0)
	CNS infection, n (%)	3 (13.0)	1 (5.3)	1 (16.7)
	CSF fistula, n (%)	2 (8.7)	2 (10.5)	1 (16.7)
	Pneumonia, n (%)	1 (4.3)	2 (10.5)	1 (16.7)
	Wound infection, n (%)	1 (4.3)	0 (0.0)	0 (0.0)
	SVT, n (%)	0 (0.0)	1 (5.3)	0 (0.0)
	DVT, n (%)	1 (4.3)	0 (0.0)	0 (0.0)
Exitus		0 (0.0)	2 (10.5)	1 (16.7)

CNS: central nervous system, CSF: cerebrospinal fluid, SVT: sinus venous trombosis, DVT: deep vein thrombosis

meningiomas were headache (19 patients) and vertigo (7 patients), with only 1 patient presenting with hearing loss. In schwannomas, the most common presenting complaint was also headache (11 patients), followed by hearing loss (7 patients) (Table 3).The most frequently observed findings during examination in the entire population were hearing loss (29.1%) and facial palsy (9.1%). In 61.8% of patients, neurological examination was normal. Further details are provided in Table 1. Hearing loss was present in 12 among schwannoma patients in contrary to 3 in meningioma patients had. Both schwannoma

and meningioma groups had 2 cases of facial palsy at the time of presentation (Table 3).

52.7% of tumors were located on the right side and one patient had bilateral tumors. The average diameter of the PCA tumors in this study was 33.60 ± 10.62 mm (Table 1). Gross total resection was achieved in all cases.

During the postoperative period, new neurological deficits or complications developed in 26 patients (47.3%) (Table 2). The number of patients who developed facial palsy was 14 (25.4%), with 1 having a primary meningioma and 13 having a schwannoma. Eight patients completely recovered during follow-up. Three patients (5.5%) developed dysphagia, all of which were temporary and resolved completely. In addition, 7 patients (12.7%) developed central nervous system (CNS) infections, 5 (9.1%) had CSF leakage, and 5 (9.1%) had pneumonia. Overall 9 of the meningioma patients, 13 of the schwannoma patients, and 2 of the epidermoid tumor patients had one or more complications. The postoperative complications observed in our series are listed in Table 2 and Table 3.

The mean follow-up period of the cases was 19.49 ± 21.61 months. A total of 5 patients (9.1%) died. One case had a metastatic tumor, and 2 cases were lost in the early period due to infections. The condition of 6 patients (10.9%) was worse than the preoperative period. These were patients who developed postoperative facial palsy and did not recover. In 65.5% of the patients (n=36), there was no difference between the preoperative condition and the last follow-up. Among these patients, 29 did not have neurological deficits initially. The condition of 8 patients was better at the last follow-up compared to the preoperative period (Table 2).

DISCUSSION

Analysis of the data regarding the surgical treatment of PCA tumors in our department revealed that the majority of cases were seen in females. The most common presenting complaint was headache, and the most frequent examination finding was hearing loss. However, most patients did not have any examination findings. When examining the histopathological types, the most commonly observed tumors were meningiomas and schwannomas. While gross total resection was achieved in all patients, cranial nerve injury was more frequent in vestibular schwannomas.

PCA tumors constitute 5-10% of all brain tumors, with vestibular schwannomas accounting for 70-90%, meningiomas for 5-15%, and epidermoid tumors for 6% of PCA tumors (9). Interestingly, in our series, it was observed that the number of meningioma cases slightly exceeded the number of schwannoma cases. This may be due to the relatively small size of the population or characeristics of the region. Samii et al. identified neurofibromatosis type 2 in 82 out of 962 cases with bilateral schwannomas in their series (10). In our series,

bilateral schwannoma was only observed in 1 patient, but neurofibromatosis was not present.

Some clinical differences between acoustic and non-acoustic tumors have been demonstrated in the literature (11, 12). Compared to vestibular schwannomas, audiovestibular symptoms (hearing loss, tinnitus, vertigo) are less common in meningiomas, whereas cerebellar symptoms, facial palsy, and hydrocephalus are more frequent in the latter (11-13). Similarly, in our series, 7 out of 19 schwannoma cases presented with hearing loss, while only one of the 23 meningioma cases described hearing loss. In terms of neurological evaluation, hearing loss was detected in 12 cases in the first group and only in 3 cases in the second group. None of the epidermoid tumor cases in our series had a history of recurrent aseptic meningitis. An important finding was that 71% of patients with meningiomas exhibited no positive examination findings. Considering this, patients with complaints but no examination findings are recommended to be evaluated with imaging studies to avoid misdiagnosing these cases.

The goal in treatment of vestibular schwannomas is gross total tumor resection while preserving neurovascular structures (8). Gross total resection rates of 97-99% and mortality rates of around 1% were reported in the literature (10, 14). Samii et al. reported that the cochlear nerve can be preserved in 39.5% of cases, and the facial nerve can be preserved in 61-70% of cases (10). The rate of CSF fistula development ranges from 2% to 30% (8). In our center, our primary goal is gross total resection in all PCA tumors regardless of pathology. As a result, the gross total resection rate was 100%. There were 2 exitus. Facial nerve injury occurred in 13 patients, and 8 of them recovered during the follow-up period. Temporary dysphagia developed in one patient.

Similar to schwannomas, the goal of surgical treatment for meningiomas is to achieve the widest safe resection -including resection of dural attachments and hyperostotic bone- while preserving cranial nerves, (9, 15). The reported rates for gross total resection, mortality, temporary/permanent facial palsy, and dysphagia are 45-86%, 0-5%, 30%/10%, and 2-12%, respectively (16). Gross total resection was achieved in all meningioma cases in our series. One patient had permanent facial palsy, while two patients experienced temporary swallowing difficulties. The lower incidence of cranial nerve involvement in meningiomas compared to vestibular schwannomas explains the lower occurrence of cranial nerve related complications in the postoperative period. In addition, three cases of CNS infection, two cases of CSF fistula, one case of pneumonia, one case of wound infection, and one case of deep vein thrombosis were detected. Also, the rate of patients that experienced surgical complications was lower in meningioma

patients compared to schwannoma patients, however no statistical analysis was performed in this regard. No patient with meningioma died postoperatively.

The definitive surgical treatment of epidermoid tumors require complete excision of the tumor including the tumor capsule (9). However, due to the tight adherence of the capsule to neurovascular structures, safe and complete excision can be challenging, and recurrence is possible (9). The gross total resection rate ranges from 33% to 88%, and postoperative complications may include facial palsy (0-23%), hearing loss (8-10%), and swallowing problems (0-10%) (17, 18). In our series, gross total resection was achieved in all six cases of epidermoid tumors, and no cranial nerve related complications were observed. 1 patient died.

Malignant tumors are characterized by the rapid onset of symptoms, and their treatment is challenging due to the invasion of vital structures in the region. Malignant lesions in this localization have a poor prognosis, and while complete removal is not impossible, it is difficult to achieve (19).

CONCLUSION

PCA tumors constitute a significant group of intracranial tumors. Surgical treatment is an important option in the management of these tumors. With advances in surgical techniques and instruments, gross total resection is largely achieved, and although neurovascular complications still occur, permanent damage rarely occurs.

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Assessment of the Relationship between Vitamin D Deficiency and the Development of Hyperemesis Gravidarum

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Abstract

Object: Hyperemesis gravidarum, the leading cause of hospitalization in the first trimester, is observed in 0.3% to 3.6% of all pregnant women worldwide. Vitamin D is a significant vitamin for human health, and vitamin D deficiency in the pregnant women population in Turkey is a common pathology. In this context, this study was carried out to assess the relationship between vitamin D deficiency and the development of hyperemesis gravidarum.

Methods: The population of this prospective, single-center, case-controlled study consisted of pregnant women diagnosed with hyperemesis gravidarum. In the end, 23 pregnant women with hyperemesis gravidarum were included in the patient group, and 30 healthy pregnant women with demographic characteristics that match those with hyperemesis gravidarum were included in the control group. The Vitamin D and hematocrit levels were compared between the two groups.

Results: There was no significant difference between the patient and control groups in the serum vitamin D (p = 0.760) and hematocrit (p = 0.149) levels. Overall, only 9 (17%) of the 53 pregnant women had sufficient (> 20 ng / ml) vitamin D. There was no significant difference between the patient and control groups in the number of patients with vitamin D deficiency.

Conclusion: The study findings did not indicate a correlation between vitamin D deficiency and hyperemesis gravidarum. Further large-scale studies are needed to establish the absence of a relationship between vitamin D deficiency and hyperemesis gravidarum. On the other hand, the fact that only 17% of the pregnant women who participated in this study had sufficient vitamin D revealed the need to emphasize using vitamin D supplements in pregnant women as early as possible in the first trimester.

Keywords: Hyperemesis gravidarum, nausea, pregnancy, vitamin D, vomiting

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INTRODUCTION

Hyperemesis gravidarum (HG) is a pregnancy complication characterized by severe nausea, vomiting, fluid-electrolyte imbalance, acid-base imbalance, malnutrition, and weight loss (1). HG is commonly diagnosed based on weight loss of more than 3 kg or 5% of the body weight compared to before pregnancy and continuous (more than three times a day) vomiting with ketonuria that cannot be attributed to any other condition (2,3). HG is observed in 0.3% to 3.6% of all pregnant women worldwide and is the leading cause of hospitalization in the first trimester (4-6). The factors that potentially play a role in the etiology of HG reportedly are psychogenic factors, hormonal factors, smoking-alcohol use, gastric passage, lower esophageal sphincter pressure, and genetic factors (7).

The most important hormone that plays a role in the etiology of HG is thought to be beta human chorionic gonadotropin (βhCG). βhCG levels, as the symptoms of HG, reach a maximum in the 12th week and then regress and plateau (8). However, symptoms of HG are more severe in pregnancies with high βhCG levels, such as molar pregnancy, pregnancies affected by Down's syndrome, and multiple pregnancies (9).

In a study evaluating patients with HG, a correlation was found between the severity of the HG symptoms and the βhCG levels (10). By regulating the production and release of IL and hCG, tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6) produced by trophoblasts play an essential role in the etiology of HG (11). It was reported that pregnant women with HG had significantly lower type-1 helper (Th1)-to-type-2 helper (Th2) ratios than healthy pregnant women, and hormonal changes were implicated in this significant difference (12). HG is more prevalent in younger and first-time pregnant women, as well as those living in developed nations and urban areas, receiving estrogen-based treatment, and suffering from movement disorders and migraine (13). The adverse effects of HG on the fetus have not been clearly demonstrated. Then again, it is one of the most common causes of hospitalization during pregnancy, associated with maternal physical morbidity and negative psychological consequences (14).

Vitamin D is an essential vitamin for human health. A significant portion of the vitamin D in the body is synthesized endogenously in the skin by ultraviolet B (UVB) rays, whereas a small portion is taken with food. The vitamin

D3 synthesized in the skin turns into 25-hydroxy vitamin D in the liver, subsequently forming the primary form of vitamin D. This process, which has a half-life of 2 to 3 weeks, is considered in determining the vitamin D levels in the blood (15,16). Vitamin D deficiency in the pregnant population in Turkey is a common pathology. In a recent study, the incidence of vitamin D insufficiency in pregnant women was reported as high as 81.3% indifferent districts (17). The American College of Obstetricians and Gynecologists (ACOG) underlines that serum vitamin D levels of >30 ng/mL are required in pregnancy and recommends taking 1000-2000 IU vitamin D supplement daily in case of vitamin D insufficiency (18).

There are studies on the role of various factors in the etiopathogenesis of HG (19-23). For example, one study showed that βhCG levels increased as vitamin D levels decreased (24). It can be said that such studies indicate a possible mediating role of vitamin D in the etiopathogenesis of HG.

In view of the foregoing, this study was carried out to assess the relationship between vitamin D deficiency and the development of HG, one of the most common causes of hospitalization in the first trimester of pregnancy, significantly affecting the quality of life.

METHODS

Population and Sample

The population of this prospective, single-center, case-controlled study consisted of 53 pregnant women diagnosed with HG during the first 12 gestational weeks at Bakırköy Dr. Sadi Konuk Training and Research Hospital, Gynecology and Obstetrics Clinic between November 2019 and May 2020. The study protocol was approved by the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (23.12.2019/2019-25-03). Informed consent was obtained from all study participants. Participants' demographic and clinical data, i.e., their age, body mass index (BMI) values, pregnancy data, comorbidities, and the medications they have been using, were queried using a questionnaire form. 5 ml of venous blood samples were taken from all 53 cases, stored in tubes containing ethylene diamine tetra acetic acid (EDTA) solution, and sent to the biochemistry laboratory for analysis. To this end, first, the plasma in the samples was separated via centrifugation carried out at 3000 rpm for 5 minutes, and then the total vitamin D level was analyzed using UniCel DxI immunoassay kits (Beckman Coulter, Brea, CA, 92821, US) utilizing the paramagnetic particle-based chemiluminescence immunoassay method. In addition, a hematocrit test was requested for each patient, and their urine density and ketone positivity data were obtained from the results of the complete urinalysis and recorded. Consequently,

pregnant women with persistent (more than four times a day) vomiting with ketonuria and 5% or more weight loss compared to before the pregnancy were prediagnosed with HG were included in the patient group. Patients with multiple pregnancies, trophoblastic diseases, any systematic disease history (diabetes, hypertension, and thyroid diseases), psychiatric illness, inflammatory disease, antiemetics use, and patients that received any medical treatment with a potential effect on their hormone profile were excluded from the study. In the end, 23 pregnant women were included in the HG group. The results of the power analysis conducted based on literature data indicated that the minimum number of cases included in the study must be 52. Therefore, 30 healthy pregnant women with demographic characteristics that match the pregnant women with HG were included in the control group.

Statistical Analysis

Statistical analyses were carried out using the SPSS Statistics 17.0 (Statistical Package in the Social Sciences for Windows, Version 17.0, SPSS Inc., Chicago, IL, U.S., 2008), NCSS 11 (Number Cruncher Statistical System, version 11, NCSS LLC, Kaysville, Utah, US, 2016) and MedCalc 18 (MedCalc, version 18, MedCalc Software bv, Ostend, Belgium, 2018) software packages. Continuous variables were expressed as mean ± standard deviation and median and minimum-maximum values, whereas categorical variables were expressed

as frequency and percentage values. Relationships between categorical variables were assessed using Pearson's chi-squared test. Independent samples t-test and Mann-Whitney U test were used to compare two groups with continuous independent variables determined to conform and not to conform to the normal distribution, respectively. The probability (p) statistics of ≤ 0.05 were deemed to indicate statistical significance.

RESULTS

The results of the study did not reveal any significant difference between the patient and control groups in terms of mean age, BMI value, gestational week, vitamin D level, and hematocrit value (p = 0.874, p = 0.552, p = 0.760, and p = 0.149, respectively) (Table 1).

Table 1. Distribution of participants' demographic and clinical characteristics by the patient and control groups

	Healthy Pregnant Women (Control Group)	Pregnant Women with HG (Patient Group)	
	Mean± SD Median (min.–max.)	Mean±SD Median (min.–max.)	*p*-value
Age (year)	(n=30) 28.17±5.37	(n=23) 28.39±4.69	0.874
BMI (kg/m²)	(n=30) 25.82±4.19	(n=23) 26.51±4.2	0.552
Gestational week (week)	(n=30) 11.98±1.93	(n=23) 12.01±2.63	0.962
Vitamin D level (ng/ml)	(n=30) 12.38 (7.19-28.36)	(n=23) 14.4 (5.7-53.13)	0.760*
Hematocrit (%)	(n=30) 34.9±2.35	(n=23) 35.91±2.56	0.149
Urine density (g/l)	(n=30) 1016±6.94	(n=23) 1022.13±9.55	0.009

Abbreviations: HG: Hyperemesis Gravidarum, SD: standard deviation, min.: minimum, max.: maximum, BMI: body-mass index
Student's t-test,
*: Mann-Whitney U test

On the other hand, there was a significant difference between the groups in urine density (p = 0.009) and ketone positivity in the urine. Only 17% of the 53 pregnant women who participated in this study had sufficient (> 20ng / ml) vitamin D.

DISCUSSION

Contrary to most studies available in the literature, which found a significant difference between pregnant women with HG and healthy pregnant women in vitamin D levels and attributed this difference to the weakened immune system of HG patients, no significant difference was found in vitamin D level between the patient and control groups included in this study.

Gürbüz et al., who found that vitamin D levels were significantly lower in cases with HG and in cases without HG (24), attributed this difference to the increase in gastric inflammation caused by vitamin D deficiency resulting in more severe complaints such as nausea and vomiting.

In contrast, in a prospective study that compared vitamin D and C-reactive protein (CRP) levels between 30 healthy cases and 30 HG cases, Yılmaz et al. found that the vitamin D levels were lower in the patient group than in the control group, yet this difference was not significant (25). The authors of the said study attributed the lack of significant difference between the patient and control groups in vitamin D levels to the relatively small size of

their sample. In the results of our study, no significant difference was found between vitamin D levels in HG and healthy pregnant women, similar to the study of Yılmaz et al. However, unlike in our study, vitamin D levels were higher in the HG group than in healthy pregnant women.

A number of recent studies suggested a relationship between vitamin D deficiency and many maternal and fetal problems. In light of this information, this study was carried out based on the hypothesis that pregnant women with HG would have significantly lower 25 (OH) vitamin D levels compared to healthy pregnant women. However, the results of the study proved this hypothesis wrong.

It has been speculated that HG might be associated with elevated βhCG levels and excessive increase in cellular immunity (Th cells). Vitamin D, an immunomodulatory vitamin, regulates cellular immunity and has auxiliary effects on immune tolerance mechanisms during pregnancy. The relevant literature data, taken together with the results of this study, suggest that vitamin D deficiency cannot increase T-cellular immunity through the said mechanisms, thus that vitamin D deficiency cannot serve as a primary factor, yet may have a role secondary to elevated βhCG levels in the development of HG.

"Vitamin D Support Program for Pregnant Women" has been implemented in Turkey since 2011. Accordingly, pregnant women are

given 1200 IU / day of vitamin D orally starting from the second trimester till the end of the first six months of the lactation period. Nevertheless, vitamin D deficiency was detected in both patient and control groups included in this study. The fact that only 17% of the pregnant women who participated in this study had sufficient vitamin D revealed the need to monitor pregnant women closely and emphasize using vitamin D supplements in pregnant women as early as possible in the first trimester.

Limitations of the Study

The primary limitations of this study were its relatively small sample size and the fact that βhCG levels were not evaluated.

CONCLUSION

The etiology of HG has not been fully elucidated yet. There are conflicting results in the literature on the relationship between vitamin D deficiency and the development of HG. Then again, considering that vitamin D deficiency is common among pregnant women, they should be given vitamin D supplements as early as possible in the first trimester. Further large-scale studies are needed to corroborate the findings of this study and shed more light on the etiopathogenesis of HG.

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Determining University Students' Anxiety and Problem Solving Skills in the COVID-19 Pandemic Process

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Abstract
Objective: This study is a descriptive cross-sectional study that was conducted to assess the problem-solving skills and anxiety levels of all students who agreed to participate in the study at the vocational school of health services.
Methods: The population of the study included 1800 students from all departments of the 2021-2022 academic year health services vocational school at a state university in Konya, and the sample included 356 students who voluntarily agreed to participate in the study and provided informed consent. Frequency, percentage, mean, standard deviation, t-test, one-way analysis of variance Kruskal-Wallis H, and Mann-Whitney U tests were used to analyze the data.
Results: When the total mean scores of the Problem-Solving Inventory (PSI) were compared based on the variables of gender, department of education, class, childhood location, income level, family type, and status of receiving problem-solving education, no statistical significance was found. The mean approach PSI score of those with chronic diseases, on the other hand, showed a statistically significant difference. The Generalized Anxiety Disorder (GAD) score was found to be statistically significantly higher in smokers, those with chronic diseases, and those with low income (p-value<0.05).
Conclusion: It is important to plan initiatives and, if necessary, revise curricula to improve the problem-solving and anxiety-management abilities of future healthcare professionals.
Key words: Problem-solving inventory, Anxiety, University student

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*Note: The summary of this research was presented as a poster presentation at the Internal Medicine Congress held in Belek/Antalya on October 19-23, 2022.

INTRODUCTION

One of the fundamental functions of the brain's natural intelligence is problem-solving. In addition to being one of the most important components of a person's cognitive process, problem-solving is a cerebral process used to seek a solution to a specific problem or to achieve a specific goal. This process involves the interaction of other cognitive processes such as abstraction, research, learning, decision-making, inference, analysis, and synthesis to solve a problem (1-4). The problem-solving process is made up of a series of behaviors, such as gathering information about the perceived and defined problem, determining and applying the most appropriate coping skills in the face of the challenges encountered while solving the problem, as well as how the experiences are perceived (5). Dealing with problems in life necessitates knowledge and skills. It is reported that regardless of how complex and difficult the problem is if the individual has the necessary knowledge and skills, they could indeed find the most appropriate approach to solving the problem (6).

The COVID-19 pandemic has affected almost every aspect of life and altered the social dynamics globally (4, 7). According to the literature, the Covid-19 pandemic causes negative emotional reactions such as anxiety, fear, and anger, especially in different age groups, raises stress levels, and increases susceptibility to psychological disorders such as anxiety disorders, depressive disorders, post-traumatic stress disorder, and it has been linked to a variety of psychological symptoms suicidal thoughts (8), insomnia, and so on (9-17). Another significant effect of the pandemic has been a profound impact on the entire educational system, including health education. Knowledge gained in practice-based health fields must be put into action. During the pandemic period, however, applications that require skills are either attempted to be learned on a mannequin or simulation in laboratories or are passed without any application (7).

According to the literature, cognitive status, psychological adjustment, social-emotional competence level, self-confidence, decision-making style, effective communication skills, academic and social self-esteem, self-perception, creative thinking, imperturbability, assertiveness (18), age, gender, family income, residential area, parents' education and employment status (19) can all influence individuals' problem-solving skills. In fact, according to a study conducted to evaluate university students' problem-solving skills, university students evaluate their problem-solving skills more positively as their families' monthly income, perceived academic success, and satisfaction with the department they study increase; another study on the same subject found that variables such as school type, age, gender, and father's occupation influenced students' perception of their problem-solving skills, whereas mother's

occupation and parental education levels had no effect (20). The purpose of this study is to identify the factors that influence the anxiety and problem-solving skills of students in the vocational school of health services during the COVID-19 pandemic.

The hypotheses of the research are listed below.

H0: According to the sociodemographic characteristics of the students, there is no relationship between their anxiety and their problem solving skills.

H1: There are differences in anxiety levels according to the sociodemographic characteristics of the students.

H2: There are differences in problem solving skills according to the sociodemographic characteristics of the students.

METHODS

Design

This is a descriptive and relationship-seeking study that was carried out to assess the relationship between problem-solving skills and anxiety levels of students in the vocational school of health services.

Sample and Setting

This study was conducted in a vocational school of health services in Turkey's Central Anatolia region between April and June 2022. The research population consisted of first and second-year students (n=1800) in 2021-2022. The minimum number of participants was calculated using Cohen's formula, which is used for calculating sample size for known target groups, and the result was p=0.50, and q=317 with a 95% confidence interval (α=0.05 table value 1.96), and d=0.05 sampling error. Students had to be actively attending school (obligatory attendance) and give their consent to take part in the study to meet the inclusion criteria. Three hundred fifty-six students who met the inclusion criteria volunteered for the study.

Data Collecting

Due to the COVID-19 outbreak, data were gathered through an online survey. The health services vocational school students were informed about the study, and they signed an informed consent form. In two months, data were collected online using the "Personal Information Form", "Problem-Solving Inventory", and "Generalized Anxiety Disorder" scale. Completing the questionnaires takes an average of 15-20 minutes.

Instruments

Personal Information Form

The researchers created the form in accordance with the current literature. It contains fourteen questions about the participants' sociodemographic characteristics (age, gender, department, class, family type, economic situation, where they lived for a long time, where they live now, chronic disease condition, smoking, alcohol use, and whether there is a change in the amount of consumption during the pandemic) (21)

Problem-Solving Inventory (PSI)

The Problem-Solving Inventory is a Likert-type self-assessment questionnaire consisting of 35 items scored between 1 and 6, which measures an individual's self-perception of problem-solving abilities. Heppner and Petersen's 1982 inventory was translated into Turkish by Şahin and Heppner (1993). The scoring excludes the use of items 9, 22, and 29. Reverse scoring is used for items 1, 2, 3, 4, 11, 13, 14, 15, 17, 21, 25, 26, 30 and 34. After evaluating the remaining 32 items, the scale yields the lowest possible score of 32 and the highest possible score of 192. For the scale's evaluation, no cut-off point was specified. A high total score on the inventory indicates that the individual believes they are inadequate at problem-solving, whereas a low total score indicates that the individual believes they are adequate at problem-solving. The inventory is divided into three subscales: The "Problem-solving confidence" subscale (5, 10, 11, 12, 19, 23, 24, 27, 33, 34, 35) assesses self-perceived confidence in solving problems. The "approach-avoidance" subscale (1, 2, 4, 6, 7, 8, 13, 15, 16, 17, 18, 20, 21, 28, 30, 31) refers to the assessment of initial problem-solving efforts. The "personal control" subscale (13, 14, 25, 26, 27, 32) measures an individual's ability to control their emotions, refer to them in the future, and actively seek out various alternative solutions. In the inventory adaptation process, the total Cronbach's alpha coefficient was calculated to be 0.88 (3).

Generalized Anxiety Disorder Scale (GAD-7)

GAD-7 is a brief self-reported test developed by Spitzer et al. according to DSM-IV-TR criteria (10). It is a 7-item Likert type quartet scale (0=none, 1=many days, 2=more than half of the days, 3=almost every day) that assesses the experiences asked in the scale items during the last 2 weeks. The total scores of 5, 10, and 15 obtained on the scale are cut-off points for mild, moderate, and severe anxiety, respectively. Patients with a total score of 10 and above should be investigated using other methods and the diagnosis should be confirmed. When the threshold for the total score is selected as 10, the sensitivity for the diagnosis of GAD is 89% and the specificity is 82% (22).

Data Analysis

The SPSS 22.0 package program was used to analyze the data obtained in this study. A total of 356 associate degree candidates took part in the survey. Demographic data frequency and percentage distributions are provided. Using the Cronbach alpha value, the questionnaire's reliability analysis was obtained. The Cronbach alpha coefficient measures the homogeneity of Likert-type scale items. The higher the alpha coefficient of the relevant scale, the more it can be interpreted that the items in this scale are consistent with each other and the scale consists of items that examine related features. The Pearson Chi-Square test was used to examine the relationships between variables. The Kolmogorov-Smirnov test was used to determine whether the form is parametric or non-parametric

(to examine the data's compliance with the normal distribution), and the Levene test was used to determine variance homogeneity. For variables that satisfy both of these assumptions, a parametric test will be used, and for those that do not, a non-parametric test will be used. To compare the two groups, the independent two-sample t-test or Mann-Whitney U test was used. When comparing more than two groups, one-way analysis of variance (ANOVA) or the Kruskal-Wallis H test was used. In post hoc tests, the Tukey test or Mann-Whitney U test in pairs was used to compare groups with differences. The level of significance was set at 0.05.

Validity and Reliability Analysis

The validity and reliability analysis revealed that the problem-solving inventory (32 questions) had a Cronbach alpha coefficient of 0.706 and the generalized anxiety disorder (7 questions) had a Cronbach alpha coefficient of 0.879. It was determined that both scales, for which validity and reliability studies had previously been conducted, are reliable for this study as well.

Ethical Value

Before beginning the study, the ethics committee (approval dated March 2022 and numbered 2022/07), the Ministry of Health's scientific research permission for Covid-19 period research, and institutional permission were all obtained. The students were informed about the purpose of the study, and their permission to participate was obtained.

RESULTS

Sociodemographic Characteristics of Students:

The average age of the students participating in the research was 20±2.1 (Min 18–Max 40). Of the participants in the study, 291 (81.7%) were female and 65 (18.3%) were male. 135 (37.9%) of the students were in the 1st grade and 221 (62.1%) of them were in the 2nd grade (Table 1). While 77 (21.6%) of the students participating in the study were in the Audiometry department, 13 (3.7%) were studying in the Anesthesia department. 68 (19.1%) of the participants had extended families, and 288 (80.9%) had nuclear families. Considering the distribution by income, 47 (13.2%) participants' income was more than their expenses, 98 (27.5%) participants' income was less than their expenses, and 211 (59.3%) participants' income was equal to their expenses. 41 (11.5%) of the participants' families lived in the village, 77 (21.6%) in the district, and 238 (66.9%) in the city center. During the education period, 19 (5.3%) of the participants lived with their friends, 118 (33.1%) in the dormitory, and 219 (61.5%) with their families. While 30 (8.4%) of the 356 students participating in the study had a chronic illness, 326 (91.6%) did not have a chronic illness. Of the participants, 69 (19.4%) were smokers, and 18 (5.1%) were drinking alcohol. While internet use increased in 337 (94.7%) of the participants during the pandemic, phone use increased in all of them (Table 1).

Table 1. Sociodemographic characteristics of the participants (n=356)

Variable	n	%
Gender		
Female	291	81.7
Male	65	18.3
Grade		
1st grade	135	37.9
2nd grade	221	62.1
Department		
Operating Room Services	22	6.2
Anesthesia	13	3.7
Dialysis	15	4.2
Physiotherapy	25	7.0
First and Emergency Aid	17	4.8
Audiometry	77	21.6
Medical Imaging	17	4.8
Medical Imaging Evening Education	75	21.1
Elderly Care	36	10.1
Disabled Care and Rehabilitation	30	8.4
Child Development	29	8.1
Family Type		
Extended Family	68	19.1
Nuclear Family	288	80.9
Family Income Level		
Income is more than expenses	47	13.2
Income is equal than expenses	211	59.3
Income is less than expenses	98	27.5
Long-term Residence		
Village	41	11.5
District	7	21.6
City	238	66.9
Current Residency		
Dormitory	118	33.1
With parents	219	61.5
With Flat-mates	19	5.3
Chronic Disease		
Yes	30	8.4
No	326	91.6
Smoking		
Yes	69	19.4
No	287	80.6
Have you smoked more since the pandemic started?		
Yes	40	11.2
No	316	88.8
Do you use alcohol?		
Yes	18	5.1
No	338	94.9
Has your alcohol consumption increased during the pandemic?		
Yes	9	2.5
No	347	97.5
Has the time you spend on the Internet increased during the pandemic period?		
Yes	337	94.7
No	19	5.3
Has the time you spend on your mobile phone increased during the pandemic period?		
Yes	356	100.0
No	0	0.0
Total	356	1000

Average Scores of Students:

The average score from the problem-solving inventory for all students was 90.30, with a standard deviation of 11.91. The average score on the generalized anxiety disorder scale was 16.09, with a standard deviation of 4.39. The average score on confidence in problem-solving, one of the subscales of the problem-solving inventory, was 28.98, with a standard deviation of 4.81; the average score on the approach-avoidance subscale was 47.23, with a standard deviation of 8.30; and the average score on personal control was 14.05, with a standard deviation of 3.35. (Table 2).

Table 2. Problem-Solving Inventory and Generalized Anxiety Disorder total and sub-dimension mean scores of students (n=356)

Scale	X ±SD	Min-Max
Problem-Solving Inventory	90.30±11.91	60.00-127.00
Problem-Solving Confidence	28.98±4.81	18.00-47.00
Approach Avoidance	47.23±8.30	27.00-68.50
Personal Control	14.05±3.35	5.00-22.00
Generalized Anxiety Disorder	16.09±4.39	7.00-28.00

The Correlation Between the Problem-Solving Inventory and the Generalized Anxiety Disorder Scale:

The problem-solving inventory and generalized anxiety disorder scale were found to have a weak positive correlation (r=0.107), which was statistically significant (p-value=0.044) (Table 3).

The Generalized Anxiety Disorder Scale and the Problem-Solving Inventory in Relation to Student Sociodemographic Characteristics:

There was no statistically significant difference in the mean scores of any scale based on the students' gender, class, family type, place of residence, or alcohol use (p-values >0.05). There was a statistically significant difference in the mean scores of generalized anxiety disorder based on income status (p-value<0.05). The Mann-Whitney test was used to determine the difference between the groups in pairs. There was no statistical difference between the groups whose income was more than their expenses and those whose income was less than their expenses as a result of the test, however, the group whose income was equal to their expenses had a lower generalized anxiety disorder score.

Table 3. Correlation between the Results of Problem-Solving Inventory and Generalized Anxiety Disorder

		Problem-Solving Inventory	Generalized Anxiety Disorder Scale
Problem-Solving Inventory	p-value r	1	
Generalized Anxiety Disorder Scale	p-value r p-value	**0.107** **0.044**	1

There was a statistically significant difference in the mean general anxiety disorder score based on smoking (p-value<0.05). Smokers had a statistically significant higher score for generalized anxiety disorder. There was a statistically significant difference in the mean approach-avoidance score based on chronic disease status (p-value<0.05). In those without chronic disease, the approach-avoidance score was found to be statistically significantly higher.

There was a statistically significant difference in the mean approach problem-solving inventory scores based on chronic disease conditions (p-value<0.05). The score on the problem-solving inventory was found to be statistically significantly higher in those who did not have chronic illnesses. There was a statistically significant difference in the mean general anxiety disorder ores based on chronic disease conditions (p-value0.05) (Table 4).

Table 4. Generalized Anxiety Disorder Scale, Problem-Solving Inventory Total and Subscale Mean Scores in Relation to Sociodemographic Characteristics of Students (n=356)

Basic characteristics			Problem-Solving Inventory x±SD		Problem-Solving Confidence x±SD		Approach Avoidance x±SD		Personal Control x±SD		Generalized Anxiety Disorder x±SD	
Gender	Female	65	91.89±12.01	t: 1.193[2]	28.43±4.92	t:8764.00[1]	48.86±8.41	t:1.754[2]	14.60±3.10	t: 1.147[2]	15.49±34.41	t:8910.500[1]
	Male	291	89.94±11.88	p: 0.234	29.10±4.79	p:0.354	46.86±8.25	p:0.080	13.93±3.40	p:0.149	16.23±4.39	p: 0.463
Grade	1st grade	135	90.18±11.91	t:-0.147[2]	28.88±5.19	t:14364.500[1]	47.27±8.27	t:0.081[2]	14.02±3.41	t:-0.149[2]	15.65±4.31	t:13601.500[1]
	2nd grade	220	90.37±11.94	p:0.884	29.04±4.58	p:0.556	47.20±8.34	p:0.936	14.07±3.32	p:0.882	16.36±4.43	p: 0.160
Family Type	Extended	68	89.90±12.34	t:-0.304[2]	29.02±4.55	t:-0.427[2]	46.84±8.52	t: -0.427[2]	14.02±3.66	t:-0.073[2]	16.16±4.75	t: 9756.000[1]
	Nuclear	288	90.39±11.83	p:0.761	28.97±4.88	p:0.686	47.32±8.26	p: 0.670	14.06±3.28	p:0.942	16.07±4.31	p:0.962
Chronic Disease	Yes	30	85.96±11.05	t:**-2.092**[2]	28.46± 4.38	t:4693.50[1]	43.80±7.91	t:**-2.381**[2]	13.70±2.96	t:-0.607[2]	18.23±5.47	t: **3639.500**[1]
	No	325	90.70±11.92	p:**0.037**	29.03±4.85	p:0.715	47.54±8.28	p:**0.018**	14.08±3.39	p:0.544	15.89±4.24	p: **0.020**
Economic Status	Income is more than expenses	47	87.75±12.43	t: 1.191[4]	28.12±4.87	t:1.598[3]	45.30±8.42	t:2.030[4]	14.31±3.05	t:2.626[4]	17.14±4.96	t: **8.572**[3]
	Income is equal than expenses	211	91.22±11.95	p: 0.148	29.05±4.86	p:0.450	47.86±8.56	p:0.133	14.30±3.28	p: 0.074	15.51±4.20	p: **0.014**
	Income is less than expenses	97	89.52±11.45		29.24±4.68		46.78±7.55		13.39±3.57		16.83±4.36	
Longest Residence	Village	40	92.77±12.52	t:1.025[4]	12.52±5.00	t:0.475[3]	49.15±9.00	t: 1.279[4]	13.75±3.54	t:0.526[3]	15.85±4.15	t: **3639.500**[3]
	District	77	89.60±12.24	p:0.360	12.24±4.68	p:0.789	46.66±8.09	p: 0.280	14.01±3.79	p:0.769	15.54±3.62	p: **0.020**
	City	238	90.10±11.70		11.70±4.83		47.09±8.24		14.12±3.17		16.31±4.65	
Smoking	Yes	69	90.65±11.95	t: 0.273[2]	29.13±4.57	t: 9290.000[1]	46.75±8.37	t: -0.533[2]	14.76±3.13	t: 1.971[2]	17.63±4.68	t: **7410.500**[1]
	No	286	90.21±11.92	p: 0.785	28.94±4.87	p: 0.424	47.34±8.30	p: 0.594	13.88±3.38	p: 0.051	15.72±4.25	p: **0.001**
Alcohol Use	Yes	18	91.00±10.60	t: 0.255[2]	28.88±4.14	t: 2947.00[1]	46.83±8.37	t: -0.209[2]	15.27±2.94	t: 1.589[2]	18.66±5.05	t: 2358.000[1]
	No	337	90.26±11.99	p: 0.799	28.98±4.85	p: 0.823	47.25±8.31	p: 0.835	13.99±3.36	p: 0.113	15.98±4.34	p: 0.106

DISCUSSION

The COVID-19 outbreak had an impact on all aspects of society around the world, both directly and indirectly. Schools were closed for extended periods of time in order to control the pandemic and protect students from COVID-19. Students who were isolated at home for an extended period of time and had to attend online classes experienced a variety of emotional stressors. Due to the rapid spread of COVID-19, college students who received a large amount of negative information were more likely to develop psychological maladjustment. As a result, it is critical to pay close attention to the psychological state of university students who have been isolated at home for an extended period of time and to provide timely and appropriate interventions to protect and improve their mental health (4).

Problem-Solving Skills of Students

One of the most important aspects of a person's cognitive process is problem-solving. In healthcare, problem-solving skills necessitate critical thinking abilities that allow knowledge to be applied to find solutions23. The ability to solve problems effectively is a critical step in the health care process that promotes creative thinking (24). The mean problem-solving inventory score in our study was 90.30±11.91. The mean problem-solving inventory pre-test score was 87.55±2.65 in the study conducted by Kanbay (25) et al. (2017) and 90.65±19.03 in the study conducted by

Bayram (24) et al. (2022). The mean problem-solving inventory score was reported as 100.31±17.3 in a study that examined the factors influencing the problem-solving skills of undergraduate nursing program students. Health professionals with strong problem-solving abilities can help to improve health care quality by ensuring the successful implementation of the care process. The students' moderate problem-solving abilities demonstrate that their education and experience, as well as the methods they employ, are insufficient. According to the World Health Organization (WHO), healthcare professionals must be able to take the necessary precautions and use a problem-solving approach while providing appropriate care to individuals (26). The problem-solving abilities of the research participants were found to be moderate in this study, as in many other studies in the literature. A moderate level of problem-solving ability can reduce the content and quality of care, negatively affecting quality, effectiveness, efficiency, transformation, professionalism, autonomy, and power (27-29).

Anxiety Levels of Students

One of the most distinctive psychological consequences of the COVID-19 pandemic is anxiety. University students in general, and especially students studying medicine, are the most affected. The current study discovered a mean anxiety score of 16.09±4.39. This indicates a high level of anxiety. Furthermore,

in our study, the prevalence of high-level anxiety was found to be 35.4%. This result is consistent with the literature. Several systematic reviews and meta-analyses have been conducted to investigate the prevalence of anxiety in college students in general during the Covid-19 crisis. In their study, Batra et al (30) discovered a 39.4% prevalence of anxiety in university students, Wang et al (31) discovered a 31% prevalence discovered. Because anxiety impairs interpersonal communication and empathy, this can have a negative impact on their academic performance, professionalism, and empathy toward patients during their education.

Do Sociodemographic Characteristics Affect Students' Anxiety Levels and Problem-Solving Skills?

The study investigated whether gender, economic status, school year, long-term residence, family type, chronic disease, smoking, and alcohol use affect respondents' scale scores. According to the findings, there was no statistically significant difference in total problem-solving inventory scores based on gender, school year, longest place of residence, smoking status, economic status, or family type. Also, Fu et al (2021) found no significant difference between gender and mean Problem-Solving Inventory score, which is consistent with the findings of other studies (4). In line with the results of this study, the H2 hypothesis was accepted.

Those with a high income, those who spent the majority of their lives in the city center, those with chronic diseases, and those who smoked had higher anxiety scores in the study, and the difference was statistically significant. In line with the results of this study, the H1 hypothesis was accepted accordingly Male students and those living in extended families had higher anxiety score averages, but there was no statistical significance. In line with earlier studies (4), the current study did not detect any gender-related differences that were statistically significant. As a result of the COVID-19 pandemic, male and female college students are experiencing similar stresses and negative emotions. Furthermore, we discovered that first-year students were more anxious than second-year students, but this difference was not statistically significant. Academic pressure is greater for more senior students, and some are facing graduation, employment, and application, among other things, but we believe that the COVID-19 pandemic is inextricably linked to a variety of factors affecting their development. In contrast to previous research, we discovered that college students with low economic status were less likely to experience anxiety symptoms than those with higher economic status. This could be due to the higher life expectancy of students with higher incomes. In this study, a weak positive (r=0.107) relationship was found between the problem solving inventory and generalized

anxiety disorder, and this relationship was found to be statistically significant (p-value=0.044) (Table 4). Ho hypothesis is rejected

CONCLUSION

Initiatives should be planned to improve prospective health care providers' self-perceptions of problem-solving skills and anxiety management, and curricula should be revised as needed. To mitigate the psychological damage caused by the COVID-19 pandemic, university students should receive timely and appropriate psychological interventions. The regulation of the psychological state of students who receive health education will affect the quality of care they will provide to patients after graduation in this process.

Limitations of the Study

This research is a descriptive cross-sectional study conducted in order to evaluate the problem-solving skills and anxiety levels of all students who accepted to participate in the research in vocational school of health services. That is, it is based on students' self-reports and is not taken from their medical records. Therefore, personal reports often provide objective indicators. sample size; A larger sample of students could have yielded more reliable results by including the social and health departments of different faculties.

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RESEARCH ARTICLE

Surgical Removal of Endometriomas Adversely Affects Ovarian Reserve: Comparison of Serum FSH, AMH and AFC Before and After Cystectomy

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Abstract

Objective: Surgical removal of endometriomas, even if performed in experienced hands, leads to a decrease in ovarian reserve in varying degrees depending on age. This study was designed to determine the pre- and post-surgical changes of ovarian reserve markers in patients who underwent endometrioma cystectomy.

Methods: Gözde Akademi Hospital gynecology outpatient clinic with the diagnosis of symptomatic ovarian endometrioma was included in the study. Fourteen normal-ovulatory women aged between 21-36 were included in the study. In addition to serum anti-Mullerian hormone (AMH), follicle-stimulating hormone (FSH), and estradiol levels, antral follicle count (AFC) was evaluated before and 3 months after cystectomy. Ovarian damage was avoided as much as possible during endometrioma surgery.

Results: After endometrioma cystectomy, serum AMH levels were significantly decreased (3.21 ± 1.1 ng/mL vs 1.9 ± 0.6 ng/mL; p= 0.02). There was no significant change in serum FSH (5.97 ± 1.6 mIU/mL vs 7.34 ± 0.55 mIU/mL, p=0.08) and estradiol (37.8 ± 9.44 pg/mL vs 32.9 ± 10.7 pg/mL, p=0.56) values measured three months after surgery. Similarly, there was no significant change in AFC values before and after surgery (4.12 ± 2.80 vs 4.89 ± 3.06, p=0.24).

Conclusion: Endometrioma cystectomy leads to a significant decrease in AMH levels, which is the main ovarian reserve marker, but does not affect AFC and FSH values.

Keywords: Endometrioma, Cystectomy, AMH, FSH, Estradiol.

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INTRODUCTION

Endometriosis is an important reproductive tract disease with a frequency of approximately 10% in women of reproductive age, accompanied by pelvic pain and subfertility. Although it can be treated to some extent with conservative approaches in single women, it is very difficult to manage in infertile couples. Ovarian endometrioma is an important complication of endometriosis and there is no general consensus on its treatment (1,2). Endometrioma is a blood-filled pseudocyst formation that occurs due to close contact between the endometrial foci in the peritoneum and the ovarian surface epithelium (3,4). Retrograde menstruation, small invaginated cysts, and corpus luteum metaplasia have also been implicated in the formation of endometrioma (5). The location of endometriomas close to the ovarian cortex may cause damage to the primordial follicles in this area. The most important feature that keeps endometrioma on the clinician's agenda is its harmful effects on ovarian reserve. Since endometrioma occupies a place in the ovarian cortex, it both restricts the location of the follicles and can reduce the ovarian reserve by disrupting its blood supply. The fact that the ovarian cortex of patients with endometrioma contains fewer follicles than healthy individuals or the opposite ovary is important evidence that these cysts cause follicle damage (6,7). Increased cortical fibrosis and follicular atresia in areas close to endometrioma are further evidence that endometrioma itself negatively affects ovarian reserve (1,2).

If an ovarian endometrioma causes a decrease in ovarian reserve, surgical removal should lead to recovery of the reserve. However, clinical studies and observational data have not led to a consensus that endometrioma surgery fully restores ovarian reserve. While some studies have reported that ovarian reserve improves after endometrioma cystectomy (8), others have suggested that cystectomy has no clear effect on reserve or is harmful (1,2). In light of recent meta-analyses, it has been emphasized that both endometrioma and endometrioma surgery lead to a decrease in ovarian reserve (9). Endometrioma reduces the reserve by restricting the location of the follicles and impairing oxygenation. Endometrioma surgery disrupts the reserve by removing healthy cortical tissue (1,2).

Serum and ultrasonographic markers can be used alone or in combination to detect ovarian reserve. Serum anti-müllerian hormone (AMH), FSH, and estradiol are considered the

most reliable biomarkers (10). Ultrasonographically measured antral follicle count (AFC) is another important ovarian reserve marker (11). AMH and AFC are more sensitive in determining ovarian reserve than other markers. This study was planned to determine the changes in serum (AMH, FSH, estradiol) and ultrasonographic (AFC) markers of ovarian reserve before and after endometrioma cystectomy in patients with uni- or bilateral symptomatic endometrioma.

METHODS

Fourteen patients who applied to Gözde Akademi Hospital gynecology outpatient clinic with the diagnosis of symptomatic ovarian endometrioma were included in the study. All participants exhibited different symptoms related to endometrioma (pelvic pain, subfertility, etc.). Therefore, a decision was made for laparoscopic ovarian endometrioma cystectomy. The ages of the patients ranged from 21 to 36. The BMI values of the participants were taken into account (24.8 ± 10.6 kg/m2) to prevent possible dilutional changes in serum AMH levels. Endometrioma diagnosis was made by transvaginal USG. It was recorded whether the cyst was uni- or bilateral. To measure serum AMH, FSH and estradiol levels, blood samples were taken from all patients before and three months after surgery in the follicular phase of the cycle. After an overnight fast, cubital venous blood was collected from all participants in a sitting position. Serum AMH, FSH and estradiol levels were measured by electro-chemiluminescence immunoassay (ECLIA) method with Roche Cobas e602 (Roche Diagnostics GmbH, Germany) immunoassay analyzer. AFC was calculated in the early follicular phase and with TV-USG. Follicles larger than 2-6 mm in both ovaries were counted and recorded. Patients with BMI values >30 kg/m2, those with concurrent non-endometriotic ovarian cysts, PCOS patients, those who had previous ovarian or pelvic surgery, and those who used hormonal therapy in the last 6 months were excluded from the study.

Endometrioma Cystectomy: Laparoscopy was performed under general anesthesia using the four-port laparoscopy technique. The contents of the endometrioma were aspirated through a small cautery incision made by the antimesenteric side. The endometrioma capsule was removed by grasping forceps. If there was no bleeding, cauterization was not performed. Bipolar cautery was used in patients with bleeding. Endometriosis foci detected in the peritoneum and on the ligaments were cauterized or excised. During the surgical procedure, care was taken not to damage the healthy ovr tissue. The removed cyst components were sent to the pathology.

Statistical Analysis: Statistical Package for Social Sciences version 21.0 (SPSS, Chicago, IL, USA) was used for the analysis of all

collected data. Whether the data were normally distributed was tested with Shapiro-Wilk. Normally distributed data were analyzed with paired samples t-test, and parameters that were not normally distributed were analyzed with

Wilcoxon test. The correlation between ovarian reserve markers and demographic data was calculated using Spearman's test. While the results were presented as mean+ SD, p<0.05 was considered statistically significant.

Table 1: Patients characteristics

Demographic features*	Participants (n=14)
Age (years)	32.4±11.2
BMI (kg/m^2)	25.8±10.6
Application complaint	
Severe dysmenorrhea, n (%)	6 (42.8%)
Subfertility/infertility, n (%)	5 (35.7%)
Dysmenorrhea + subfertility, n (%)	3 (21.4%)
Laterality	
Unilateral, n (%)	10 (71.4%)
Bilateral, n (%)	4 (28.5%)
Endometrioma size (mm)	43.6 ± 9.32 (34-52)
AMH (ng/mL)	
Before surgery	3.21 ± 1.1
After surgery	1.9 ± 0.6
FSH(mIU/mL)	
Before surgery	5.97 ± 1.6
After surgery	7.34±0.55
AFC	
Before surgery	4.12 ± 2.80
After surgery	4.89 ±3.06
Estradiol (pg/mL)	
Before surgery	37.8 ±9.44
After surgery	32.9 ±10.7
Values was presented as mean ± SD, or n (%).	

RESULTS

Endometrioma cystectomy was successfully performed in all participants without serious complications. Of the 14 participants, 4 had bilateral (28.5%) and 10 had unilateral endometrioma (71.4%). The patients were discharged after one day of observation. No menstrual irregularity was detected in the early postoperative period and at the end of 3 months. Three patients gave a history of spotting vaginal bleeding on the first and second postoperative days. Demographic data and pre-postoperative ovarian reserve marker values of the patients are shown in Table 1. After endometrioma

cystectomy, serum AMH levels were significantly decreased (3.21 ± 1.1 ng/mL vs 1.9 ± 0.6 ng/mL; p= 0.02). There was no significant change in serum FSH (5.97 ± 1.6 mIU/mL vs 7.34±0.55 mIU/L, p=0.08) and estradiol (37.8 ±9.44 pg/mL vs 32.9 ±10.7 pg/mL, p=0.56) values measured three months after surgery. Similarly, there was no significant change in AFC values before and after surgery (4.12 ± 2.80 vs 4.89 ±3.06, p=0.24).

The AFC value on the endometrioma side was lower than the ovarian AFC on the healthy side (4.12 ± 2.80 vs 5.66 ±2.30, p<0.01). The

change in AFC values was similar at the postoperative third month. A positive and significant correlation was found between AMH values and AFC both before (r=0.467, p=0.03) and after surgery (r=0.490, p=0.02). No significant correlation was found between other parameters.

DISCUSSION

Although many hypotheses regarding the formation of endometrioma have been put forward, a common consensus has not been established so far. The unclear etiology of endometrioma has also led to heterogeneous results regarding its effects on reproductive outcome. While some studies report that the ovary on the endometrioma side responds less to ovarian stimulation than the healthy ovary, there are also studies reporting that there is no difference between the ovaries (1,2). In another study, it was reported that women with endometrioma had lower AMH levels than those without endometrioma in the same age group (2). The bilateral and severe stage of endometrioma leads to a more significant decrease in ovarian reserve markers. However, the low AFC and AMH values may vary depending on the size of the cyst and the severity of the disease. In addition, it has been emphasized that AFC may show a false-negative decrease (1,2) since the cyst distorts the ultrasonographic appearance.

In the presence of endometrioma, decreased area for follicle placement in the ovarian cortex and low blood flow may decrease AMH and AFC levels. Indeed, the presence of fibrosis, inflammation and low blood flow in the cortical area adjacent to the cyst may lead to a decrease in the follicle pool and decrease in AFC, especially AMH (12,13). If subfertility due to endometrioma is due to the space-occupying effect of the lesion, surgical removal of the cyst should lead to recovery of ovarian reserve. To test this, we evaluated the main ovarian reserve markers, AMH, FSH, E2, and AFC, before and three months after surgery in patients who underwent endometrioma cystectomy. If the space-occupying effect of the cyst is the main cause of subfertility, AMH, E2, and AFC should increase and FSH should decrease after surgery. However, our results did not fully meet our expectations. After endometrioma cystectomy, serum AMH levels decreased, but there was no significant change in AFC, FSH, and estradiol levels. Post-surgery AMH reduction may be an indication that cystectomy leads to deterioration in ovarian reserve. Removal of healthy cortex tissue during cystectomy may lead to a decrease in AMH. The presence of cortical tissue and preantral follicles in cystectomy material is evidence of surgery's damage to healthy ovarian tissue (1,2). However, the absence of a significant change in AFC led us to question the space-occupying effect of the cyst. Similarly, the fact that FSH and estradiol values remained the same in the postoperative period did not support

the idea that cystectomy had a negative effect on ovarian resection.

We can list the possible reasons why the AFC remains stable despite the decrease in AMH value after endometrioma cystectomy. The disappearance of the compression effect of the endometrioma on the preantral follicles in the post-cystectomy period may have allowed them to become functional. The re-functioning of follicles released from pressure after surgery suggests that the AFC pool is not seriously affected by surgery (2). Although the follicle under the pressure of endometrioma maintains its vitality, these follicles may not be able to fulfill their AMH secretion task. We believe that surgery should not be delayed due to the risk of losing the vitality of the follicles in endometriomas that have not undergone surgery for a long time. Since changes in FSH and estradiol levels are long-term effects of endometriomas, it may be accepted as normal for their levels to remain unchanged after surgery. The positive correlation between AMH and AFC is evidence that these two markers work in coordination. No matter how experienced the surgeon is, a decrease in reserve can occur. Cauterization of unpredictable bleeding, the presence of accompanying peritoneal and deep endometriosis, and bilaterality may be the reason for the discrepancy in AMH and AFC results. AMH reduction can be minimized thanks to the necessary care and attention to be

shown during cystectomy. In addition, since the age range of the participants is variable, AMH and AFC mismatch may have occurred. In a recent study (14), it was reported that laparoscopic endometrioma resection increased FSH levels while decreasing serum AMH levels. The FSH results of this study are inconsistent with ours. We measured FSH levels at the third-month post-cystectomy. The other study measured it three days after surgery. The reason for the inconsistency may be the difference in FSH measurement times. Decreased estradiol levels due to early cautery damage may have led to an increase in FSH. After three months, histomorphological and functional improvement in the ovary may have normalized FSH levels. The lack of international standardization of AMH values does not allow us to make a clear discussion about whether there is a decrease in post-surgical levels (15). On the other hand, the fact that AMH has a stronger effect in determining the response to ovarian stimulation compared to basal FSH concentrations weakens the clinical significance of unchanged FSH levels after endometrioma surgery (16).

Despite the small number of cases and the short follow-up period, our study showed that endometrioma cystectomy did not cause a significant change in AFC, despite a decrease in serum AMH levels. If the number of AFCs is sufficient, the decrease in AMH may not mean much. Whether there is a decrease in AFC in

long-term follow-up should be investigated extensively. We did not evaluate ovarian reserve marker changes according to whether the endometrioma is unilateral or bilateral. This can be a handicap. However, since the distribution of patients into groups was not homogeneous, statistical analysis results would not be very objective. However, we can expect a further decrease in AMH values in bilateral cases. By including cyst size and individual ovarian reserve, it will be possible to interpret ovarian reserve marker changes more objectively in bilateral endometriomas. In conclusion, in symptomatic endometriomas, the clinician should decide in light of treatment guidelines and based on the patient's past clinical and fertility history.

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