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ORIGINAL ARTICLE

Evaluation of Status of Getting ill with SARS CoV-2 and the Knowledge of Using and Attitudes of Personal Protective Equipment at Pre-Hospital Emergency Care Services Employees

Hastane Öncesi Acil Sağlık Çalışanlarının COVID-19 Enfeksiyonu Geçirme Durumları ile Kişisel Koruyucu Ekipman Kullanımı Hakkında Bilgi ve Tutumlarının Değerlendirilmesi

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ABSTRACT

Objective: The present study aimed to evaluate the knowledge level of healthcare personnel working in pre-hospital emergency care services in Konya province regarding the coronavirus disease 2019 (COVID-19) infection and the use of personal protective equipment (PPE) during the pandemic.
Material and Methods: A total of 410 healthcare personnel working in pre-emergency care services in Konya province were included in the study. The data were collected through a questionnaire developed by the researcher inquiring about the demographic data, whether they caught (COVID-19) or not, knowledge about COVID-19, and knowledge and attitudes regarding the use of PPE.
Results: The rate of individuals who experienced mild infection was 27.1%, and those who experienced severe disease were 5.6%. It was determined that 83.7% of the healthcare personnel were using PPE. The most commonly used PPE were gloves (90.8%), and the least were visors and eyeglasses (43.8%). When the frequency of the COVID-19 symptoms was analyzed according to age, the symptoms were more frequent in the age group of 40 years and above, and the symptom frequencies were seen to increase with age.
Conclusion: It was concluded that the healthcare personnel had received in-service training about COVID-19 and had sufficient knowledge. The rate of PPE use was high, and there was no difference between males and females in catching COVID-19 infection.

Keywords: COVID-19, SARS-CoV-2, Personal protective equipment, Pandemics

ÖZ

Amaç: Bu çalışmanın amacı Konya ili hastane öncesi Acil Sağlık Hizmetlerinde görev yapan sağlık personelinin, pandemi sürecinde Covid-19 enfeksiyonu ve kişisel koruyucu ekipman kullanımı ile ilgili bilgi, tutum ve davranışlarını incelemektir.
Gereç ve Yöntem: Bu çalışmaya Konya ili Acil Sağlık Hizmetlerinde görev yapan 410 sağlık personeli dâhil edildi. Veriler araştırmacı tarafından hazırlanan; demografik bilgileri, Covid-19 geçirip geçirmediğini, Covid-19 bilgisi ve KKE (Kişisel Koruyucu Ekipman) bilgi ve tutumlarını sorgulayan bir anket aracılığıyla toplanmıştır.
Bulgular: Araştırmaya katılan bireylerden Covid-19 enfeksiyonunu hafif geçirenlerin oranı %27,1, ağır geçirenlerin oranı %5,6 olarak belirtilmiştir. Sağlık personelinin %83,7'si KKE kullandığını belirtmiştir. Personelin eldiven, tulum/önlük, N95/FFP3 maske, cerrahi maske ve siperlik/gözlük kullanım oranları sırasıyla %90,8; %65,4; %64,4; %62,4 ve %43,8 olduğu bilgisine ulaşılmıştır. Sağlık personelinin yaşlarına göre COVID-19 semptom görülme sıklığı incelenmiş, 40 yaş üstü personelde semptomların daha sık görüldüğü belirtilmiştir. Yaşın artmasıyla semptomların görülme sıklığının arttığı gözlenmiştir.
Sonuç: Sağlık personelinin Covid-19 hakkında hizmet içi eğitim aldığı ve yeterli bilgiye sahip olduğu ayrıca KKE kullanım oranlarının yüksek olduğu sonucuna varılmıştır.

Anahtar Kelimeler: Covid-19, SARS-CoV-2, kişisel koruyucu ekipman, pandemi

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified in Wuhan, China, in 2019 (1). Coronaviruses (CoV) are single-strand positive chain RNA viruses that belong to the coronavirus species of the Coronaviridea family (2). Coronaviruses are a large virus family, which may lead to mild infections such as the common cold or severe infections such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) (3). The incubation period is 2-14 days, and contamination occurs via droplets, contact, and aerosols, and also from asymptomatic individuals (4). According to South Korea's and Germany's data, most infections are transferred from asymptomatic subjects (5, 6). SARS-CoV-2 has affected the whole world in a short time due to its rapid and easy transmission. The first case was detected in Turkiye at the beginning of March 2020 (7).

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The whole population is susceptible to COVID-19 infection and the healthcare workers are the group with the highest risk. The studies on the working perception of healthcare workers during pandemics emphasize the importance of using PPE to feel safe and ready (8). In a study from China, healthcare workers were said to be protected from infection when they were provided a proper PPE and proper training about PPE use, including "protective clothes, masks, gloves, face visors and coveralls" (9).

With this study, we aimed to detect the deficiencies, make recommendations, and contribute to the literature about knowledge and education regarding COVID-19, skills, and attitudes toward PPE use among healthcare providers during pandemics when these issues are of great importance.

Material and Methods

Study Design and Population

A cross-sectional model was used for the study. The study was conducted on healthcare personnel working at pre-hospital emergency care services in the province and districts of Konya. The sample consisted of 410 health personnel (physician, ambulance and emergency care technician (AECT), emergency medical technician (EMT), health officer, nurse, and midwife) who were working at the emergency care services centers, logistic units, and command and control center (CCC) of Konya Province Ambulance Services Directorate. After having obtained the required permissions from the Scientific Researches Committee of the Directorate-General for Health Services (date:15.09.2020/number:2020-09-14T20 08 53), Konya Provincial Directorate of Health (date:10.11.2020/ number:86737044-806.01.03), the ethics committee approval had been obtained from Selcuk University Medical School Non-interventional Clinical Researches Ethics Committee (date:30.09.2020/number:2020/18), and verbal consents were obtained from volunteer participants.

The data were collected through face-to-face interviews. The questionnaire form developed by the researchers included 33 questions inquiring about socio-demographic information (gender, age, title, working experience, educational status, the unit where s/he worked, etc.), whether s/he got COVID-19, knowledge about COVID-19 and PPE. The questions in the survey consist of both yes/no and multiple-choice questions. Open-ended questions were not asked in the survey. All questions were analyzed according to the answers given by the personnel participating in the survey.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 21.0 software. The statistics of health personnel were given as frequencies and percentages. The associations between the categorical variables were analyzed using the chi-square test. The ANOVA test and the t-test were used for the comparison of the means. A p-level of <0.05 was accepted as statistically significant.

Results

The demographic characteristics, titles, educational status, and working units of the participants are presented in Table 1. No statistically significant relationship was observed between gender infected with COVID-19 (p>0.05) (Table 2). A statistically significant difference was determined between the symptoms and age (p<0.05). When the symptom differences were analyzed according to age, the signs were more frequent among individuals 40 years and above (p<0.05) (Table 3). Gloves were found as the most frequently used PPE (90.8) when making an intervention or transferring the patient, and visors/ eyeglasses were the least used PPE (43.8%) (Table 4).

Table 1. Distribution of socio-demographic details of healthcare personnel.

Details		n	%
Sex, n (%)	Female	223	54.4
	Male	187	45.6
Age (years), n (%)	20-30	146	35.6
	30-40	193	47.1
	>40	71	17.3
Participants, n (%)	Physician	10	2.4
	AECT	144	35.1
	EMT	211	51.5
	Other	45	11.0
Work experience (years), n (%)	0-5	35	8.5
	5-10	153	37.3
	10-15	143	34.9
	>15	79	19.3
Educational level, n (%)	High school	36	8.8
	Associate degree	174	42.4
	Bachelor degree	177	43.2
	Post-Graduate degree	23	5.6
Working Unit, n (%)	Station	338	82.4
	CCC	64	15.6
	Other	8	2.0
Status of Receiving In-Service Training for Covid-19, n (%)	Yes-face to face	19	4.6
	Yes- online	378	92.2
	No	13	3.2
PPE usage, n (%)	Yes	343	83.7
	No	3	.7
Total		410	100.0

AECT: Ambulance Emergency Care Technician
EMT: Emergency Medical Technician
CCC: Command Control Center

Table 2. COVID-19 infection status findings by sex.

No Don't know			Suffering from COVID-19 Infection				Total	x^2	p
			Yes (mild)	Yes (severe)					
Sex	Female	n	117	31	61	14	223		
		%	55.5	47.7	55.0	60.9	54.4		
	Male	n	94	34	50	9	187	1.675	.643
		%	44.5	52.3	45.0	39.1	45.6		
Total		n	211	65	111	23	410		
%			51.5	15.9	27.1	5.6	100.0		

Table 3. Multiple comparison of the incidence of symptoms according to age of healthcare personnel with COVID-19 infection.

Age	Age range	Mean Difference	p-Value
20-30	30-40	-.17702	.524
	>40	-.86475	.000
30-40	20-30	.17702	.524
	>40	-.68773	.003
>40	20-30	.86475	.000
	30-40	.68773	.003

Table 4. Rates of PPE used by healthcare professionals when intervening/transferring patients with a contagious disease.

PPE	n	%
Gloves	179	90.8
Surgical mask	123	62.4
N95/FFP3 mask	127	64.4
Overalls/apron	129	65.4
Visor/eyeglasses	106	43.8
Total	197	100

Discussion

COVID-19 significantly affected health services worldwide; a remarkable increase in demand for healthcare services, and the need for PPE and its importance increased. Despite being the group with the highest risk for exposure and contamination with the virus, the lack of studies in the literature investigating the knowledge and attitudes of health personnel about COVID-19 infection and PPE use has urged us to carry out this study, and it was aimed to contribute to the literature. In such a time when the knowledge and attitudes of health personnel are of great importance, our study, which was conducted with 410 healthcare workers, has obtained data about the ability of participants about COVID-19 infection and PPE, the attitudes toward PPE use, education about COVID-19, and being infected with COVID-19 through a questionnaire. The finding that the education rates about COVID-19 and PPE were high and the personnel had sufficient knowledge, and the vast majority of the personnel were using PPE despite it being complicated and restrictive was promising.

Studies investigating the working perception of healthcare workers during the pandemic emphasize the importance of PPE education to feel safe and ready (8). In a study conducted in Henan in 2020, it was stated that 89% of healthcare workers had sufficient knowledge about COVID-19 infection (10). Healthcare workers reported that they had difficulty providing services when using PPE and putting on and taking off the PPE. They stated that blurred eyeglasses were challenging when performing procedures such as intubation and anesthesia (11). Healthcare workers remarked additional worries about PPE such as communication difficulty, physical disturbance, fatigue, restriction, heat, and dehydration. They reported continued providing care despite the high number of patients and short break time (9). In our study, when the PPE used by the personnel when intervening in patients with a contagious disease was examined, the rate of PPE use was observed high. According to the results of our study, we can state that although PPE is complicated and restrictive, most health personnel prefer to use them and thereby try to protect themselves and their environment from the risk of contamination.

When the COVID-19 in-service training status of the health personnel participating in our study was evaluated, we found that 96.8% received (online or face-to-face) training. We suggest that the high rate of in-service training resulted from their having completed their in-service training, and from the institutions to which the personnel is affiliated directing the health personnel to receive training.

Healthcare workers are the group with the highest risk for COVID-19 infection. In a study from Italy, 20% of healthcare workers who provided care for COVID-19 patients were infected within the first two months (12). In a study from Spain, 419 out of 4393 COVID-19 patients (9.5%) were healthcare workers (13). In a survey conducted in the USA in 2020, the rate of healthcare workers was 5.9% among 6760 COVID-19 patients (14). In our study, the rate of subjects who had a mild COVID-19 infection was 27.1% (n.111) and the rate of those who had a severe infection was 5.6% (n:23). We suggest that healthcare workers are at greater risk than the general population for infection and contamination.

In our study, no statistically significant relationship was determined between gender and contracting a COVID-19 infection ($p>0.05$). In a study from Turkiye , 48% of positive cases reported were male (15). The rates of males and females were reported close in similar studies (16). Many studies in the literature support our findings; however, different results may have arisen from sample characteristics, sample size, and methodologies. While different data are available for the COVID-19 pandemic by gender, they mostly show an equal number of cases between the genders. Still, the evidence suggests that male death rates are higher (17).

The COVID-19 pandemic has caused many people to become infected and many people to die worldwide, but the most commonly affected were the middle-aged and elderly individuals. A study conducted in Brazil in 2020 reported that 131 out of 2070 individuals (6.3%) who tested positive for COVID-19 died, and 1939 people (93.7%) survived. The mortality risk was higher for elderly people and those with comorbidities (18). Elderly individuals are more likely to become infected due to physiological changes that occur with age and underlying health conditions (19-21). In a study including 140 community-infected COVID-19 patients, most of the patients were reported as middle-aged and elderly (22). When the difference in symptoms according to age groups of the health personnel who participated in our study and had a COVID-19 infection was examined, it was observed that the symptoms were more common when personnel over 40 had COVID-19 infection compared to other age groups. The incidence of symptoms increased as the age increased ($p<0.05$) (Table 4). Since our study included personnel working in the emergency healthcare system, an assessment could not be made

of those over 65. Despite those explained above, the result obtained in our study supports the studies in the literature, and it was observed that the symptoms of the elderly personnel were more severe ($p<0.05$). Old aged adults also have additional factors, including malnutrition, comorbid conditions, decreased mucosal barrier efficiency, loss of the cough reflex and physical changes in the urinary tract (23). It can be stated that the older the age, the higher the adverse effects and risks of diseases (20). While some studies on the incidence of symptoms parallel to our analysis, others have shown different results. The change in the prevalence of the symptoms of COVID-19 with increased age and the fact that the participants in our study were younger adults may explain the difference in the incidence and course of symptoms. Furthermore, in some questionnaire studies, asking the symptoms with open-ended questions may make it difficult to remember all the symptoms at the first stage. We suggest that writing down the frequently seen symptoms in items made it easier to place them in our study.

Conclusion

According to the survey results, we can say that healthcare personnel over the age of 40 infected with COVID-19 had more symptoms. We may also say that the personnel received in-service training and had sufficient knowledge about COVID-19 infection and PPE; they prefered using PPE to protect themselves, their environment, and patients from contamination risk and continued to provide care to patients.

Ethics Committee Approval: Ethical approval for this study was obtained from the Scientific Researches Committee of the Directorate-General for Health Services (date:15.09.2020/number:2020-09-14T20 08 53), Konya Provincial Directorate of Health (date:10.11.2020/number:86737044-806.01.03), Selcuk University Medical School Non-Interventional Clinical Researches Ethics Committee (date:30.09.2020/ number:2020/18).

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ORIGINAL ARTICLE

Determination of Daily Fluid Intake Levels and Affecting Factors of Elderly Individuals Living at Home

Evinde Yaşayan Yaşlı Bireylerin Günlük Sıvı Alım Düzeyleri ve Etki Eden Faktörlerin Belirlenmesi

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ABSTRACT

Objective: In this study, it was aimed to determine the daily fluid intake and the factors affecting the fluid intake of elderly individuals living at home.
Method: This descriptive study collected data from a total of 91 elderly individuals. The sociodemographic characteristics form, daily fluid intake determination form, Edmonton Vulnerability Scale, Katz Activities of Daily Living Scale and Perceived Well-being Scale were used to collect data. For the fluid consumption status, the body surface area of the elderly individuals, the amount of fluid they should take daily, and the amount of fluid consumption deficiency were calculated.
Results: It was determined that the elderly individuals consumed an average of 1247.25 ± 428.71 milliliters of fluid per day and the average daily fluid deficit was 1065.60 ± 417.91 milliliters. It has been determined that elderly individuals are in the middle-frail border, semi-dependent in activities of daily living, and their well-being is low. In addition, it has been determined that elderly individuals do not want to go to the toilet frequently, have the most constipation problems due to lack of fluid consumption, and consume the most liquid between meals.
Conclusion: It has been determined that elderly individuals consume half as much fluid as they should daily are in the moderate fragility limit, are semi-dependent in daily living activities, and have low well-being. It has been determined that elderly individuals who use less than four drugs, live with their spouse, have been hospitalized before, and do not have a chronic disease consume more fluids.

Keywords: Elderly, dehydration, nursing, fluid consumption

ÖZ

Amaç: Bu çalışmada evde yaşayan yaşlı bireylerin günlük sıvı alımlarının ve sıvı alımını etkileyen faktörlerin belirlenmesi amaçlanmıştır.
Yöntem: Tanımlayıcı tipteki bu araştırmada toplam 91 yaşlı bireyden veri toplanmıştır. Verilerin toplanmasında sosyodemografik özellikler formu, günlük sıvı alımını belirleme formu, Edmonton Duyarlılık Ölçeği, Katz Günlük Yaşam Aktiviteleri Ölçeği ve Algılanan İyi Oluş Ölçeği kullanılmıştır. Sıvı tüketim durumu için yaşlı bireylerin vücut yüzey alanı, günlük almaları gereken sıvı miktarı ve eksik sıvı tüketimi miktarı hesaplanmıştır.
Bulgular: Yaşlı bireylerin günde ortalama 1247,25 ± 428,71 mililitre sıvı tükettiği, ortalama günlük sıvı açığının ise 1065,60 ± 417,91 mililitre olduğu belirlenmiştir. Yaşlı bireylerin orta-kırılgan sınırda oldukları, günlük yaşam aktivitelerinde yarı bağımlı oldukları ve iyilik hallerinin düşük olduğu belirlenmiştir. Ayrıca yaşlı bireylerin sık sık tuvalete gitmek istemedikleri, sıvı tüketiminin az olmasından dolayı en çok kabızlık sorunu yaşadıkları ve en fazla sıvıyı öğün aralarında tükettikleri tespit edilmiştir.
Sonuç: Yaşlı bireylerin günlük alması gereken sıvı miktarının yarısı kadar sıvı tükettikleri, orta kırılganlık sınırında oldukları, günlük yaşam aktivitelerinde yarı bağımlı oldukları ve iyilik hallerinin düşük olduğu belirlenmiştir. Dörtten az ilaç kullanan, eşiyle birlikte yaşayan, daha önce hastaneye yatmış, kronik bir hastalığı olmayan yaşlı bireylerin daha fazla sıvı tükettiği belirlenmiştir.

Anahtar Kelimeler: Yaşlı, dehidrasyon, hemşirelik, sıvı tüketimi

Introduction

Frailty is defined as a functional loss in multiple organs or systems, decreased physiological reserve, and decreased defense against stressors. The emergence of fragility reveals negative health consequences such as the increase in the frequency of falls in the elderly, the prolongation of hospital stay, the need to receive special care services, and the increase in health costs and morbidity (1).

A slow and progressive dehydration process and hyperosmotic stress disorder occur in individuals during aging (2). More than 60% of the human body consists of water. As people age, the water content in the body decreases below 50% (3). If adequate hydration levels are not maintained and regulated, this decrease can have adverse effects on the body. Therefore, although water is necessary at every stage of life, its importance increases with old age (4).

In the absence of fluid intake, death occurs much faster within a few days to a week than in the absence of any other nutrient. High mortality rates due to dehydration and hyponatremia among older adults have been reported in the literature (5). Other risk factors such as changes in the body's physiological and hormonal systems, inactivity, visual impairment, and urinary

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incontinence predispose the elderly to dehydration (6).

Clinical manifestations of dehydration include dry mouth (tongue grooves, dry mucous membranes), weight loss, decreased skin turgor, constipation, orthostatic hypotension, and increased urine concentration. It is known that dehydration is associated with many chronic health problems in elderly people such as falls, fractures, confusion, delirium, pressure ulcers, poor wound healing, constipation, urinary tract infections, heat stress, infections, kidney stones, and kidney failure (7). In some individuals, the loss of as little as 2-3% of body fluid can cause physical and cognitive impairment. Elderly individuals are at the risk of dehydration due to not feeling hungry or thirsty, decreased thirst, decreased renal perfusion, changes in sensitivity to antidiuretic hormones and neurocognitive changes. In addition, access to water and fluids may be reduced in older individuals. The elderly have problems such as oropharyngeal dysphagia (OD), which may cause dehydration and malnutrition due to a lack of fluid and food intake (8).

Although various studies have shown that the elderly are at high risk for health problems related to dehydration, there is little information about the conditions that affect the appropriate amount of fluid intake in the elderly (9). It is emphasized that the factors affecting fluid intake variability in the elderly and the daily fluid intake associated with adequate hydration status should be determined (3). We think that determining the factors affecting the daily fluid intake of the frail elderly will contribute to the literature. For this reason, this study aims to determine the factors affecting the daily fluid intake of frail elderly people.

Materials and Methods

The pattern of the research

The research was conducted with individuals aged 70 and over admitted to a secondary-level public hospital for outpatient treatment. Questionnaire forms were used to collect research data. Research data were collected between April 2022 and October 2022.

The power level and effect size calculations were calculated in the study with G*Power Version 3.1.7. Since the population of the study is not known exactly, the power and sample level of the study was calculated based on the study of Dönmez and Demir (2022) (10). Dönmez and Demir's research was conducted with 98 participants. Accordingly, it can be seen that at least n=69 participants, who are planned to be included in the study, can represent the study with 80% power (values of 0.70 and above are valid in studies and 0.80 is expected to be quite sufficient). In addition, it was determined that the effect size level of the study was 0.37 (0.10 small, 0.25 medium, and 0.40 large effect size) (10).

Inclusion Criteria

Individuals aged 70 years and older who meet at least one frailty criterion and can walk independently (with the possibility of ambulatory assistive devices without the assistance of another person) and present to a health center for outpatient treatment. Elderly individuals use only simple painkillers and antihypertensive drugs.

Exclusion Criteria

Participants with hearing or vision loss and moderate to severe cognitive impairment. Elderly individuals have been told by their physicians to restrict fluids. The elderly with diabetes and kidney failure. Elderly individuals using diuretic drugs.

Data Collection Tools

Research data; sociodemographic characteristics form, determination of daily fluid consumption form, Edmonton Vulnerability Scale, Katz Activities of Daily Living Scale, and Perceived Well-Being Scale were employed. The researcher administrated the questionnaires through face-to-face interviews with elderly individuals within the scope of the research.

Descriptive Characteristics of the Patients and Questionnaire Regarding the Disease: It was created by the researchers (11-13). It was composed of questions about the sociodemographic characteristics and illnesses of the participants. There are 13 items in the form.

Daily Liquid Consumption Amount Determination Form: It was composed of questions about the amount of daily fluid consumption by the elderly person, the time of fluid consumption, and the obstacles in front of fluid consumption. The questions were prepared by the researchers. There are 7 items in the form.

Edmonton Vulnerability Scale: It was developed by Rafson et al. in 2006 to define vulnerability (14). The validity and security study of ECO in Turkiye was carried out by Aygör and Fadıloğlu in 2018. As a result of the adaptation of the scale to Turkish society, the Cronbach alpha value was determined as 0.75 (15).

The scale consists of 11 items in total. The questions are evaluated with 0, 1, and 2 points, if the total score from the scale is 0-4, it is not fragile, if it is 5-6 points, it is vulnerable, if 7-8 points are slightly fragile, if 9-10 is moderately fragile, and if it is 11 and above, it is defined as severely fragile. In this study, the scale's Cronbach's alpha value was found as 0.91.

Katz Activities of Daily Living Evaluation Form: It was developed by Katz et al. for the evaluation of treatment and prognosis in chronic disease states and the elderly. Pehlivanoğlu et al. reported that the Turkish adaptation of the scale was reliable and the Cronbach Alpha coefficient was calculated as 0.83. Evaluation is made by giving 3 points if the elderly person can do their daily living activities independently, 2 points if they do it with help, and 1 point if they cannot do it at all. In the ADL index, 0-6 points are considered as "dependent", 7-12 points as "semi-dependent", and 13-18 points as "independent" (16). In this study, the scale's Cronbach's alpha value was 0.89.

Perceived Well-being Scale (PES): The scale was developed by Adams (1997) and its Turkish adaptation was made by Memnun (2006) (17). The Cronbach Alpha value of the scale was found as 0.84. It consists of six sub-dimensions: emotional, physical, spiritual, social, intellectual and psychological. There are a total of 36 items, six of which are in each dimension, and the answers given are in the form of a six-point Likert. While some items on the scale have positive meanings, some have negative meanings. Positive statements in the scale range from 6 to 1 changing from "Totally Agree" to "Strongly Disagree" and negative statements from 1 to 6 changing from "Totally Agree" to "Strongly Disagree" by inverting the negative statements scored with numbers. The lowest score that can be obtained from the scale is 36, and the highest score is 216. A score of 144 or less indicates low well-being, while a score above 144 indicates high well-being. It is accepted that the higher the score obtained from the scale, the higher the state of well-being. In this study, the scale's Cronbach's alpha value was determined as 0.92.

Application of Research

Elderly individuals who met the inclusion criteria of the study and agreed to participate in the study were asked to fill out the questionnaires. The data of the elderly who could fill out the questionnaires were considered valid. Then, the amount of fluid consumed by the elderly individuals in the last two days was questioned and this information was recorded in the Daily Fluid Consumption Determination Form. Questions about the amount of liquid consumed by the elderly individual included water and other liquids, and a glass calculation was made to measure it. The standard size was used in the glass calculation (water glass: 200 ml, tea glass: 100 ml). The elderly were asked to answer water, milk, fruit juice, buttermilk, herbal tea, etc. with the size of a glass of water and black tea from the size of a tea glass. Then, the body surface areas of the elderly individuals were calculated from the height and weight values, and then the amount of fluid needed daily was determined with the Gaspar formula (Body surface area x 1200 ml) (18). For example, if the individual's height is 170 cm and weight is 80 kg, the surface area is calculated as 1.96 m2. Then, when this value is multiplied by 1200 ml according to the Gaspar formula, the amount of fluid that the individual should consume daily is calculated as 2352 ml. The average of the amount of fluid taken by individuals for two days was subtracted from the amount of fluid that should be taken daily, and as a result, the amount of fluid deficiency of the individual was determined.

Data collection was terminated for that patient when the elderly could not remember their fluid intake status.

Evaluation of Data

The analysis of the data was carried out with the SPSS 23 program. Descriptive data are presented as numbers (n), mean and percentage (%). Within the scope of the research, Mann Whitney U tests Z test value was used in the evaluation of daily fluid consumption levels according to demographic variables, dehydration status and drug use.

Permissions

Permission was obtained from the ethics committee of a university with the number 2022/153. All principles o f the Declaration of Helsinki were complied with throughout the study. Informed consent was read and signed by each participant. In informed consent, the participants were assured that their participation was voluntary and that if they decided to withdraw from the study, there would be no change in the care provided by the staff.

Results

Table 1. Sociodemographic characteristics of elderly individuals and some characteristics of fluid consumption (N=91)

		n	%
Gender	Woman	55	60.4
	Male	36	39.6
Marital status	married	44	48.4
	single	47	51.6
Educational status	primary education	30	33.0
	secondary education	43	47.3
	license	18	19.7
People living with	lives alone	47	51.6
	lives with his wife	44	48.4
Number of drugs used	less than 4	38	41.8
	more than 4	53	58.2
Prior hospitalization status	Yes	73	80.2
	No	18	19.8
The state of having a chronic disease	Yes	65	71.4
	No	26	28.6
Age	74.67 ± 3.03 (min: 70, max: 80)		
Daily amount of fluid consumption (milliliters)	1247.25 ± 428.71 (min: 600ml, max-:2000ml)		
Daily fluid deficit (milliliters)	1065.60 ± 417.91 (min: 300ml, max-:1700ml)		
Fragility	7.91 ± 0.63 (min: 7, max: 9)		
GYA	11.85 ± 3.52 (min:5, max:16)		
well-being scale	141.06± 5.86 (min:132, max:148)		

The average age of the elderly individuals participating in the study was 74.67 ± 3.03 (min : 70, max : 80), 60.4 % were female, 48.4% were single , 47.3% were secondary school graduates, 51.6% lived alone. It was determined that 58.2% used more than 4 drugs, most of them were hospitalized before and 71.4% of them had at least one chronic disease. In addition, it was determined that elderly individuals consumed an average of 1247.25 ± 428.71 (min : 600ml, max : 2000ml) milliliters of fluid per day, and the average daily fluid deficit was 1065.60 ± 417.91 (min : 300ml, max : 1700ml) milliliters. Elderly individuals are 7.91 ± 0.63 (min : 7, max :9) in the middle frail limit, 11.85 ± 3.52 (min :5, max :16) in which they are semi-dependent in activities of daily living , and 141.06 ± 5.86 (min :132, max:148) where their well-being is low.

Table 2. Findings on fluid consumption characteristics of elderly individuals

		n	%
Reason for not drinking water	I forget to drink liquid	17	18.7
	I do not like to drink liquid	18	19.8
	I have pain when urinating	18	19.8
	Not to go tothe toilet often	38	41.8
Common problem	Constipation	47	51.6
	Indigestion	9	9.9
	Dry mouth	17	18.7
	Hot flashes	18	19.8
Fluid consumption time	Between meals	30	33.0
	During the meal	8	8.8
	After meals	18	19.8
	When seeing water	9	9.9
	When thirsty	26	28.6

It has beenfoundthat the elderly do not want to go to the toilet more often, they have the most constipation problems due to the lack of fluid consumption, and they consume the most liquid between meals.

Table 3. Conditions affecting daily fluid consumption of elderly individuals

		Mean ±SD	Testand *p* value
Number of drugs used	Less than 4	1361.84 ± 313.96	Z:-3.100
	More than 4	1165.09 ± 481.14	**p=0.002**
People living with	With his wife	1394.31 ± 479.36	Z:-3.059
	Alone	1109.57 ± 323.64	**p=0.002**
Prior hospitalization status	Yes	1675.00 ± 77.17	Z:-5,038
	No	1141.78 ± 413.90	**p=0.000**
The state of having a chronic disease	Yes	1160.00 ± 427.85	Z:-3.209
	No	1465.38 ± 351.78	**p=0.000**

Z: Mann Whitney U-tests

It has been determined that when the factors affecting the daily fluid intake of elderly individuals are examined, elderly individuals who use less than 4 drugs (p =0.002), live with their spouses (p=0.002), have been hospitalized before (p=0.000) and do not have a chronic disease (p=0.000) they consume too much fluid.

Discussion

This study was conducted to determine the amount of fluid intake of elderly individuals and the factors affecting the amount of fluid intake. Our findings reveal some results regarding the factors affecting the fluid consumption characteristics, fluid deficit levels and fluid intake of the elderly.

In our study, it was determined that elderly individuals consumed an average of 1247.25 milliliters of fluid per day and the average daily fluid deficit was 1065.60 milliliters. Similar studies with elderly individuals have shown similar results in this study. Güleç and Küçükgüçlü stated that 84.4% of elderly individuals take less fluid than they should take daily (19). Bennett et al. (2004) found chronic thirst symptoms in 48% and mild thirst symptoms in 26% of 185 elderly individuals (20). In a more recent study, it was reported that 72.7% of the elderly living at home and 77.1% of the elderly living in a nursing home consumed less than four glasses (800 milliliters on average) (21). Our findings are similar to other studies in the literature in this respect.

In a recent similar study, Dönmez and Demir (2022) found the average daily fluid intake of elderly individuals living at home to be 1721.4±478.6 ml. (18). Elderly individuals participating in this study consumed less liquid than the participants in Dönmez and Demir (2022). We think that this difference between the two studies is since the elderly do not want to go to the toilet more often and consume the most liquids between meals.

In our study, it was determined that the elderly who used less than 4 drugs consumed more fluids. In Güleç's (2013) study on elderly people living in nursing homes; There was no significant difference between the number of drugs consumed and water consumption (19). Muz et al. (2017) did not find a relationship between the number of drugs used and the state of dehydration (21). It has been determined that the combination of factors such as advanced age, polypharmacy, and lack of mobility, especially with the use of diuretic drugs, will increase the risk of dehydration in the elderly (22). Taking the drug with water is expected to increase water consumption. Studies indicate that elderly individuals reduce their fluid consumption due to increased urine production and fear of incontinence (23, 24). It is thought that the difference in our study may be due to the fear of urinary incontinence in elderly individuals.

In our study, it was determined that there was a significant difference between the daily fluid consumption of elderly individuals and those living together. Dönmez and Buse (2022) stated that the amount of fluid deficit decreases as much as the elderly individuals who are independent in their living activities can do, on the other hand, the amount of fluid deficit increases as the addiction of elderly individuals who are dependent in life activities increases (18). Laruiola et al. (2018) stated that there is a significant relationship between the dependent elderly and dehydration (25).

In our study, it was determined that elderly individuals who were hospitalized before and who did not have a chronic disease consumed more fluids. Fluid consumption in elderly individuals has a very important place. In particular, the decrease in the level of water reabsorption due to the effects of the drugs used on kidney functions causes a decrease in the feeling of thirst that occurs in elderly individuals during this period and ultimately leads to the elderly individuals not consuming enough fluids (21). It can be said that regular follow-ups of the elderly with chronic diseases and training of health personnel increase fluid consumption for elderly individuals.

Conclusion

In our study, it was determined that elderly individuals consumed an average of 1247.25 ± 428.71 milliliters of fluid per day, and the average daily fluid deficit was 1065.60 ± 417.91. It has been determined that elderly individuals are in the middle-frail border,

semi-dependent in activities of daily living, and their well-being is low. It has been determined that the elderly consume less liquid because they do not want to go to the toilet frequently, and they have the most constipation problems due to the lack of liquid consumption. When the factors affecting the daily fluid intake of elderly individuals are examined, it has been determined that elderly individuals who use less than 4 drugs, live with their spouses, have been hospitalized before, and do not have a chronic disease consume more fluids. In line with these results, our recommendation should be to determine the amount of fluid that elderly individuals should take and to remind elderly individuals to consume fluids.

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Ethical aspects of the research: In order to conduct the research, permission was obtained from the ethics committee of a university, number 2022/153. All principles of the Declaration of Helsinki were complied with throughout the study. All participants read and signed the informed consent form.

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ORIGINAL ARTICLE

Investigation of Cytokines, Biochemical Parameters and Oxidative Stress Levels in Serum of Patients with Acute Pancreatitis

Akut Pankreatitli Hastaların Serumlarında Sitokinler, Biyokimyasal Parametreler ve Oksidatif Stres Düzeylerinin Araştırılması

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ABSTRACT

Objective: This study aimed to find new serum biochemistry parameters, especially for the early identification of severe Acute Pancreatitis (AP). In the study, serum cytokine levels (TNF-A, IL-1, IL-6, IL-10, IL-21), biochemical parameters (Aquaporin-1, Hepcidine, Iron, Zinc, Copper, Nitric Oxide, C-Reactive protein) and oxidative stress parameters analysis were performed.
Method: A total of 46 patients with AP and 46 healthy controls were included in this study. Serum cytokine levels, biochemical, and oxidative stress parameters by the ELISA method and CRP by the immunoturbidimetric method were measured.
Results: When patients with AP and control groups were compared, all studied parameters were found statistically significant ($p<0.05$). However, IL-1 was insignificant ($p>0.05$). Therefore, the Mann-Whitney U test, which is a non-parametric test, was deemed appropriate to determine whether there was a significant difference between the patient and control groups.
Conclusions: Investigating the role of cytokines, oxidative stress and other biochemical parameters in the pathogenesis and course of the disease may contribute to a better understanding of the disease process and its therapeutic value. It showed a significant increase in oxidative stress parameters and biochemical parameters such as aquaporin-1, hepcidin, lipase, and amylase, which may help in the diagnosis of AP.

Keywords: Acute pancreatitis, cytokine, oxidative stress, some other biochemical parameters

ÖZ

Amaç: Bu çalışma, özellikle şiddetli AP'nin erken teşhisi için yeni serum biyokimya parametreleri bulmayı amaçladı. Çalışmada serum sitokin seviyeleri (TNF-A, IL-1, IL-6, IL-10, IL-21), biyokimyasal parametreler (Aquaporin-1, Hepsidin, Demir, Çinko, Bakır, Nitrik Oksit, C-Reaktif protein) ve oksidatif stres parametreleri analizi yapıldı.
Yöntem: Bu çalışmaya AP'li toplam 46 hasta ve 46 sağlıklı kontrol dahil edildi. ELISA yöntemi ile serum sitokin düzeyleri, biyokimyasal ve oksidatif stres parametreleri, immünotürbidimetrik yöntemle de CRP ölçüldü.
Bulgular: AP'li hastalar ve kontrol grubu karşılaştırıldığında çalışılan tüm parametreler istatistiksel olarak anlamlı bulundu ($p<0.05$). Ancak IL-1'in önemsiz olduğu bulundu ($p>0.05$). Bu nedenle hasta ve kontrol grupları arasında anlamlı fark olup olmadığını belirlemek için parametrik olmayan bir test olan Mann-Whitney U testi uygun bulunmuştur.
Sonuç: Sitokinlerin, oksidatif stresin ve diğer biyokimyasal parametrelerin hastalığın patogenezindeki ve seyrindeki rolünün araştırılması, hastalık sürecinin ve tedavi edici değerinin daha iyi anlaşılmasına katkı sağlayabilir. AP tanısında yardımcı olabilecek aquaporin-1, hepsidin, lipaz ve amilaz gibi oksidatif stres parametrelerinde ve biyokimyasal parametrelerde önemli bir artış gösterdi.

Anahtar Kelimeler: Akut pankreatit, sitokin, oksidatif stres, diğer bazı biyokimyasal parametreler

Introduction

Acute pancreatitis (AP) is an inflammatory disease of the exocrine pancreas with highly variable severity, ranging from self-limited disease to severe progressive disease with organ dysfunction and death (1,2). There is no intervention to modify the progression or severity of pancreatitis. What distinguishes pancreatitis from other diseases of the gastrointestinal tract is its tendency to amplify the localized process by inducing a general systemic inflammatory response. TNF-a is produced by macrophages and is associated with acute and chronic inflammation and autoimmune diseases (3). A study conducted in mice with TNF-a deficiency has shown that TNF-a plays an important role in the regulation of embryo development. Interleukin-1 (IL-1) regulates the differentiation of lymphoid cells in autoinflammatory, autoimmune, infectious and degenerative diseases and potentiates the effect of neutrophils and macrophages (4). IL-6 is a pleiotropic cytokine with complex roles in inflammation and metabolic disease. Within the pancreatic islet, IL-6 stimulates secretion by a-cells of the prosurvival incretin hormone glucagon-like peptide 1 and acts directly on β-cells to stimulate insulin secretion in vitro (5,6). It allows to prevent diabetes and delay the progression to insulin dependence. IL-6 can be produced by and act on multiple tissues in the body (6), therapeutic pirfenidone treatment increases IL-10 secretion from macrophages before changes in histology and modulates the immune

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phenotype of inflammatory cells with reduced levels of inflammatory cytokines (7).

C-reactive protein (CRP) is an acute phase protein that reflects a measure of the acute phase response, a good indicator of inflammation, its secretion mainly dependent on IL-6. Persistently elevated hepcidin (HEPC) levels caused by IL-6 block the iron (Fe) transporter ferroportin in macrophages, hepatocytes, and intestinal epithelial cells, leading to Fe deficiency and anemia of chronic inflammation (8,9). In lymphocytes, IL-6 stimulates B-cell differentiation into immunoglobulin-producing cells. IL-10 is a cytokine with anti-inflammatory properties and important immunoregulatory functions, and an essential regulator of the immune system. It is a potent suppressor of antigen presenting cells and lymphocytes (9).

IL-21 is mainly produced by natural killer, T cells, and CD4+ T cells. All CD4+ T helper subsets can produce varying amounts of IL-21 depending on the stimulation context and cytokine environment, promoting inflammation and the immune response (10).

Nitric oxide (NO), Proinflammatory mediator bradykinin (BK), induces NO production in vascular endothelial cells, BK has been shown to elicit Ca2+ signals. It is a signaling molecule that plays a key role in the pathogenesis of inflammation (11).

The hepatic peptide hormone HEPC is the main regulator of Fe absorption and tissue distribution. Fe levels are controlled by the liver peptide hormone HEPC. Defects in HEPC regulation contribute to the pathogenesis of many Fe disorders (12,13).

Zinc (Zn) is a key element in numerous proteins and plays an important role in cell functions in defense against free radicals and repair of DNA damage. AP is a chronic inflammation of the pancreas that results in progressive fibrosis of the pancreas, ultimately resulting in malnutrition-associated pancreatic exocrine insufficiency (PEI) (14,15). Adversely affect the development and function of T and B cells, phagocytosis, intracellular killing and cytokine production (15).

Oxidative stress occurs in response to oxidative damage produced by the body's antioxidant and scavenging activities by a harmful stimulant. AP plays a role in the etiopathogenesis of many diseases such as cancer (16,17).

Copper (Cu) produced by the portal circulation is mainly absorbed by the liver, excess Cu can trigger oxidative damage, reactive oxygen stress generation, and damage biological molecules (18).

Aquaporins (AQPs) are a family of water-permeable transmembrane proteins. In mammals, they are broken down into classical aquaporins that are permeable to water glycerol and urea (19,20). AQPs assure crucialphysiological functions in both the exocrine and endocrine pancreas. Indeed, they are involved in pancreatic juice and insulin secretion. The possible role of AQPs in the development of inflammatory processes is highlighted (21).

In our study, TNF-a, IL-1, IL-6, IL-10, IL-21, NO, CRP, biochemical parameters: AQP-1, HEPC, Fe, Zn, Cu and oxidative stress levels were measured in patients with AP. By looking at these parameters, it is possible to contribute to the parameters that may cause the etiology of the disease and, as a result, to the studies on treatment.

Material and Methods

Patients and healthy control groups

A total of 46 patients with AP and 46 healthy controls were included in this study. Patients, diagnosed with AP in the gastroenterology department of the Harran University Hospital Internal Diseases Department, participated in our study. Patients admitted to the hospital with abdominal pain in the first 2 days of diagnosis of AP and patients who did not have any additional chronic diseases were included. 64 U/L (min:25, max:294), lipase average value is 1404.69±1900.99 U/L (min:11, max:6000). The study included 38 men and 54 women. The total sample of the patient group was 46, and the mean age for both genders was (43±19). For the control group, we recruited control groups from 46 volunteers. We recruited 19 men and 27 women in the healthy control group without any current disease history or pathological condition, and the mean age of the control group was 46 ± 13 years for both sexes. When we collected the blood, we transferred it to the gel (biochemistry tubes) tube. We were careful in obtaining blood samples from the patient and control groups to minimize hemolysis as hemolysis can greatly affect the validity of test results. The blood was centrifuged at 4000 rpm for 10 minutes and the serum was separated. We then collected the supernatant (plasma) without sediment and then stored it in the freezer.

In our study, the blood samples of the patients were centrifuged at 4000 rpm and the serum samples were stored in a deep freezer at -80°C. The samples taken were studied with the principle of ELISA to analyze the levels of TNF-a, IL-1, IL-6, IL-10, IL-21, AQP-1 and HEPC. Measurement of the total antioxidant status (TAS) were made using brand commercial kits (Rel Assay Diagnostic, Gaziantep) on a microplate reader system (Varioskan Lux; Thermo Scientific). Briefly, free radical reactions were initiated by the Fenton reaction and monitored by absorbance of the dianisidyl radicals. This reaction was measured spectrophotometrically at 660nm. Using this method, the antioxidative effect was measured as the relative amount of free dianisidyl radicals. The precision of this test has high accuracy (<3% error rate). The data were expressed in mmol Trolox equivalent/L. Measurement of the total oxidative status (TOS) were made using brand commercial kits (Rel Assay Diagnostic, Gaziantep) on a microplate reader system (Varioskan Lux; Thermo Scientific) according to the method of Erel. Briefly, oxidants present in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. The oxidation

reaction is enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion makes a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically (at 530nm), is related to the total amount of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide (H_2O_2), and the results are expressed as µmol H2O2 equivalent/L.Then to calculate the oxidative stress index (OSI), the resulting TAS units were converted to mmol/L, and the OSI value was calculated according to the following formula: OSI (arbitrary unit) = TOS (mmol H_2O_2 equivalent/L)/TAS (mmol Trolox equivalent/L) (22,23).

Principle of NO

NO in the samples rapidly decomposes into nitrate and nitrite. Spectrophotometric quantification of nitrite using Griess reagent is sensitive but does not measure nitrate. Reduction of nitrate to nitrite is performed using the NADH-dependent enzyme nitrate reductase, followed by spectrophotometric analysis measurement of total nitrite at 545nm with Griess reagent (21).

Principle of Fe, Zn, Cu and CRP

In our study, the Fe Atellica device was used. It is measured spectrophotometrically by combining with ferrosine to release a colored chromophore that absorbs at 571/658 nm. Zn changes the red-orange color of 5-Br-PAPS to light pink under alkaline conditions. The change in absorbance at 548 nm is proportional to the total Zn level in the sample. Cu in the samples changes the red-orange color of DiBr-PAESA to purple under acidic conditions. The change in absorbance at 572 nm is proportional to the total Cu concentration in the sample. Consolidation occurs when the serum containing CRP is mixed with the latex reagent, turbidity is measured at 571 nm.

Statistical analysis

The conformity of the data to the normal distribution in the patient and control groups was tested with Shaphiro Wilk. Student's t test was used to compare the normally distributed features in the parameters while the non-normally distributed groups were compared using the Mann Whitney U test. The Sperman correlation coefficient was examined for the relationship between the parameters. Mean ± standard deviation values for numerical variables are given as descriptive statistics. SPSS Windows version 24.0 package program was used for statistical analysis and $p<0.05$ was considered statistically significant.

Results

Since all the p-values were less than 0,05, the participants in the patient group had statistically signicantly higher concentrations of AQP-1, HEPC, TOS, and Cu (31.18 ± 10.76 U/L; 107.12 ± 36.15 ng/ml; 16.77 ± 4.02 µmol H2O2 equiv/L; 127.31±28.32µg/dl) compared to the control group (5.51 ± 2.80 U/L; 32.65 ± 7.50 ng/ml; 11.49 ± 2.47 µmol H2O2 equiv/L; 88.77±22.07µg/dl), respectively. On the other hand, the participants in the patient group had statistically signicantly lower concentrations of TAS, Fe, and Zn (1.14 ± 0.14 mmol Trolox equiv/L; 33.79±16.32 µg/dl; 73.75±15.36µg/dl) compared to the control group (1.46± 0.18 mmol Trolox equiv/L; 79.10 ± 32.52 µg/dl; 88.57±14.66 µg/dl), respectively.

Since all the p-values were less than 0,05, the participants in the patient group had statistically signicantly higher concentrations of TNF-a , IL-1, IL-6, IL-10, IL-21, CRP, and NO (86.59 ± 32.45 ng/L; 37.73 ± 14.09 pg/L; 131.51± 21.43 ng/L; 189.66 ± 103.44 pg/L; 190.13 ± 152.96 ng/L; 3.16±1.91 mg/dl; 58.32±9.83 µmol\L) compared to the control group (35.15 ± 10.04 ng/L; 21.43 ± 7.27 pg/L; 50.58 ± 20.82 ng/L; 87.07 ± 14.15 pg/L; 64.37 ± 22.63 ng/L; 0.61±0.56mg/dl; 28.79±2.71 µmol\L), respectively.

The correlation coefficient (r) values were calculated among the ten variables; TNF-alpha, IL-10, IL-1, IL-6, IL-21, AQP-1, HEP-C, TAS, TOS, OSI. Fe, Zn, Cu, CRP, and NO were used in the study. In the correlation analysis for the control group, TNF-alpha levels increase with increasing of NO levels (r=0.394, p=0.031). A statistically significant negative correlation was shown between IL-10 levels and IL-1 levels (r=-0.476, p=0.008). A significant negative correlation was detected between IL-6 levels and the levels of AQP-1 (r=-0.368, p=0.045). IL-21 levels were negatively correlated with Cu levels (r=-0.388, p=0.034). A moderate negative significant correlation was shown between TAS levels and TOS levels (r=-0.646, p=0.000). A high negative significant correlation was seen between TOS levels and OIS levels (r=-0.723, p=0.000).

For the patient group, TNF-alpha levels increased with increasing levels of IL-10, IL-21 and HEP-C (r=0.504, p=0.001; r=0.363, p=0.017; r=0.537, p=0.000), respectively. IL-10 levels increased with increasing the levels of IL-21 and HEP-C (r=0.427, p=0.004; r=0.393, p=0.009), respectively. A significant positive correlation was obtained between IL-1 levels and Fe levels (r=0.305, p=0.047). IL-6 levels were positively correlated with levels of IL-21 and HEP-C (r=0.368, p=0.015; r=0.310, p=0.043), respectively. AQP-1 levels were positively correlated with the levels of Fe and Zn (r=0.413, p=0.006; r=0.302, p=0.049), respectively. A significant positive correlation was detected between TAS levels and OSI levels (r=0.437, p=0.003). A significant high positive correlation was found between TOS levels and OSI levels (r=0.855, p=0.000). The Fe levels are positively correlated with the levels of Zn (r=0.317, p=0.038). A significant moderate positive correlation was provided between Zn levels and CRP levels (r=0.560, p=0.000). A significant positive correlation was computed between CRP levels and NO levels (r=0.436, p=0.003).

Table 1: Descriptive statistics of AQP-1, HEPC, TAS, TOS, OSI, Fe, Zn, and Cu

Parameters	Control group (n=46)			Patient group (n=46)			**p-value**
AQP-1 (U/L)	10.58	10.52	5.51 2.80	1.26	47.64	31.18 10.76	*p*<0.01
HEPC (ng/ml)	14.85	42.63	32.65 7.50	55.22	250.78	107.12 36.15	*p*<0.01
TAS (mmol Trolox equiv/L)	10.06	10.74	1.46 0.18	0.72	10.45	1.14 0.14	*p*<0.01
TOS (μmolH_2O_2 equiv/L)	90.11	22.15	11.49 2.47	70.6	25.6	16.77 4.02	*p*<0.01
OSI (Arbitrary units)	0.55	10.56	0.79 0.21	0.67	20.33	1.49 0.41	*p*<0.01
Fe (μg/ dl)	32	184	79.10 32.52	30	66	33.7916.32	*p*<0.01
Zn (μg/dl)	60.4	116.2	88.5714.66	51.4	18.9	73.75	*p*<0.01
Cu (μg/dl)	63	130.9	88.77	81.5	245.1	127.31	*p*<0.01

Table 2: Descriptive statistics of TNF-a, IL-1, IL-6, IL-10, IL-21, CRP, and NO

Parameters	Control group (n=46)			Patient group (n=46)			**p-value**
TNF-a (ng/L)	12.98	60.85	35.15 10.04	48.07	172.33	86.59 32.45	*p*<0.01
IL-1 (pg/L)	4.09	35.17	21.43 7.27	20.44	84.16	37.73 14.09	*p*<0.01
IL-6 (ng/L)	24.53	91.16	50.58 20.82	80.11	174.95	131.51 21.43	*p*<0.01
IL-10 (pg/L)	45.72	115.72	87.07 14.15	91.83	679.06	189.66 103.44	*p*<0.01
IL-21 (ng/L)	10.26	17.30	64.37 22.63	0.26	940.63	190.13 152.96	*p*<0.01
CRP (mg/dl)	0.05	20.17	0.61	0.10	60.84	3.16	*p*<0.01
NO (μmol\L)	23.16	34.27	28.792.71	39.12	75.27	58.32	*p*<0.01

Table 3. Correlation matrix of the variables for control group.

	IL-10	IL-1	IL-6	IL-21	AQP-1	HEPC	TAS	TOS	OSI	Fe	Zn	Cu	CRP	NO
TNF-a	0.067 (0.727)	0.060 (0.753)	-0.220 (0.243)	0.042 (0.824)	0.091 (0.631)	0.160 (0.399)	-0.292 (0.117)	0.088 (0.643)	0.296 (0.112)	-0.057 (0.763)	0.002 (0.993)	0.006 (0.973)	0.217 (0.250)	**0.394*** (0.031)
	IL-10	**-0.476**** (0.008)	-0.141 (0.457)	0.064 (0.737)	0.299 (0.109)	-0.322 (0.082)	0.206 (0.274)	-0.180 (0.340)	-0.239 (0.204)	-0.031 (0.871)	-0.123 (0.518)	0.047 (0.806)	0.281 (0.132)	-0.044 (0.817)
		IL-1	0.283 (0.129)	0.003 (0.986)	-0.036 (0.851)	0.322 (0.082)	-0.185 (0.328)	0.191 (0.311)	0.191 (0.312)	0.186 (0.324)	0.034 (0.859)	-0.033 (0.863)	-0.167 (0.378)	0.037 (0.845)
			IL-6	-0.233 (0.216)	**-0.368*** (0.045)	0.145 (0.445)	0.181 (0.338)	0.106 (0.576)	-0.023 (0.903)	-0.092 (0.627)	-0.082 (0.665)	0.226 (0.229)	0.141 (0.458)	-0.242 (0.197)
				IL-21	0.233 (0.214)	-0.071 (0.708)	-0.297 (0.111)	-0.006 (0.973)	0.270 (0.149)	0.064 (0.736)	-0.035 (0.854)	**-0.388*** (0.034)	0.024 (0.899)	0.347 (0.061)
					AQP-1	-0.153 (0.420)	-0.147 (0.439)	0.010 (0.960)	0.071 (0.709)	0.235 (0.211)	0.045 (0.813)	-0.103 (0.588)	0.195 (0.301)	0.356 (0.053)
						HEPC	-0.133 (0.485)	0.012 (0.952)	0.143 (0.452)	0.359 (0.051)	-0.135 (0.478)	-0.019 (0.921)	0.170 (0.370)	0.107 (0.573)
							TAS	-0.017 (0.928)	**-0.646**** (0.000)	-0.200 (0.290)	-0.086 (0.650)	0.237 (0.208)	-0.043 (0.822)	-0.263 (0.160)
								TOS	**0.723**** (0.000)	0.124 (0.513)	-0.036 (0.852)	-0.147 (0.439)	0.077 (0.685)	0.108 (0.569)
									OSI	0.222 (0.237)	-0.039 (0.836)	-0.222 (0.238)	0.106 (0.576)	0.255 (0.173)
										Fe	-0.152 (0.422)	-0.063 (0.741)	0.009 (0.962)	0.161 (0.396)
											Zn	0.127 (0.502)	-0.092 (0.630)	-0.117 (0.539)
												Cu	0.218 (0.248)	-0.102 (0.593)
													CRP	0.056 (0.770)

p-values (in parentheses) are presented bolded if *p* ** and *p* *

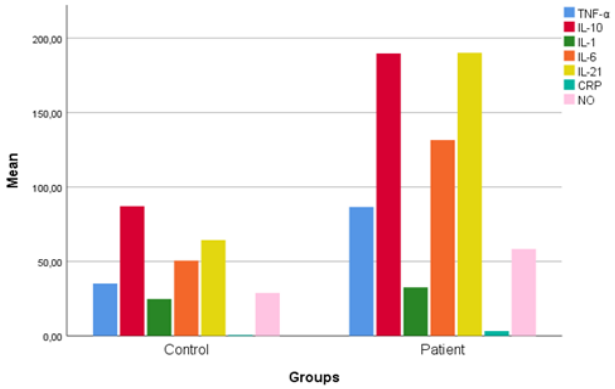

Figure 1: Comparison of TNF-a, IL-10, IL-1, IL-6, IL-21, CRP, and NO

Discussion

AP is one of the most common diseases of the gastrointestinal tract and its prognosis mainly depends on the development of organ failure and peri pancreatic necrosis infection (1,2). It has led to the identification of new molecular therapeutic targets such as TNF-a and interleukin-6, both of which are important activators of the inflammatory response in AP (24).

Severe acute pancreatitis is associated with high morbidity and mortality. Early severity classification remains a formidable problem that must be tackled to improve outcomes. We aim to find new plasma cytokines for the early diagnosis of severe AP according to the revised Atlanta criteria. Acute pancreatitis is now divided into two distinct subtypes, necrotizing pancreatitis and interstitial edematous pancreatitis, based on the presence or absence of necrosis, respectively. Since the cytokine profiles of the patients, especially TNF- and IL-6, are distinctive for severe AP, these parameters were analyzed.

TNF-a is a central regulator of inflammation, a proinflammatory cytokine secreted by monocytes and macrophages (25). Kylänpää et al. showed that TNF-a directly damaged the cells of multiple organs in AP and caused ischemia, hemorrhage, necrosis, inflammation and edema (25). Serum TNF-a levels were not considered to be a good indicator of disease severity because the liver can rapidly clear TNF-a before it enters the general circulation. Gasiorowska et al. have shown that TNF-a levels also increased in patients with chronic pancreatitis (26). In our study, TNF-a levels in AP patients significantly increased when compared to the control group (Table 2, $p<0.05$ Figure 1). TNF-a, a key regulator of proinflammatory cytokines, is thought to play an important role in the pathogenesis of AP (26).

CRP belongs to the pentraxin protein family of hepatic origin and serves as the main component of any inflammatory reaction (27). CRP is secreted in response to IL-6 and TNF-a proinflammatory cytokines. It plays a role in innate immunity by facilitating the phagocytosis of damaged and foreign cells (28). IL-6 is animportant proinflammatory cytokine involved in inflammation and immune responses. In vitro, Beringer et al. showed increased secretion of IL-6 from human pancreatic periacinar myofibroblast cells in the presence of several inflammatory mediators TNF-a, IL-17, IL-1β and growth factors, which served as an early marker (28). In our study, CRP levels increased significantly when compared to the control group (Table 2, $p<0.05$; Figure 1). Additionally, it was observed that TNF-a and IL-6 significantly increased compared to the control group (Table 2, $p<0.05$, Figure 1). After having been synthesized in a local lesion in the initial stage of inflammation, IL-6 moves through the bloodstream to the liver, where it then secretes a broad range of acute phase proteins such as CRP (28). On the other hand, IL-6 reduces the production of fibronectin, albumin and transferrin. It can be suggested that treatments for IL-6 should be used to prevent organ damage (29).

IL-1 is an important cytokine for autoinflammatory, autoimmune, infectious and degenerative diseases. IL-1 induction plays a role in the pathogenesis of acute pancreatitis (30). Resaher revealed that IL-1β could induce trypsin activation and reduce cellular viability of pancreatic acinar cells and release cytokines IL-1 from inflamed pancreatic tissue with the development of distant organ dysfunction (29).

In our study, IL-1 levels were found significantly higher when compared to the control group (Table 2, $p<0.05$, Figure 1). IL-1 promotes the recruitment of inflammatory cells at the site of inflammation by inducing the expression of adhesion molecules on endothelial cells and the release of chemokines by stromal cells (29).

IL-10 is an essential regulator of the immune system because of its anti-inflammatory properties and its role in re-establishing the immune system (30). Zhou et al. showed that IL-10 attenuated the inflammatory response and reduced TNF-a secretion in acute pancreatitis. It has been confirmed that IL-10 attenuates the severity of inflammation in AP by reducing serum amylase and TNF-a secretion as well as pancreatic pathological score (31).

IL-10 levels were found significantly higher when compared to the control group (Table 2, $p<0.05$, Figure 1). IL-10 appears to be a potent negative feedback regulator by influencing the control and resolution of inflammation through autocrine and paracrine mechanisms. Because of these effects, IL-10 may play an important role in the diagnosis and treatment of the disease (32).

IL-21 is involved in the differentiation and proliferation of β-cells and thus in the formation and maturation of antibodies. Linnebacher et al. associated an increased septic risk in AP patients with IL-21-related polymorphisms (32). IL-21 levels in AP patients were found significantly higher compared to the control group (Table 2, $p<0.05$, Figure 1). As IL-21 is a potent antitumor agent, making it a promising candidate for the development of therapeutic tools, an increased risk of septic shock in AP patients with high levels of IL-21 may be considered (11,33).

The ability of NO to limit endothelial activation and inhibit leukocyte adhesion is the anti-inflammatory properties of AP. It has been observed that NO synthase inhibitors increase ultrastructural degenerative changes in pancreatic acinar cells in the course of acute pancreatitis, demonstrating the protective role of endogenous NO in this disease (34,35). In our study, we observed that NO levels were significantly higher compared to the control group (Table 1, $p<0.05$, Figure 1) NO is produced at high levels during human inflammatory reactions. NO is proinflammatory at low concentrations by inducing vasodilation and recruitment of neutrophils, while at high concentrations it downregulates adhesion molecules, suppresses activation, and induces apoptosis of inflammation (34). The fact that the level of damage and the increase in NO in pancreatic cells are in parallel may be an important marker for diagnosis, and amino acids such as lysine and arginine may be effective for treatment by affecting NO levels. While Emerald et al. showed that increased NO levels were protective from the disease (35), Andican et al. showed the opposite (34).

The hepatic peptide hormone HEPC is the main regulator of Fe absorption and tissue distribution (13). HEPC reduces Fe entry into plasma from absorbing duodenal cells and Fe recycling macrophages by blocking Fe production and degrading Fe producing ferroportin. Wang et al. found decreased serum Fe levels in patients with AP (detected by a secretin test) compared to controls (14). Fe regulates HEPC homeostasis, HEPC production is suppressed in case of deficiency, and HEPC increases during infection. Therefore, Fe levels are found significantly low because HEPC impairs Fe absorption. Xu et al. found increased Fe levels, but did not find a significant difference (13). In another study, Julián-Serrano et al. reported low Fe levels, but they could not find a significant difference (36). Further studies on Fe and HEPC in patients with AP may be a better guide for understanding the subject.

AQP-1 is a glycoprotein responsible for rapid passive water transport across the biological membrane. In acute or chronic pancreatitis, which are considered inflammatory syndromes, patients are implicated in many pancreatic diseases, including pancreatitis, cystic fibrosis, and cancer. Arsenijevic et al. showed decreased levels of AQP1 in a rat model of acute pancreatitis and a mouse model exhibiting exocrine pancreatic insufficiency (20). Pancreatitis can cause multi-organ failure, including lung and colon, showing altered expression of AQPs (37). In a study that invastigateing the role of AQP1 in the pathophysiology of pancreatitis, it was found that AQP1 expression decreased in both ductal and acinar cells in a cerulein-induced pancreatitis model (38). This suggests that low AQP1 levels may contribute to exocrine insufficiency. In our study, AQP1 levels were significantly higher in serum when compared to the control group (Table 1, $p<0.05$). In the course of AP, AQP1 cells in the ducts and acini were damaged as a result of acute inflammation. AQP1 levels were high in patients with AP. It can also be thought that AQP1 plays a role in the passage of water to the pancreas, because fluid therapy plays the most important role in patients with AP. It can be predicted that treatments that increase the levels of AQP1 in the pancreas may facilitate fluid passage and improve the course of the disease (20,39).

Zn plays a crucial role in the immune system. It is necessary to facilitate the coordination of immune activation during responses to infection. Recent studies have reported that Zn deficiency increases organ damage, systemic inflammation and mortality in sepsis. Muneoka et al. have shown that Zn has a number of effector mechanisms that may play a role in the development of acute and chronic pancreatitis (15).

Since AP severity is mediated by inflammatory cells, Zn deficiency may also worsen the disease by stimulating the inflammatory response (15). In our study, Zn levels were found significantly lower compared to the control group (Table 2, $p<0.05$; Figure 1). Zn can trigger ROS production through mitochondrial and extra mitochondrial pathways. A few studies in isolated mitochondria show that the cation interferes with the activity of the electron transport chain, inhibiting cellular respiration (17). An abnormal Zn metabolism is accompanied by severe oxidative stress due to increased free radical production. As a result, it can be expected that Zn supplements may improve the prognosis in AP patients by increasing antioxidant levels.

Cu is necessary for the human body to maintain the daily stability of organs and metabolic processes. It plays a role in glucose metabolism and synthesis and release of proteins and enzymes (19). Lener et al. found that high Cu levels appear to be associated with pancreatic cancer. They report that high Cu levels may result in higher ROS levels, which affects the risk of development and progression of pancreatic cancer (40). In our study, Cu levels were found significantly higher compared to the control group (Table 2, $p<0.05$; Figure 1). Cu can trigger the generation of ROS and consequent damage to biological molecules. The inflammatory response is closely linked to oxidative stress. Further studies on Cu in AP will elucidate the possible mechanisms (19,40).

AP is a complex inflammatory disease caused by more than one etiology, the pathogenesis of which has not been fully elucidated. Oxidative stress is important for regulation of signaling pathways associated with inflammation, recruitment of inflammatory cells, release of inflammatory factors, and other processes, and plays a key role in the emergence and development of AP. In recent years, antioxidant therapy, which suppresses oxidative stress by scavenging reactive oxygen species, has become the research topic of AP. However, conventional antioxidant drugs have problems such as poor drug stability and low delivery efficiency that limit their clinical translation and application. Nanomaterials bring a whole

new opportunity for antioxidant treatment of AP. Antioxidant drugs including small size, good stability, high permeability and long retention effect can be used not only as effective carriers but also directly as antioxidants. After discussing the relationship between oxidative stress and AP first, we focused on demonstrating its effects on oxidative stress-related indicators in pathological conditions. This provides references for follow-up research and encourage clinical practice (41) .

Oxidative stress occurs in response to oxidative damage when the body's antioxidant and scavenging activities cannot cope with active oxidants produced by a harmful stimulant (42). Robles et al. have shown that oxidative stress plays a critical role in the pathogenesis and various complications of pancreatitis (43). In our study, the TOS was found significantly higher compared to the control group. On the other hand, T-AOC were found significantly lower compared to the control group. (Table 2, $p<0.05$ Figure 1). It has revealed the mechanism by which oxidative stress can cause chronic inflammation, which in turn mediates many chronic diseases, including cancer, diabetes, and cardiovascular, neurological, and pulmonary diseases (43).

TNF-a is an inflammatory cytokine. On the other hand, IL-10 is an anti-inflammatory cytokine. As shown in Table-3 there is a statistically significant positive correlation between TNF-a and IL-10 ($r=0.504$, $p<0.01$). IL-1 is a cytokine that increases in inflammation and Fe is a decreasing element in inflammation, so there is a positive correlation between IL-1 and Fe ($r=0.305$, $p<0.05$). HEPC is an acute phase reactant synthesized in the liver that increases in inflammation, and there is a positive correlation between TNF-a and ($r=0.537$, $p<0.01$). IL-21 and IL-10 are anti-inflammatory cytokines and there is a positive correlation between IL-10 and IL-21 ($r=0.427$, $p<0.01$). IL-10 is a cytokine secreted to suppress inflammation, and there is a positive correlationbetween between IL-10 and HEPC ($r=0.537$, $p<0.01$). AQP-1 is a cell membrane protein involved in the transport of water molecules. In AP disease, blood levels increase as inflammatory events destroy the cell membrane. The level of Fe decreases in inflammatory events. In the study, there is a positive correlation between AQP-1 and Fe, ($r=0.413$, $p<0.01$). IL-1 is a cytokine that increases in inflammation. Fe is an element that decreases in case of inflammation. In our study, there is a positive correlation between IL-1 and Fe ($r=0.305$, $p<0.05$). NO is a molecule secreted to prevent damage to organs by the effect of vasodilation in inflammatory events. CRP is one of the main proteins involved in inflammation. There is a strong/moderate statistically significant positive correlation between CRP and NO, ($r=0.436$, $p<0.01$).

IL-6 is an inflammatory cytokine. HEPC is an inflammatory acute phase reactant. There is a statistically significant negative correlation between IL-6 and HEPC ($r=-0.310$, $p<0.05$). Zn is an antioxidant element and its deficiency increases the tendency to inflammatory conditions. AQP-1 levels are increased in inflammatory conditions. There is a negative correlation between AQP-1 and Zn ($r=-0.302$, $p<0.05$). Zn is an antioxidant element, and its levels may increase in inflammatory conditions. Fe, on the other hand, decreases due to the increase in HEPC levels in inflammatory conditions. There is a negative correlation between Fe and Zn, ($r=-0.387$, $p<0.05$). CRP is an acute phase protein that increases in inflammation. Zn deficiency causes inflammatory reactions. There is a strong statistically significant positive correlation between Zn and CRP, ($r=0.560$, $p<0.01$).

Conclusion

In the pathogenesis of oxidative stress acute pancreatitis, the generation of ROS directly oxidizes various biomolecules, exacerbating the oxidative load through a respiratory burst due to the recruitment of ROS-producing inflammatory cells in the pancreas, thereby causing further damage. TNF-a, IL-1β and IL-6 are proinflammatory cytokines. AP has a multifactorial and complex etiology. It is an important factor in the pathogenesis of AP. At the same time, the levels of these cytokines can be a guide for diagnosis and treatment in patients with Acute Pancreatitis. The predicted and concentrations of inflammatory cytokines released from the pancreas may provide new clues for the elucidation of the roles of pancreatitis in the pathophysiological processes and the development of new treatment protocols. As a result of our study in AP patients, oxidative stress levels increase while antioxidant defense levels decrease. For this reason, we can hope that treatments that reduce oxidative stress levels or increase antioxidant levels can improve the course of the disease.

Ethical statement: The study protocol was approved by the Harran University, Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (protocol number: 2019/03; March 11, 2019). Our study was planned in accordance with the criteria set in the Helsinki Declaration. Informed consent forms were obtained from both AP patients participating in the study and healthy controls.

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

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ORIGINAL ARTICLE

Retrospective Evaluation of Adult Hydatid Cyst Cases

Erişkin Kist Hidatik Vakalarının Retrospektif Değerlendirilmesi

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ABSTRACT

Aim: The aim of this study was to evaluate the characteristics of adult patients followed up for hydatid cysts disease.
Method: Patients over the age of 18 years who were diagnosed with hydatid disease, between January 2015 and September 2021 were included in the study. The clinical, laboratory and radiologic characteristics of the patients were evaluated retrospectively.
Results: The study included 66 patients. Of the patients 59.1% were female and the mean age was 40.9±15.60 years. The most common presenting symptom was abdominal pain (42.4%). The most common sites of involvement were the liver (78.8%) and lung (18.2%). The majority of patients had solitary cysts (84.8%). The most common finding in laboratory tests was elevated total IgE (74.1%). The indirect hemagglutination test was positive in 77.4% of the patients tested.
Conclusion: In our study, it was concluded that hydatid cysts are most commonly seen in the liver, often with single organ involvement, and that elevated total IgE in laboratory diagnosis may be helpful in the diagnosis of hydatid cyst disease although it does not make a definitive diagnosis.

Keywords: Hydatid cyst, liver, cystic echinococcosis, parasitic infection

ÖZ

Amaç: Bu çalışmanın amacı kist hidatik nedeniyle takip edilen erişkin hastaların özelliklerini değerlendirmektir.
Yöntem: Çalışmaya Ocak 2015-Eylül 2021 tarihleri arasında kist hidatik tanısı konan 18 yaş üstünde hastalar dahil edildi. Hastalara ait klinik, laboratuvar, radyolojik özellikler retrospektif olarak değerlendirildi.
Bulgular: Çalışmaya 66 hasta dahil edildi. Hastaların %59,1'i kadın cinsiyette olup, yaş ortalaması 40,9±15,60 yıldı. Hastaların en sık tarifledikleri başvuru semptomu karın ağrısıydı (%42,4). En sık tutulum yeri sırasıyla karaciğer (%78,8) ve akciğerdi (%18,2). Hastaların büyük çoğunluğunda soliter kist (%84,8) vardı. Laboratuvar tetkiklerinde en sık saptanan bulgu total IgE yüksekliğiydi (%74,1). İndirekt hemaglütinasyon testi, test edilen hastaların % 77,4'ünde pozitif olarak saptandı.
Sonuç: Çalışmamızda kist hidatiğin en sık karaciğerde görüldüğü, sıklıkla tek organ tutulumu şeklinde olduğu, laboratuvar tanısında total IgE yüksekliğinin kist hidatik hastalığı kesin tanısını koydurmasa da tanıya yardımcı olabileceği sonucuna varıldı.

Anahtar Sözcükler: Kist hidatik, karaciğer, kistik ekinokokkoz, paraziter enfeksiyon

Introduction

Hydatid disease (HD) is one of the most important parasitic diseases in terms of both human and animal health and economics. It is a common disease in Turkiye, which is one of the countries where animal husbandry is widespread (1,2). HD affects more than one million people worldwide and causes a financial loss of more than three billion dollars every year (3). HD is caused by the larvae of dog and fox tapeworms (cestodes), which are species of Echinococcus. Echinococcus granulosus and Echinococcus multilocularis are the main species infecting humans and cause cystic echinococcosis and alveolar echinococcosis in humans. Both clinical presentations may show a chronic, severe course and mortality may be observed as a result of inappropriate and inadequate treatment (4). HD is most commonly found in the liver and lungs. The final host of E. granulosus is animals such as wolves, dogs and jackals, and the intermediate hosts are herbivorous animals such as cattle, sheep, and humans. Transmission to humans usually occurs through close contact with dogs, hands contaminated with dog feces, or contaminated food (5). Humans are incidental intermediate hosts for Echinococcus species and humans cannot transmit the disease. In HD, cysts may remain in the affected organ for years without symptoms. Although symptoms related to the liver and lungs are more common, they may vary according to the affected organ (6). In addition to clinical symptoms and findings, radiologic tests including ultrasonography (USG), computed tomography (CT), direct radiography and magnetic resonance imaging (MRI), serologic tests, and direct diagnostic and molecular methods are utilized in the diagnosis. Most asymptomatic patients are diagnosed incidentally (7). Although many serologic tests can be used, indirect hemagglutination (IHA) and enzyme-linked immunosorbent assay (ELISA) tests are preferred (8). In this study, we aimed to retrospectively evaluate the clinical, laboratory and radiologic features of adult HD patients.

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Material and Methods

Patients older than 18 years of age who were followed up in the Infectious Diseases and Clinical Microbiology Clinic of Van Yüzüncü Yıl University Faculty of Medicine between January 2015 and September 2021 with a diagnosis of HD were included in the study. Information about the patients was obtained from the hospital information management system and archival records. Age, gender, clinical symptoms, radiologic imaging, laboratory tests and treatment protocols were evaluated retrospectively. Biochemical values (alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), direct bilirubin (D.bilirubin), total bilirubin (T.bilirubin) and gamma-glutamyl transferase (GGT)) and total IgE levels of the patients were also analyzed.

In the diagnosis of HD, radiologic methods (including USG, CT, and MRI) were used in addition to serologic methods (9). Liver-localized HDs were categorized radiologically according to the Gharbi classification (10).

Statistical analysis: SPSS Statistics 23.0 package program was used for data analysis. Categorical variables were expressed as a percentage (%) and frequency (n). Mean±standard deviation values of normally distributed variables and median values of non-normally distributed variables were given. The shapiro-Wilk test was used for normality assumption.

Ethics committee approval: This study was conducted with the approval of the ethics committee of Van Yüzüncü Yıl University Non-Interventional Research Ethics Committee dated 08.11.2019 and numbered 19-141. All procedures in the study were performed according to the World Medical Association Declaration of Helsinki.

Results

The study included 66 patients, 39 (59.1%) women and 27 (40.9%) men. The mean age of all patients was 40.9±15.60 years, the mean age of women was 41.5±15.6 years and the mean age of men was 39.8±15.75 years. The most common clinical symptoms at initial presentation were abdominal pain (n=28, 42.4%), pruritus, nausea, and vomiting (8 patients each, 12.1%). Eighteen of these patients (27.3%) had no symptoms (Table 1). The most common organ involved was the liver (n=52, 78.8%), followed by the lung (n=12, 18.2%) and kidney (n=8, 12.1%). Single-organ involvement was observed in 58 patients (87.9%) and the most commonly involved organ was the liver (n=46, 69.7%) (Table 2). When the size of the cysts were evaluated, it was found that the cysts were 13 cm in the kidney, 12 cm in the liver, 9 cm in the lung, and 5 cm in the brain. Regarding the number of cysts seen in the organs, 56 patients (84.8%) had solitary cysts, 9 patients (13.6%) had two cysts and one patient (1.5%) had multiple cysts. The most common laboratory tests at initial presentation were total IgE (74.1%), C-reactive protein (CRP) (66.7%), and GGT elevations (41.5%) (Table 3). The hydatid cyst IHA test was positive in 77.4% of the patients tested (Figure 1).

Table 1. Distribution of HD patients' symptoms

The initial symptoms	n	%	The initial symptoms	n	%
Abdominal pain	28	42.4	Expectoration	3	4.5
Nausea	8	12.1	Sweating	2	3
Vomiting	8	12.1	Dysuria	2	3
Itching	8	12.1	New shivering or shaking (rigors)	1	1.5
Fever	6	9.1	Chest pain	1	1.5
Loss of appetite	6	9.1	Constipation	1	1.5
Weight loss	6	9.1	Abdominal swelling	1	1.5
Pain in his/her back, under the ribs	4	6.1	Headache	1	1.5
Fatigue	4	6.1	Seizures	1	1.5
Shortness of breath	4	6.1	Hematuria	1	1.5
Cough	3	4.5	No symptoms	18	27.3

Table 2. HD organ involvement sites

Organ	n	%	Organ	n	%
Liver (Total)	52	78.8	Kidney (Single)	6	9.1
Lung (Total)	12	18.2	Liver+Lung	5	7.6
Kidney (Total)	8	12.1	Liver+Kidney	1	1.5
Liver (Single)	46	69.7	Lung+Kidney	1	1.5
Lung (Single)	6	9.1	Brain	1	1.5

Table 3: Abnormal laboratory findings of the HD patients

Laboratory findings	n (Total)	n (+)	%	Labo-ratory findings	n (Total)	n (+)	%
Leukocytosis	66	17	25.8	Increased ALP levels	41	11	26.9
Eosinophilia	66	16	24.2	Increa-sed GGT levels	41	17	41.5
Anemia	66	20	30.3	Increased T.bilirubin levels	60	4	6.7
Thrombocyto-penia	66	1	1.5	Increased D.bilirubin levels	60	2	3.3
Increased CRP levels	66	44	66.7	Increased creatinine levels	64	0	0
Increased AST levels	65	26	40	Increased Total IgE levels	58	43	74.1
Increased ALT levels	64	16	25				

***ALT:** Alanine transaminase; **AST:** Aspartate aminotransferase; **ALP:** Alkaline phosphatase; **D.bilirubin:** Direct bilirubin; **T.bilirubin:** Total bilirubin; **GGT:** Gamma-glutamyl transferase

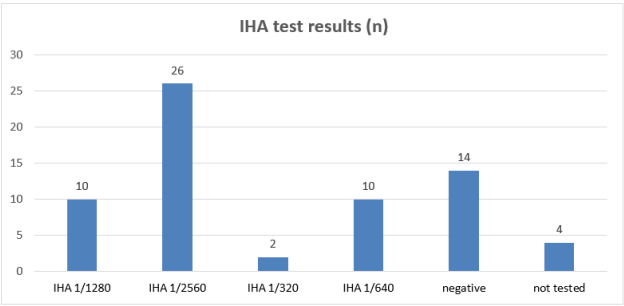

Figure 1. IHA test results of the patients

Of the cysts located in the liver, 39 (75%) were categorized according to the Gharbi classification. The cysts were mostly classified as type 1 (n=11, 28.2%) and type 2 (n=10, 25.6%) (Table 4).

Table 4. Gharbi classification of liver hydatid cysts

Gharbi classification	n	%	Gharbi classification	n	%
Type 1	11	28.2	Type 5	4	10.3
Type 2	10	25.6	Type 1-2	1	2.6
Type 3	8	20.5	Type 3-4	1	2.6
Type 4	4	10.3			

Patients with liver involvement mostly underwent PAIR (percutaneous aspiration, injection, and re-aspiration) (19.7%) while lung and other organ involvement underwent open surgical intervention (Table 5). All patients were treated with albendazole 2x400 mg for an average of 3-6 months in non-surgical patients and one week before and one month after the procedure in surgical patients.

Tablo 5. Summary of treatments for HD patients

Method	n	%	Method	n	%
PAIR*	13	19.7	Wedge resection (Lung)	1	1.5
Cystectomy	8	12.1	Decortication, Cystotomy + Capitonage	1	1.5
PAIR+ Cystectomy	4	6.1	Treatment refusal	4	6.1
Nephrectomy	2	3	Only medical treatment	31	47
Lung lobectomy	2	3			

*__PAIR:__ percutaneous aspiration, injection, and re-aspiration

Relapse was detected in three patients (4.5%). One of these patients had been previously followed up and surgically treated for liver HD, but two years later lung HD was detected and albendazole and surgical treatment were repeated. In two patients with liver HD (one of them underwent PAIR and the other underwent cystectomy in the first follow-up), the surgical procedure was repeated due to relapse.

Discussion

According to the data of the Ministry of Health of the Republic of Turkiye, there has been an increase in the number of reported cases of HD, which is one of the notifiable infectious diseases in our country. While the number of cases was 408 in 2008, it reached 1,867 by the end of 2019. While the number of cases reached the highest rate, especially between 2016-2017, it is seen that the number of cases reported after 2016 exceeded 1,700. However, it is thought that this increase is not a real increase and is related to the 2015 year-end regulation of the surveillance of infectious diseases mandatory to be notified by the Ministry of Health (1). Although it has been shown that HD can be observed at any age, it has been reported that the disease usually becomes symptomatic years after contact in childhood (6). In the HERACLES study, it was found that the prevalence of HD increased gradually with age in Turkiye (11). Güreser et al. (12) reported that 75% of the patients were over 40 years of age. In the study by Türkoğlu et al. (13), the mean age of the patients was found as 40.6 years. In our study, 59% of the patients were female and 41% were male. The mean age of all patients was 40.9 years and the result is similar to the literature.

Primary infection is always asymptomatic initially. Small cysts may remain asymptomatic for years although not permanently. The incubation period in HD is uncertain and probably lasts for months or years. The disease becomes symptomatic when the cysts rupture or show mass effect. More than 90% of cysts are found in the liver, lungs, or both. Symptomatic cysts can be found in kidney, spleen, peritoneal cavity, skin and muscles (2-3%) and more rarely in heart, brain, vertebral column and ovaries (≤ 1%). The clinical presentation depends not only on the organ involved but also on the size of the cysts, their location within the organ, mass effect and complications due to cyst rupture and secondary infection. Common complications include rupture of the biliary tract and secondary cholangitis, biliary obstruction, intracystic or subphrenic abscess formation, intraperitoneal rupture (with or without anaphylaxis), rupture of the bronchial tree and broncho-biliary fistula development (14). Alveolar echinococcosis presents later than the cystic form. Liver and mostly right lobe involvement is observed in 99% of HD patients. Multiorgan involvement is seen in 13% of the cases as lung, brain, and spleen involvement in addition to liver. Although HD is rarely multivesicular, it is generally unilocular (1). Clinically, epigastric pain and cholestatic jaundice are observed in one-third of the patients, and faint symptoms such as fatigue and weight loss are also observed (4). In a multicenter study conducted in Turkiye, it was reported that the most common presenting complaints were abdominal pain, nausea, and vomiting and 18.2% of the patients were asymptomatic. It was shown that the majority of patients were diagnosed between 2-6 months after the onset of complaints. Also, in this study liver involvement was the most common (90%), 89.4% of patients had single-organ involvement, and 50% of patients with multiple-organ involvement had lung involvement together with the liver (6). Türkoğlu et al. (13) found that 75.6% of the patients were symptomatic and abdominal pain (65.6%), cough (23.3%), chest pain (19.4%) and nausea and vomiting (14.4%) were the most common symptoms. It was observed that 73.1% of the patients had single organ involvement and 26.9% had multi-organ involvement, liver (64.3%) and lung (29.3%) were the most commonly involved organs, and bone, kidney, omentum, mesentery, brain, spleen, bladder, muscle, and adrenal gland were also involved. Öztürk-Durmaz et al. (15) determined that 80.2% had solitary cysts and 19.8% had more than one cyst, 87.4% involved the liver, 4.9% the spleen, 3.9% mesenteric adipose tissue, 1.9% the kidney and 1.9% the lung. In a study conducted in Italy, it was reported that 57% of 10,682 patients who underwent surgical procedures with a diagnosis of HD between 2001 and 2012 were over the age of 60, and the cysts were found in the liver (83.6%) and lung (8.4%) (16). In an observational study conducted in Iran, it was stated that 61% of cysts were in the liver and 20% in the lung, 53% had solitary cysts, 18% had two cysts, 7% had three cysts and 8% had more than three cysts (17). In our study, 72.8% of the patients were symptomatic and 27.2% were asymptomatic. Abdominal pain (42.4%) was most commonly described at the initial

presentation. The most commonly involved organ was the liver (78.8%) while the lung (18.2%) and kidney (12.1%) were the other commonly involved organs. Single organ involvement was present in 87.9% of the patients and the liver (69.7%) was the most commonly affected organ, and the cysts were mostly solitary (84.8%). It is noteworthy that kidney involvement was higher than in the current literature, especially in terms of organs with cysts.

Serologic tests are used together with radiologic imaging such as USG, CT, MRI, and direct radiography to make the diagnosis of HD. If HD is suspected on radiologic imaging, serologic tests must be performed (5). The sensitivity of serologic tests is reported to be 88-96% in liver cysts, 50-56% in the lung, and 25-26% in other organ involvement. The most commonly used serologic tests are IHA, ELISA, IFA and immunoblotting tests. IHA is important in both diagnosis and monitoring of treatment and is used to monitor the efficacy of treatment in the postoperative period (18). In the study by Türkoğlu et al. (13), serologic tests (IHA and/or IFA) were performed in 66% of the patients, and positivity was found in 70.7% of the patients. In the study of Öztürk-Durmaz et al.(15), 52 (50.4%) of 103 patients underwent the IHA test, and positivity was established in 27 (51.9%). In the study of Akkaya Işık et al. (6), IHA test positivity was 81.8%. In our study, the hydatid cyst IHA test was performed in 93.9% of the patients and 77.4% were positive and this rate is similar to the literature.

There are no biochemical and hematologic diagnostic tests specific to HD. Elevated bilirubin and transaminases may be observed in patients with liver involvement and biliary obstruction. In patients with cyst leakage or rupture, eosinophilia may be observed in the hemogram or peripheral smear, unlike in patients with cyst membrane integrity (19). In the study by Akkaya Işık et al. (6), the most common laboratory finding was anemia (25.3%) while eosinophilia was detected in 19%, AST in 15%, ALT in 19% and elevated T.bilirubin in 11%. In the study of Güreser et al. (12), GGT (28%), ALT (16%), AST (16%), and ALP (13%) elevations and eosinophilia were found in 19%. In our study, elevated total IgE (74.1%), CRP (66.7%), and GGT (41.5%) levels were especially prominent at the first presentation to the clinic. Eosinophilia was present in 24.1% of the patients.

While surgery was the only option in the treatment of HD until the 1980s, the combination of chemotherapy with benzimidazole compounds (albendazole 10-15 mg/kg/g, mebendazole 40-50 mg/kg/g) and the PAIR method gained priority (4). After the widespread use of benzimidazole compounds, it has been observed that one third of the patients receiving treatment recovered completely, and 30-50% had a significant regression in cyst size (20). In HD, if the cyst is intact, complete recovery can be achieved with surgery. Complete removal of the cyst is extremely important in terms of prevention of scattering of cyst contents and prevention of complications. Pericystectomy, marsupialization, capitonage and resection may be necessary depending on the location of the cyst. In patients who cannot be operated, PAIR can be performed in solid or multiple cysts located in the liver, spleen, kidney, abdominal cavity and bone (4). Chemotherapeutic agents can be used as an adjuvant to surgical treatment before surgery, after surgery, or both. A course of chemotherapy before the surgical procedure sterilizes the cysts and facilitates the surgical procedure by reducing their tension while a short course of chemotherapy after surgery reduces the risk of recurrence (21). In a study conducted in India, only 9.4% of patients who used albendazole before surgery and 96.9% of patients who did not use albendazole before surgery had live cysts during surgery. In the same study, the recurrence rate was found as 18.75% in patients who did not receive albendazole treatment and 4.2% in those who did (22). In a study conducted in Turkiye, recurrence was in only one of 98 patients (1.02%) who received preoperative and postoperative albendazole (23). In a meta-analysis by Smego et al. (24), 769 patients who underwent PAIR with albendazole/mebendazole (ALB/MBZ) treatment were compared with 952 patients who underwent surgery alone and it was concluded that PAIR with ALB/MBZ treatment was more effective, had lower morbidity and mortality rates, lower risk of recurrence and shorter hospital stay. In our study, the PAIR procedure was performed the most (19.7%). While 12% of the patients underwent cystectomy, 47% did not require any surgical intervention. All of the patients were given albendazole treatment, which was started one week before the procedure and continued until one month after the procedure in patients who did undergo surgery and for 3-6 months in patients who did not undergo surgery. Recurrence developed in three patients followed up clinically, so these patients were given albendazole treatment and the surgical procedure was repeated.

Conclusion

HD remains an important health problem in Turkiye. The diagnosis may be missed due to the lack of symptoms for a long time. In our study, it was observed that HD was most commonly seen in the liver and mostly in the form of single-organ involvement and that elevated total IgE was helpful in the laboratory diagnosis, although not diagnostic. HD should be kept in mind in patients presenting with abdominal pain and elevated total IgE.

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ORIGINAL ARTICLE

Radiological Imaging and Analysis of Laboratory Values in Case of Acute Ischemic Stroke

Akut İskemik İnme Vakalarında Radyolojik Görüntüleme ve Laboratuvar Değerlerinin Analizi

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ABSTRACT

Aim: The rate of death and disability due to acute ischemic stroke ranks second in the world. In this study it was planned to analyze the demographic characteristics and additional diseases in the etiology as well as radiological imaging and laboratory values in patients with ischemic stroke.
Material Method: This study was conducted retrospectively by analyzing the patients hospitalized in the emergency department with the diagnosis of ischemic stroke between 01.01.2022 and 31.12.2022. Routine laboratory values, lipids, vitamin levels, radiological imaging and tests for etiology were analyzed in the patients.
Results: One hundred seventy-seven patients were analyzed in the study. 53.1% of the patients were male. The mean age was 75±12.75 years. The most common comorbidities were hypertension, diabetes and hyperlipidemia. As ischemic infarction, involvement was most common in the areas fed by the middle cerebral artery. In the carotid and/or vertebral doppler ultrasonography performed in the patients, plaque was observed in the vessels at a rate of 83.1%. According to the transthoracic echocardiographic findings, 79.3% of the patients were found to have heart valve pathology. Pathologically the majority of patients had hyperglycemia, vitamin D deficiency and low HDL cholesterol levels. Thrombolytic therapy was applied in six patients and three patients benefited and one patient died due to bleeding. 13.6% of the patients were treated in the intensive care unit.
Conclusion: The risk of ischemic stroke increases in advanced age. Hypertension and diabetes are among the most important risk factors. Vitamin D and vitamin B12 deficiency and folic acid deficiency pose a risk in terms of atherosclerosis. At the same time, low HDL cholesterol levels increase the risk of stroke. These factors which are considered as preventable causes in etiology should be controlled with treatment.

Keywords: Emergency department, Acute ischemic stroke, Cerebrovascular disease

ÖZ

Amaç: Akut iskemik inmeye bağlı ölüm ve sakatlık oranı dünyada ikinci sırada yer almaktadır. Bu çalışmada, iskemik inme geçiren hastalarda demografik özellikler ve etiyolojide yer alan ek hastalıklar ile yapılan radyolojik görüntüleme ve laboratuvar değerlerinin analizinin yapılması planlandı.
Materyal Metod: Bu çalışma retrospektif olarak 01.01.2022-31.12.2022 tarihleri arasında acil servisten iskemik inme teşhisi ile hastaneye yatırılan hastaların analizi ile yapılmıştır. Hastalarda rutin laboratuvar değerleri, lipitler, vitamin düzeyleri, radyolojik görüntülemeler ve etiyolojiye yönelik testler analiz edilmiştir.
Bulgular: Çalışmada 177 hasta analiz edildi. Hastaların %53,1'i erkekti. Yaş ortalaması 75±12,75 oldu. Ek hastalık olarak en sık hipertansiyon, diyabet ve hiperlipidemi olduğu görüldü. İskemik infarkt olarak en sık orta serebral arterin beslediği alanlarda tutulum görüldü. Hastalarda yapılan karotis ve/veya vertebral doppler ultrasonografide damarlarda %83,1 oranında plak olduğu görüldü. Transtorasik ekokardiyografi bulgularına göre hastaların %79,3'ünde kalp kapak patolojisi olduğu saptandı. Hastalarda patolojik olarak çoğunlukta hiperglisemi, D vitamini eksikliği ve HDL kolesterol seviyesinde düşüklük olduğu gözlendi. Altı hastada trombolitik tedavi uygulandı ve üç hasta fayda görürken bir hasta kanama gelişerek öldü. Hastaların %13,6'sı yoğun bakımda tedavi edildi.
Sonuç: İskemik inme görülme riski ileri yaşlarda artmaktadır. Hipertansiyon ve diyabet en önemli risk faktörlerindendir. Vitamin D ve vitamin B12 eksikliği ile folik asit eksikliği ateroskleroz açısından risk arz etmektedir. Aynı zamanda düşük HDL kolesterol düzeyi de inme riskini artırmaktadır. Etiyolojide önlenebilir nedenler olarak değerlendirilen bu faktörler tedavi ile kontrol altına alınmalıdır.

Anahtar Kelimeler: Acil servis, Akut iskemik inme, Serebrovasküler hastalık

Introduction

Stroke is a disease that occurs after focal loss of function in the brain and generally develops due to vascular causes (1,2). The lifetime risk of stroke is 25% in adults over the age of 25 (3). The second most common cause of disability and death in the world is stroke (4). Although the symptoms last longer than 24 hours, partial or complete recovery can be seen over time, while on the other hand, they can also result in disability and death. The clinic usually develops suddenly and is related to vascular pathologies (1,2). Strokes are divided into hemorrhagic and ischemic. The rate of ischemic stroke is higher than 87% (1,2,5). The most common causes in etiology are atherothrombotic and cardioembolic causes. Fat and plaques accumulating in the vascular tissue cause clot formation and cause atherothrombotic-induced ischemic stroke (2). Infarct

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due to embolism occurs as a result of occlusion of the vessel by embolism in a distal area in the collateral arterial structure. The heart and proximal arteries may be sources of embolism (6). In some patients, ischemic stroke may develop due to vascular tissue disorders, coagulation disorders and disorders of hemoglobin tissue (7). In cases where adequate nutrition cannot be provided due to the deterioration of blood flow in the brain tissue, permanent damage begins to develop rapidly. The brain cannot be adequately nourished due to a complete or partial decrease in blood flow. Perfusion in the brain may also decrease in conditions such as hypotension, heart failure and blood loss. In ischemic strokes, the infarct area should be detected by imaging methods and the etiology should be investigated (6,7).

When the risk factors in etiology are examined, two groups emerge. While gender, age and race are in the unchangeable risk group, habits such as hypertension, diabetes, coronary artery diseases, dyslipidemia, atherosclerosis, obesity, alcohol and smoking are in the modifiable risk group (4). The incidence of ischemic stroke can be reduced by eliminating modifiable causes or by properly treating the diseases currently under treatment.

Current studies on ischemic stroke should be done and new data should be added to the literature. In this study, we planned to analyze the demographic characteristics and additional diseases in the etiology as well as radiological imaging and laboratory values of patients hospitalized with the diagnosis of ischemic stroke in the emergency department.

Material and Methods

This descriptive study was conducted retrospectively among patients who were diagnosed with acute cerebrovascular disease and received inpatient treatment in the adult and pediatric emergency department of a secondary care hospital. Before the study, Nevşehir Hacıbektaş Veli University non-interventional clinical research publication ethics committee approval was obtained with the decision number 2023/6 dated 19.04.2023.

The study population consisted of patients hospitalized with the diagnosis of 'cerebrovascular disease' in the neurology service, other services and intensive care units of the hospital between 01.01.2022 and 31.12.2022. Among the patients, those diagnosed with cerebrovascular disease due to hemorrhagic reasons (epidural, subdural, ventricular, subarachnoid hemorrhage) were excluded from the study. The data obtained in the analysis of the patients were accessed through the program called SISOFT operating system used in the hospital information operating system. Age, gender, admission times and known comorbidities of the patients were analyzed. Apart from the hemogram and biochemical parameters that are routinely evaluated in the patients, blood levels of vitamin B12, vitamin D, iron, folate, triglyceride, LDL, HDL and INR were analyzed. Brain CT (computed tomography) diffusion MR (magnetic resonance) images and doppler ultrasonography (USG) images of the carotid and vertebral arterieswere evaluated through reports prepared by radiologists. Transthoracic echocardiography (ECHO) reports made by cardiologists were accessed. The treatments and results were obtained from the epicrisis reports recorded on the information operating system of the patients. During the process the records of 244 patients were reviewed and 67 patients were excluded from the study due to missing data. Of the repetitive applications in the same year, only the first application was evaluated. The planning of the study is shown in figure 1.

Statistical Method

Statistical Package for Social Sciences for Windows 21.0 (SPSS 21.0) was used to analyze the data. After the data were entered into the system, age ranges and application time intervals were created. Additional disease data were combined. Laboratory values were divided into three classes as low, normal and high. As statistical analysis, descriptive statistics (frequency, percentage distribution) and chi-square test were used to compare categorical variables between the two groups. Results were evaluated as mean ± SD, or frequency (percentage), and $p < 0.05$ was considered statistically significant at the 95 percent confidence interval.

Results

Data of 177 patients were analyzed in this study. 53.1% of the patients were men. The lowest age of the patients was 24, the highest was 96 and the mean age was 75±12.75. Looking at the age ranges, the lowest number of applications was between the ages of 20-40 and the highest number of applications was between the ages of 60-80 (Table 1). No patient under the age of 20 was diagnosed with ischemic stroke. When the patient applications were analyzed by time period, it was observed that the most common application was in October (13%), the most common day was Friday (17.5%) and the most common time of application was between 08.00-15.59 hours (57.5%). The patients' previous and diagnosed diseases were examined. The most common comorbidity was hypertension (59.5%) followed by diabetes mellitus (37.2%) (Table 1).

Laboratory data of the patients were analyzed. It was observed that blood glucose level was above the normal range in 143 (80.8%) patients. Vitamin D levels and HDL levels were below the normal range in 132 (74.6%) and 116 (65.5%) patients respectively. Blood sodium, potassium, AST, ALT, white blood cell, hemoglobin, thrombocyte and INR values were within the normal range in most of the patients. Blood laboratory analysis results are given in table 4 and figure 2. Vitamin D levels were compared according to gender and no significant difference was found (Chi-square: 3.816, $p>0.05$). HDL cholesterol levels were compared according to gender and there was no significant difference(Chi-square: 6.179, $p>0.05$). Vitamin D levels were compared according to age and no significant difference was observed (Chi-

square: 70.516, p>0.05). HDL levels in blood were compared according to age, and HDL levels were lower especially over 65 years of age (Chi-square: 221.736, p<0.001).

Table 1. Analysis of demographic data

Demographic Data	Number of Patients (n) / Ratio (%) / Standard Deviation (SD)		
Gender			
Male	94 (53.1)		
Female	83 (46.9)		
Average Age	75 ± 12.75		
Age Ranges	Male	Female	Total
0-20	0 (0)	0 (0)	0 (0)
20-40	5 (2.8)	2 (1.1)	7 (3.9)
40-60	14 (7.9)	6 (3.4)	20 (11.3)
60-80	57 (32.2)	49 (27.7)	106 (59.9)
>80	18 (10.2)	26 (14.7)	44 (24.9)
Additional illness		(n / %)*	
Hypertension		106 (59.5)	
Diabetes Mellitus		66 (37.2)	
Hyperlipidemia		43 (24.2)	
Coronary Artery Disease		33 (18.6)	
Presence of Atrial Fibrillation		32 (18)	
Past Ischemic Stroke		37 (20.9)	
Past Embolism /Thrombosis		4 (2.2)	
Past Surgical Operation		5 (2.8)	
Other **		27 (15.2)	
No Additional Disease		32 (18)	

*This is the ratio given according to the total number of patients.

**Asthma, Chronic obstructive pulmonary disease, Chronic kidney failure, Cancer disease

According to CT reports, 67% of patients had old or new infarct findings in imaging. According to the diffusion MRI reports, the most infarct areas were seen in the regions fed by the middle cerebral artery (30%). According to the results of the comparative analysis between demographic data and imaging methods, cerebellar infarction development was significantly higher in male patients (p<0.001, Chi-square: 14.198). No significant differences were observed in the comparison of the affected regions in the brain according to gender and age ranges (p>0.05) (Table 3). According to carotid and vertebral doppler USG reports, intravascular plaques were observed in 83.1% of the patients (Table 3). According to the results of transthoracic echocardiography performed by cardiologists, heart valve pathology was detected in 79.3% of the patients. The mean heart ejection fraction (EF) rate of the patients was 60% ±9.24, and the EF rate was between 40-60% in 88.7% of the patients.

Table 2. Analysis of the laboratory values of the patients after admission

Parameter*	Average	Lowest	Highest	Normal range (n/%)**	Standard range
Glucose	132±80.30	65	550	30 / 16.9	70-100 mg/dL
Urea	40±26.44	1.92	212	81 / 45.8	16-38 mg/dL
Creatinine	0.89±0.80	0.06	7.70	73 / 41.2	0.5-0.9 mg/dL
Sodium	139±3.01	129	148	153 / 86.4	135-145 mmol/L
Potassium	4.3±,0.54	3.2	6.5	153 / 86.4	3.5-5.1 mmol/L
AST	18±17.45	8	163	153 / 86.4	0-32 U/L
ALT	14±13.25	3	78	156 / 88.1	0-33 U/L
CRP	5.3±35.07	0.1	311	86 / 48.6	0-5 mg /dL
WBC	7.9±3.98	3.9	33	130 / 73.4	4.3-10.7 10^3/ mm^3
Hemoglobin	14±1.85	8.4	18	151 / 85.3	11.7-17.2 g/dL
Platelet	242±97.35	54	812	158 / 89.3	150-450 10^3/ mm^3
INR	1.1±0.36	0.1	3.6	138 / 78	0.8-1.22
Vitamin B12	288±216.36	19	2000	129 / 72.9	191-633 ng/dL
Vitamin D	14±10.32	2	72	42 / 23.7	20-50 µg/dL
Iron	59±31.06	9	188	146 / 82.5	33-193 µg/dL
Folate	7.53±6.42	0.5	79	160 / 90.4	3.8-16 µg/dL
Tryglicéride	129±74.7	57	531	149 / 84.2	0-200 mg/dL
LDL	104±37.95	8	267	136 / 76.8	0-130 mg/dL
HDL	15.27	5	144	116 / 65.5	45-100 mg/dL

*AST: Aspartate transaminase, ALT: Alanine aminotransferase, CRP: C-Reactive protein, WBC: White blood cell, INR: International normalized ratio, LDL: Low density lipoprotein, HDL: High density lipoprotein

**Number and rates of patients with laboratory values within the normal range

It was observed that the heart valve pathology increased as the age of the patients increased, and the comparative data were significant (Chi-square: 21.155, p<001). Comparative analysis between the findings of carotid and vertebral doppler USG results and age ranges showed significant results (p<0.001, 37.415). According to these results, there were more plaques and stenosis in the 60-80 age range (Table 3).

Intravenous thrombolytic administration was performed in six of the analyzed patients, considering the duration of admission and indication requirement. One of the patients showed complete recovery and two showed significant improvement. While positive response was not obtained in two patients at the end of the treatment, death occurred in one patient with bleeding into the ventricle. 13.6% of the patients were followed in the intensive care unit (24 patients) while the other patients were followed up in the service. A total of two patients resulted in death. Comparative analysis of patient hospitalizations according to demographic data, imaging results and laboratory data is given in table 4.

Table 3. Diffusion MRI, carotid and vertebral doppler ultrasonography and transthoracic echocardiography findings and comparative analysis by age and sex

Results*	Gender (n / %)		Statistical Analysis (p value/ chi square)	Age Range (n /%)				Statistical Analysis (p value/ chi square)	Total (n %)
Ischemic Area	Male	Female		20-40	40-60	60-80	>80		
MCA areas	24 (45.2)	29 (54.8)	0.174 / 1.845	0 (0)	5 (9.4)	30 (56.6)	18 (34)	0.161 / 5.154	53 (30)
Thalamic area	20 (50)	20 (50)	0.655 / 0.200	0 (0)	3 (7.5)	29 (72.5)	8 (20)	0.206 / 4.568	40 (22.6)
Cerebellar area	18 (90)	2 (10)	0.000 / 14.198	3 (15)	3 (15)	11 (55)	3 (15)	0.042 / 8.200	20 (11.3)
Lacunar area	1 (33.3)	2 (66.7)	0.601 / 0.476	0 (0)	1 (33.3)	1 (33.3)	1 (33.3)	0.598 / 1.879	3 (1.7)
Pons area	5 (71.5)	2 (28.5)	0.450 / 0.982	0 (0)	0 (0)	6 (86)	1 (14)	0.522 / 2.251	7 (3.9)
Other cortical areas	27 (50)	27 (50)	0.626 / 0. 301	4 (7)	8 (14)	28 (52.6)	14 (26.4)	0.254 / 4.065	54 (30.5)
Carotid and Vertebral Doppler USG									
Normal	16 (64)	9 (36)	0.305 / 3.624	4 (16)	7 (28)	12 (48)	2 (8)	0.000 / 37.415	25 (14.1)
Plaques	77 (52)	70 (48)		2 (1,3)	12 (8.1)	91 (61.9)	42 (28.7)		147 (83.1)
Shortness	1 (25)	3 (75)		1 (25)	0 (0)	3 (75)	0 (0)		4 (2.3)
Thrombus	0 (0)	1 (100)		0 (0)	1 (100)	0 (0)	0 (0)		1 (0.5)
Transthoracic Echocardiography									
Heart Valve Pathology									
Yes	69 (49)	72 (51)	0.028 / 4.483	2 (1.4)	12 (8.5)	86 (60.9)	41 (29.2)	0.000 / 21.155	141 (79.7)
No	25 (69.4)	11 (30.6)		5 (13.8)	8 (22.2)	20 (55.5)	3 (7.5)		36 (20.3)
Ejection Fraction Ratio									
0-20	0 (0)	0 (0)	0.957 / 0.087	0 (0)	0 (0)	0 (0)	0 (0)	0.000 / 32.519	0 (0)
20-40	1 (50)	1 (50)		0 (0)	0 (0)	2 (100)	0 (0)		2 (1.1)
0-60	84 (53.5)	73 (46.5)		2 (1.2)	17 (10.8)	97 (61.7)	41 (26.3)		157 (88.7)
>60	9 (50)	9 (50)		5 (27.7)	3 (16.7)	7 (38.9)	3 (16.7)		18 (10.2)

*MCA: Main Cerebral Artery, USG: Ultrasonography

Table 4. Comparison of patients' ward and intensive care unit hospitalizations with demografic data, laboratory data and imaging results

	Service (n/%)	Intensive Care (n/%)	Statistical Analysis
Gender			
Male	83 (47)	11 (6.5)	p=0.512, Chi square: 0.590
Female	70 (39.5)	13 (7)	
Age Ranges			
0-20	0 (0)	0 (0)	p=0.007, Chi square: 9.301
20-40	7 (4)	0 (0)	
40-60	20 (11)	0 (0)	
60-80	93 (52)	13 (7)	
>80	33 (19.5)	11 (6.5)	
Ischemic Area			
Main cerebral artery areas	38 (22.5)	15 (8.5)	p=0.001, Chi square: 11.796
Thalamic area	37 (21)	3 (1.5)	p=0.295, Chi square: 1.619
Cerebellar area	18 (10)	2 (1)	p=0.622, Chi square: 0.244
Lacunar area	3 (1.5)	0 (0)	p=0.489, Chi square: 0.479
Pons area	7 (4)	0 (0)	p=0.596, Chi square: 1.343
Other cortical areas	50 (28)	4 (2)	p=0.153, Chi square: 2.509
Carotid Doppler Ultrasonography			
Normal	24 (13.5)	1 (0.5)	p=0.350, Chi square: 3.280
Plaques	124 (70.5)	23 (13)	
Shortness	4 (2)	0 (0)	
Thrombus	1 (0.5)	0 (0)	
Transthoracic Echocardiography			

Heart Valve Pathology			
Yes	119 (67.5)	22 (12.5)	p=0.172, Chi square: 2.470
No	34 (19)	2 (1)	
Ejection Fraction Ratio			
0-20	0 (0)	0 (0)	p=0.194, Chi square: 3.277
20-40	1 (0.5)	1 (0.5)	
40-60	135 (76.5)	22 (12.5)	
>60	17 (9.5)	1 (0.5)	
Laboratory Paremeter*			
Glucose			
Low	4 (2)	0 (0)	p=0.325, Chi square: 2.250
Normal	28 (16)	2 (1)	
High	121(68.5)	22 (12.5)	
Urea			
Low	2 (1)	0 (0)	p=0.331, Chi square: 0.212
Normal	73 (41)	8 (4)	
High	78 (46)	16 (8)	
Creatinine			
Low	15 (8.5)	4 (2)	p=0.348, Chi square: 2.110
Normal	66 (37.5)	7 (3.5)	
High	72 (40.5)	13 (7)	
Sodium			
Low	19 (11)	4 (2)	p=0.033, Chi square: 6.383
Normal	134 (75.5)	19 (11)	
High	0 (0)	1 (0.5)	
Potassium			
Low	6 (3.5)	1 (0.5)	p=0.022, Chi square: 7.637
Normal	136 (76)	17 (10)	
High	11 (6.5)	6 (3.5)	
AST			
Low	0 (0)	0 (0)	p=0.016, Chi square: 5.770
Normal	136 (76)	17 (10)	
High	17 (10)	7 (4)	
ALT			
Low	0 (0)	0 (0)	p=0.434, Chi square: 0.612
Normal	136 (76)	20 (11.5)	
High	17 (10.5)	4 (2)	
CRP			
Low	0 (0)	0 (0)	p=0.001, Chi square: 11.325
Normal	82 (46)	4 (2)	
High	71 (40.5)	20 (11.5)	
WBC			
Low	5 (3)	0 (0)	p=0.019, Chi square: 7.907
Normal	117 (66)	13 (7.5)	
High	31 (17.5)	11 (6)	
Hemoglobin			
Low	23 (13)	1 (0.5)	p=0.122, Chi square: 4.204
Normal	129 (72.5)	22 (13)	
High	1 (0.5)	1 (0.5)	
Platelet			
Low	12 (7)	1 (0.5)	p=0.799, Chi square: 0.449
Normal	136 (76)	22 (13)	
High	5 (3)	1 (0.5)	
INR			
Low	1 (0.5)	0 (0)	p=0.757, Chi square: 0.558
Normal	118 (67)	20 (11.5)	
High	34 (19)	4 (2)	

Vitamin B12			
Low	33 (19)	4 (2)	
Normal	109 (61)	20 (11.5)	p=0.304, Chi square: 2.380
High	11 (6.5)	0 (0)	
Vitamin D			
Low	115 (65.5)	17 (9.5)	
Normal	36 (20)	6 (3.5)	p=0.585, Chi square: 1.072
High	2 (1)	1 (0.5)	
Iron			
Low	23 (13)	8 (5)	
Normal	130 (73)	16 (9)	p=0.028, Chi square: 4.809
High	0 (0)	0 (0)	
Folate			
Low	10 (6)	3 (1.5))	
Normal	139 (78)	21 (12.5)	p=0.437, Chi square: 1.658
High	4 (2)	0 (0)	
Trygliceride			
Low	0 (0)	0 (0)	
Normal	128 (84.5)	20 (11.5)	p=0.903, Chi square: 0.015
High	4(2)	4 (2)	
LDL			
Low	0 (0)	0 (0)	
Normal	118 (66)	18 (10)	p=0.798, Chi square: 0.053
High	35 (20)	6 (4)	
HDL			
Low	100 (57)	16 (8)	
Normal	52 (30.5)	8 (4)	p=0.921,Chi square: 10.165
High	1 (0.5)	0 (0)	

*AST: Aspartate transaminase. ALT: Alanine aminotransferase. CRP: C-Reactive protein. WBC: White blood cell. INR: International Normalized Ratio. LDL: Low density lipoprotein. HDL: High density lipoprotein

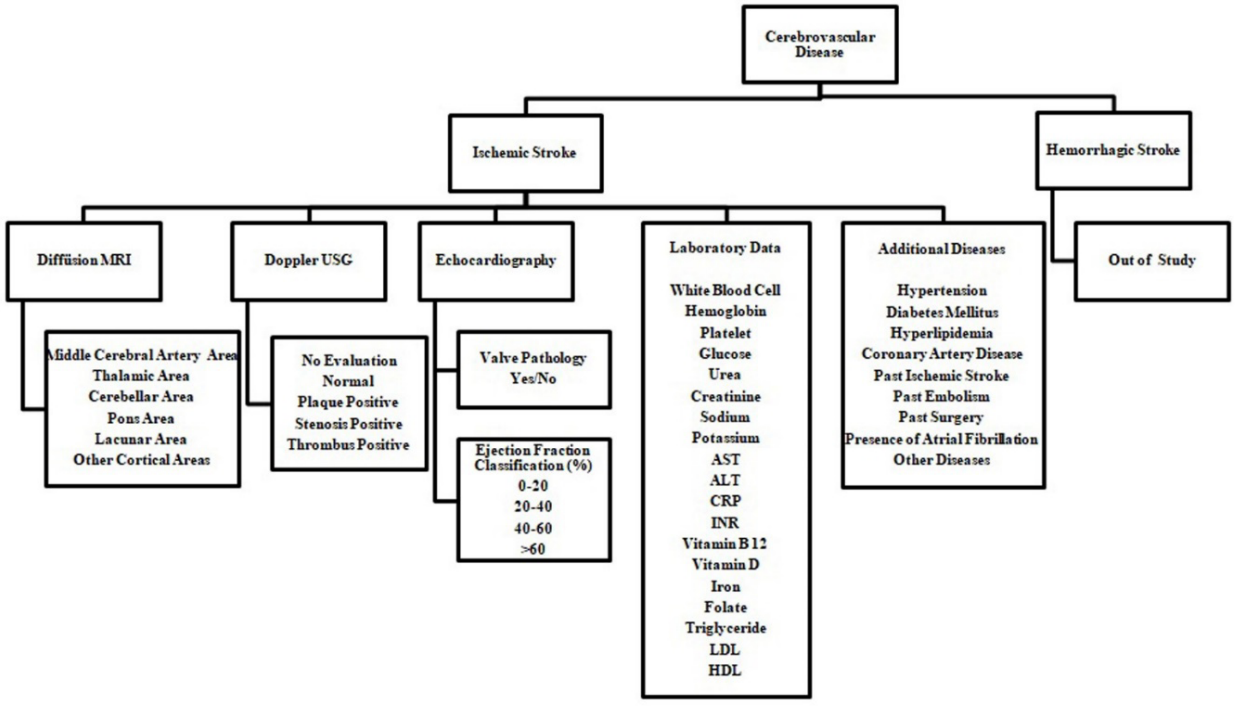

Figure 1. Study Plan

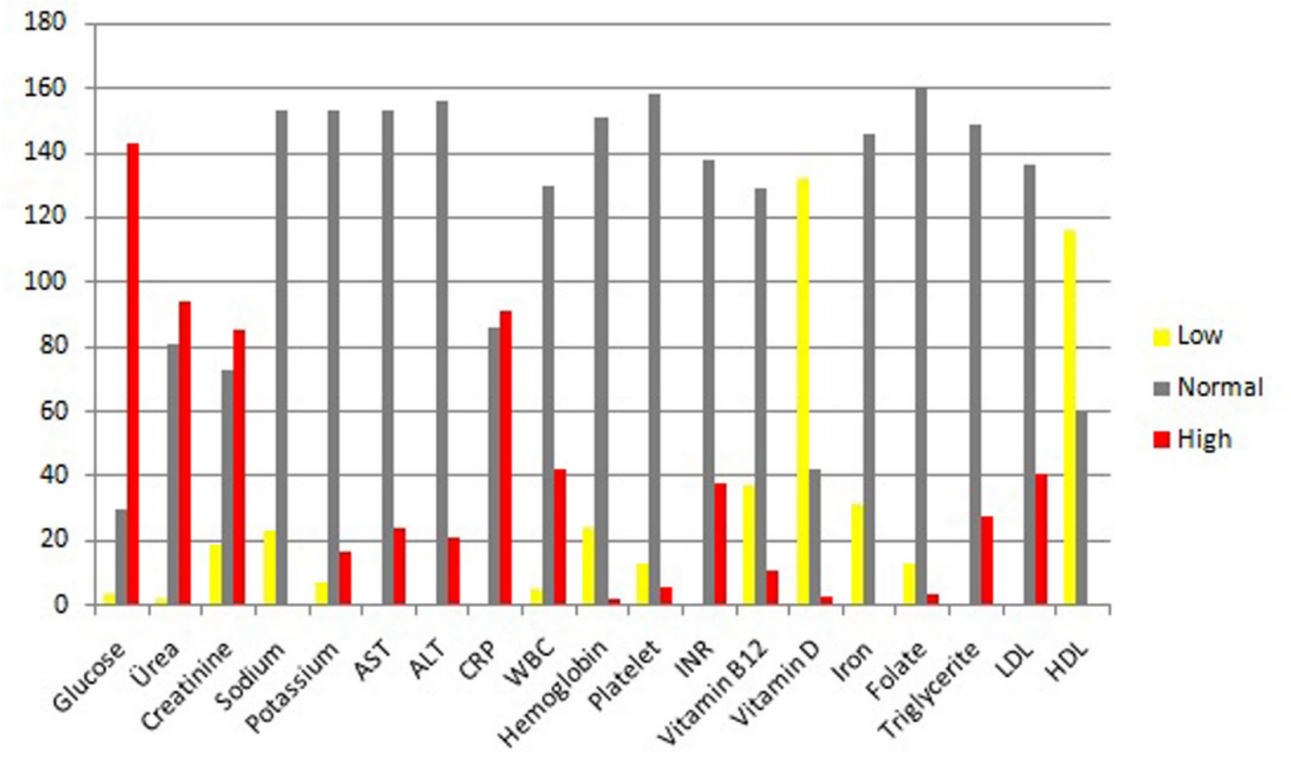

Figure 2. Distribution of patient numbers according to laboratory data

Discussion

Ischemic strokes constitute approximately 80-85% of patients evaluated with acute cerebrovascular disease. The most common causes of ischemic stroke are hypoperfusion, atherothrombosis and embolism. The most common cause of ischemic strokes caused by cardiac causes is atrial fibrillation (8).

Age is an important factor in stroke and it has been reported that 70% of patients with stroke are over 65 years of age (9). In our study, the mean age was 75±12.75 years and the highest number of admissions was in the 60-80 age range. In similar studies conducted on the subject, the mean age range was 60-80 years and our study is compatible with the literature (10-14). In a study by Kiyan et al. it was observed that 5% of ischemic stroke cases were young patients who had stroke under the age of 45 years (15). In our study, the number of patients under 45 years of age was 4.5%. In a similar study, the rate of patients under 45 years of age was found as 6.55% (10).

In similar studies in which stroke patients were analyzed, the rate of male patients was higher (10,13-15). Similarly, 53.1% of the patients were male in our study. In a study conducted by Mozaffarian et al., it was analyzed that stroke was more common in males than females at younger ages, and in patients over 75 years of age, stroke was more common in the female gender (16). Similarly, in our study, 70.3% of patients under the age of 60 years were male and 60% of patients over the age of 80 years were female. Likewise, Öztürk et al. reported that the cases seen after the age of 80 years were mostly in the female gender in their study (14).

In our study, we observed that hypertension and diabetes were the most common comorbidities in stroke patients. In the study conducted by Soyudogru et al., hypertension and diabetes were the most common comorbidities in patients who had a stroke, as in our study (10). Inan et al. reported in a study they conducted that hypertension was the most common cause with a rate of 46% in young patients with ischemic stroke (17). In the study of Morkavuk et al. in which they examined vitamin D levels in patients with ischemic stroke, it was found that 85.2% of the patients had hypertension and 53.7% had diabetes (18). The data in our study was similar to the data in the literature.

In this study, we wanted to examine the laboratory values of ischemic stroke cases. As a result, we observed high blood glucose levels in 143 (80.7%) patients. Studies show that high glucose levels have an effect on survival and clinical prognosis of patients (19, 20). In our study, the mean glucose level was 132±80.30 mg/dL, and there was no significant difference in the comparison between glucose levels and intensive care admissions (Table 4). In the study of Aksoy et al., glucose level was measured as 124.83±50.72 mg/dL, and no significant difference was found between patients with poor prognosis and patients with good prognosis (p=0.009), (13). Glucose level may vary according to additional diseases and differences between hunger and satiety. In studies to be carried

out on the subject, long term follow up of patients and analysis of glucose values by monitoring them at certain periods will be beneficial.

There are studies showing that acute phase reactants are effective in mortality and restroke in ischemic stroke. Some studies show that C-reactive protein (CRP) levels are effective in predicting one year survival after stroke (21, 22). On the contrary, there are studies showing that CRP levels are not significant in stroke (23, 24). In our study, the CRP level was 5.3±35.07. Similarly, in a study comparing CRP and internal carotid artery intima thickness in ischemic stroke patients, the mean CRP level was measured as 7.95±3.81 (25). High levels of CRP in the blood may indicate that plaques in the vessels may become unstable and atherosclerosis may develop. In a study, it was seen that the unstableness and size of the plaques in the carotid vessels were associated with the elevation of CRP (26). In our study, the number of patients with plaque in the vessels was 147 and no significant relationship was found between the elevation of CRP and the number of patients with plaques (p=0.083). In the study conducted by Şengül et al., there was no significant relationship between high CRP and plaque formation in 21 patients (p=0.380) (25). In our study, an evaluation was made between CRP level and intensive care admissions and no significant relationship was found (Table 4). In addition, it was observed that the CRP level was high in patients due to reasons such as infection and malignancy. It would be more appropriate to examine the effect of CRP level in ischemic stroke in more comprehensive studies and in isolation in patients without additional disease.

It is stated that hematological parameters are effective on prognosis in ischemic stroke, and hemogram tests are routinely performed because they are fast and inexpensive. However, since the clinical course of patients is affected by many factors, it is not meaningful to evaluate them alone(27). In our study, white blood cell count was 7.9±3.98 103/mm3, hemoglobin was 14±1.85 g/dL, and platelet was 242±97.35 103/mm3. Aksoy et al. in their study, the laboratory value of white blood cell count was 7.58±2.41 103/mm3, hemoglobin was 12.8±1.70 g/dL and platelet was 239.87±68.42 103/mm3 in patients with good prognosis, and in patients with poor prognosis, white blood cell count was 9.26±4.18 103/mm3, hemoglobin was 13.07±1.91 g/dL and platelet was 248.25±73.63 103/mm3 (13). They reported that there was a significant correlation between the height of white blood cell and poor prognosis (p>0.05) (13). In the study of Kaşıkçı et al., in surviving patients white blood cell was 11.12±4.48 103/mm3, hemoglobin was 11.37±2.43 g/dL and platelet was 258.63±128.18 103/mm3, and they found in patients who ended in death that white blood cell count was 11.31±7.45 103/mm3, hemoglobin 11.65±1.93 g/dL and platelet was 286.79±106.96 103/mm3 (28). They stated that there was no significant relationship between hematological parameters between surviving and deceased patients (28). In our study an evaluation was made between the patients admitted to the intensive care unit and the patients hospitalized in the ward and no significant differences were found in terms of hemogram values (white blood cell; p=0.585, hemoglobin; p=0.924, thrombocyte; p=0.442).

Homocysteine plays an important role in the development of atherogenic events and this is due to thrombus formation resulting from endothelial damage and platelet activation (29). Vitamin B12 plays an important role in the functioning of enzymes activated in the homocysteine remethylation pathway (30). Therefore, vitamin B12 deficiency is considered as a risk factor in the occurrence of ischemic stroke. In this study, we found that 20.9% of the patients had low vitamin B12 levels. Another factor affecting homocysteine level is folic acid level. In this study, we found that 7.7% of the patients had folate levels below the normal range. Comparative analysis between vitamin B12 and folate levels and homocysteine levels could not be performed because homocysteine levels could not be measured in the center where our study was conducted.

Studies have reported that vitamin D plays an important role in maintaining the integrity of the blood brain barrier and is a good neuroprotective agent (31,32). In our study, the mean blood vitamin D level was 14±10.23µg/dL. Vitamin D level was low in 132 (74.5%) of the patients. In a study, it was reported that low vitamin D level in patients with hypertension, dense plaque in the vessels as a result of carotid doppler and low HDL cholesterol level posed a cardiovascular risk (18). In our study, it was observed that vitamin D levels were low in patients with low HDL cholesterol, valvular pathology in the heart, and plaque on carotid and/or vertebral doppler examination. According to a study conducted by Manouchehri et al. in 2017, the risk of ischemic stroke increased 7-fold in people with vitamin D deficiency (33). Longer-term and large-scale studies are needed to indicate that vitamin D poses cardiovascular risk and is an important factor in stroke.

According to studies that analyzed lipid parameters as factors increasing the risk of stroke, high total cholesterol and LDL cholesterol and low HDL cholesterol increase the risk of stroke (34). In our study, mean triglyceride level was 129±74.7 mg/dL, LDL cholesterol level was 104±37.95 mg/dL and HDL cholesterol level was 15.27 mg/dL. HDL cholesterol levels were low in 116 (65.5%) of the patients. In the study conducted by Yılmaz et al., no statistically significant differences were found between the triglyceride, LDL and HDL cholesterol levels measured in the patient and control groups (35). Aksoy et al., on the other hand, measured the mean triglyceride level as 155.15±78.40 mg/dL and LDL cholesterol level as 121.03±33.04 mg/dL in patients with a good prognosis (13). In the same study, mean triglyceride level was measured as 152.42±71.30 mg/dL and LDL cholesterol level as 113.81±33.31 mg/dL in patients with poor prognosis, and no statistical difference was found between good and poor prognosis (13). Yucel et al. examined lipid parameters in patients with and without hypertension in their study

and reached the similar values in our study, and they found that HDL cholesterol level was below the normal value in the majority of patients (36). According to the results of the same study, total cholesterol and LDL cholesterol levels were found significantly higher in patients with hypertension compared to those without but there was no significant relationship between blood lipid parameters and prognosis in general (36). In our study, lipid levels and intensive care hospitalizations were compared and no significant difference was found (Table 4).

In this study, all patients underwent brain CT and diffusion MR imaging. In particular, brain CT evaluation was used to exclude hemorrhagic stroke cases. Infarct areas seen in the patients were classified based on radiological evaluations. According to the results of our study, it was observed that infarcts were most common in the areas fed by the middle cerebral artery. In similar studies, Soyudogru et al. reported according to the evaluation made with MR imaging that infarct was most common in the middle cerebral artery area with a rate of 53.2% (10), Kıyan et al., on the other hand, evaluated with CT imaging in their study and found 15.3% of infarcts in the anterior cerebral artery area(15). In the study conducted by Uzar et al. in young patients who had a stroke, it was found that infarcts were more common in the middle cerebral artery area with a rate of 39.6% (37). Naess et al. stated in their study that infarcts were more common in the middle cerebral artery area with a rate of 62.5% (38).

In our study, 147 patients (83.1%) had plaques in their vascular structures in the carotid and/or Doppler USG examinations of the patients. Similarly, Damar et al. found in their study that 76% of the patients had plaques in the vascular structure (39). Uncu et al. examined the carotid and vertebral artery doppler USG results in patients in their study and found 40% stenosis and occlusion (40).

Atrial fibrillation is the most common cardiac arrhythmia in adults. Impairment of atrial myocardial function causes clot formation in the left atrium and indirectly increases the risk of ischemic stroke (41). In our study, we found that 18% of the patients received treatment for atrial fibrillation. At the same time, 79.7% of the patients who underwent transthoracic echocardiography were found to have heart valve pathology. Kiyan et al. observed 11.3% of atrial fibrillation in electrocardiography (ECG) results of stroke patients (15). In the study of Aksoy et al., the rate of patients who received atrialfibrillation treatment was 11% (13). In the study conducted by Inan et al. on young ischemic stroke patients, the rate of atrial fibrillation was found as 3.3% (17). Diker et al. reported the rate of atrial fibrillation as 62.5% in patients with recurrent stroke (42).

In ischemic stroke, intravenous tPA therapy is an effective treatment when applied to the appropriate patient. Hemorrhages seen after treatment are the most common clinical concern and may occur within the first 36 hours (43). In our study, tPA treatment was applied in six patients, three of them recovered, two did not benefit and one patient developed bleeding and resulted in death. Our patient who developed bleeding was an 83-year-old female patient. Eren et al. observed in their study on patients who received thrombolytics that hemorrhage developed in 12 of 97 patients (44). Since our study is a retrospective study, it was insufficient to evaluate the future outcomes of patients who received thrombolytic therapy.

Conclusion

As a result, the risk of ischemic stroke increases with advanced age. Hypertension and diabetes are among the most important risk factors. Vitamin D and vitamin B12 deficiency and folic acid deficiency pose a risk in terms of atherosclerosis. At the same time low HDL cholesterol levels increase the risk of stroke. These factors, which are considered as preventable causes in etiology, should be controlled with treatment. More studies should be done on the application of thrombolytic therapy and the treatment process should be accelerated by early diagnosis in patients. There are differences between studies in the literature. Therefore, there is a need for more comprehensive studies on laboratory, imaging and treatment applications related to ischemic stroke patients.

Ethics committee approval: Before the study, Nevşehir Hacıbektaş Veli University non-interventional clinical research publication ethics committee approval was obtained with the decision number 2023/6 dated 19.04.2023.

Conflict of Interest: The authors declared no conflict of interest.

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Authors' contribitions to the article: M.A. and N.B. constructed the main idea and hypothesis of the study. M.A. developed the theory and arranged/ edited the material and method section. M.A. has done the evaluation of the data in the Results section. Discussion section of the article written by M.A. and N.B. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

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ORIGINAL ARTICLE

Determination of Factors Affecting Sleep Quality in Postoperative Patients and Improvement of Correctible Causes

Postoperatif Hastalarda Uyku Kalitesini Etkileyen Faktörler ve Düzeltilebilecek Nedenlerin Saptanması

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ABSTRACT

Patients who had postoperative major abdominal surgery and major cardiovascular surgery were included in our study. A total of 103 patients were included in the study. Patients were evaluated with the Pitssburg sleep quality index questionnaire between five and seven days postoperatively. All questionnaires and scales were administered by the same researcher without specifying the participant's name in order to maintain consistency. After explaining the scope and purpose of the study, written consent of all participants was obtained. Pittsburg sleep quality index is a 19-item self-report scale that evaluates sleep quality and disorder. It consists of 24 questions, 19 questions are self-report questions, 5 questions are questions to be answered by the spouse or roommate. The 18 scored questions of the scale consist of 7 components. Subjective Sleep Quality, Sleep Latency, Sleep Duration, Habitual Sleep Efficiency, Sleep Disorder, Sleeping Drug Use, and Daytime Dysfunction. Each component is evaluated over 0-3 points. The total score of the 7 components gives the scale total score. The total score ranges from 0 to 21. A total score greater than 5 indicates "poor sleep quality". In our study, we aimed to investigate whether anesthetic agents, concomitant diseases, type of surgery, and some biochemical parameters affect sleep quality in postoperative patients. The diseases we investigated included hypertension, chronic obstructive pulmonary diseases, asthma, heart failure, cerebrovascular diseases, thyroid function disorders, diabetes mellitus, chronic kidney diseases, and chronic kidney failure. We also evaluated the sociocultural levels of the patients as an important part of the study. Educational status of our patients, literacy rates and occupations were also important to us. In our study, we showed that anesthetic agents [hypnotic and opioid] had no effect on sleep quality, and sleep quality was worse in cardiovascular surgery cases, although it was not statistically significant. We showed that a long operation time (5 hours and more) impairs postoperative sleep quality, thyroid diseases affect sleep quality badly, and sleep disorders are more common especially in patients with COPD. We think that sleep has a very important place in accelerating the recovery process of postoperative patients and that sleep disorders should be questioned better and that postoperative patients with sleep disorders should definitely seek psychological and medical help.

Keywords: sleep quality, pittsburg sleep quality index, postoperative sleep quality

ÖZ

Çalışmamıza postoperatif major abdominal cerrahi geçiren ve major kalp damar cerrahi vakası geçiren hastalar dahil edilmiştir. Çalışmaya toplam 103 hasta dahil edilmiştir. Hastalar postoperatif beş ile yedi gün arasında Pitssburg uyku kalitesi indeksi anketi ile değerlendirilmiştir. Tüm anket ve ölçekler tutarlılığı korumak amacıyla aynı araştırmacı tarafından ve katılımcı ismi belirtilmeden uygulanmıştır. Çalışmanın kapsam ve amacı açıklandıktan sonra bütün katılımcıların yazılı izinleri alınmıştır. Pittsburg uyku kalitesi indeksi uyku kalitesini ve bozukluğunu değerlendiren, 19 maddelik bir özbildirim olceğidir. 24 sorudan oluşur, 19 soru özbildirim sorusu, 5 soru eş veya oda arkadaşı tarafından yanıtlanacak sorulardır. Ölçeğin puanlanan 18 sorusu 7 bileşenden oluşur. Oznel Uyku Kalitesi, Uyku Latensi, Uyku Süresi, Alışılmış Uyku Etkinliği, Uyku Bozukluğu, Uyku İlacı Kullanımı ve Gündüz İşlev Bozukluğudur. Her bir bileşen 0-3 puan uzerinden değerlendirilir. 7 bileşenin toplam puanı ölçek toplam puanını verir. Toplam puan 0-21 arasında değişir. Toplam puanın 5'ten büyük olması "kötü uyku kalitesini" gösterir. Biz çalışmamızda postoperatif hastalarda uyku kalitesini anestezik maddeler, yandaş hastalıklar, cerrahi türü, bazı biyokimyasal parametrelerin etkileyip etkilemediğini araştırmayı hedefledik. Araştırdığımız hastalıklar arasında hipertansiyon, kronik obtruktif akciğer hastalıkları, astım, kalp yetmezliği serebrovasküler hastalıklar, tiroid fonsiyon bozuklukları, diyabetes mellitus kronik böbrek hastalıkları, kronik böbrek yetmezliği bulunmaktaydı. Aynı zamanda hastaların sosyokültürel düzeylerini de çalışmanın önemli bir parçası olarak değerlendirdik. Hastalarımızın eğitim durumları okuma yazma oranları ve meslekleri de bizim için önemliydi. Çalışmamızda anestezik maddelerin [hipnotik ve opioid] uyku kalitesi üzerine bir etkisi olmadığın uyku kalitesinin istatistiksel olarak anlamlı olmasa da kalp damar cerrahisi vakalarında daha kötü olduğunu gösterdik. Ameliyat süresinin uzun olmasının (5saat ve üzeri) postoperatif uyku kalitesini bozduğunu, tiroid hastalıklarının uyku kalitesini kötü etkilediğini ve özellikle koahı olan hastalarda uyku bozukluğunun daha sık olduğunu gösterdik. Postoperatif hastaların iyileşme sürecinin hızlandırılması için uykunun çok önemli bir yer teşkil ettiğini ve uyku bozukluklarının daha iyi sorgulanması gerektiğini ve mutlaka uyku bozukluğu olan postoperatif hastaların psikolojik ve medikal yardım alması gerektiğini düşünüyoruz.

Anahtar Kelimeler: uyku kalitesi, pittsburg uyku kalitesi indeksi, postoperatif uyku kalitesi

Introduction

Sleep; in addition to being a reversible state of unconsciousness, is not just a state of inactivity that allows the body to rest, but also an active regeneration period that prepares the whole body for life. Sleep is one of the basic and indispensable daily life activities that affects the quality of life and health of individuals, and

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it is a concept with physiological, psychological and social dimensions. Sleep is a fundamental element in strengthening physical growth and academic performance (1).

Sleep is not a temporary interruption of daily life or wasted time. It is an active period that is important to renew mental and physical health every day and covers one third of our lives.

There are about 85 types of sleeping sicknesses most of which cause a decrease in quality of life and deterioration in a person's health. Sleep disorders are public health problems as they can cause traffic and occupational accidents. Some sleep disorders cause difficulty falling or staying asleep. Other sleep disorders cause excessive daytime sleepiness. Problems with the body's biological clock cause people to be sleepy at the wrong time of day. Sleep walking, bedwetting, nightmares and other problems can also disrupt sleep. Some sleep disorders are life-threatening (2,3).

Sleep quality is affected by various factors and altered routine status of a person perioperatively effects sleep in the postoperative period, definitely. In this study, we aimed to investigate the factors affecting postoperative sleep quality and determine the correctible causes.

Material and Methods

This study is a prospective, nonrandomized analysis of patients who underwent cardiac surgery or abdominal surgery between January 2013 and June 2013 at a single center. The study was approved by the Institutional Medical Advisory Board.

After explaining the scope and purpose of the study, written consent of all participants was obtained. Demographical data were collected from the hospital database and patients were evaluated with the Pittsburgh sleep quality index questionnaire between five and seven days postoperatively. Patients hospitalized for seven days are either those with postoperative infection or other complications. The normal average hospitalization day is about five days. The patients were interviewed directly at the patient bed. All questionnaires and scales were administered by the same researcher without specifying the participant's name in order to maintain consistency. Anesthetic agents, type of surgery, biochemical parameters, chronic diseases such as hypertension, chronic obstructive pulmonary disease, asthma, heart failure, cerebrovascular disease, thyroid dysfunction, diabetes mellitus, chronic kidney disease; socio-cultural levels and educational status (i.e. literacy rates and occupation) were investigated as potential factors affecting sleep quality.

Pittsburgh Sleep Quality Index (PSQI):

Pittsburgh Sleep Quality Index: PSQI was developed by Buysse et al. (10) and adapted into Turkish by Ağargun et al. (11). PSQI is a 19-item self-report scale that assesses sleep quality and disturbance over the past month. It consists of 24 questions: 19 self-report questions, 5 questions to be answered by the spouse or roommate. The 18 questions of the scale consist of 7 components; Subjective Sleep Quality, Sleep Latency, Sleep Duration, Habitual Sleep Efficiency, Sleep Disorder, Sleeping Drug Use, and Daytime Dysfunction. Each component is evaluated over 0-3 points. Scoring; If it has not happened in the last month, it's 0, if it is less than once a week, it is 1, if it is once or twice a week, it is 2, and if it is three or more times a week, it is 3. The sleep quality evaluation asked in the survey is; It is scored as very good 0, fairly good 1, fairly bad 2, very bad 3.

The total score of the 7 components gives the scale total score. The total score ranges from 0 to 21. A total score greater than 5 indicates "poor sleep quality".

Statistical Analysis

Statistical analyzes were performed in IBM SPSS for Windows Version 21.0 package program (Statistical Package for the Social Sciences, International Business Machines, Inc., Armonk, New York, USA). Numerical variables were summarized as mean ± standard deviation and median [min – max], and categorical variables were summarized as numbers and percentages. Parametric test assumptions (normality and homogeneity of variances) were checked before the groups were compared in terms of numerical variables. Whether there was a difference between two independent groups in terms of numerical variables was investigated by t-test in independent groups if parametric test assumptions were met. If the parametric test assumptions were not met, the Mann-Whitney U test was used. The difference between the groups in terms of categorical variables was examined with the chi-square test or Fisher exact test. Significance level was taken as $p<0.05$.

Results

A total of 103 patients were included in the study. Mean age was 53.35±13.9 years. Sixty-seven patients were male (65%). Of 103 patients, according to PSQI, 53 (51,45%) patients had poor sleep quality and 50 (48,55%) patients had good sleep quality, postoperatively.

Age, marital status, sex, obesity, hypertension, diabetes, alcohol consumption and smoking did not have any significant impact on sleep quality in our study. The socioeconomic status of the patients was also evaluated and their education level was also questioned. Sleep quality of high school graduates and individuals with higher education level was better than the patients with lower education (Table 1).

The anesthetic drugs used were divided into those used in induction and those used in maintenance. No significant difference was found when the drugs used in induction were divided into those using midazolam and those not using midazolam (p:0,576). When the drugs used in maintenance were evaluated, no significant difference was found between the use of desflurane-sevoflurane and the use of desflurane and midazolam p:0,761) (Table 2).

Table 1. Comparison of good and bad results according to marital status, age and gender

		Good sleep (n=50)	Poor sleep (n=53)	p
Gender F/M (%)		14/36 (28/72)	22/31 (41.5/58.5)	0.219
Age (years)		52.5±14.0	54.2±13.8	0.530
Marital status (Single /married) (%)		8/42 (16/84)	4/49 (7.5/92.5)	0.303
Height		171.9±7.5	169.6±7.5	0.120
Weight		75.8±7.5	72.9±10.2	0.102
BMI		25.5±2.7	25.6±3.7	0.845
Obesity		12 (24)	10 (18.9)	0.693
High school and university (+/-)(%)		21/29 (42/58)	35/18 (66/34)	0.024
Education status (%)	Literate	5 (10)	14 (26.4)	0.045
	Primary school	5 (10)	11 (20.8)	
	Middle school	11 (22)	10 (18.9)	
	High school	21 (42)	15 (28.3)	
	University	8 (16)	3 (5.7)	

BMI. body mass index; percentages in brackets.

Table 2. Effect of anesthetic substances on sleep quality

		Good sleep (n=50)	Poor sleep (n=53)	p-value
Drug used	Propofol(%)	14 (28)	16 (30.2)	0.628
	Penthotal(%)	4 (8)	7 (13.2)	
	Midazolam(%)	32 (64)	30 (56.6)	
Induction (nonmidazolam / with midazolam) (%)		18/32 (36/64)	23/30 (43,4/56,6)	0.572
Drug used (maintenance)	Sevoflurane(%)	11 (22)	15 (28.3)	0.761
	Desflurane(%)	9 (18)	9 (7)	
	Midazolam-desflurane(%)	30 (60)	29 (54.7)	
Drug used (maintenance)	Fentanyl(%)	31 (62)	27 (50.9)	0.351
	Remifentanil(%)	19 (38)	26 (49.1)	

Table 3. Parameters evaluated in the evaluation of good and bad sleep

		Good sleep (n=50	Poor sleep (n=53)	p-value
Operation time (hours)		4.8±1.4 4 [3 – 8]	5.7±2.5 5 [3 – 14]	0.053
Hypertension		32 (64)	35 (66)	0.992
Diabetes mellitus		12 (24)	17 (32.1)	0.489
COPD		3 (6)	13 (24.5)	0.020
Chronic renal diseases/ failure		1 (2)	7 (13.2)	0.041
Guatr		-	5 (9.4)	0.047
Cerebrovascular diseases		1 (2)	1 (1.9)	1.000
Time to fall asleep (minutes)		19.5±11.3 15 [5 – 60]	67.4±39.4 60 [10 – 180]	<0.001
Awakening hour in the morning (time)		7.5± 0.7 8 [6 – 9]	6.3±1.0 6 [3 – 8]	<0.001
Duration of night sleep(hours)		7.6±0.7 8 [6 – 9]	5.3±1.3 5 [2 – 8]	<0.001
Hematocrit (%)		30.4±4.6 29.5 [22 – 41]	30.5±4.1 29.7 [23.8 – 39]	0.853
Urea (mg/dL)		44.8±20.9 43 [8 – 132]	47.8±27.2 50 [3 – 148]	0.942
Creatinine (mg/dL)		1.02±0.36 0.98 [0.41 – 2.02]	0.95±0.52 0.86 [0.30 – 2.70]	0.147
Surgery type	Cardiovascular	30 (60)	31 (58.5)	1.000
	Abdominal	20 (40)	22 (41.5)	
Effective Sleep	Very good	29 (58)	1 (1.9)	**<0.001**
	Good	21 (42)	17 (32.1)	
	Bad	-	23 (43.4)	
	Very bad	-	12 (22.6)	

COPD, chronic obstructive pulmonary disease; Percentages in brackets

The postoperative sleep quality of patients who underwent surgery over five hours or more duration was worse but not statistically significant (p:0.053).

The effect of the presence of chronic obstructive pulmonary diseases (COPD) on sleep quality was also evaluated. It was determined that the presence of COPD had a negative effect on sleep quality (p:0,020). Thirteen of 16 COPD patients had impaired sleep quality (Table 3).

In this study, it was established that sleep quality was impaired in patients with chronic renal failure (p:0.041) and goiter (p:0.047).Contrary to expectations, sleep quality was better in patients with high school or higher education level (p:0,024) (Table 1) . Another finding was that people with good sleep had a shorter time to fall asleep. Individuals with poor sleep woke up earlier in the morning. People with good sleep took longer to actually sleep at night. Individuals with bad sleep had a higher rate of bad and very bad effective sleep. Individuals with good sleep had a higher rate of subjective and very good sleep.

Discussion

Patients underwent major abdominal surgery had better sleep quality, which made us think that cardiopulmonary bypass had a bad effect on sleep. This finding is supported by the Hedges et al.'s study comparing patients who underwent coronary bypass surgery in terms of cardiopulmonary bypass use, PSQI revealed that sleep quality was better in patients who underwent off-pump coronary bypass surgery. (4)

Many sleep studies have shown that sleep quality deteriorates as age increases due to the decreased REM duration (5). In this study, we did not find a good or bad effect of age on sleep quality (p: 0,530). This insignificance may be due to the younger cohort population of our study (6), which leads to the suggestion of new studies with a wider and older age range.

The presence of COPD significantly affects sleep quality. Thirteen of 16 postoperative patients with COPD in our study had poor sleep quality (p:0.020). In many large patient studies conducted by Douglas et al., they showed that patients with COPD, interstitial lung disease or asthma had significantly disturbed sleep, and they attributed this to lung diseases, concomitant obstructive sleep apnea syndrome, hypoxia and hypoventilation during sleep (5-7). Lung capacity, which is already limited may decrease further with the opening of the abdomen and thorax in the operations performed, with the contribution of pain and atelectasis, and the sleep quality deteriorates with the increase in hypoxia and night coughing.

Studies conducted in hemodialysis patients with chronic kidney disease and chronic kidney failure have shown that sleep quality is impaired due to the frequent occurrence of itching and restless legs syndrome (8-10). In a study conducted by Saeedi et al. on 82 hemodialysis patients, they showed that patients who were given a one-month sleep hygiene treatment had a better sleep quality when evaluated with the PSQI one month later (11). In sleep hygiene treatment, patients were told and taught what they should and should not do before going to sleep. Edalat et al., in their study on 115 hemodialysis patients, found that 85% of the patients had sleep disorders. In addition, they showed that the duration of hemodialysis, diabetes and age had no effect on sleep quality (12). Harris et al. attributed sleep disturbance to cytokines that cause pain in hemodialysis patients. In addition, Pai et al. attributed sleep disturbance in hemodialysis patients to a higher prevalence of depression and a higher prevalence of anemia (10). Han et al.'s study suggests that PSQI score can be used as a predictor of all-cause mortality in dialysis patients and the cutoff applied to predict mortality was higher than the traditional diagnostic point. This is the first study in which a new cutoff has been investigated and used to predict the relationship of SQ measured by PSQI and all-cause mortality (13).

Although, the relationship of hypertension with poor or good sleep quality in our study could not be shown, the study by Yuan et al. showed that poor sleep quality is a bad risk factor for early-onset hypertension in young and middle age (14). Concurrently, our findings in this study support abovementioned manuscripts as chronic renal disease and chronic renal failure significantly affect sleep quality (p:0,041). (Table 4)

We also aimed to investigate whether anesthetic substances have an effect on postoperative sleep quality. Hypnotic drugs used in induction were propofol, pentothal and midazolam. The ones used in the maintenance were sevoflurane and desflurane. The opioids used in maintenance were remifentanil and fentanyl. No statistically significant difference was found between any of these drugs on sleep quality. Contrarily in the literature; Wenk et al. found that patients who were administered fentanyl-based anesthesia slept better than patients who were administered remifentanil-based anesthesia, and showed that the sleep of patients who received remifentanil in the first three weeks postoperatively was disrupted and returned to normal in the next three weeks (15). The fact that we could not find a difference in our study may have been due to the shorter postoperative follow-up period.

Smoking is known to prolong the time it takes to fall asleep. It is known that smokers have shorter sleep times and, accordingly, worse subjective sleep quality, which leads to deterioration in daytime functions and lengthens the time to fall asleep (16). In our study, no sleep disturbance was found in patients who used alcohol and cigarettes; however, this might be due to the small number of patients and the lack of reporting.

Obesity is known to be a predisposing factor for COPD and sleep apnea syndrome. In the study of Hung et al., it was found that obesity and female gender increase sleep disorders (17). In our study, patients with a body mass index of 30 and above were considered obese, and the effect of obesity on sleep quality was

investigated. A total of 22 patients were considered obese, and 12 of these patients had good sleep quality and 10 had poor sleep. No significant difference was found between the two groups (p:0.693).

The effect of the length of the operation was also evaluated. Sleep quality was worse in surgeries of 5 hours or more (p:0,053). Although it is not statistically significant, the long duration of the operation impairs sleep quality due to the presence of perioperative complications, the size of the operation field and pain were the causes of this sleep disorder.

As a result, contrary to the few studies conducted, it is found that anesthetic agents had no effect on postoperative sleep quality in this cohort. When comorbid diseases were evaluated, it was found that the rate of sleep disturbance was higher in patients with chronic renal disease and failure, due to the frequency of itching and restless legs syndrome, pain rates and chronic anemia.

The presence of COPD impairs postoperative sleep quality, and the sleep quality of patients with preoperative and postoperative COPD can be improved with aggressive treatment and with devices that will keep the airway open at night in patients with sleep apnea syndrome. Only two of 103 patients included, requested medical and psychological help for sleep disorders.

Limitations:

This study was limited by the small sample size and lack of a control group. Postoperative short follow-up limited the observation of effects of surgery on sleep quality in the long term. This was a single-center experience; therefore, outcome interpretation is limited by institutional bias. Implications of this study need further investigation.

Conclusion

Sleep has a very important place in accelerating the recovery process of postoperative patients. Preoperative assessment for sleep disorders is crucial for better postoperative course. Sleep quality is very important both to prevent future diseases and to increase the quality of life, particularly in patients with chronic diseases.

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ORIGINAL ARTICLE

Evaluation of Subclinical Atherosclerosis in Patients with Psoriatic Arthritis

Psöriatik Artrit Tanılı Hastalarda Subklinik Aterosklerozun Değerlendirilmesi

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ABSTRACT

Background/Aims: Psoriatic arthritis (PsA) with peripheral and axial involvement; It is a heterogeneous disease that can cause enthesitis, dactylitis, and nail and skin involvement. The persistence of inflammation in psoriasis may lead to comorbidities such as PsA, cardiovascular disease and metabolic syndrome. Our study aimed to detect subclinical atherosclerosis and prevent possible morbidity and mortality in PsA patients with no known risk factors.
Methods: Fifty-eight patients were evaluated in our study, and 33 patients diagnosed with PsA who met the diagnostic and inclusion criteria constituted the study group. There are 25 healthy individuals of similar age in the control group. Age, gender, disease duration, medical treatment used for the disease, low-density lipoprotein, triglyceride, and total cholesterol levels monocyte-lymphocyte ratio and carotid intima-media thickness (CIMT) obtained from carotid ultrasonography were recorded. Hematological parameters and CIMT were statistically evaluated in the patient and control groups. In addition, correlation analysis was performed to evaluate CIMT, hematological parameters and disease duration. The relationship between PsA and atherosclerosis was evaluated.
Results: A comparison was made between the study and control groups regarding age, triglyceride, low-density lipoprotein, and monocyte-lymphocyte ratio, and no statistically significant difference was observed (p>0,05). Monocyte-lymphocyte ratio, monocyte and lymphocyte count were found to be high in the study group and there was a statistically significant difference (p<0.05). CIMT was higher in the study group and this difference was statistically significant (p<0.05).
Conclusion: Patients with PsA have an increased risk of atherosclerosis compared to the healthy population without any risk factors. CIMT measurements and serum hematological markers have been found useful in predicting this risk. This awareness will be useful in the follow-up of patients and in taking precautions against morbidities that may develop.

Keywords: Psoriatic arthritis, carotid intima-media thickness, subclinical atherosclerosis, ultrasonography

ÖZ

Amaç: Periferik ve aksiyel tutulumlu psöriatik artrit (PsA); entezit, daktilit, tırnak ve deri tutulumuna neden olabilen heterojen bir hastalıktır. Psöriazis de inflamasyonun devam etmesi, PsA, kardiyovasküler hastalık ve metabolik sendrom gibi komorbiditelere yol açabilir. Çalışmamızda bilinen bir risk faktörü olmayan PsA hastalarında subklinik aterosklerozu saptamak, olası morbidite ve mortaliteyi önlemek amaçlandı.
Gereç-Yöntem: Çalışmamızda elli sekiz hasta değerlendirilmiş olup tanı ve katılma kriterlerine uygun 33 PsA tanılı hasta çalışma grubunu oluşturmaktadır. Kontrol grubunda benzer yaşta 25 sağlıklı birey bulunmaktadır. Yaş, cinsiyet, hastalık süresi, hastalık için kullanılan medikal tedavi, düşük dansiteli lipoprotein, trigliserid ve total kolesterol değerleri, monosit-lenfosit oranı, karotis doppler ultrasonografi ile elde edilen karotis intima-media kalınlık (KIMK) ölçüm sonuçları kaydedildi. Hasta ve kontrol grubunda hematolojik parametreler ve KIMK istatistiksel olarak incelendi. Ayrıca KIMK ile hematolojik parametreler ve hastalık süresini değerlendirmede korelasyon analizi yapıldı. PsA ile ateroskleroz arasındaki ilişki istatistiksel olarak incelendi.
Bulgular: Çalışma ve kontrol grupları arasında yaş, trigliserit, düşük dansiteli lipoprotein ve monosit-lenfosit oranı açısından karşılaştırma yapıldı ve istatistiksel olarak anlamlı bir fark gözlenmedi (p>0,05). Monosit/lenfosit oranı, monosit ve lenfosit sayısı çalışma grubun da yüksek bulunmuş olup istatistiksel olarak anlamlı fark saptanmıştır (p<0,05). KIMK çalışma grubunda daha yüksekti ve bu fark istatistiksel olarak anlamlıydı (p<0.05).
Sonuç: PsA'li hastalar, herhangi bir risk faktörü olmayan sağlıklı popülasyona kıyasla artmış ateroskleroz riskine sahiptir. KIMK ölçümleri ve serum hematolojik belirteçleri bu riski ön görmede faydalı bulunmuştur. Bu farkındalık hastaların takibinde ve gelişebilecek morbiditelere karşı önlem alınmasında faydalı olacaktır.

Anahtar Kelimeler: Psöriatik artrit, karotis intima media kalınlığı, subklinik ateroskleroz, ultrasonografi

Introduction

Psoriatic arthritis (PsA) is a chronic autoinflammatory disease that can occur with various clinical phenotypes. It is most commonly seen in people with psoriasis disease. Among the spondyloarthropathies, it is the group that significantly affects the life of the patients and is significantly associated with cardiovascular mortality (1). As a result of increasing awareness and knowledge about the immunological mechanism, psoriasis is increasingly accepted as a disease with systemic effects, different from skin and joint involvement (2). It has been suggested that proinflammatory cytokines are effective in atherogenesis and peripheral insulin resistance. Results compiled from various retrospective and prospective cohort studies and imaging methods show that psoriasis and PsA are associated with increased cardiovascular risk (3,4). Coronary artery disease and ischemic cerebrovascular diseases remain the leading causes of death worldwide (5). It is important to detect subclinical atherosclerosis, which is involved in the common etiopathogenesis of

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these two diseases. Atherosclerosis is a multifactorial, chronic inflammatory disease that can affect all parts of the arterial system, characterized by the deterioration of blood supply to organs and limbs such as the heart, brain, and extremities as a result of the narrowing of the lumen of the progressive lesion involving the intima and media layers of the vascular wall (6).

Carotid intima-media thickness (CIMT) is used to detect early atherosclerosis in the demonstration of vascular pathologies that may occur in the future(7,8). Ultrasonographic findings of CIMT correlate with histological findings (9). Studies have also shown that increased CIMT is associated with pathologies such as myocardial infarction and ischemic stroke (10).

Hypercholesterolemia plays a significant role in the development of atherosclerosis. The impact of lipoproteins such as low-density lipoprotein (LDL) and VLDL in the formation of atherosclerosis has been demonstrated in numerous studies (11). It is indisputable that dyslipidemia is a significant risk factor for atherosclerosis. Additionally, in recent years, several studies have shown that inflammation, alongside dyslipidemia, also constitutes an important risk factor (12). There are many markers indicating inflammation. The proportional results of data obtained after blood cell counts provide us with information about inflammation. The effectiveness of the monocyte-to-lymphocyte ratio (MLR), previously obtained by the ratio of monocyte count to lymphocyte count, has been demonstrated in studies concerning the progression and severity of PsA in patients with psoriasis (13). Furthermore, the relationship between MLR and subclinical atherosclerosis has been highlighted in numerous studies (14,15).

This study aims to evaluate subclinical atherosclerosis in patients with psoriatic arthritis using ultrasonography and hematological parameters.

Material and Methods

Our study was approved by the relevant unit of our institution (decision no: 2023-05/03). After ethics committee approval, medical records were analyzed retrospectively between January 2020 and March 2023. Patients who applied to the rheumatology clinic of the university hospital between January 2022 and March 2023 and had a confirmed diagnosis of PsA according to the internationally accepted were included in the study. The data of 58 patients were examined retrospectively. Exclusion criteria were Diabetes Mellitus, Hypertension, Presence of Coronary Artery Disease, Hyperlipidemia diagnosis, body mass index above 30, and smoking. 33 patients diagnosed with PSA and meeting the criteria formed the study group. The control group comprised 25 healthy individuals of similar age and without any disease. An automatic blood counter (Beckman Coulter LH 780, USA) was used for the analysis of hematological parameters. The enzymatic colorimetric method (Roche Diagnostics, Mannheim, Germany) was used to measure LDL and triglyceride concentrations. In routine carotid ultrasonography (US) in our institution, CIMT is found by taking the average of 3 different measurements from the posterior wall, 1 cm distal to the common carotid artery bulb level (Figure 1).

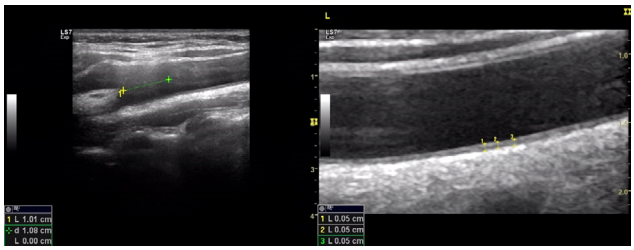

Figure 1. Measurement of common CIMT in carotid artery Doppler ultrasonography

The Laboratory and ultrasonographic findings of individuals in the patient and control groups were evaluated. Patients' age, gender, disease duration, medical treatment used for the disease, LDL, triglyceride levels, lymphocyte and monocyte count, MLR, and CIMT measurements were recorded.

Statistical analysis:

SPSS 22.0 was used for data analysis. Visual and analytical methods analyzed the normality of the variables. For quantitative data suitable for normal distribution, a t-test was performed on independent groups according to the number of groups. For quantitative data unsuitable for normal distribution, analyses were made using the Mann-Whitney U test according to the number of groups. The Spearman Correlation test was used to correlate the data in the patient group. The error level was taken as 0.05.

Results

Fifty-eight patients were evaluated in our study, and 33 patients diagnosed with psoriatic arthritis who met the diagnostic and inclusion criteria constitute the study group. There are 25 healthy individuals of similar age in the control group. Of the 33 patients in the study group, 15 were female, and 18 were male. Of those in the control group, 12 were female and 13 were male. The median age was 45 (32-55) in the study group and 40 (33-51 years) in the control group. There was no significant difference between the groups in terms of age (p:0.47) and gender (p:0.84) (p>0.05).

In the patient group, 14 people were using biologic agents (9 secukinumab, 1 ixekizumab, 1 tofacitinib, 1 adalimumab), 11 patients were using conventional synthetic DMARDs (9 methotrexate, 1 leflunomide), and 8 patients were using NSAIDs (Figure 2).

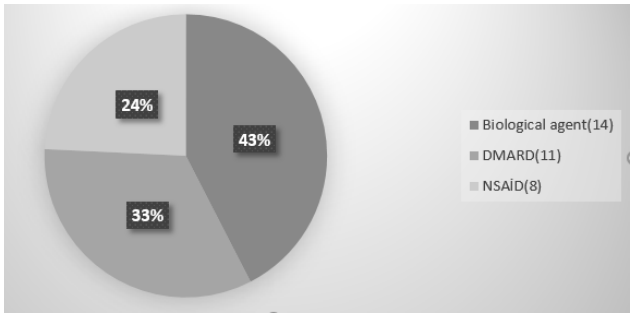

Figure 2. Drug use in the patient group

No significant difference was found when the study and control groups were compared in terms of LDL and triglyceride values (p>0.05). When the study and control groups were compared, CIMT, lymphocyte and monocyte counts were found statistically significant and high in the patient group (Table 1).

Table 1: Comparison of laboratory and imaging results of patient and control groups

	Patient Group	Control Group	P value
LDL count(mg/dl)[a]	119.42±34.84	112.12±22.44	0.36
Triglyceride count (mg/dl)[b]	103(52-178)	97(47-169)	0.41
Monocyte count (10^9/L)[a]	0.6±0.17	0.5±0.14	0.016*
Lymphocyte count (10^9/L)[b]	2.36(1.27-4.19)	1.77(1.48-2.86)	0.018*
MLR[a]	0.26±0.08	0.24±0.06	0.2
Right CIMT (mm)[b]	0.70(0.40-1)	0.43(0.30-0.53)	0.0001*
Left CIMT (mm)[b]	0.70(0.50-1)	0.43(0.27-0.53)	0.0001*

LDL: Low-density lipoprotein, MLR: Monocyte/lymphocyte ratio, CIMT: Carotid intima-media thickness

***p<0.05**: Statistically significant

[a]: Values are given as mean±standard deviation.

[b]: Values are given as median (min-max).

Spearmen correlation analysis was performed to evaluate the relationship between CIMT and disease duration. A positive correlation was found between right and left CIMT and disease duration, and the results were statistically significant (p<0.05)(Table 2).

Table 2: The relationship between CIMT and disease duration, lymphocyte, monocytes, and MLR

	MLR	Lymphocyte	Monocyte	Disease Duration
Right CIMT (mm)	r:0.08 p:0.53	r:0.11 p:0.39	r:0.12 p:0.35	r:0.454** p: 0.008*
Left CIMT (mm)	r:0.079 p:0.55	r:0.20 p:0.13	r:0.21 p:0.11	r:0.472** p:0.006*

CIMT: Carotid intima-media thickness, MLR: Monocyte/lymphocyte ratio

*p<0.05: Statistically significant

**r: Correlation coefficient

Discussion

In this study, subclinical atherosclerosis was investigated in patients diagnosed with PsA. CIMT was found to have increased in patients diagnosed with PsA. A positive correlation was found between CIMT and disease duration.

Psoriatic arthritis belongs to the spondyloarthritis group and exhibits a heterogeneous clinical presentation often associated with psoriasis. Patients with PsA may experience various comorbidities alongside skin and joint involvement. Particularly notable is the heightened risk of cardiovascular disease within this patient population (4).

Ultrasonographic measurement of CIMT is a non-invasive, reproducible, and sensitive test for detecting subclinical vascular disease and assessing cardiovascular risk factors (16). CIMT has been widely utilized in numerous studies to identify atherosclerosis presence in rheumatological diseases (17,18).

In a meta-analysis conducted by Bai et al., the presence of subclinical atherosclerosis in patients diagnosed with ankylosing spondylitis (AS) was investigated, and it was concluded that AS patients were at high risk. It was emphasized that these patients might require early evaluation and intervention (18). In a systematic review investigating the presence and prevalence of subclinical atherosclerosis in patients with PsA, it was concluded that CIMT was higher in patients with PsA compared to healthy controls. It was found that increased CIMT was correlated with disease activity parameters (19). In Eder et al.'s study, a positive correlation was found between inflammation intensity and disease duration. Compatible with this, our study found a positive significant correlation between CIMT and disease duration. These results also show the relationship between PsA and atherosclerosis (20).

Monocyte-to-lymphocyte ratio has been used in many studies and has been associated with many diseases (21-24). MLR is a marker that has been studied and shown to be important in malignancies (22), rheumatological (24), cardiovascular (21) and psychiatric (23) diseases. Dincer et al. found in their study in patients with PsA that MLR was high and it was associated with disease activity (24). In the study conducted by Si et al., MLR was stated as an independent risk factor for subclinical atherosclerosis and it was stated that it might be useful in the diagnosis of coronary artery disease (21). In our study, we investigated the effect of monocyte-to-lymphocyte ratio on the development of subclinical atherosclerosis in patients with PsA. When we compared the monocyte-to-lymphocyte ratio between the control group and the patient group, no significant difference was found. In addition, there was a low positive correlation with CIMT, but this correlation was not statistically significant. We think that this result is due to the relatively low clinical disease activity of the patients included in the study. We believe that there is a need for studies in which more patients are included, patients are classified according to disease activity, and additionally, different serum inflammation markers are used.

Conclusion

This study had some potential limitations. First of all, the study was single-center and conducted with a relatively small study population. The second limitation is that it was designed retrospectively. Finally, numerical differences between the patient and control groups emerged due to the study being conducted within a specific time frame. We believe that studies with long-term follow-up in a larger patient population are required.

As a result, it was found that subclinical atherosclerosis increased in patients with PsA who did not have a known cardiovascular risk factor, compared to the healthy population. Considering the relationship between atherosclerosis and the duration of diagnosis, as emphasized in our study, an awareness of cardiovascular problems is essential in the follow-up

of patients with PsA. To prevent possible morbidity and mortality in this patient group, necessary tests should be performed, prophylactic measures should be taken, diet and lifestyle changes should be explained, and a treatment plan should be made, if necessary, by consulting the relevant departments.

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Ethical approval: The ethics committee approval of the study was obtained from Sivas Cumhuriyet University Medical Faculty Hospital Clinical Research Ethics Committee with the number 2023-05/03.

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ORIGINAL ARTICLE

Resistance Rates of *Mycobacterium tuberculosis* Complex Isolates to First-line Anti-tuberculosis Drugs: A 5-Year Retrospective Study

Mycobacterium tuberculosis Kompleks İzolatlarının Birinci Basamak Anti-tüberküloz İlaçlara Direnç Oranları: 5 Yıllık Retrospektif Araştırma

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ABSTRACT

Background/Aim: Tuberculosis (TB) remains a major global health problem with a high morbidity and mortality rate, approximately a quarter of the population is infected with tuberculosis. Drug susceptibility testing is an essential tool to identify and manage drug-resistant tuberculosis. This study was conducted to evaluate the drug susceptibility pattern of Mycobacterium tuberculosis complex strains isolated from a university hospital.
Methods: A total of 10900 samples sent to the microbiology laboratory with the suspicion of tuberculosis clinically between January 2018 and January 2022 were analyzed retrospectively. The automated BACTEC MGIT 960 (Becton Dickinson, USA) was used for sample culture and susceptibility testing. The obtained data were statistically analyzed with the Statistical Package for Social Sciences (SPSS version 20).
Results: Out of the 154 isolated positive samples, males and females constituted equal parts of the study population (50%). The majority of tuberculosis cases were in the age group of 56–75 years (42.2%). Pulmonary tuberculosis was detected in 139 (90.3%) of the patients while extrapulmonary TB cases were observed in 15 (9.7%) patients. As a result of susceptibility studies on positive samples, isoniazid resistance was 5.2%; streptomycin resistance 1.3%; ethambutol resistance was detected at a rate of 0.6% while no rifampicin resistant sample was found. Both streptomycin and isoniazid resistance were seen together in 1.3% of the samples.
Conclusion: A similar resistance pattern of the first-line antituberculosis drugs was observed in other studies conducted in different provinces of Turkiye. The absence of multi-drug resistant and extensively drug-resistant tuberculosis in our study indicates that the tuberculosis surveillance program implemented in our region was successful.

Keywords: Mycobacterium tuberculosis complex, tuberculosis, anti-tuberculosis drug, drug susceptibility testing.

ÖZ

Giriş/Amaç: Tüberküloz, yüksek morbidite ve mortalite oranı ile önemli bir küresel sağlık sorunu olmaya devam etmektedir ve nüfusun yaklaşık dörtte biri tüberküloz ile enfektedir. İlaç duyarlılık testleri, ilaca dirençli tüberkülozu tanımlamak ve yönetmek için önemlidir. Bu çalışmada, bir üniversite hastanesinden izole edilen Mycobacterium tuberculosis kompleks suşlarının ilaca duyarlılık paterninin değerlendirilmesi amaçlanmıştır.
Yöntemler: Ocak 2018-Ocak 2022 tarihleri arasında tüberküloz şüphesi ile mikrobiyoloji laboratuvarına gönderilen toplam 10900 örnek retrospektif olarak incelenmiştir. Örneklerin kültürü ve duyarlılık testleri için BACTEC MGIT 960 (Becton Dickinson, ABD) otomatize sistem kullanılmıştır. Elde edilen veriler Statistical Package for Social Sciences (SPSS version 20) ile istatistiksel olarak analiz edilmiştir.
Bulgular: Pozitif olarak bulunan 154 hastada erkek ve kadın oranı eşit olarak bulunmuştur. Tüberküloz olgularının çoğunluğu 56-75 yaş grubunda (%42,2) olup, hastaların %90,3'ünde akciğer tüberkülozu saptanırken, %9,7 oranında akciğer dışı tüberküloz tespit edilmiştir. Pozitif örneklerde yapılan duyarlılık çalışmaları sonucunda izoniazid direnci %5,2; streptomisin direnci %1,3; etambutol direnci %0,6 oranında tespit edilirken, rifampisin dirençli örnek bulunmamıştır. Örneklerin %1,3'ünde hem streptomisin hem de izoniazid direnci birlikte görülmüştür.
Sonuç: Türkiye'de farklı illerde yapılan diğer çalışmalarda birinci basamak antitüberküloz ilaçlarda benzer direnç paterni gözlenmiştir. Çalışmamızda çok ilaca dirençli tüberküloz ve yaygın ilaca dirençli tüberküloz suşlarının bulunmaması, bölgemizde uygulanan tüberküloz gözetleme programının başarılı olduğunu göstermektedir.

Anahtar Kelimeler: Mycobacterium tuberculosis kompleksi, tüberküloz, anti-tüberküloz ilaç, ilaç duyarlılık testi.

Introduction

Tuberculosis (TB) is a communicable disease caused by Mycobacterium tuberculosis complex, an organism that spreads slowly and broadly in the lungs creating hard nodules with the possibility of infecting other organs in the body (1). TB has affected humans for over 5000 years (2) and continued to be among the top ten causes of death due to an individual infectious agent until the COVID-19 pandemic (3). The latest World Health Organization (WHO) 2022 Global TB report estimates an incidence rate of 10.6 million new TB cases and 1.6 million deaths globally (4). In 2020, the incidence of tuberculosis in Turkiye was 15 cases per 100,000 people. Statistics provided by the WHO and the European Centre for Disease Prevention and Control (CDC), show that the rate of tuberculosis cases in Turkiye has witnessed a gradual decline, with a mean

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annual change (-4.5%) between 2016–2020 (5).

The disease is transmitted through the inhalation of infected aerosols. TB bacilli have a unique ability to survive intracellularly. After being taken up by alveolar macrophages, which in most cases kill the entering bacteria, some may avoid being killing and remain inactive for a long period of time until the development of a favorable environment. The critical point in TB treatment is the completion of the treatment within the expected period which is at least six months (6). Two groups of drugs are used. First-line drugs e.g. (isoniazid, rifampicin, pyrazinamide, and streptomycin), most effective and least toxic for use in the treatment of TB, while the second-line therapeutic drugs, less effective, more expensive and have higher toxicities and more difficult to tolerate, e.g. (rifabutin, cycloserine, amikacin, capreomycin, para-aminosalicylic acid, levofloxacin and gatifloxacin) are the drugs available (7). A 4–6-month uptake of anti-TB drug can successfully treat 85% of patients with TB (4). Shortly after the implementation of streptomycin in clinical use, drug resistance to anti-TB drugs developed (3).

The emergence of drug-resistant Mycobacterium tuberculosis strains is one of the major public health problems of this century (8). Multidrug-resistant TB (MDR-TB) is the condition in which M. tuberculosis develops resistance to the first-line anti-TB drugs, isoniazid, and rifampicin, simultaneously whereas extensively drug-resistant TB (XDR-TB) is identified as resistant to secondary anti-TB injectable drugs and fluoroquinolones in addition to MDR-TB (9). In 2020 the nationwide incidence of multidrug-resistant/ rifampicin-resistant tuberculosis (MDR/RR-TB) was 3.3% in new cases and 18% in formerly treated cases (1). According to the instruction of the American Thoracic Society and the CDC, drug susceptibility testing must be done for at least the first-line anti-TB drugs in all older and new TB cases to guarantee the proper treatment for patients and to hinder the development of anti-TB drugs resistance (10). Drug susceptibility testing is critical for recognizing and managing drug-resistant TB (11). This study was intended to assess the drug susceptibility pattern of Mycobacterium tuberculosis complex strains isolated from the university hospital in Konya, Turkiye through 5 years of results.

Material And Methods

Study design

This laboratory-based descriptive retrospective study was conducted at a university hospital in Turkiye, and approved by the Ethics Committee of the Necmettin Erbakan University (Decision no. 2023/4443). The study was carried out using presumptive TB patient records who were referred to different health centers between January 2018 and January 2022. Epidemiological, clinical, and laboratory data were collected from the lab database and registration books. Over the five years, a total of 10900 samples were received for culture for Mycobacteria, patients with positive automated culture results at any age were selected. Any repeated samples for confirmation or follow-up were not included in the study. Culture and susceptibility to anti-TB drugs results of isolated Mycobacterium tuberculosis complex were reviewed.

Microbiological methods

All procedures in the laboratory were carried out in Class II biosafety cabins using the required personal protective equipment. Sterile samples such as pleural fluid and cerebrospinal fluid which were obtained with aseptic techniques, were handled without being decontaminated; whereas other samples such as sputum, bronchoalveolar lavage (BAL), and abscess were examined after homogenization and decontamination with N-acetyl-L-cysteine and sodium hydroxide (10). The material obtained after the preliminary preparation was inoculated on BACTEC MGIT 960 TB automated system (Becton Dickinson, USA) and Löwenstein-Jensen (LJ) medium according to the recommendations of the manufacturer. The Ehrlich-Ziehl-Neelsen (EZN) staining method was used for acid-fast bacilli (AFB) detection in direct smear preparations (12). Cultures were left for incubation for up to 42 days (10). Drug susceptibility testing was achieved by BACTEC MGIT 960 following the manufacturer's procedures (13). Reference strain H37RV (ATCC 27294) was used as a quality control of culture and drug susceptibility test, and the strain was sensitive to all standard anti-TB drugs (10).

Statistical analysis

The obtained data were statistically analyzed by The Statistical Package for Social Sciences (SPSS version 20). Continuous variables were described as mean ± Standard deviation (SD) while descriptive statistics were used to calculate the frequency and percentage of age categories, gender, organism isolated, sensitivity and resistance.

Results

The number of male and female patients was equal in 154 positive samples (77 males, 77 females). The mean ± standard deviation of the participant age was 57.87± 20.872 (range 1 year to 93 years). The majority of TB cases were in the age group 56–75 years (42.2%), whereas the lowest TB cases were at the age of ≤ 15 years (2.6%), followed by 16–35 years (15.6%), ≥ 76 years (19.4%), and 36–55 years (20.1%) as illustrated in figure 1. The obtained clinical samples were distributed as the following: Sputum 94 (61%), bronchoalveolar fluid 44 (28.6%), pleural effusion 5 (3.2%), body fluids 4 (2.6%), biopsy 2 (1.3), gastric juice, drainage fluid, cerebrospinal fluid, urine and abscess 1 (0.6%). Pulmonary TB was detected in 139 (90.3%) of the patients, while extrapulmonary TB cases were observed in 15 (9.7%) as shown in Table 1.

Of the total isolated strain 101 (65.6%) samples were detected positive using EZN staining method and 111 (72%) samples were evaluated positive by growing on the LJ medium. As Table 2 demonstrates, the susceptibility pattern against first-line anti-tuberculosis drugs, 145 (94.1%) of the isolated strains were sensitive to all tested drugs. Only isoniazid resistance was detected in 6 samples, both isoniazid and streptomycin

resistance in 2 samples, and ethambutol resistance in one sample. Among the first-line antituberculosis drugs, the highest resistance was isoniazid with 5.2%, followed by streptomycin resistance with 1.3% and ethambutol resistance with 0.6%. (Table 2). Neither rifampicin resistance nor multidrug resistance has been observed in this study.

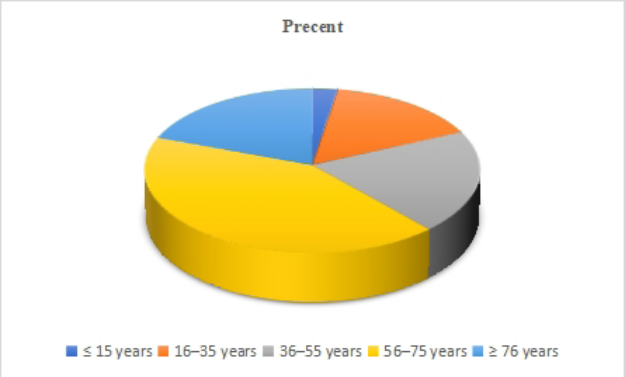

Fig 1: The distribution of tuberculosis-positive patients by age

Table 1: Distribution of *Mycobacterium tuberculosis* isolated strains according to clinical samples

	n (%)
Pulmonary TB	139(90.3)
Sputum	94(61)
Bronchoalveolar fluid	44(28.6)
Gastric juice	1(0.6)
Extrapulmonary TB	15(9.7)
Pleural effusion	5(3.2)
Biopsy	2(1.3)
Drainage	1(0.6)
CSF	1(0.6)
Body Fluids	4(2.6)
Urine	1(0.6)
Abscess	1(0.6)
Total	154(100)

Table 2: The susceptibility pattern of *Mycobacterium tuberculosis* complex isolates to first-line anti-tuberculosis drugs by years

	2018	2019	2020	2021	2022	Total
Characteristics	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Tested isolate	41 (100)	19 (100)	28 (100)	26 (100)	40 (100)	154 (100)
Sensitive to anti-TB drugs	38 (92.6)	14 (73.7)	28 (100)	23 (88.5)	40 (100)	146 (94.8)
Resistance to any drug	3 (7.3)	5 (26.3)	0 (0)	3 (11.5)	0 (0)	8 (5.2)
Streptomycin	0 (0)	2 (10.5)	0 (0)	0 (0)	0 (0)	2 (1.3)
Isoniazid	3 (7.3)	3 (15.8)	0 (0)	2 (7.7)	0 (0)	8 (5.2)
Rifampicin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethambutol	0 (0)	0 (0)	0 (0)	1 (3.8)	0 (0)	1 (0.6)
Single drug Resistant						
Streptomycin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Isoniazid	3 (7.3)	1 (2.4)	0 (0)	2 (7.7)	0 (0)	6 (3.9)
Rifampicin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethambutol	0 (0)	0 (0)	0 (0)	1 (3.8)	0 (0)	1 (0.6)
Poly Resistant						
Streptomycin and Isoniazid	0 (0)	2 (10.5)	0 (0)	0 (0)	0 (0)	2 (1.3)
Multidrug-Resistant						
Isoniazid and Rifampicin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Discussion

Mycobacterium tuberculosis complex is a group of diverse bacteria species that cause TB, a serious chronic infection recognized by the high rate of morbidity and mortality (14,15). Globally, around 25% of the population is infected with TB (16), with an annual death rate of 1.6 million people in 2021 according to WHO reports (4). TB mortality has surpassed that of acquired immunodeficiency syndrome (AIDS), making Mycobacterium tuberculosis the leading infectious agent that threatens human well-being (16). TB control strategies have been massively hindered by the emergence and transmission of antituberculosis-resistant strains, specifically rifampicin-resistant and MDR-TB isolates despite the striking declines in the prevalence of TB in recent years (17). The estimated annual incidence of RR-TB in new cases was 3.4% (18). Performing drug susceptibility testing not only assists to identify MDR-TB/ RR-TB but also provides a solid base for clinicians to prescribe the appropriate regimens (19). Our study was conducted to evaluate the antimicrobial susceptibility patterns of Mycobacterium tuberculosis complex strains over the past five years.

This study revealed an equal prevalence of TB among males and females (50%) which is consistent with studies conducted in central Ethiopia and Pakistan (13,20). This can be explained by the equivalent involvement of both genders in the community and the exposure to the same environment. However the ratio differs from the results obtained by Quezel-Guerraz et al and Al-Shahrani et al (21,22), stating that TB has a higher incidence in men due to greater exposure to the surrounding, alcohol-abusing and other factors that may constitute a risk to acquire the bacterium. Despite many studies in the literature have reported that tuberculosis is common among young people (22–25), in our study the vast majority of TB cases were in the age group 56–75 years (42.2%), With aging, many elements can play a crucial role in acquiring TB such as suppressed immune system due to drugs or other conditions, higher tendency to respiratory diseases, and activation of latent TB infection. The most frequent clinical manifestation of TB infections was pulmonary TB 139 (90.3%) while extrapulmonary cases were only 15 (9.7%), in accordance with many previous literature (12,13,25–27). Since the primary location of the bacteria is the lungs, extrapulmonary involvement is expected to be low. In addition, the atypical course of extra-pulmonary infections makes it more difficult to diagnose, which may be one of the reasons for the low rates. In our study, 65.6% of the samples detected positive by automated culture were found positive by EZN staining method. EZN staining positivity rate was which is in line with studies done by Behcet et al and Balcı et al (12,26). Although direct microscopy examination is broadly used in TB diagnosis, the sensitivity varies according to numerous factors such as the density of bacilli in the sample, decontamination procedures and the examiner experience.

Regarding antimicrobial resistance, 5.2% of

Mycobacterium tuberculosis complex isolates were resistant to at least one of the tested antituberculosis drugs. This rate is lower to some extent than the registered frequencies in Turkiye (26–28). This disparity can be due to the difference in the geographical region of the country, population, and sample size. In studies conducted in Turkiye in recent years, the resistance rates have been reported as 3.2-9.4% for isoniazid, 1.8-10.3% for streptomycin, 0-3.6% for ethambutol and 0-1.8% in the range for rifampicin 10,26–29%, which are comparable with the findings in our study where the detected resistance against isoniazid, streptomycin, and ethambutol, was 5.2%, 1.3%, and 0.6% respectively, and no resistance was observed against rifampicin. Among the tested drugs, isolated strains displayed high resistance against isoniazid, followed by streptomycin, and poly resistance of both drugs (1.3%) was also observed. The wide resistance of these regimens was attributed to their extensive implication in prophylaxis and treatment. Moreover, streptomycin is used in the treatment of conditions other than TB. The absence of rifampicin resistance is contradictory to a study conducted in the same province (30), the disparity can be explained by the difference in the sensitivity of the automated system used at the time of the study. Supported by the study conducted in Eastern Anatolia (27), no MDR was also observed in our study which can be accredited to the successful TB control strategies or low rifampicin resistance rate despite the high isoniazid resistance.

Conclusion

Despite the similar resistance pattern of the first-line antituberculosis drugs to other studies performed in different provinces in Turkiye, lower resistance against TB regimens was observed in our study. In addition to the absence of RR-TB and MDR strains, the finding is a good suggestion for the effective TB surveillance program in Konya province. Stating the fact that the study finding is based on a single-center experience, hence, more studies are required to reflect the real situation in the province.

Ethical aspects of the research: This laboratory-based descriptive retrospective study was conducted at a university hospital in Turkiye, and approved by the Ethics Committee of the Necmettin Erbakan University (Decision no. 2023/4443).

Author contributions: Assoc. Prof. Fatma Esenkaya Taşbent: Generating ideas for the article, supervising, taking responsibility for executing the project, and intellectually examining the study content before submission. Doc. Stud. Sondos A. A. Ibnouf: Data Collection, Processing, and Reporting, Logical interpretation and presentation of findings, conducting the literature review, and writing the article.

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ORIGINAL ARTICLE

Degenerated (Ancient) Schwannomas: Unraveling Unusual Locations and Treatment Management

Dejenere (Eski) Schwannomlar: Olağandışı Yerleşimlerin Çözülmesi ve Tedavi Yönetimi

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ABSTRACT

Introduction: Schwannomas, originating from Schwann cells in peripheral nerve sheaths, exhibit diverse clinical manifestations and unpredictable behavior. Among them, ancient schwannomas, with distinctive degenerative features, present in atypical locations and pose diagnostic challenges. This study explores their unique characteristics and implications for diagnosis and management.
Material and Methods: The study was designed as a retrospective analysis of 7 adult patients aged ≥18 years diagnosed with paraspinal, presacral, sacral, or para-aortic tumors, and all histologically confirmed as ancient schwannomas. Data for analysis were collected from patients treated and followed up at Ankara City Hospital between April 2017 and December 2022. Ethical approval and informed consent were obtained before inclusion in the study.
Results: The most common symptoms included the presence of a local lump (71,4%) and localized or radiating pain (57,1%). Notably, one patient (14,2%) was incidentally diagnosed during the evaluation process. Surgical intervention played a crucial role in the management of these tumors, with 71,4% of patients underwent complete resection while 28,5% underwent subtotal resection. Tumor recurrence occurred in 42,8% of cases, prompting the administration of radiotherapy as part of the treatment strategy. Imaging findings, particularly on MRI, played a crucial role in the accurate identification of ancient schwannomas. These tumors displayed isointensity on T1-weighted images and heterogeneous hyperintensity on T2-weighted images, along with distinctive heterogeneous contrast enhancement.
Conclusion: Ancient schwannomas exhibit unique histological features and distinctive MRI characteristics, differentiating them from other nerve sheath tumors. Early diagnosis and complete surgical resection offer favorable outcomes. Awareness of this entity is essential for managing peripheral nerve sheath tumors effectively.

Keywords: Schwannoma, Ancient, Benign tumor, neural tumors, Schwann cells.

ÖZ

Giriş: Periferik sinir kılıflarındaki Schwann hücrelerinden kaynaklanan Schwannomlar, çeşitli klinik belirtiler ve öngörülemeyen davranışlar sergilerler. Bunlar arasında, belirgin dejeneratif özelliklere sahip olan eski schwannomlar atipik lokasyonlarda bulunur ve tanısal zorluklar oluşturur. Bu çalışma, bunların benzersiz özelliklerini ve tanı ve yönetim için etkilerini araştırmaktadır.
Gereç ve Yöntemler: Çalışma, paraspinal, presakral, sakral veya para-aortik tümör tanısı konan ve histolojik olarak antik schwannom olduğu doğrulanan ≥18 yaşındaki 7 yetişkin hastanın retrospektif analizi olarak tasarlanmıştır. Analiz için veriler, Nisan 2017 ile Aralık 2022 tarihleri arasında Ankara Şehir Hastanesinde tedavi ve takip edilen hastalardan toplanmıştır. Çalışmaya dahil edilmeden önce etik onay ve bilgilendirilmiş onam alınmıştır.
Bulgular: En sık görülen semptomlar lokal bir kitlenin varlığı (%71,4) ve lokalize veya yayılan ağrı (%57,1) idi. Özellikle, 1 hastaya (%14,2) değerlendirme sürecinde tesadüfen tanı konuldu. Cerrahi müdahale bu tümörlerin yönetiminde önemli bir rol oynamış, hastaların %71,4'üne tam rezeksiyon, %28,5'ine ise subtotal rezeksiyon uygulanmıştır. Vakaların %42,8'inde tümör nüksü meydana gelmiş ve bu da tedavi stratejisinin bir parçası olarak radyoterapi uygulanmasını gerektirmiştir. Görüntüleme bulguları, özellikle de MRG, eski schwannomların doğru tanımlanmasında çok önemli bir rol oynamıştır. Bu tümörler T1 ağırlıklı görüntülerde izointensite ve T2 ağırlıklı görüntülerde heterojen hiperintensite ve belirgin heterojen kontrast artışı göstermiştir.
Sonuç: Antik schwannomlar benzersiz histolojik özellikler ve ayırt edici MRG özellikleri sergileyerek diğer sinir kılıfı tümörlerinden ayrılırlar. Erken tanı ve tam cerrahi rezeksiyon olumlu sonuçlar sağlamaktadır. Bu antitenin farkında olmak, periferik sinir kılıfı tümörlerini etkili bir şekilde yönetmek için gereklidir.

Anahtar Kelimeler: Schwannoma, Antik, Benign tümör, nöral tümörler, Schwann hücreleri.

Introduction

Schwannomas, benign nerve sheath tumors arising from Schwann cells, have long intrigued medical researchers and clinicians with their diverse clinical manifestations and unpredictable behavior (1). Among the intriguing subsets of these tumors are the degenerated (ancient) Schwannomas, which exhibit distinctive histopathological characteristics, and they are found in atypical locations within the body (2). This article delves into the enigmatic world of degenerated Schwannomas, shedding light on their unique features, unusual occurrences, and the implications these atypical presentations hold for diagnosis, treatment and patient

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care. Conventional Schwannomas, though generally benign, can still cause significant morbidity due to their location and compressive effects on surrounding structures (3). However, degenerated Schwannomas present an additional layer of complexity, as their histological alterations give rise to a fascinating set of challenges for clinicians and pathologists alike (4). While much research has been conducted on typical Schwannomas, there remains a knowledge gap concerning the less common degenerated variants.

Typically, these tumors are most commonly observed between the ages of 20 and 50 and present with clinical features that include the presence of a palpable mass, reduced nerve function, and localized pain (5). While Schwannomas can develop from any central or peripheral nerve within the body, they are notably absent in the olfactory and optic nerves (5). Among the regions with the highest prevalence of Schwannomas are the head, neck, mediastinum, retroperitoneum and the inner surface of the extremities. Interestingly, the vestibulocochlear nerve (CN VIII) stands out as the most frequent cranial nerve from which these tumors originate.

In clinical practice, both computed tomography (CT) and magnetic resonance imaging (MRI) have demonstrated their value by providing information about potential malignant attributes, the existence of local or distant metastases and any neural entanglement. However, there is no distinctive imaging trait specific to Schwannomas, making it essential to rely on histopathological analysis for an unequivocal diagnosis. On a macroscopic level, Schwannomas are identifiable by their flesh-colored appearance and well-defined masses or large cysts enclosed by a collagenous capsule (4). Prominent histopathological characteristics encompass the presence of Verocay bodies, hyalinized vessels, and variable zones exhibiting Antoni A (densely packed spindle fibers) and Antoni B (less dense, microcystic, hypocellular regions containing macrophages and collagen) (1). Immunohistochemical analysis usually demonstrates widespread, robust expression of pericellular type IV collagen and S-100 protein (1,4).

As the understanding of Schwannomas continues to evolve, their association with neurocutaneous syndromes and the role of NF2 tumor suppressor gene suppression are subjects of ongoing research. Moreover, the intricate interplay between clinical features, imaging findings and histopathological insights holds paramount importance in facilitating accurate diagnosis and guiding optimal treatment strategies.

Throughout this article, we will explore the distinct morphological changes seen in degenerated Schwannomas, which set them apart from their conventional counterparts. Ancient schwannoma, a rare subtype of schwannoma, displays a distinctive histological profile featuring hemorrhage, nuclear hyperchromatism, calcification, cystic degeneration pleomorphism and myxoid stroma (2). The presence of these atypical characteristics can create diagnostic challenges, potentially leading to misdiagnosis as a malignant tumor. Understanding the unique attributes of ancient schwannomas is crucial for accurate identification and appropriate management of this benign but diagnostically deceptive neoplasm. Additionally, we will investigate the intriguing phenomenon of degenerated Schwannomas occurring in atypical locations within the body. This unusual propensity for localization raises important questions about the underlying pathogenesis and may have crucial implications for their clinical management.

In the following pages, we will explore the intricacies of degenerated Schwannomas, presenting a comprehensive analysis of their histopathological features, clinical manifestations, diagnostic challenges and therapeutic options. It is expected that this article will not only pique the interest of researchers and clinicians but also offer valuable insights that will shape the future management of these captivating tumors.

Materıal and Methods

Study Design and Patient Selection:

This retrospective study was conducted at tertiary education and research hospitals to investigate prognostic factors, patient characteristics and outcomes of ancient schwannomas in adult patients aged ≥18 years. The study focused on 7 individuals diagnosed with paraspinal, presacral, sacral or para-aortic tumors. All cases were histologically proven to be ancient schwannomas. The data for analysis were collected from patients treated and followed up at Ankara City Hospital and Erol Olçok Training and Research Hospital between April 2017 and December 2022. Ethical approval was obtained from the Institutional Review Board, and written informed consent was obtained from each patient before inclusion in the study.

Data Collection and Preoperative Assessment:

All patients underwent computed tomography (CT) and/or magnetic resonance imaging (MRI) with contrast enhancement scans both prior to and following their surgical procedures. Individuals under the age of 18 and those with a diagnosis of conventional Schwannomas were not included in the study. Prior to surgery, comprehensive preoperative blood tests, extensive neurological assessments, and cranial imaging were routinely conducted to identify any preoperative symptoms. The primary symptoms evaluated included visual abnormalities, cranial nerve dysfunction, instability in gait, motor deficiencies, cognitive impairments, sensory disruptions, and the most commonly reported symptom, localized pain.

Treatment Approach:

Every patient underwent a maximal safe extended surgical resection, and radiotherapy was integrated into the treatment protocol. A minimally invasive approach was employed as an operative technique

to achieve maximal tumor removal. The primary focus was on preserving root function during the resection of intraspinal tumor extensions, with emphasis on utilizing intraoperative neurophysiologic monitoring. For intraspinal extensions spanning up to 3 spinal levels, a unilateral hemilaminectomy technique was utilized. This involved retaining paravertebral muscles on the tumor side to access the hemilaminae, which were then removed using a high-speed pneumatic drill to expose the dural sac.

In cases of paraspinal tumors, often dorsolaterally positioned due to their origin from the dorsal root, a posterior or posterolateral approach was employed. Resection of dumbbell tumors presented additional challenges, necessitating a combination of techniques such as multilevel laminectomy, costotransversectomy and anterior exposure involving neck dissection, thoracotomy, or retroperitoneal exposure.

Ensuring a watertight closure, the dura mater was sutured with 4–0 wire, and additional reinforcement was provided using fibrin glue and epidurally applied fat. In instances requiring laminectomy, a bilateral muscle dissection was performed, followed by removal of laminae to expose and open the dural sac for tumor removal under the operating microscope. Notably, spinal instability did not necessitate instrumentation in any of the cases.

The surgical procedures were categorized into four groups as follows: 1) complete resection, involving the removal of over 95% of the tumor; 2) subtotal resection, characterized by the removal of tumor mass ranging from >50% to <95%; 3) partial resection, indicating the surgical extraction of less than 50% of the tumor; and 4) biopsy. The date of the surgery was regarded as the point of diagnosis.

Statistical Analysis:

Data analysis was performed using IBM SPSS 25.0 (Armonk, NY: IBM Corp.) and MedCalc 15.8 (MedCalc Software bvba, Ostend, Belgium) statistical package programs. Descriptive statistical methods including frequency, percentage, mean, standard deviation, median, and min-max values were utilized to compare qualitative data.

Results

Between 2017 and 2022, a total of 7 adult patients underwent surgical intervention for tumors located in different regions: 2 patients had lumbar paraspinal tumors, 1 had cervical paraspinal tumor, 1 had thoracic paraspinal tumor, 1 had presacral tumor, 1 had sacral tumor, and 1 had para-aortic tumor. The mean age at the time of surgery was 50,1±9 years, and 3 of the patients (42,8%) were male. Among the presenting symptoms, 5 patients (71,4%) experienced a local lump, 4 patients (57,1%) reported localized or radiating pain, 2 patients (28,5%) presented with urinary disturbances, and 3 patients (42,8%) reported tingling sensations. Notably, 1 patient (14,2%) was incidentally diagnosed during the evaluation process (Table 1).

The average maximum diameter of the tumors was measured at 7,4 ± 2,2 cm. In fact, intramuscular schwannomas were frequently associated with the presence of entering and exiting nerves, whereas such nerve involvement was not observed in cases of ancient schwannomas.

Among the patients, 5 (71,4%) underwent complete resection while 2 patients (28,5%) underwent subtotal resection. Following the initial surgeries, 3 patients (42,8%) experienced tumor recurrence, prompting the administration of radiotherapy as part of the treatment strategy (Table 1).

Table 1: Patient characteristics, radiologic findings and pathologic anomalies

Patients	Age	Sex	Localisation	Preop Symptoms	Surgical Resection	MRI Findings	Diameter (cm)	Pathologic findings	Outcome	Complications
1	55	F	Lumbal Paraspinal	Lump, Pain, Tingling sensation	Complete	Split Fat sign, denervation change	11,2	cystic degeneration, fibrosis, lobulation	Cure	None
2	44	F	Lumbal Paraspinal	Lump, Tingling sensation	Complete	Split Fat sign, denervation change	6,5	fibrosis, stromal edema, pleomorphism	Cure	None
3	34	F	Sacral	Lump, urinary disturbances	Complete	Split Fat sign, denervation change	5,4	xanthomatous change, perivascular hyalinization, hyperchromasia	Recurrence, RX	None
4	48	M	Cervical paraspinal	Pain, lump, Tingling sensation	Complete	Split Fat sign, denervation change	8,7	cystic degeneration, fibrosis, perivascular hyalinization, hyperchromasia	Cure	None
5	56	M	Thoracal Paraspinal	Pain, Lump	Complete	Split Fat sign, denervation change	9,1	xanthomatous change, stromal edema, pleomorphism	Cure	None
6	61	M	Pre-sacral	Pain, urinary retention	Subtotal	Split Fat sign, denervation change	6,7	cystic degeneration, fibrosis, lobulation, pleomorphism	Recurrence, RX	None
7	53	F	Para-aortic	Incidentally	Subtotal	Split Fat sign, denervation change	4,7	cystic degeneration, fibrosis, lobulation, pleomorphism	Recurrence, RX	None

M:Male, F:Female, MRI: Magnetic Resonance Imaging, Rx: radiotherapy

Upon examination of MRI findings, all patients exhibited the split fat sign and denervation changes. Ancient schwannomas appeared isointense on T1-weighted images and displayed heterogeneous hyperintensity on T2-weighted images (Figure 1). Furthermore, these tumors exhibited distinctive heterogeneous contrast enhancement, which aided in their differentiation from other lesions (Figure 2). The "split fat sign" refers to the characteristic appearance of an area of fatty tissue being split or displaced by an adjacent mass or tumor (6,7). This sign is often seen in certain soft tissue masses, particularly nerve sheath tumors like schwannomas, where the mass disrupts the normal distribution of fat, resulting in a visible separation or splitting of the fatty tissue. The split fat sign can be helpful in distinguishing certain benign tumors, like schwannomas, from other soft tissue lesions during radiological evaluation (6).

Ancient schwannomas are recognized for their unique degenerative traits, which encompass cystic alterations, fibrosis, stromal edema, xanthomatous transformations and perivascular hyalinization (6) (Figure 3). These modifications are ascribed to the extended growth of the tumor, resulting in vascular insufficiency, that is why they are referred to as "ancient." Despite these changes, ancient schwannomas demonstrate a behavior akin to typical schwannomas. Under microscopic examination, they display regions of cellular density intertwined with a myxoid matrix. However, these cellular areas tend to become sclerotic or fibrotic and may experience degenerative transformations over time, potentially leading to the formation of hematomas and cysts (6,7). The absence of mitoses, cohesive clusters of spindle-shaped cells, and positive immunostaining with S100 help differentiate ancient schwannomas from malignancies (8). Surgical excision is essential for establishing a definitive diagnosis and achieving cure, with complete resection preserving surrounding structures whenever possible. Symptoms of compression such as pain and numbness are common presentations necessitating surgical intervention for these benign tumors.

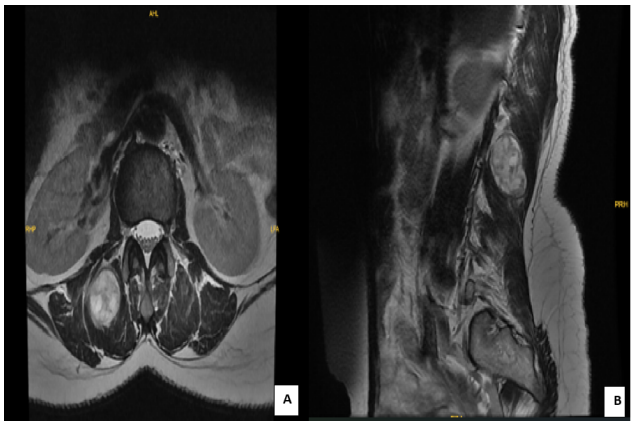

Figure 1: 55-year-old female patient who presented with axial lumbalgia and lump, tingling sensation diagnosed with paraspinal intramuscular mass, non-contrast lumbar MRI was performed. T2 weight MRI showed an encapsulated mass in the right paravertebral muscle. A) axial section, B) sagittal section.

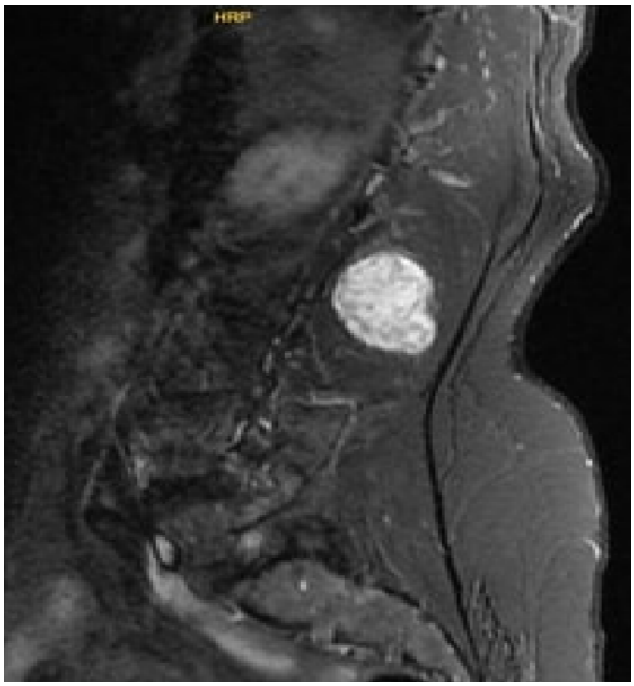

Figure 2: Contrast lumbar MRI was performed on the same patient. It showed well-circumscribed spherical tumor with homogeneous contrast enhancement.

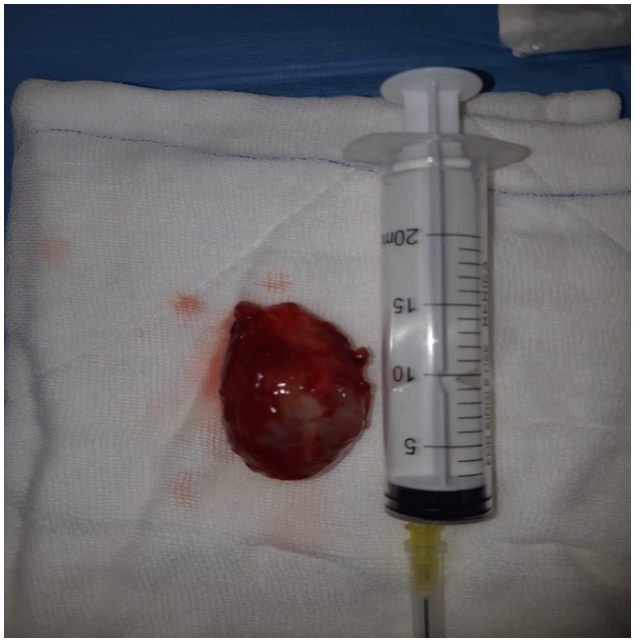

Figure 3: Gross pathological examination of thoracal paraspinal tumour, the 9,1 cm mass revealed a cystic, flesh-tan, focal hemorrhagic and mottled solid mass with yellow, viscous fluid compatible with schwannoma.

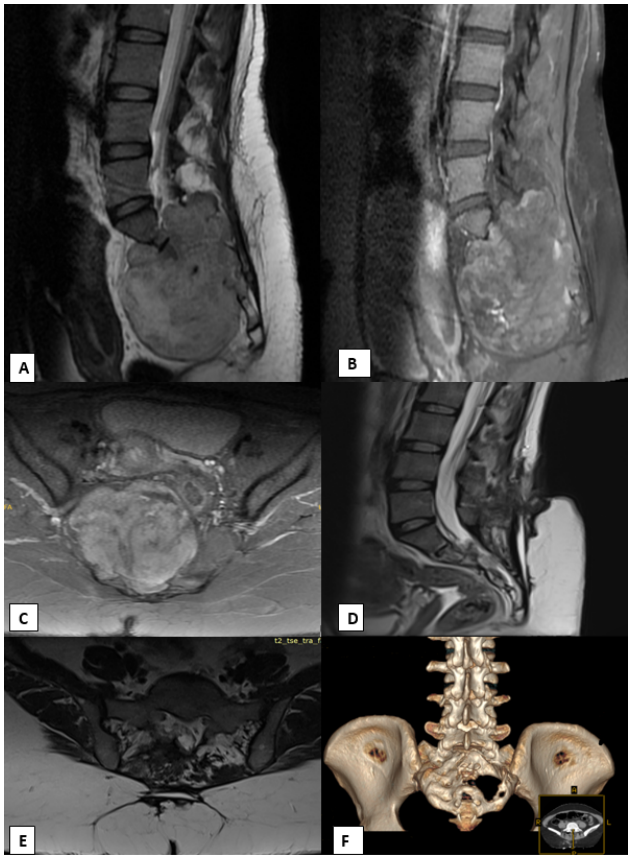

Figure 4: A)Sagittal MRI scan displaying a giant sacral mass in a 34-year-old female patient. The mass appears with heterogeneous intensity on T2-weighted imaging (T2WI). B) Sagittal contrast-enhanced MRI scan revealing the sacral mass. C) Axial contrast-enhanced MRI scan providing an additional view of the sacral mass. D) Postoperative sagittal T2-weighted MRI scan showing the outcome after the excision of the sacral mass. E) Postoperative axial T2-weighted MRI scan displaying the result of the surgical removal of the sacral mass. F) Postoperative 3D computed tomography images of the sacral region, offering a comprehensive visualization of the surgical outcome.

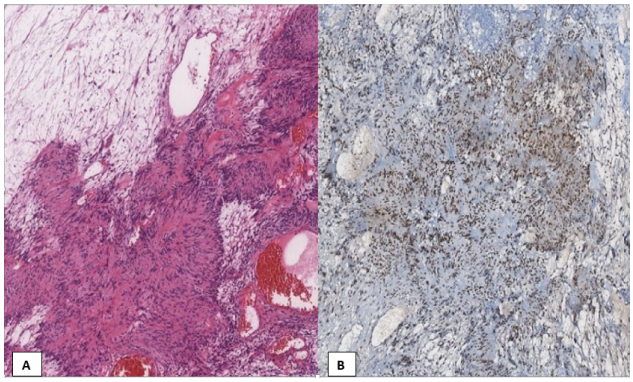

Figure 5: Monotonous spindle cells that form a palisade-like structure in a few focal areas around the vessels that are intact. A) Hematoxylin and Eosin-stained tumor, widespread bleeding, hyalinization and degeneration are observed within the tumor (×10). B) Immunohistochemical staining showed diffuse S-100 positivity and activity with SOX10. Staining with CD34 was negative.

Discussion

Schwannomas, alternatively termed neurilemmomas, are benign tumors that arise from Schwann cells found in the peripheral nerve sheaths, specifically within soft tissues (1). Typically originating from sensory nerves, they may occasionally have a motor nerve origin. The head and neck as well as the extremities are the most common sites of origin. Because of the ample areolar space available, these tumors frequently manifest later, causing compression effects and degenerative alterations. Typically, the clinical progression is gradual and prolonged, with rare occurrences of malignant transformation. Histologically, schwannomas exhibit distinctive features with Antoni A areas, featured by highly cellular spindle-shaped cells, and Antoni B areas, showing a myxoid stroma (5).

Schwannomas, rare encapsulated tumors, are typically found in peripheral nerves of the limbs, head and neck. Extraspinal locations of ancient schwannomas are not very common. Their occurrence in the para-aortic localisation is infrequent, constituting 0,7% to 2.7% of all primary schwannomas, and 0.5% to 1.2% of all para-aortic tumors (9). Retroperitoneal locations are also rarely described in the literature (10). This retroperitoneal localization predominantly affects individuals in their mid-50s, with a slightly higher prevalence in females (2:3 ratio) (11). Various types of schwannomas, including cellular, glandular, epithelioid, melanotic and ancient variants have been identified. Despite their rarity and diverse presentations, the understanding of these tumor types is crucial for accurate diagnosis and appropriate management.

One of the infrequent variations of schwannomas is the ancient schwannoma, which was initially documented by Ackerman and Taylor in 1951 (12). These tumors account for just 0.8% of all soft tissue neoplasms (13). Ancient schwannomas display distinctive degenerative features, including cystic changes, fibrosis, stromal edema, xanthomatous alterations and perivascular hyalinization. Additionally, degenerative nuclear modifications such as pleomorphism, lobulation, and hyperchromasia may be evident. These alterations are attributed to the extended growth or "aging" of the tumor, resulting in vascular insufficiency, that is why they are termed "ancient schwannomas." Despite these degenerative changes, ancient schwannomas exhibit behavior similar to typical schwannomas. Under microscopic examination, they exhibit areas of cellularity interspersed with a myxoid matrix although the cellular regions tend to become sclerotic or fibrotic, potentially leading to the development of hematomas and cysts over time. In particular, the nuclear palisades commonly seen in classic schwannomas are absent in ancient schwannomas. Although nuclear atypia and hyperchromasia are frequent in these tumors, differentiating them from malignancy can be established by the absence of mitotic activity and the preservation of cohesive clusters of spindle-shaped cells. Additional diagnostic confirmation can be achieved through flow cytometry, which assesses DNA ploidy, and immunostaining with S100 protein, further supporting their benign neural origin (6,7,13) (Figure 5).

Ancient schwannomas typically manifest with symptoms related to compression, such as pain

and numbness, necessitating surgical removal for a conclusive diagnosis. A complete surgical excision of the tumor, whenever possible while safeguarding adjacent structures, serves as a curative approach. In this discussion, we have presented two instances of the uncommon pathological condition of ancient schwannomas originating in the retroperitoneum. These tumors are characterized by slow growth and a benign course, often causing pressure-related symptoms. Surgical resection remains the primary treatment, and if there is suspicion of the diagnosis prior to surgery, since recurrences are rare, it is vital that all surrounding structures be protected.

Ancient schwannomas exhibit distinct MRI characteristics that set them apart from other nerve sheath tumors, particularly neurofibromas and malignant lesions. On T1-weighted images, ancient schwannomas appear isointense while on T2-weighted images, they display heterogeneous hyperintensity. Additionally, these tumors exhibit heterogeneous contrast enhancement. Interestingly, these imaging features can sometimes evoke concerns of malignancy during the initial evaluation due to their resemblance to certain malignant tumors.

In contrast, neurofibromas typically present with slightly hyperintense or isointense signals on T1-weighted images while on T2-weighted images, they show heterogeneous hyperintensity with homogeneous contrast enhancement. Understanding these distinctive MRI patterns is essential in accurately differentiating ancient schwannomas from other nerve sheath tumors and preventing misdiagnoses.

When confronted with MRI findings resembling malignancy, clinicians should be aware of the unique radiological features associated with ancient schwannomas, enabling prompt and precise diagnosis, and guiding appropriate management strategies.

Conclusion

In conclusion, ancient schwannomas represent a rare and intriguing subset of soft-tissue tumors. While their degenerative changes can mimic malignancy, meticulous histological examination and immunostaining help confirm their benign nature. Early diagnosis and complete surgical resection with preservation of surrounding structures offer excellent prognosis, making awareness of this entity crucial for clinicians managing patients with peripheral nerve sheath tumors.

Author Contributions

Conceptualization: GG, EÇ, SG, Investigation:GG, EÇ, YŞ, ZD, Project administration: GG, AD, SG, Resources: EÇ, YŞ, ZD, EI, BT, Surgery: GG, AD,EI,BT, Writing – original draft: EÇ, YŞ, ZD, Writing – review & editing: GG, AD

Disclosure Statement

All authors declare that they have no conflict of interest to disclose.

Ethics Statement

This study was approved by the Institutional Review Board (TUEK E1-23-3858), and written informed consent was obtained from each patient.

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ORIGINAL ARTICLE

Attitudes of Teachers towards Individuals with Mental Health Problems and Affecting Factors

Öğretmenlerin Ruh Sağlığı Sorunu Olan Bireylere Yönelik Tutumları ve Etkileyen Faktörler

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ABSTRACT

Aim: Teachers are in a good position to provide first aid to students with mental health problems. The aim of the study is to determine the attitudes of teachers towards individuals with mental health problems and the factors affecting them.
Materials-methods: The research, which is a cross-sectional descriptive study, was conducted with teachers reached online via social media. Sociodemographic information form, Hospital Anxiety-Depression Scale and Community Attitudes towards the Mentally Illness Scale were applied to the teachers through Google forms. The data were evaluated with the SPSS 20 statistical program. A p value of <0.05 was considered statistically significant.
Results: In this study, 477 teachers were participated. Psychological Counseling and Guidance (PCG) teachers' "mental health ideology" (19.24±3.99) and "goodwill" scores (18.07±3.16) were found lower than the scores of preschool and classroom teachers (p=0.001; p=0.014). The goodwill score of male teachers (20.27±3.66) was higher than that of female teachers (19.38±3.19). The risk of anxiety was in 17.00% of the teachers participating in the study and the risk of depression was in 27.62%. The goodwill approach of teachers with anxiety risk to those with mental problems was lower than those without anxiety risk (p=0.003).
Conclusion: It is noteworthy that the attitudes of teachers towards individuals with mental health problems are at a moderate level, and that the attitudes of teachers who are especially young, women and who frequently encounter these patients are negatively affected.

Keywords: Teacher, Mental Health Problem, Anxiety, Depression

ÖZ

Amaç: Öğretmenler ruh sağlığı sorunları olan öğrencilere yardım sağlama konusunda iyi bir konumdadırlar. Çalışmanın amacı öğretmenlerin ruh sağlığı sorunu olan bireylere yönelik tutumlarını ve bunları etkileyen faktörleri belirlemektir.
Gereç-Yöntem: Kesitsel tanımlayıcı bir çalışma olan araştırma, sosyal medya üzerinden online olarak ulaşılan öğretmenler ile yapıldı. Öğretmenlere Google formları aracılığıyla sosyodemografik bilgi formu, Hastane Anksiyete-Depresyon Ölçeği ve Ruhsal Sorunlu Bireylere Yönelik Toplum Tutumları Ölçeği uygulandı. Veriler SPSS 20 istatistik programı ile değerlendirildi. p<0,05 değeri istatistiksel olarak anlamlı kabul edildi.
Bulgular: Bu çalışmaya 477 öğretmen katılmıştır. Psikolojik Danışmanlık ve Rehberlik öğretmenlerinin "ruh sağlığı ideolojisi" (19,24±3,99) ve "iyi niyet" puanlarının (18,07±3,16) okul öncesi ve sınıf öğretmenlerinin puanlarından daha düşük olduğu belirlendi (p=0,001; p=0,014). Erkek öğretmenlerin iyi niyet puanının (20,27±3,66) kadın öğretmenlere göre (19,38±3,19) daha yüksek olduğu bulundu. Araştırmaya katılan öğretmenlerin %17,00'inde anksiyete riski, %27,62'sinde ise depresyon riski saptandı. Anksiyete riski taşıyan öğretmenlerin ruhsal sorunu olanlara karşı iyi niyet yaklaşımı, anksiyete riski olmayan öğretmenlere göre daha düşüktü (p=0,003).
Sonuç: Öğretmenlerin ruh sağlığı sorunu olan bireylere yönelik tutumlarının orta düzeyde olduğu, özellikle genç, kadın ve bu hastalarla sıklıkla karşılaşan öğretmenlerin tutumlarının olumsuz etkilendiği dikkat çekmektedir.

Anahtar Kelimeler: Öğretmen, Ruh Sağlığı Sorunu, Anksiyete, Depresyon

Introduction

Mental disorders manifest themselves as inconsistent feelings, thoughts and behaviors of individuals, and as problems in their relations with individuals (1). Throughout history, negative attitudes and approaches have been observed in society towards people with mental illness in different cultures and periods. People with mental problems are usually stigmatized as strange, frightening, and dangerous and are ostracized, and even undergo hostile attitude (2). Stigmatization is considered as a person's trivialize in society due to incompatible behaviors which are opposed to social norms and criteria, and as evaluation disreputable and defective (3). Even today, people with mental illness do not want to go to the doctor because they are disapproved, alienated and stigmatized as "crazy" not only by society but also themselves. These diseases are hidden due to this drawback. Since these negative attitudes and beliefs provoke hitches and delays in treatments of these patients, awareness raising and education is necessary against stigma. After all, people with mental illness and their family and society which they live in is damaged. However, one of the most important steps in the treatment is adaptation of these patients to social life. Preventing wrong attitudes and behaviors will increase adaptation to society and success in the treatment process (4,5). In a study investigating the attitudes of occupational groups towards mental illnesses, it was

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determined that the occupational groups with the most negative beliefs were mukhtar, police officers, teachers and healthcare professionals, respectively (6). In studies discussing attitudes and behaviors, it was found that the attitudes of healthcare professionals towards people with mental illness were positive (7,8). In a study conducted with lecturers of a university, it was determined that the participants had an understanding and protective approach towards the ones with mental illness (9). In another study conducted with medical students and lecturers of them, it was found that the students had more stigmatizing attitudes than the lecturers, and their tolerance increased after taking psychiatry rotation (10).

Many psychiatric problems emerge during adolescence period. Worldwide, mental illnesses affect 10-20% of children and teenagers (11). Given that children spend most of their times at school, teachers are in a unique position to recognize psychiatric problems and to support student's call for help (12). Because teachers are one of the occupational groups which most frequently encounter people with mental illness (6). Teachers' having sufficient knowledge about mental illnesses and telling the right attitudes and behaviors to their students can ensure that individuals with mental illnesses are accepted, supported by the society, and protected from negative situations (13,14). For this reason, it is important to determine the attitudes and behaviors of teachers, who constitute the most important part of community education, towards individuals with mental problems. There are few studies conducted with teachers in this field in our country Turkiye. In this context, with this study, it was aimed to determine the attitudes of teachers across the country towards individuals with mental problems and the factors affecting them, and to evaluate the reflection of their own mental state on their attitudes.

Material and Methods

In this descriptive study, it was planned to reach the number of samples that could represent all teachers across the country through the internet, social media and communication networks. Thus, it was calculated that at least 377 teachers should be reached in the study with a 5% margin of error and a 95% confidence interval. After the approval of the ethics committee, the purpose of the study was explained by making announcements through different social networks in a period of about three months, and volunteers were asked to fill in the questionnaire form in the link given and forward this link to the teachers they knew. The survey form created with Google forms was anonymous and voluntary consent was requested. In the first part of the three-part questionnaire, there was the sociodemographic information form for the teachers, the Hospital Anxiety-Depression Scale in the second part, and the Community Attitudes towards Mental Illness Scale in the third part.

Sociodemographic Information Form: The form included 16 items about the sociodemographic characteristics of the participants, questions about their professional careers, and their encounters with individuals with mental problems.

Hospital Anxiety Depression Scale (HADS): It was developed by Zigmond and Snaith (1983) to determine an individual's risk of anxiety and depression (15). Turkish validity and reliability study was conducted by Aydemir et al. (16). Seven questions (odd numbers) of the scale, which consists of 14 items, measure anxiety and seven questions (even numbers) measure the risk of depression. Questions answered on a four-point Likert scale are scored between 0 and 3. The cut-off point of HADS was determined as 10 for anxiety (HAD-A) and seven for depression (HAD-D).

Community Attitudes to Mental Illness (CAMI) Scale: The Turkish validity and reliability of the scale, developed by Taylor and Dear (1979), was performed by Bag and Ekinci (2006) (17,18). The five-point Likert scale is scored as Totally Agree (1) and Strongly Disagree (5). Cronbach's alpha value was calculated as 0.72 in the scale consisting of 21 items. The scale has three sub-dimensions.

Goodwill Sub-Dimension: It expresses the willingness to be kind to those with mental health problems and to understand and share their feelings. It consists of nine items; Items 2, 6, 11, 18, and 20 are scored straight; items 4, 9, 13, and 16 are reverse scored. A high score in the sub-dimension indicates a positive attitude.

Community Mental Health Ideology Sub-Dimension: It is about maintaining the care and treatment of individuals with mental disorders by gaining acceptance in the community. It consists of ten items; Items 3, 7, 12, 15, and 19 are scored straight while items 5, 10, 14, 17, and 21 are reverse scored. A high score in the sub-dimension indicates a positive attitude.

Fear/Exclusion Sub-Dimension: It expresses the concept of fear of individuals with mental illness and keeping them away from society. It consists of two items; item 1 is scored straight; item 8 is scored reverse. A high score from the sub-dimension indicates a negative attitude.

Statistical Analysis

While evaluating the data obtained through Google forms in the study, the mean and standard deviation values of the numerical data were calculated. Compliance with normal distribution was evaluated with Kolmogorov-Smirnov test, categorical and numerical data were compared with appropriate statistical analyzes such as Chi-square, Student-t test, and One-way anova test. A value of $p<0.05$ was considered statistically significant. Pearson correlation analysis was used to determine the relationship between variables.

Results

A total of 477 teachers from various regions of Turkiye participated in the study. The mean age of the participants was 40.46±10.84 (22-72) years, and the time they spent in the teaching profession was 15.66±10.35 (1-42) years. 37.94% (n=181) of the teachers were women, 82.87% (n=395) were married, and 90.56%

(n=432) had nuclear families. The sociodemographic characteristics of the teachers, more than half of whom (57.23%; n=273) live in Central Anatolia, are given in Table 1.

Table 1. Sociodemographic features of the participants

		mean ± SD	
Age (year)		40.46±10.84 (22-72)	
Time spent in the profession		15.66±10.35 (1-42)	
		n	%
Gender	Male	181	(37.94)
	Female	296	(62.06)
Marital status	Married	395	(82.87)
	Single	82	(17.13)
Family structure	Nuclear	432	(90.56)
	Extended	39	(8.19)
	Broken	6	(1.25)
Region where he/she spent most of his/her life	Central Anatolia	273	(57.23)
	Eastern Anatolia	32	(6.70)
	Southeastern Anatolia	18	(3.77)
	Marmara	35	(7.33)
	Aegean	63	(13.24)
	Mediterranean	36	(7.54)
	Black Sea	20	(4.19)
Occupational Branch	Preschool	55	(11.53)
	Religious culture	103	(21.59)
	Classroom teaching	52	(10.90)
	PCG	54	(11.32)
	Others	213	(44.65)
Current working status	State Agency	410	(85.95)
	Private Industry	22	(4.61)
	Retired	14	(2.95)
	Not working	31	(6.49)
Institution he/she is working at	Kindergarten	23	(4.82)
	Primary Education	267	(55.97)
	Secondary/High School	166	(34.80)
	Others	21	(4.4)
Income status	Income less than expenses	86	(18.0)
	Income equal to expenses	242	(50.7)
	Income more than expenses	149	(31.2)

*PCG: Psychological Counseling and Guidance

CAMI Scale Cronbach's alpha coefficient was calculated as 0.799. The mean of the community mental health ideology sub-dimension of the participants' CAMI Scale was 21.68±4.83 points, the mean of goodwill sub-dimension was 19.71±3.40 points, and the mean of fear/exclusion sub-dimension was 6.53±1.49 points.

It was found that the average score (19,24±3,99) of the teachers whose vocational branches were PCG in the community mental health ideology, sub-dimension of the CAMI Scale was lower than the preschool (22,11±4,59) and classroom teaching branches (22,75±5,35) (p=0.001; p=0.014). The mean score of the community mental health ideology sub-dimension was that of those who encountered a student with a psychiatric disorder during their professional life (21.11±4.62) and those who had a family member with a psychiatric disorder (20.21±4.26). These mean scores were lower than those who did not encounter people with psychiatric disorders. (p=0.004; p=0.003).

The mean score of the male teachers' goodwill sub-dimension (20.27±3.66) was higher than the female teachers' goodwill score (19.38±3.19) (p=0.007). Teachers whose professional branch was PCG (18.07±3.16) and who had a family member with a psychiatric disorder 18.95±3.33) had lower mean score of goodwill sub-dimension (p<0.05) (Table 2).

Table 2. Comparison of CAMI Scale sub-dimensions and sociodemographic characteristics

	CAMI Scale		
	Community Mental Health Ideology	Goodwill	Fear/Exclusion
	Mean ± SD	Mean ± SD	Mean ± SD
Sex			
Male	22.10±4.83	20.27±3.66	6.48±1.39
Female	21.42±4.82	19.38±3.19	6.56±1.55
p	0.133	0.007	0.587
Marital status			
Married	21.76±4.78	19.91±3.34	6.52±1.46
Single	21.28±5.06	19.76±3.54	6.57±1.63
p	0.412	0.005	0.765
Occupational branch			
Preschool[a]	22.11±4.59	19.64±2.82	6.45±1.39
Religious culture[b]	20.87±4.76	19.84±3.37	6.56±1.46
Classroom teaching[c]	22.75±5.35	20.42±3.57	6.54±1.40
PCG[d]	19.24±3.99	18.07±3.16	6.76±1.92
Others[e]	22.31±4.77	19.92±3.47	6.47±1.43
p	0.001[cd], 0.014[ad]	0.016[b], .003[cd]	0.772
Having family members who have mental problems			
Yes[f]	20.21±4.26	18.95±3.33	6.46±1.38
No[g]	21.92±4.86	19.91±3.35	6.59±1.52
I don't know[h]	24.54±5.02	20.27±3.97	5.96±1.39
p	0.004[fg], 0.001[fh]	0.031[fg]	0.102
Your encounter with a student who has a psychiatric illness in your professional life			
Yes	21.11±4.62	19.47±3.37	6.58±1.49
No	22.73±5.09	20.29±3.36	6.41±1.50
I don't know	22.90±4.92	19.77±3.61	6.52±1.48
p	0.003	0.066	0.567

** CAMI: Community Attitudes to Mental Illness

Anxiety risk was found in 17.00% (n=81) and depression risk in 27.62% of the teachers participating in the study. It was determined that the mean score of the goodwill sub-dimension (18.70±3.19) of the participants who were at high risk of anxiety was lower than those who did not have the risk of anxiety (19.92±3.41) (p=0.003). There was no statistically significant difference between the participants in terms of depression risk and mean scores of community mental health ideology score, goodwill score and fear/exclusion score (p>0.05) (Table 3).

There was a positive, weak-strength, and significant relationship between the participants' goodwill sub-dimension score and age and time spent in the profession (r=0.146; r=0.154; p=0.001). A negative, weak, and significant correlation was found between the fear/exclusion sub-dimension score of the scale and age and time spent in the profession (r=-0.097; r=-0.090; p=0.035). As age and time spent in the profession increased, the score of goodwill towards individuals with mental problems increased, and the scores of fears of individuals and exclusion decreased (Table 4).

Table 3. Comparison of the participants' depression and anxiety risk status and CAMI scale sub-dimensions

		CAMI Scale		
		Community Mental Health Ideology	Goodwill	Fear/Exclusion
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
HAD-A				
≤10 points, No anxiety	396(83.00)	21.64±4.75	19.92±3.41	6.55±1.49
≥11 points, have anxiety	81(17.00)	21.88±5.25	18.70±3.19	6.42±1.50
	p	0.687	0.003	0.474
HAD-D				
≤7 points, No depression	345(72.38)	21.51±4.69	19.84±3.36	6.60±1.50
≥8 points, have depression	132(27.62)	22.11±5.18	19.38±3.50	6.35±1.44
	p	0.225	0.182	0.104

* CAMI: Community Attitudes to Mental Illness

**HAD: Hospital Anxiety and Depression

Table 4. Correlation between CAMI Scale sub-groups

		CAMI Scale		
		Community Mental Health Ideology	Goodwill	Fear/Exclusion
HAD-A	r	0.062	-0.100*	-0.056
	p	0.175	0.030	0.220
HAD-D	r	0.074	-0.054	-0.087
	p	0.106	0.243	0.058
Age	r	0.049	0.146**	-0.097*
	p	0.287	0.001	0.035
Time in the profession	r	0.069	0.154**	-0.090*
	p	0.130	0.001	0.048

* CAMI: Community Attitudes to Mental Illness

**HAD: Hospital Anxiety and Depression

Discussion

Mental health treatment services are increasing every year and mental health related diseases constitute an important part of health services in Türkiye as well as all over the world. In the sustainability of these services, the attitude of the society towards sick individuals is very important. The attitude of teachers, which is the most important part of community education, towards individuals with mental problems is an important factor in evaluating and improving community attitudes. This study, which was conducted to determine the attitudes of teachers towards individuals with mental problems and the factors affecting them, is important because it is one of the few studies in the field.

In the study, the mean score of teachers' community mental health ideology was 21.68±4.83 points, the mean score of goodwill was 19.71±3.40 points, and the mean score of fear/exclusion was 6.53±1.49 points. The mental health ideology score of the nurses working in the psychiatric hospital was 22.80±5.89, the goodwill score was 19.65±3.58, and the fear/exclusion score was 6.78±1.60 (7). Since the frequency of encountering these individuals by nurses and teachers is higher than the general population, similar results can be seen. However, in a population-based study, the mean score of community mental health ideology (29.0±4.0) and goodwill mean score (27.8±3.8) of adults were higher than teachers and nurses, and the mean score of fear/exclusion (6.1±1.7) was found lower (19). In the study of Karaca et al., in which they examined the attitudes of different occupational groups towards mental illnesses with another scale, it was found that the general attitude towards individuals with mental problems was at a moderate level, and the highest attitude scores were in health workers and teachers (6). In another study on the attitudes and behaviors of the society towards mental health problems, it was stated that half of the participants had a generally negative attitude towards mental illnesses (20).

In the study, the mental health ideology score and goodwill score of those who encountered students with psychiatric disorders throughout their professional life and those who had psychiatric patients in their families were lower than those who did not encounter psychiatric disorders. Karaca et al. found that those who had a mental illness or a family member with a mental illness were less likely to find these patients dangerous and to be ashamed of them than those who did not have mental illness (6).

About one-fifth of the teachers who participated in the present study were found at risk for anxiety and about one-third at risk for depression. Those at high risk of anxiety had a more negative attitude of goodwill than those at low risk. It has been observed that there is a positive and significant relationship between the negative attitude towards individuals with mental problems and the level of professional burnout in nurses working in psychiatric hospitals (7). Yuksel et al. found that lecturers who knew someone with a mental illness had a more protective and humanistic approach towards these patients (9). In the present study, mental health ideology and goodwill scores of PCG branch teachers were lower than those of preschool and classroom teaching branches. Although the opposite is expected, it can be thought that the fact that PCG teachers encounter these patients more frequently affects their attitudes negatively.

Tumer et al. examined adults' attitudes towards mental illness and those with mental illness. In their studies, it was determined that the mean scores of goodwill, fear/exclusion of women were higher than that of men (19). In the study of Babicki et al., it was stated that women were more concerned about those with mental illness than men and were more afraid of such patients (21). In another study, it was revealed that the gender of the lecturers did not affect their views on mental illnesses and psychiatric patients (9). In Bilge et al.'s study (2011), it was revealed that the attitudes towards individuals with mental problems were similar between the genders, but only the goodwill sub-dimension score was higher in males. In the present study, it was found that male teachers had higher goodwill towards these individuals than

female teachers (5). It can be said that male teachers are more understanding and accepting of those with mental illness than women.

In this study, as age and time spent in the profession increased, the score of goodwill towards individuals with mental problems increased, and the scores of fears of individuals and exclusion decreased. On the contrary, in the study of Yuksel et al., lecturer's attitudes towards psychiatric patients did not change with their age and time spent in the profession (9). Again, it is stated in other studies that elderly individuals believe that people with mental health problems are more aggressive, less intelligent than other people and that they should be socially restricted (22,23).

Conclusion

As a result; it was seen that teachers' attitudes towards individuals with mental problems were at a moderate level in terms of scores. It was observed that the attitudes of young teachers, female teachers and teachers who frequently encountered these patients were negative. In a study investigating the knowledge levels of teachers on basic health issues, it was found that female teachers and teachers who graduated from health-related faculties had higher levels of health knowledge. In the study, it was concluded that teachers' knowledge levels on this subject should be increased so that students can exhibit more positive health-related behaviors (24). The first symptoms of psychiatric diseases usually appear in childhood and adolescence (25). Early detection of mental illnesses can be achieved by teachers' awareness of mental health problems and accompanying symptoms (26). Especially in developing countries where child and adolescent mental health services are inadequate, teachers are needed more in this regard (27). However, studies have found that teachers' mental health literacy levels are low (26,28).

In order for teachers to better understand the mental health problems of young people; in particular, their knowledge about mental illnesses and their treatments needs to be improved. There is a need for in-service training for identification and referral, and the assignment of school psychologists to deal with students' mental health problems (29).

The limitation of this study is that beliefs about different mental illnesses were not evaluated separately and only volunteers participated in the study.

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ORIGINAL ARTICLE

The Relationship Between Uric Acid/HDL Ratio and Monocyte/HDL Ratio and Glycemic Control in Male Type 2 Diabetic Patients

Erkek Tip 2 Diyabetik Hastalarda Ürik Asit/HDL Oranı ve Monosit/HDL Oranı ile Glisemik Kontrol Arasındaki İlişki

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a major health problem worldwide. As glycemic control worsens, the risk of both microvascular and macrovascular complications increases. The aim of this study is to investigate the relationship between blood glucose regulation and two different parameters: uric acid/HDL ratio (UHR) and monocyte/HDL ratio (MHR) in male subjects with type 2 diabetes.
Methods: In this retrospective study, a total of 166 male patients diagnosed with type 2 diabetes and 83 healthy adult men as a control cohort were included. Diabetic male participants were equally divided into two subgroups: the group with uncontrolled blood glucose (HbA1c levels exceeding 7, n=83) and the group with good glycemic control (HbA1c levels at or below 7, n=83). Our analysis included assessment of several serum markers, including triglyceride, high-density lipoprotein (HDL), uric acid, low-density lipoprotein (LDL), neutrophil, lymphocyte, monocyte, white blood cell, hemoglobin and platelet levels. In addition, uric acid/HDL ratio, body mass index and monocyte/HDL ratio were compared.
Results: Creatinine levels were normal in all study participants and ages were similar in the groups. Triglyceride levels were significantly higher in diabetic patients compared to the healthy group (P<0.001). In contrast, diabetic patients had lower HDL levels than healthy subjects (P=0.002). Serum uric acid levels were lower in the blood glucose unregulated group than in the blood glucose well-regulated group and healthy subjects (P<0.001). UHR was lower in the blood glucose unregulated group compared to the blood glucose well-regulated group and healthy subjects (P=0.003). White blood cell, neutrophil and lymphocyte counts were higher in diabetic patients than in the healthy group (P<0.001, P<0.001, P=0.002). Platelet count and MHR values were higher in the blood glucose-unregulated group compared to the blood glucose-regulated group and healthy subjects (P=0.007).
Conclusion: Increased MHR and decreased UHR levels are associated with uncontrolled blood glucose regulation in male patients with type 2 diabetes.

Keywords: Type 2 diabetes mellitus, Uric acid/HDL ratio, Monocyte/HDL ratio, HbA1C

ÖZ

Amaç: Tip 2 diabetes mellitus (T2DM) dünya çapında önemli bir sağlık sorunudur Glisemik kontrol kötüleştikçe, hem mikrovasküler hem de makrovasküler komplikasyon riski artar. Bu çalışmada amacımız, tip 2 diyabet tanısı almış erkek bireylerde kan şekeri regülasyonu ile iki farklı parametre arasındaki ilişkiyi araştırmaktır: ürik asit/HDL oranı (UHR) ve monosit/HDL oranı (MHR).
Yöntem: Bu retrospektif araştırmada, tip 2 diyabet tanısı konmuş toplam 166 erkek hasta ve kontrol kohortu olarak 83 sağlıklı yetişkin erkek çalışmaya dahil edilmiştir. Diyabetik erkek katılımcılar eşit olarak iki alt gruba ayrıldı: kan şekeri kontrol altında olmayan grup (7'yi aşan HbA1c seviyeleri, n=83) ve iyi glisemik kontrolü olan grup (7 veya altında HbA1c seviyeleri, n=83). Analizimiz, yüksek yoğunluklu lipoprotein (HDL), trigliserit , düşük yoğunluklu lipoprotein (LDL), ürik asit, nötrofil, lenfosit, monosit, beyaz kan hücresi, hemoglobin ve trombosit seviyeleri dahil olmak üzere çeşitli serum belirteçlerinin değerlendirilmesini kapsamıştır. Ayrıca, UHR, vücut kitle indeksi ve MHR karşılaştırılmıştır.
Bulgular: Çalışma kapsamında tüm katılımcıların kreatinin düzeyleri normaldi. gruplarda yaşlar benzerdi. Trigliserid düzeyleri diyabetik hastalarda sağlıklı grubuna kıyasla belirgin şekilde yüksekti (P<0.001). Buna karşılık, diyabetik hastaların HDL seviyeleri sağlıklı bireylerden daha düşüktü (P=0.002). Serum ürik asit düzeyleri, kan şekeri düzenlenmemiş grupta, kan şekeri iyi düzenlenmiş gruptan ve sağlıklı bireylerden daha düşüktü. (P<0.001). Kan şekeri düzenlenmemiş grupta, kan şekeri iyi düzenlenmiş gruba ve sağlıklı bireylere kıyasla UHR daha düşüktü (P=0.003). Beyaz kan hücreleri, nötrofil ve lenfosit sayıları diyabetik hastalarda sağlıklı gruptan yüksek bulundu (P<0.001, P<0.001 ve P=0.002). Trombosit sayısı ve MHR değerleri kan şekeri regüle olmayan grupta kan şekeri regüle edilen gruba ve sağlıklı bireylere kıyasla daha yüksek bulunmuştur (P=0.007).
Sonuç: Tip 2 diyabetli erkek hastalarda artmış MHR ve azalmış UHR düzeyleri kontrolsüz kan şekeri regülasyonu ile ilişkilidir.

Anahtar Kelimeler: Tip 2 diabetes mellitus, ürik asit/HDL oranı, Monosit /HDL oranı, HbA1C.

Introduction

Type 2 diabetes mellitus (T2DM) poses a formidable global health challenge, with complications arising in both the microvascular and macrovascular domains as glycemic control worsens. Hemoglobin A1c (HbA1c) continues to serve as the primary retrospective marker to assess glycemic management, but the inability to monitor daily blood glucose fluctuations remains a persistent concern (1, 2). High-density lipoprotein (HDL) acts by reducing proinflammatory responses triggered by monocytes, effectively restricting monocyte proliferation, activation and migration, and plays a role in the anti-oxidant mechanism. In contrast, reduced levels of HDL in the bloodstream imply a worsening metabolic profile and are a component of the metabolic syndrome

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(3, 4). Uric acid, a product of purine metabolism, acts as an endogenous antioxidant, but its elevation often accompanies renal disorders. Patients with T2DM often have elevated levels of uric acid. (4). Elevated uric acid is associated with hypertension, chronic kidney disease and cardiovascular disease in diabetes (5-7). There are also studies showing that low serum urate levels are associated with poor glycemic control (8, 9).

The uric acid/HDL ratio(UHR) is emerging as a parameter closely linked to the metabolic syndrome, with a body of research highlighting its predictive potential (3, 10).

Monocytes and macrophages play crucial roles in damage to pancreatic islet cells, islet inflammation and impaired insulin signaling in T2DM. In addition, the interaction between lipid metabolism and hematopoiesis is also of interest. (11, 12). The monocyte/HDL-cholesterol ratio (MHR) has been proposed as an indicator of ongoing low-grade metabolic inflammation and has been suggested in subsequent studies to be used as a marker for cardiovascular disease and chronic kidney disease(13, 14). In a study on MHR in DM, it was found higher in nephropathic patients(15).

The aim of this study was to examine the correlation between the uric acid/HDL ratio, monocyte/HDL ratio, and glycemic control in male patients diagnosed with T2DM, and compare these results with those of the control group.

Material And Methods

Study Design

This study retrospectively examined a group of 166 male patients diagnosed with diabetes at a single center. These individuals were enrolled after their visits to the Internal Medicine outpatient clinic at City Training and Research Hospital from January 1, 2021, to June 1, 2022. For comparative analysis, an additional 83 healthy adult males were included as a control cohort. The diabetic male patients were then evenly distributed into two groups: those with less-than-ideal glycemic control (HbA1c levels surpassing 7) and those with commendable glycemic control (HbA1c levels at or below 7). Only men were included in the study to eliminate possible gender-related differences in blood parameters, including uric acid, monocyte and lipid parameters. In addition, only male gender was included in the study in order to reduce the difference between male and female gender in the effect of hormones such as testosterone and estrogen on lipid profile and uric acid.

Exclusion criteria were applied to individuals with malignancies, those using furosemide, thiazide, acetylsalicylic acid, losartan group drugs, cholesterol-lowering drugs, patients with other autoimmune disorders, patients with coronary artery disease, chronic kidney disease or gout. The control group excluded diabetes mellitus by conducting a 75-gram oral glucose tolerance test following the diagnostic guidelines established by the American Diabetes Association. All patients included in the study and those in the control group were selected from individuals whose BUN, creatinine and GFR values were within normal limits to avoid affecting uric acid values.

Patient records provided essential demographic details, weight measurements, and height data. The body mass index (BMI) of all diabetic patients and the control group was calculated. Data regarding biochemical parameters were extracted from the hospital's comprehensive database. The uric acid/HDL ratio was derived by dividing the uric acid value by the HDL cholesterol value for all participants, including those in the control group. The monocyte/HDL ratio was established by dividing the count of monocytes by the HDL level, which was measured through a complete blood count analysis.

Blood studies were conducted using the Abbott Architect 16200 autoanalyzer (Abbott Inc., Princeton, NJ, USA) following a mandatory fasting period of at least 8 hours. As per the classification outlined by the World Health Organization, patients were further stratified into categories of normal weight (BMI < 24.99), overweight (BMI between 25 and 29.99), and obese (BMI > 30).

Statistical analysis

To evaluate the data, various statistical tests were applied. The normality of variables was examined using the Shapiro-Wilk test. For normally distributed variables, descriptive statistics were presented as mean± standard deviation, and group comparisons were performed using the One-Way Analysis of Variance (ANOVA) test for the three independent groups. Non-normally distributed variables were presented as median (minimum-maximum) values and Kruskal Wallis H test was used for comparisons between three independent groups. Categorical variables were presented as frequencies and percentages, and comparisons between groups were assessed using the Pearson chi-square test. Additionally, Pearson's correlation analysis was employed to explore associations between UHR, MHR, FBS, and HbA1c.

All statistical analyses were performed using the IBM SPSS Statistics 22.0 software, with the significance level set at a=0.05.

Ethics statement

The study was conducted in accordance with the Helsinki principles, and approval was obtained from the Mersin University Ethics Committee on 06.07.2022, numbered 2022/455.

Results

All participants in this investigation consisted exclusively of males, with diabetes durations ranging from 1 to 30 years. No statistically significant disparity in age was evident across the groups (P = 0.073). Additionally, all participants displayed blood creatinine levels within the normal range.

In the comparison between diabetic patients and

the control group, triglyceride levels were significantly higher (P < 0.001) while LDL levels did not show a significant difference (P = 0.095). In contrast, the control group exhibited higher HDL levels than the diabetic patients (P = 0.002).

White blood cell (P < 0.001), neutrophil (P < 0.001) and lymphocyte counts (P = 0.002) were all higher in diabetic patients compared to the control group. No significant difference was found between the three groups in terms of monocyte count (P=0.123). The platelet count was significantly higher in the group with poor glycemic control compared to both healthy subjects and the group with good glycemic control (P = 0.007).

Serum uric acid levels were lower in the poorly glycemic controlled diabetic group compared to the control group and the well glycemic controlled diabetic group (P < 0.001).

Table 1. Demographic, clinical data and statistical analysis results of the groups

Parameters *Mean±SD **Median(-min-max)	Group 1 Control group (n=83)	Group 2 Well-controlled T2DM (n=83)	Group 3 Poorly controlled T2DM (n=83)	Test	P value
Age (years) **	51(29-75)	56(33-70)	55(29-70)	5.246	0.073
T2 DM duration**	0	4(1-18)	6(1-30)	3.014	0.083
Fasting blood sugar (mg/dL) **	92(50-99)	123(11-172)	213(105-394)	194.34	<000.1
HbA1c (%)**	5.5(4.6-6.2)	6.7(5.5-7)	9.6(7.5-14.6)	212,22	<000.1
Total cholesterol(mg/dL)*	185.05±33.734	186.16±36.72	201.65±46.41	4.618	0.011
Triglyceride (mg/dL) **	128(94-258)	186(49-500)	208(72-762)	35.02	<000.1
HDL-C (mg/dL) **	47(29-75)	43(27-89)	41(23-72)	12.41	0.002
LDL-C(mg/dL) *	110.14±29.366	100.6±28.73	109.82±37.33	2.372	0.095
Uric acid (mg/dL) **	5.2(3.4-9.2)	5(2.2-8.5)	4.1(2.4-8)	31.17	<000.1
WBC $\cdot 10^3$ cells/IL**	6.6(4.5-11)	7.4(2.24-13)	8.5(4.8-14)	26.84	<000.1
Hemoglobin (g/dL) **	14.8(12.6-17)	14.4(12-17)	15(11-17)	2.747	0.253
Platelet count (k/mm3) **	224(155-395)	228(154-379)	249(150-500)	9.805	0.007
Neutrophil count $\cdot 10^3$ **	3.8(2.1-7.8)	4.3(2.5-9.7)	4.9(2-9)	23.67	<000.1
Lymphocyte count $\cdot 10^3$**	2(1-3.41)	2.4(1.07-3.6)	2.3(0.9-4.9)	12.17	0.002
Monocytes- count $\cdot 10^3$ **	0.40(0.14-2.31)	0.41(0.14-0.96)	0.45(0.23-0.81)	4.194	0.123
BMI (kg/m^2)**	26.23(17.51-51.78)	26.98(18.59-38.82)	26.98(18.93-38.75)	3.137	0.208
UHR**	0.12(0.05-0.28)	0.12(0.03-0.24)	0.10(0.04-0.21)	11.97	0.003
MHR**	0.0090(0.0027-0.0436)	0.0092(0.0033-0.0255)	0.0109(0.0047-0.0352)	9.818	0.007

UHR levels for well- and poorly-controlled diabetic patients and control subjects were at 12%, 10%, and 12%, respectively. UHR was lower in the poorly glycemic-controlled diabetic group compared to healthy subjects and the well-glycemic-controlled diabetic group (P = 0.003). Subsequent post hoc Tukey testing revealed no significant difference in UHR levels between well-controlled T2DM and control groups (p = 0.801). Nevertheless, UHR levels showed significant variation between well and poorly controlled diabetic patients (p = 0.006) and between poorly controlled diabetic patients and control subjects (p = 0.006).

As for MHR levels in well- and poorly-controlled diabetic patients and control subjects, they measured at % 0.90, %0.92, and %1.09, respectively. These differences in MHR among the study groups also held statistical significance (p = 0.007). Post hoc Tukey analysis revealed no statistically significant difference in MHR levels between well-controlled T2DM and control groups (p = 0.199). The MHR level was significantly higher in poorly controlled diabetic patients than in the well-controlled group (p = 0.027) and the control group (p = 0.027). Please refer to Table 1 for a comprehensive breakdown of demographic, clinical data, and detailed statistical analysis results.

Spearman's correlation analysis showed a significant weak negative correlation between UHR and fasting blood glucose (r = -0.147, p = 0.02) and HbA1c (r = -0.152, p = 0.016). Conversely, MHR showed a significant weakly positive correlation with fasting blood glucose (r = 0.128, p = 0.044) and HbA1c (r = 0.217, p = 0.001). A detailed presentation of the statistical results is given in Table 2.

Table 2. Correlation of UHR and MHR with various parameters

		UHR	MHR
Fasting blood glucose	r	-0.147	0.128
	p	0.02	0.044
Hba1c	r	-0.152	0.217
	p	0.016	0.01
Body mass index	r	0.99	0.133
	p	0.120	0.074

Discussion

In the literature, study results regarding uric acid levels in diabetic individuals are contradictory. Uric acid, aside from its association with gout, has been linked to cardiovascular diseases, metabolic syndrome and T2DM in various studies (16, 17). Moreover, soluble uric acid has been implicated in vascular endothelial dysfunction, cell senescence and heightened levels of free oxygen radicals(18-20). Hyperuricemia shows a positive correlation with diabetes mellitus, hypertension and chronic kidney disease while paradoxically offering some protection against neurodegenerative diseases(21-25). However, one study is the first to provide evidence that hypouricemia is associated with decreased kidney function in men (26). A previous study reported that serum uric acid levels were lower in individuals with diabetes, and this association was greater among men(8). In another study, uric acid levels were found lower in type 1 diabetic individuals with poor glycemic control than in well-controlled type 1 diabetic individuals and control group (9). In our study, uric acid levels were lower in the diabetic male group with uncontrolled

blood glucose than in healthy male individuals and well-regulated diabetic male patients. We think that the results in our study may be due to the uricosuric effect of hyperglycemia in the diabetes group with poor glycemic control. In addition, the age difference between healthy subjects and diabetic patients and the difference in creatinine levels between the groups in a previous study conducted only with male subjects may have affected the results (25). Our study revealed no significant difference in age and creatinine levels between the groups.

Low levels of HDL are not only indicative of poor metabolic status but also a component of metabolic syndrome(3). In previous studies, HDL levels were low in diabetics(27, 28). In our study, we observed that HDL levels were significantly lower in the diabetes group with poor glycemic control than in both the diabetes group with good glycemic control and the control group. These results were similar to the literature.

The UHR serves as a parameter associated with impaired metabolic status. A previous study indicated that the UHR was higher in patients with impaired glycemic control compared to those with good glycemic control. (25). In several studies, UHR was found higher in individuals with diabetic metabolic syndrome compared to those without metabolic syndrome (10, 29). Another study showed increased UHR in those with diabetic kidney damage compared to those without(30). In the previous study, UHR was significantly positively correlated with poor glycemic control in diabetic male subjects (25). In our study, on the contrary, a weak negative correlation was observed between UHR and blood glucose and HbA1C. Therefore, it can be said that UHR decreases as blood glucose regulation worsens. However, due to the low correlation, other factors that may have an effect should not be ignored.

Investigations into the interaction between lipid metabolism and hematopoiesis have revealed that HDL attenuates monocyte-induced proinflammatory effects by inhibiting monocyte proliferation, activation and migration (11, 12, 31). MHR has emerged as a potential marker of low-grade metabolic inflammation; subsequent studies suggest its use as a marker of inflammation in cardiovascular disease and chronic kidney disease (14, 32, 33). MHR has been investigated in diabetic complications in previous studies. In several studies, MHR was found higher in individuals with diabetic nephropathy and retinopathy than in those without nephropathy and retinopathy. (34, 35) . One study reported higher MHR in those with diabetic metabolic syndrome than in those without(36). In a previous study, it was determined that MHR was higher in diabetic patients compared to the control group (37). In our study, a significant difference was detected between the control group and the poorly glycemic controlled diabetes group in terms of MHR, whereas no difference was observed between the control group and the well glycemic controlled diabetes group. In our study, MHR showed a significant weak positive correlation with fasting blood glucose and HbA1c ($r = 0.128$, $p = 0.044$; $r = 0.217$, $p = 0.001$). These results are similar to the literature, but in previous studies, MHR was positively associated with diabetic complications. In our study, diabetic complications were excluded. This study is the first study in the literature to evaluate MHR without diabetic complications. However, only male diabetic individuals were included in the study, which was a limitation of the study.

Multiple studies conducted on healthy individuals have established connections between uric acid levels and serum triglycerides (28, 38). In another study, uric acid was also found to have a significant positive correlation with triglycerides and a negative correlation with HDL in diabetic patients(39) . In our study, a low level significant positive correlation was found between triglyceride level and uric acid ($r=0.262$, $p<0.001$). These results are similar to the literature.

Our study has several important limitations. The first one is the retrospective design of the study. The other is that only male individuals were included to eliminate the effect of gender on the parameters. The third is the small number of the study population.

Conclusion

In conclusion, high MHR and low UHR and low serum uric acid level are associated with impaired blood glucose regulation in diabetic male subjects. Impaired blood glucose regulation is also known to lead to diabetic complications if prolonged. Therefore, diabetic male individuals with high MHR and low UHR levels should be considered to have unregulated blood glucose and should be evaluated for more effective blood glucose regulation therapies. Further prospective studies are needed to provide additional information to these findings.

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ORIGINAL ARTICLE

Does Burnout Due to COVID-19 Affect Resilience? The Sample of Doctors in Turkiye

COVID-19 Nedeniyle Yaşanmış Tükenmişlik Dayanıklılığı Etkiledi Mi? Türkiye'deki Doktorlar Örneği

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ABSTRACT

Objective: The consequences of the coronavirus pandemic on doctors are significant. This study was conducted to determine the resilience or burnout status of physicians, the characteristics that make a difference on them and whether burnout predicts resilience.
Method: The study was conducted with a quantitative method and a general survey model. 246 physicians were reached in the descriptive cross-sectional study. The volunteers with ethical permission were ensured to be able to answer all questions before collecting the data obtained with the principle of voluntary participation.
Results: Age range, income perception, whether they like their profession or not, and whether they are satisfied with the unit they work in are the variables that make a difference in the levels of resilience and burnout of physicians. Self-efficacy, family and social network, coping, and adaptation scores of the physicians in the study were above average in terms of their resilience. Personal achievement and satisfaction with the unit they work predict resilience.
Conclusion: In order to increase the resilience of doctors in extraordinary conditions such as pandemics, conditions such as ensuring that they are satisfied with their workplace and supporting their personal success should be created.

Keywords: Physicians' resilience, physicians' burnout, Turkiye

ÖZ

Amaç: Koronavirüs pandemisinin doktorlar üzerindeki sonuçları önemlidir. Bu çalışma hekimlerin yılmazlık veya tükenmişlik durumlarını, onlar üzerinde fark yaratan özellikleri ve tükenmişliğin yılmazlığı yordayıp yordamadığını belirlemek amacıyla yapılmıştır.
Yöntem: Araştırma nicel yöntemle ve genel tarama modeliyle gerçekleştirildi. Tanımlayıcı kesitsel araştırmada 246 hekime ulaşıldı. Gönüllü katılım ilkesi gözetildi. Verileri toplamadan önce etik izin alındı.
Bulgular: Hekimlerin yılmazlık ve tükenmişlik düzeylerinde farklılık yaratan değişkenleri; yaş aralığı, gelir algısı, mesleğini sevip sevmeme ve çalıştıkları birimden memnun olup olmama durumları oluşturmuştur. Araştırmaya katılan hekimlerin öz yeterlilik, aile ve sosyal ağ, başa çıkma ve uyum puanları dayanıklılık açısından ortalamanın üzerinde çıkmıştır. Kişisel başarı ve çalıştıkları birimden duyulan memnuniyet, dayanıklılığı yordamaktadır.
Sonuç: Pandemi gibi olağanüstü durumlarda doktorların dayanıklılıklarının arttırılması için işyerlerinden memnun olmalarının sağlanması, kişisel başarılarının desteklenmesi gibi koşullar oluşturulmalıdır.

Anahtar Kelimeler: Hekimlerin yılmazlığı, hekimlerin tükenmişliği, Türkiye

Introduction

The COVID-19 epidemic has brought health-related circumstances into the public eye, particularly in terms of the caliber and number of institutions and the people who work there. The sickness spread faster than was expected (1). In this instance, there was no time for disease control or surveillance (2, 3). Several factors such as the initial absence of a heightened workload and limited scientific knowledge about the disease, challenges in obtaining personal protective equipment for healthcare personnel, concerns about contracting the disease, the dynamic nature of patient prognosis, ethical dilemmas related to patient prioritization due to increased demand for medical equipment, and the perception of healthcare workers as being at risk for the disease, which leads to decisions about both excluding and including them in the treatment process come into play (4-11). Burnout among medical staff may have resulted from everything said. According to the literature, burnout can have a negative impact on a person's dedication to their organization as well as their physical, mental and social health. It can also traumatize a person's social identity (12). On the other side, the research asserts that difficult experiences can help people become resilient, and that having a high level of resilience has a protective effect on people (13). Resilience is described as the capacity of an individual to manage risk, adversity and stress despite exposure to a significant stressor that may contribute to a number of physical, behavioral, cognitive and emotional symptoms (14). The health system started to change and transform with the health reforms that started to be implemented in Turkiye in 2003. Access to health services has become easier, everyone has been covered by health insurance, and the quality of services has increased since the reforms. Institutions have been revised in terms of infrastructure and equipment. While

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the satisfaction of citizens with health services was 54% in 2007, this rate was 70% in 2016. Ongoing regulations have been made on the establishment of hospitals, increasing bed capacities, human resources, quality and accreditation status, reimbursement systems and institutional structures of health systems. The localization of hospitals in only certain regions was prevented and a balanced distribution was ensured in Turkiye with the reform. The health insurance system, which was at different levels before, was also changed and a balance was established between all citizens in the use of health insurance. 83.7% of its citizens could receive health insurance in 2014, the premiums of the remaining 16.3% were covered by the state, so all of its citizens were included in health insurance. Hospitals were included in national/international accreditations. A performance-based additional payment system was initially introduced and then a full-time labor law was enacted to prohibit physicians from working both in the private sector and the public in order to reduce physicians' part-time work. At the same time, the number of health personnel in the public sector has increased and equality in access to health has been ensured by initiating compulsory service practice and family medicine practice. The fact that all these reforms implemented in Turkiye were completed before the pandemic gave both the management and its citizens confidence in the pandemic (15).

Our aim in the study was to determine whether doctors are resilient or burned out in this process, to reveal what makes a difference on these, and to see whether burnout is predictive of resilience. At the same time, our aim is to determine the direction and size of the predictive effect of burnout on resilience.

Material and Methods

Type of Study

The research is quantitative, a general screening model and cross-sectional.

Population and Sample of the Study

The formula (N*t2*p*q) / [d2*(N-1) + t2*p*q) was used to determine the sample size, and p = 0.80, q = 0.20, and d = 0.05 were taken into account. The minimum number of individuals to be reached was determined as 246 individuals. As of 2020, there were 165.363 physicians working in Turkiye. The data were gathered from "volunteer participants who stated that they did not have any psychiatric disease diagnosed by the physician" in accordance with the Helsinki Declaration standards, and the participants were informed by the information text at the top of the data collection form.

Data Collection Tools

•Personal Information Form (contains independent variables): The purpose of this form is to gather information about the participants' age, gender, education, occupation, habits and status with regard to chronic diseases. It also intends to find out whether the participants' households contain anyone else who falls into the diagnostic individual category.

•Resilience Scale for Adults (RSA): Savi Cakar et al. carried out the Turkish validity and reliability assessment of the scale, which Ryan and Caltabiano published in 2009 under the title "The Resilience in Midlife Scale (RIM-S)" in 2014. The scale attempts to assess the degrees of resilience in people between the ages of 35 and 60 who must adjust to significant changes or hardships. The 25 components that made up the original scale are divided into five sub-scales. These include Self-Efficacy (SE), Perseverance (P), Internal Locus of Control (ILC), Family and Social Networks (FSN), and Coping and Adaptation (CA) respectively. From 20 to 100 points can be calculated using the scale. By combining the results of all items in the RSA test after eight of them, a total RSA score can be determined. (16). Savi et al. reported the Cronbach's Alpha value of the scale as 0.71. In this study, it was 0.87.

•Maslach Burnout Inventory (MBI): It was preferred to employ the Maslach and Jackson (1986) MBI, the Turkish adaption and validity-reliability study of which was carried out by Ergin (1992) to ascertain the participants' burnout level. The scale has a total of 22 items and assesses burnout using three subscales: personal achievement (PA), desensitization (D) and emotional burnout (EB). Every sub-scale is evaluated independently. For each item, the EB, D, and PA sub-scale scores are calculated as follows: never (0), very rarely (1), occasionally (2), frequently (3) and always (4). The high level of burnout is indicated by the high score in the EB and D subscales and the low score in the PA subscale. The expressions related to EB (Emotional Burnout) and D (Depersonalization) tend to be negative while statements regarding PA (Personal Accomplishment) are typically positive. In this study, we derive four distinct evaluation scores, which include general burnout and sub-scale scores, from the Maslach Burnout Inventory (MBI). The Cronbach's Alpha values for the MBI in this study are recorded at 0.89.

Ethics

Written approval for the study was acquired from the Ministry of Health Scientific Research Platform (03/06/2020-E.9355, number: 9234550/044/), as well as the scientific research ethics committee of a nearby institution (03/06/2020-E.9355) (2020-11-03T16_07_24.xml). In order to use scales in the study, permission was obtained through e-mail from the authors who conducted the Turkish validation study of the scale. According to the Helsinki Declaration's requirements and the information statement at the top of the research form, the data were gathered from "volunteer participants who reported not having any psychiatric illness diagnosed by a physician." In accordance with the idea of volunteering, every participant provided their informed consent.

Statistical Analysis

The SPSS-22 program was used to examine the research's data, and statistical analysis, error checks, and table creation were carried out. Number

and percentage values were given in statistical evaluations. Prior to normality analyses, lost data, and extreme value extractions were performed. Afterward, histogram drawings were made to comply with the normal distribution, skewness, and kurtosis values were examined and Kolmogorov-Smirnov analyses were performed. Chi-square analysis was conducted to determine whether sociodemographic characteristics made a difference in terms of resilience and burnout. On the other hand, multivariate hierarchical regression analysis was conducted to determine the effect of burnout on resilience. $p < 0.05$ was considered as a statistical significance level.

Results

Sociodemographic Characteristics of Participants

The ages of the participants in the study ranged from 24 to 60 years old, with a mean age of 35.75 ± 7.05 (Min - Max: 24 - 60 years). The profession's typical length of service is 11.05 ± 7.32 years (from 1 to 37 years). Table 1 displays a few sociodemographic traits of the individuals. As can be seen, 24.4 percent of doctors and 93.5 percent of their friends reported that they caught Covid-19.

Comparison of RSA and MPI Scores and Sociodemographic Characteristics of the Participants

Table 2 shows the distribution of RSA-MBI and sub-scale scores for physicians. The mean emotional exhaustion scores were found high. Table 3 displays a comparison of the participants' RSA and MBI scores with their sociodemographic details. This study also examined whether the MBI subscales affected burnout levels in relation to some physician traits. Accordingly;

•It was found that a number of factors contributed to the emotional burnout of physicians, including being under 35 years old ($p = 0.000$), not choosing their profession willingly and fondly ($p = 0.002$), not loving it now ($p = 0.000$), and working for 21 or more years ($p = 0.048$).

•It was found that a number of factors contributed to the desensitization of physicians, including being 35 years old or younger ($p = 0.000$), not choosing their profession voluntarily and lovingly ($p = 0.029$), not loving it now ($p = 0.000$), not being satisfied with the institution they work in ($p = 0.000$), and working for 21 years or more ($p = 0.002$).

•It was shown that being unmarried ($p = 0.031$), working for 5 years or less ($p = 0.012$), being 35 years or younger ($p = 0.000$), and not currently loving their career ($p = 0.000$) were all significant factors in the personal achievement of the doctors.

Correlation Between Participants' Resilience and Burnout Sub-Dimension Scores

We also conducted correlation analyses and found a correlation between resilience and emotional burnout ($r = -0.473$ $p = 0.000$), desensitization ($r = -0.388$ $p = 0.000$), personal achievement ($r = -0.596$ $p = 0.000$), age range ($r = 0.201$ $p = 0.001$), perception of income level ($r = -0.177$ $p = 0.003$), doing their job lovingly ($r = 0.402$ $p = 0.000$) and satisfaction with the unit they work in ($r = 0.451$ $p = 0.000$). There was no multicollinearity among the independent variables.

Predictors of Resilience

The multivariate hierarchical regression analysis (Table 4) revealed that the total resilience scale for adults were associated with emotional burnout ($\beta = -0.273$, $p = 0.000$) and personal achievement ($\beta = -0.486$, $p = 0.000$). According to Model 1, emotional burnout, desensitization and personal achievement alone explains 45% of the total variance ($F = 64.837$, $p = 0.000$). According to Model 2, age range, perception of income level, doing their job lovingly, satisfaction with the unit they work in explain 48% of total variance ($F = 31.323$, $p = 0.000$).

Table 1. Some characteristics of physicians (n = 246)

Characteristic	n	%
Gender		
Men	166	67.5
Women	80	32.5
Area of Specialty		
Fundamental Sciences	2	0.8
Internal Sciences	84	34.1
Surgical Sciences	89	36.2
No Specialty	71	28.9
Form of the institution where they are currently working		
State hospital (under the Ministry of Health)	123	50.0
University hospital	43	17.5
Private hospital	31	12.6
Primary healthcare service provider	49	19.9
Satisfaction with the unit they work in		
Very dissatisfied	25	10.2
Not satisfied	48	19.5
Indecisive	52	21.1
Satisfied	109	44.3
Very satisfied	12	4.9
Work-hour per week		
Less than 40 hours	84	34.1
41 hours or more	162	65.9

Table 2. Distribution of physicians' RSA and MBI and sub-scale scores (n = 246)

Scales and sub-scales	Number of items	Mean ± SD	Min - Max	%95 CI
SE	10	29.67 ± 8.97	3 – 40	28.55 – 30.80
FSN	4	12.50 ± 3.85	0 – 16	12.01 – 12.98
P	4	9.34 ± 3.72	0 – 16	8.87 – 9.80
ILC	3	6. 00 ± 2.29	1 – 12	5.71 – 6.29
CA	4	9.65 ± 3.10	2 – 16	9.26 – 10. 04
RSA	25	67.17 ± 16.53	23 – 100	65.09 – 69.25
EB	9	19.72 ± 7.45	0 – 36	18.78 – 20.66
D	5	7.28 ± 3.99	0 – 20	6.87 – 7.79
PA	8	11.87 ± 4.69	0 – 28	11.28 – 12.46
MBI	22	38.89 ± 12.45	4 – 73	37.32 – 40.45

Abbreviations: SE (Self-Efficacy), FSN (Family and Social Networks), P (Perseverance), ILC (Internal Locus of Control), CA (Coping and Adaptation); RSA (Resilience Scale for Adults), EB (Emotional Burnout), D (Desensitization), PA (Personal Achievement), MBI (Maslach Burnout Inventory)

Table 3: Distribution of physicians' RSA and MBI scores according to some characteristics (n = 246)

Characteristic	RSA		MBI	
	Mean Rank	Test Value	Mean ± SD	Test Value
Age range 35 years and under 36 years and older	111.38 141.80	U = 5458.50 **p = 0.001**	41.62 ± 12.79 34.75 ± 10.72	t = 4.392 **p = 0.000**
Perception of income level High income High expenses Income equals expenses	137.44[a,b] 97.63[a] 117.86[b]	KW= 9.234 **p = 0.010**	36.75 ± 13.36[a] 42.73 ± 10.53[a] 39.79 ± 11.75	F = 3.527 **p = 0.031**
Doing their job lovingly No Yes	94.21 149.21	U = 4164.00 **p = 0.001**	46.07 ± 10.41 32.58 ± 10.55	t = 10.07 **p = 0.000**
Satisfaction with the unit they work in Very dissatisfied Not satisfied Indecisive Satisfied Very satisfied	62.76[a,-b,c,d] 107.54[a,e] 100.47[b,f] 152.73[c,e,f] 148.13[d]	U = 45.949 **p = 0.001**	49.12 ± 10.19[a,b,c] 48.41 ± 8.12 40.80 ± 9.96[a] 33.01 ± 10.73 24.50 ± 11.65[c]	F = 32.381 **p = 0.000**

a,b,c,d,e indicate the groups from which the difference originates.

Table 4. Predictors of Resilience.

Variables	Resilience Scale for Adults				
	B	SD	β	t	p
Model 1					
Emotional Burnout	-0.564	0.123	-0.273	-4.580	0.000
Desensitization	-0.357	0.231	-0.092	-1.549	0.123
Personal achievement	-1.585	0.167	-0.486	-9.468	0.000
R = 0.675, R^2= 0.455, F = 64.837, p = 0.000					
Model 2					
Emotional burnout	-0.285	0.151	-0.138	-1.886	0.061
Desensitization	-0.345	0.232	-0.089	-1.488	0.138
Personal achievement	-1.531	0.172	-0.470	-8.891	0.000
Age range	-0.452	1.540	-0.015	-0.293	0.770
Perception of income level	-1.173	0.790	-0.072	-1.485	0.139
Doing their job lovingly	0.059	1.920	0.002	0.031	0.975
Satisfaction with the unit they work	2.990	0.867	0.219	3.449	0.001
R = 0.699, R^2 = 0.489, F = 31.323, p = 0.000					

Discussion

The effects of the COVID-19 pandemic, which caught the world off guard, continue. The importance of doctors, who are first responders, in solving future health problems, as in this pandemic, cannot be ignored. For this reason, it is necessary to ensure the resilience of doctors, to prevent their burnout and to reveal the characteristics that can affect the resilience of doctors. Since the COVID-19 pandemic is still a situation we are experiencing, studies investigating its effects on physicians are insufficient. The number of these studies will increase in the coming years, but the studies available in the literature are mostly burnout studies on health personnel. The aim of this research was to determine the burnout and resilience levels of doctors. In addition, the sociodemographic characteristics of the doctors, which caused the difference in burnout and resilience, were examined. Finally, the predictive features of doctors' resilience were investigated.

Physicians had a great responsibility due to the COVID-19 pandemic that started in 2020. There are many studies reporting over 50% burnout and inadequacy in various specialties. For example, there are publications reporting burnout at rates up to 40% even during medical faculty studying (17). The fact that the working order has not been determined yet may have increased anxiety in healthcare professionals due to uncertainty. Uncertainty is known to increase anxiety (18). Physicians' anxiety levels were found high when healthcare professionals were evaluated among themselves in a study conducted during the COVID-19 pandemic (19).

It was observed in this study that the variables of gender, marital status, whether they had willingly chosen their profession did not make any difference in terms of RSA ($p > 0.05$). There are studies in which the psychological resilience and sub-scales of healthcare professionals do not differ between gender, marital status and smoking habits in the literature (20). These studies support our study. Looseley et al. found in their study on physicians that there was no difference according to gender but when the sub-scales were evaluated separately, desensitization was more common in men while the feeling of decreased personal achievement was more common in women (21). In general, it was shown in a study conducted in Sweden in 2010 that the burnout rate in women was higher compared to men (women 16%, men 10%) (22). There are also studies in the literature that do not report a significant correlation between gender and burnout (23). Being single has been shown to increase the risk of burnout. Smoking and alcohol use have been observed to be ineffective on burnout (21).

Age and income level perception variables are the variables that make a difference when the characteristics of physicians scores are examined in terms of RSA. Güngörmüş et al. (2015) concluded that there was no significance between age and psychological resilience in a study conducted on 437 nursing students in a faculty of health sciences. They concluded in the same study that psychological resilience increased as income levels increased (20). It is thought according to these results that healthcare professionals increase their satisfaction with their work-life because they receive a recompense for their work.

Burnout is an important problem that affects physicians as well as all health personnel. Therefore, it is vital to identify physicians experiencing burnout and to correct the underlying problems. It was found that

individuals with high burnout rates were under 35 years old, described their expenses as high, disliked their present career, and/or were dissatisfied with the units in which they worked. According to a research with 2162 Canadian workers, men and women between the ages of 20 and 35 were more likely than other age groups to experience higher levels of burnout. (24). The highest burnout was found between 25-30 years of age when the age groups were evaluated in another study measuring the burnout level of anesthesiologists and reanimation physicians (25). The age factor is the factor that gives the most consistent results on burnout. Advanced age is thought to protect from burnout (26). It was seen when the income status was examined that the lack of income increased the burnout level in the studies conducted by Sharma and Terzi with their teams (27).

In our research, we found that emotional burnout and personal achievement negatively predicted the resilience of physicians. We determined that being satisfied with the workplace is a positive predictor of resilience. Yıldırım and Solmaz also reported that burnout in the pandemic was a negative predictor of resilience as in our study (28). In our study, we found that the depersonalization dimension was not predictive of resilience. Depersonalization was also observed in a longitudinal study conducted by Müller et al. In that longitudinal study, it was explained that depersonalization increased in 2021 compared to 2020 (29). In a study by Ferreira et al., the predictors of resilience in the covid-19 pandemic process were explained as age and education (14). In the study of Giuseppe et al., it was reported that there is a negative predictive effect between burnout and resilience (30).

Conclusion

A team, rather than a single doctor, can apply health techniques in a healthy way. The doctor is unquestionably the team's leader. Burnout and feelings of inadequacy in doctors have an impact not just on the doctor and their family but also on their entire team at work. Conflicts within the team also rise as a result of the physician's growing sense of inadequacy and fatigue over time. The entire team suffers, and along with these disagreements, other workers can also be driven into burnout. All findings indicate that physician burnout and inadequacy are significant issues that have a wide-ranging impact. A problem that affects so many people needs to be questioned and resolved together with all the underlying reasons.

Limitations

The data of this research were collected through the questionnaire. More qualitatively, participatory observation could be made to access the data. However, both the necessity of isolation and the variable working hours of physicians did not make this possible. Another limitation of the research is the collection of data over a certain time period. The research could be in the form of a cohort study. However, targeting assessment of the situation for the first data necessitated planning the research method in this way. Some data of the study are based on physicians' self-evaluation. Some physicians may have avoided or exaggerated expressing their real condition.

Declarations

This research was presented as a full-text oral presentation at the "4th International Health Sciences and Innovation Congress," which took place online in Azerbaijan between July 5 and 6, 2021.

Ethics approval and consent to participate: Received from the clinical research ethics committee of Bingol University (03/06/2020-E.9355, number: 9234550/044). The information text created within the scope of the Helsinki criteria was presented to the participants together with the questionnaire.

Consent for publication: Not applicable.

Availability of data and material: The data that support the findings of this study are available from the corresponding author [CY] upon reasonable request.

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ORIGINAL ARTICLE

The Relationship Between Acute Phase Reactants Levels at the Time of Admission and Comorbid Conditions with Mortality in Patients Diagnosed with Covid-19

Covid-19 Tanılı Hastalarda Başvuru Anındaki Akut Faz Reaktanları Düzeyi ile Komorbid Durumlarının Mortalite ile İlişkisi

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ABSTRACT

Background/aims: The covid-19 pandemic, which is a global problem, is still one of the most important health problems today. Treatment and vaccine studies are as important in predicting prognosis and mortality as early diagnosis and prevention of the disease, which continues unabated. İn this study, it was aimed to evaluate the success of laboratory values, comorbid conditions and intensive care scoring at the time of first admission in predicting the mortality of patients admitted to intensive care with the diagnosis of Covid-19.
Methods: The study was conducted in a tertiary adult emergency deparment. The study included 106 patients who were admitted to the emergency department and subsequently admitted to intensive care, had a positive Covid-19 polymerase chain reaction(PCR) test and met the inclusion criteria.
Results: The average age of 106 patients included in the study was 71.85. Of these patients, 65.09 % were male and 24.1% were female. While 29 of the patients were survivors, 77 were deceased. İn deceased patients; procalcitonin, lactate, leukocyte, neutrophil, urea, creatine, asti crpi ferritin, d-dimer values were found higher than the other group. Lymphocyte, lymphocyte percentage and pH values were significantly low. Sequential Organ Failure Score(SOFA) and Acute Physiology and Chronic Health Evaluation(APACHE) 2 scores were higher in deceased patients.
Conclusion: Ferritin, lactate, urea and pH values, comorbid conditions, Sequantial Organ Failure Score and Acute Sphysiology and Chronic Health Assessment 2 can be used to predict mortality in covid-19 disease.

Keywords: Covid-19, CRP, d-dimer, ferritin, fibrinogen

ÖZ

Amaç: Global bir problem olan covid-19 pandemisi günümüzde hala en önemli sağlık sorunlarının başında gelmektedir. Tedavi ve aşı çalışmaları hız kesmeden devam etmekte olan hastalığın erken tanınması ve önlenmesi kadar prognozu ve mortaliteyi öngörmekte bir o kadar önemlidir. Bu çalışmada covid-19 tanısı ile yoğun bakıma yatırılan hastaların ilk başvuru anındaki laboratuvar değerlerinin, komorbid durumlarının ve yoğun bakım skorlamalarının mortaliteyi öngörme başarılarının değerlendirilmesi amaçlanmıştır.
Yöntem: Çalışma üçüncü basamak erişkin acil servisinde gerçekleştirilmiştir. Çalışmaya acil servise başvuran ve akabinde yoğun bakım yatışı verilen, covid-19 polimeraz zincir reaksiyon(pcr) testi pozitif ve dahil edilme kriterlerini karşılayan 106 hasta dahil edilmiştir.
Bulgular: Çalışmaya dahil edilen 106 hastanın yaş ortalaması 71.85 idi. Bu hastaların yüzde 65,09'unu erkek, %34,1'ini kadın cinsiyet oluşturmakta. Hastaların 29'u survival iken 77'si vefat eden hastalardan oluşmakta idi. Vefat eden hastalarda; procalsitonin, laktat, lökosit, nötrofil, üre, kreatin, ast, crp, ferritin, d-dimer değerleri diğer gruba göre yüksek saptanmıştır. Lenfosit, lenfosit yüzdesi ve ph değerleri ise anlamlı düşük olduğu tespit edilmiştir. Ardışık Organ Yetmezliği Skoru(SOFA) ve Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi(APACHE) 2 skorları vefat eden hastalarda daha yüksek tespit edilmiştir.
Sonuç: Ferritin, laktat, üre ve ph değerleri, komorbid durumlar, Ardışık Organ Yetmezliği Skoru ve Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi covid-19 hastalığında mortalite öngörmede kullanılabilir.

Anahtar Kelimeler: Covid-19, CRP, d-dimer, ferritin, fibrinojen

Introduction

In December 2019, pneumonia cases of unknown etiology were detected in Wuhan, China's Hubei province. In its early stages, respiratory tract infection symptoms with acute respiratory distress syndrome (ARDS), acute respiratory failure and other serious complications occurred (1). On January 7, a new coronavirus was detected in throat swab samples taken from patients by the Chinese Center for Disease Control and Prevention (CDC). Since the pathogen was phylogenetically similar to SARS-CoV and its effects on the human body were similar, it was identified as a new enveloped beta coronavirus and named SARS-CoV-2 (2). On March 11, 2020, Covid-19 disease was declared a pandemic at the world press conference held by WHO Director General Tedros Adhanom Ghebreyesus (3). In April, approximately 1 year after the acceptance, the total number of cases worldwide reached 140,327,309 and the total number of deaths reached 3,006,828.

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Comorbid conditions are as important as demographic and genetic characteristics in terms of the incidence and severity of Covid-19 disease. There are extensive studies conducted on this subject. In a meta-analysis study based in the People's Republic of China, 1558 patients were recorded. As a result of this meta-analysis, while there was no correlation between liver disease, malignancy or kidney diseases and Covid-19, hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease and cerebrovascular disease were stated as serious risk factors (4).

In the diagnosis of Covid-19, many molecular, serological, biochemical tests and radiological imaging are used. The basis for identifying the disease is virus isolation and detection of nucleic acid. Antibody and antigen tests also play an important role in diagnosis and follow-up. Scoring such as Acute Physiology and Health Evaluation Score (APACHE) and Sequential Organ Failure Assessment Score (SOFA) are used to predict mortality in intensive care units.

In this study, it was aimed to evaluate the success of age, gender, comorbidities, venous blood gas, hemogram, acute phase reactants and biochemical parameters and APACHE 2 and SOFA scores in predicting mortality in patients diagnosed with Covid-19 in the emergency department and admitted to the intensive care unit.

Material and Methods

This research was designed as a retrospective cohort study. Patients with a definitive diagnosis of Covid-19 in the adult emergency department of a tertiary healthcare institution between 01.08.2020 and 31.10.2020, in line with the Covid-19 diagnostic guide of the Ministry of Health, were accepted into the study. This study was approved by the T.R. KTO Karatay University Clinical Research Local Ethics Committee decision number 2020/026. The inclusion criteria for the study were determined as having a definitive diagnosis of Covid-19 and being over 18 years of age, and patients whose data could not be fully accessed were excluded from the study.

In our study, 156 patients were scanned and 106 patients whose data were available were included in the study. Fibrinogen, procalcitonin, ferritin, lactate dehydrogenase, troponin I, sodium, potassium, chlorine, pH, pCO2, pO2, base deficit (be), lactate, bicarbonate, ck-mb, d-dimer, c-reactive protein (crp), platelet count (plt), leukocyte count, aspartate aminotransferase (ast) and alanine aminotransferase (alt) values, lymphocyte count, lymphocyte percentage and albumin values were examined. APACHE 2 and SOFA scores were calculated. Demographic characteristics of the patients were obtained using Structured Query Language (SQL) queries.

Kurtosis and skewness coefficients, Kolmogorov Smirnov and Shapiro-Wilk tests results, histogram and Q and Q graph analysis methods were used to examine the distribution of the data. Independent Sample t test was used for comparisons between two groups with normal distribution, and Mann Whitney U test was used for comparisons between two groups with non-normal distribution. Pearson Chi-Square test was applied to examine the difference between categorical data. ROC (Receiver Operating Characteristic) curve was used to determine the predictive values of laboratory parameters. Sensitivity and specificity values were obtained as a result of the ROC analysis and accuracy values were calculated using prevalence; accuracy was obtained using the formula = (TN + TP)/(TN + TP + FN + FP). Backward LR model and Cox Proportional Hazard Regression analysis were applied to evaluate the risks of laboratory parameters thought to have an impact on survival. Descriptive statistics of the data are described as mean±standard deviation for numerical variables with normal distribution, as Median (IQR) for numerical variables with non-normal distribution, and as frequency (percentage) for categorical variables. All statistical analyzes were analyzed and reported in IBM SPSS Statistics 22.0 program at a=0.05 significance level and 95% confidence level.

Results

The average age of 106 patients included in the study was 71.85±13,085 years. The patients included in the study were evaluated in two main groups: survival and non-survival. 65.09% (69) of the patients were male and 34.1% (37) were female. The median value of the patients' average length of hospital stay was 5 days and the interquartile range value was 7 days. When the distribution of mortality by gender was examined, it was seen that 47 (68.1%) of the male patients did not survive while 22 (31.9%) survived. In female patients, this situation was determined as non-survival 30 (81.1%) and survival 7 (18.9%). Comorbid diseases of the patients included in the study are shown in Table 1.

Table 1. *Gender and Accomanying Disease Distribution of Patients*

Variables		Non-survival (n=77)	Survival (n=29)	Test results	P-value
Age		75 (16)	69 (18)	Z=-2.336	0.019
Gender	Male	47 (%68.1)	22 (%31.9)	X^2=2.037	0.153
	Female	30 (%81.1)	7 (%18.9)		
Hospitalization (day)		4 (9)	5 (5)	Z=-0.164	0.870
Comorbidity					
	Yes	61 (%79.2)	17 (%58.6)	X^2=4.599	0.032
	No	16 (%20.8)	12 (%41.4)		
Comorbidities					
Hypertension		50 (%64.9)	14 (48.3)		
Diabetes Mellitus		35 (%45.5)	8 (%27.6)		
Cerebrovascular disease		8 (%10.4)	2 (%6.9)		
Coronary artery disease		32 (41.6)	8 (%27.6)		
Pulmonary artery disease		15 (%19.5)	4 (%13.8)		
Asthma/COPD		16 (%20.8)	3 (10.3)		
Acute/Chronic Kidney Failure		9 (%11.7)	3 (%10.3)		

COPD: Chronic Obstructive Pulmonary Disease

Any of the patients' comorbid conditions were not found significant in predicting mortality. Laboratory values thought to be related to COVID-19 in the patients included in the study and statistical analysis results between survival and non-survival patient groups are shown in Table 2.

Table 2. *Comparison of Laboratory Parameters Between Survival and Non-Survival Patients*

Laboratory Parameters	Non-survival (n=77) mean(±SD)	Survival (n=29) mean(±SD)	Test Results	P-value
PH	7.32 (0.17)	7.37 (0.10)	Z=-2.266	0.023
PC02	38.0 (15.50)	39.0 (14.70)	Z=-0.854	0.393
P02	39.0 (22.20)	37.0 (22.60)	Z=-0.510	0.610
HCO3	19.16 (±5.12)	22.64 (±6.94)	t=-2.815	0.006
BE	6.4 (6.95)	2.3 (4.60)	Z=-3.101	0.002
Lactate	3.06 (1.82)	2.19 (1.03)	Z=-4.632	0.000
Leukocyte	11.16 (7.73)	8.26 (7.07)	Z=-2.381	0.017
Hemoglobin	12.22 (±2.38)	13.03 (±2.34)	t=-1.559	0.122
PLT	223.0 (110.50)	214.0 (133.00)	Z=-0.252	0.801
LYM	0.79 (0.90)	0.88 (0.89)	Z=-0.170	0.865
Neutrophil	9.70 (7.99)	7.95 (6.40)	Z=-2.293	0.022
LYM %	7.50 (6.40)	9.80 (12.75)	Z=-1.233	0.217
Neutrophil %	88.40 (8.60)	86.20 (18.75)	Z=-1.173	0.241
Glucose	151.00 (90.50)	123.00 (82.00)	Z=-1.308	0.191
Urea	86.0 (78.00)	44.0 (39.50)	Z=-4.093	0.000
Creatine	1.52 (1.56)	1.10 (0.62)	Z=-2.892	0.004
AST	46.0 (47.00)	31.0 (24.00)	Z=-2.800	0.005
ALT	22.0 (21.50)	25.0 (35.00)	Z=-0.702	0.483
Na	133.22 (±7.29)	135.21 (±4.01)	t=2.70	0.008
K	4.66 (0.92)	4.56 (1.11)	Z=-0.315	0.752
Cl	103.40 (±7.61)	99.93 (±5.99)	t=2.21	0.029
CK MB	2.60 (4.07)	2.37 (4.34)	Z=-0.046	0.963
Troponin	48.20 (253.14)	13.99 (30.21)	Z=-3.561	0.000
CRP	154.0 (134.5)	66.2 (126.4)	Z=-2.959	0.003
Ferritin	624.0 (1005.8)	308.0 (582.5)	Z=-2.945	0.003
Procalsitonin*	0.65 (1.77)	0.33 (0.35)	Z=-3.580	0.000
Fibrinojen**	684.0 (559.0)	587.0 (489.0)	Z=-1.099	0.272
D Dimer	2.45 (6.35)	1.20 (3.10)	Z=-1.957	0.050
Apache	23.01 (±4.75)	17.90 (±3.98)	t=5.156	0.000
Sofa	11.61 (±1.20)	5.97 (±1.09)	t=22.074	0.000

*n1=68, n2=28 ** n1=71, n2=28, mean(±SD), SD; standard deviation

APACHE: Physiology and Chronic Health Assessment, AST: Aspartate Aminotransferase, ALT: alanin aminotransferase, BE: Base Deficit, CRP: C-Reactive Protein, CK: Creatine Kinase, LYM: lymphocyte, SOFA: Sequential Organ Failure Assessment

As stated in Table:1; In the patients included in the study, a significant difference was observed in terms of age and comorbidity in the variables examined in two groups: survival and non-survival. It was determined that the average age of patients who died and the number of patients with any disease were higher than those who survived.

As a result of the analysis; There was a significant difference in pH, bicarbonate, lactate, leukocyte, neutrophil, urea, creatine, ast, troponin, crp, ferritin, procalcitonin, d-dimer values and SOFA-APACHE 2 scores between two groups examined.

The results of the ROC (Receiver Operating Characteristic) analysis performed to determine the estimated values of laboratory parameters that were significant as a result of univariate statistical analysis are displayed in Table 3.

Proportional Hazard Backward LR and Cox Proportional Hazard Regression analysis were performed to evaluate the risk status of the parameters examined in the study, which were found significant as a result of univariate analysis for COVID-19 disease. The results obtained from this analysis are shown in Table:4.

According to the examination, pH is a protective factor, lactate, urea and ferritin values are risk factors, all of which have an effect on survival. A 1 unit increase in lactate, urea and ferritin levels increases mortality by 1.014, 1.007 and 1.0004 times, respectively.

Table 3. *ROC (Receiver Operating Characteristic) Analysis Results*

Variable	Cut-Off value	Sensitivity %	Specificity %	AUC (Area Under the Curve)	%95 Confidence Interval(CI)		P-value	Accuracy %
Age	>74.5	54.55	75.86	0.659	0.531	0.787	0.016	62.3
Saturation	<85.5	89.61	48.28	0.686	0.559	0.812	0.003	78.3
Respiratory Rate	>18.5	89.61	37.93	0.649	0.528	0.770	0.018	75.5
PH	<7.315	82.76	49.35	0.643	0.532	0.754	0.024	59.5
HCO_3	<22.95	58.62	81.82	0.686	0.565	0.807	0.003	75.5
Be	>6.1	55.95	82.76	0.696	0.580	0.811	0.002	60.4
Lactate	>2.68	66.23	86.21	0.793	0.699	0.886	0.000	71.7
Neutrophil	>11.02	42.86	82.76	0.645	0.526	0.763	0.022	53.8
Urea	>59.5	75.32	72.41	0.759	0.655	0.863	0.000	74.5
Creatine	>1.185	75.32	58.62	0.683	0.567	0.798	0.004	70.8
AST	>36.5	64.94	68.97	0.677	0.557	0.796	0.005	66.0
Na	>139.5	33.77	89.66	0.629	0.519	0.739	0.041	49.1
Cl	>104.5	42.86	86.21	0.658	0.545	0.771	0.013	54.7
Troponin	>35.395	63.64	75.86	0.725	0.612	0.838	0.000	67.0
CRP	>29.65	93.51	41.38	0.687	0.567	0.807	0.003	79.2
Ferritin	>138.5	90.91	37.93	0.686	0.567	0.805	0.003	76.4
Procalsitonin	>0.465	67.65	75.00	0.733	0.619	0.848	0.000	63.2
APACHE	>23.5	55.84	93.10	0.793	0.701	0.885	0.000	56.6
SOFA	>8.5	100.0	100.0	1.000	1.000	1.000	0.000	100.0

APACHE: Physiology and Chronic Health Assessment, AST: Aspartate Aminotransferase, BE: Base Deficit, CRP: C-Reactive Protein, SOFA: Consecutive Organ Failure Evaluation Score

Table 4. *Cox proportional Hazard Regression Model for Laboratory Parameters*

Variable	β	Standard Error	Wald	Hazard Ratio (HR)	%95 Confidence Interval(CI)		P-value
PH	-2.399	1.089	4.853	0.091	0.011	0.768	0.028
Lactate	0.167	0.078	4.594	1.182	1.014	1.377	0.032
Urea	0.007	0.002	12.390	1.007	1.003	1.011	0.000
Ferritin	0.000	0.000	4.076	1.0004	1.00001	1.00007	0.043

* Backward LR model was applied, p value for model significance p<0.001

Discussion

Considering that there is currently no definitive treatment for Covid-19 disease, where vaccine and vaccination studies continue unabated, reliable and rapid biomarkers are needed for early recognition and prediction of mortality. Making appropriate and timely decisions in choosing a therapeutic approach will only be possible thanks to this foresight.

Although hyperuricemia is often associated with respiratory diseases, studies showed that hypouricemia occured in severe Covid-19 disease (5). Urea level is used in clinical practice as an indirect indicator of dehydration and kidney functions. In our research, contrary to the literature, urea levels were higher in non-survival patients than in surviving patients. While the median urea value was 86 in non-survival patients, this value was calculated as 44 in surviving patients. Values above the cut-off value were determined as a risk factor and were associated with mortality.

To determine the acid-base balance and evaluate the breathing pattern, pH, bicarbonate, partial oxygen and carbon dioxide (paO2, paCO2), saturation, base deficit and lactate values were checked in blood samples taken from the arterial or venous system. In our research, it was determined that the pH value was lower in non-survival patients compared to surviving patients. Values above the cut-off value were considered as a protective factor and were associated with mortality (HR: 0.091). There are no sufficient studies in the literature on blood gases in the mortality analysis of Covid-19 disease. In the study conducted by Morne C. Bezuidenhout et al. (6), the relationship between blood gases, taken during the admission of 56 intensive care patients to the intensive care unit, and mortality was investigated. Increased pH and lower partial oxygen pressure were significantly associated with survival. In the study of Maria Viviana Carlino et al. (7), 28 patients were examined and lactate level was accepted as a predictor of admission to intensive care.

Lactate value is used as an indirect indicator of tissue perfusion. There are also studies showing that it modulates the inflammatory response in macrophages (8). In our research, lactate value was found higher in non-survival patients compared to surviving patients. Values above the cut-off value were determined as a risk factor. Its increase is associated with mortality. A one-unit increase in lactate value increases mortality by 1.182 times (HR: 1.182).

It was determined that the lymphocyte count and percentage were lower in non-survival patients than in surviving patients. There are studies in the literature showing that among all laboratory parameters, the lymphocyte percentage value can be used as the most significant and consistent parameter in predicting the progression of the disease and being used as a guide (9). However, as a result of the analyzes we made in our study, no significant difference was found in terms of mortality. In a meta-analysis, it was determined that patients with a confirmed diagnosis of Covid-19 had a tendency to have low lymphocyte counts and high neutrophil counts (10). Our results were similar to those of this meta-analysis. It was calculated that the neutrophil values in non-surviving patients were higher than the neutrophil values in surviving patients, and this is significant in terms of mortality. In another study conducted on the mortality prediction of neutrophil values, it was observed that neutrophil values in fatal cases gradually increased during the course of the disease. This increase in neutrophil values may indicate the involvement of a bacterial superinfection in Covid-19 disease and can be used as an indicator for the progression of the disease (11).

Crp value was determined higher in non-survival patients than in surviving patients. While the median CRP value was 154 in non-survival patients, this value was calculated as 66 in surviving patients and was considered significant in terms of mortality. In a meta-analysis, it was determined that high serum CRP, procalcitonin, d-dimer and ferritin levels were associated with poor prognosis and mortality in 25 studies and 5350 patients examined (12). Similar results were obtained in a study including 140 patients originating from China, and high CRP was evaluated as a poor prognosis criterion (13).

Procalcitonin value was found higher in non-surviving patients than in surviving patients. While the median procalcitonin value was 0.65 in non-survival patients, this value was calculated as 0.33 in surviving patients and was significant in terms of mortality. In studies, procalcitonin, like CRP and other acute phase reactants, was evaluated as a poor prognosis criterion and was associated with mortality (13,14). It is anticipated that it may be more useful to use it with serial measurements such as the Crp parameter.

In our study, no significant difference was detected between non-survival and surviving patients for fibrinogen value. On the other hand, d-dimer level was higher and significant in non-survival patients compared to surviving patients. Studies have predicted that d-dimer and fibrinogen values gradually increase in serial measurements in patient groups with a poor prognosis and may be an indicator of poor prognosis (15,16).

For troponin value, it was higher and more significant in non-survival patients compared to survival patients. Our study is compatible with the literature. Troponin I value, which is used as an indicator of cardiac involvement in many studies, suggests that it can be used as an indicator of poor prognosis (17-19).

In our study, ferritin value was determined higher in non-survival patients compared to surviving patients. While the median value was 624 in non-survival patients, it was calculated as 308 in survival patients and was significant. As a result of the analysis, the increase in the ferritin value, whose cut-off value was calculated as 138.5, was evaluated as a risk factor for the disease (HR: 1.004). Our study is compatible with the literature. In many studies, it has been revealed that high ferritin value is a guide in terms of deterioration in the course

of the disease and resulting in death (19,20).

In our research, APACHE II and SOFA scores, which are among the intensive care scoring systems, were higher in non-survival patients than in surviving patients. As a result of the analysis, the cut-off value was 23.5 for APACHE II and 8.5 for SOFA. The results were found significant for both scoring systems. In particular, the SOFA score has been determined to be the most effective parameter in predicting mortality with 100% sensitivity, specificity and accuracy. These values are compatible with the literature.

Conclusion

As a result, ferritin, lactate, urea and pH values, comorbid conditions, APACHE 2 and SOFA scoring systems during intensive care admission, which are the tests taken at the time of first admission to the health institution, can be used to predict mortality in Covid-19 disease.

With rapid evaluation at the first application, patients will be able to start treatment more quickly.

Ethical Aspects of the Research: This study was approved by the T.R. KTO Karatay University Clinical Research Local Ethics Committee decision number 2020/026.

Conflict of interest: no

There is no financially support.

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ORIGINAL ARTICLE

Comparison of Diagnostic Performance of PI-RADS V2 and V2.1 and Interobserver Agreement in Both Versions

PI-RADS V2 ve V2.1'in Tanısal Performansının ve Her İki Sürümdeki Gözlemciler Arası Uyumun Karşılaştırılması

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ABSTRACT

Objective: To compare the diagnostic performance for the detection of clinically significant prostate cancers and interobserver agreement between PI-RADS v2 and v2.1
Material and Method: The mpMRI images of 258 patients and 394 nodüles included in this retrospective study were obtained on 3T MR and evaluated by two radiologists according to PI-RADS v2 and v2.1. Sensitivity and specificity between v2 and v2.1 were compared. Detection rates for clinically significant prostate cancers were evaluated. Interobserver agreement was evaluated using κ statistics.
Results: PI-RADS v2.1 and v2 had higher sensitivity and lower specificity (100%, 52.38%) in the peripheral zone, and showed higher sensitivity and specificity (92.86%, 98.79%) in the transition zone for category ≥4 lesions to estimate csPCa, but no remarkable difference was found between the two versions. Interobserver agreement was statistically significant and very weak in the transition zone (κ=0.383, κ=0.279, respectively), very strong in the peripheral zone (κ=0.869) according to both classifications and they were similar.
Conclusion: The diagnostic performance of PI-RADS v2 and v2.1 were found similar in the determination of clinically significant cancers and all cancers in both zones. The clinically significant cancer detection rate in category 2+1 lesions in the transition zone was higher than in category 2 lesions but it was not statistically significant. Interobserver agreement was low in the transition zone and very strong in the peripheral zone in both versions.

Keywords: PI-RADS V2.1, clinically significant prostate cancer, interobserver agreement

ÖZ

Amaç: PI-RADS v2 ile v2.1 'nin klinik olarak anlamlı prostat kanserlerinin saptanmasına yönelik tanısal performansı ve gözlemciler arası uyumunu karşılaştırmak.
Gereç ve Yöntem: Bu retrospektif çalışmaya dahil edilen 258 hasta ve 394 nodülün mpMRI görüntüleri 3T MR'da elde edilmiş ve iki radyolog tarafından PI-RADS v2 ve v2.1'e göre değerlendirildi. V2 ve v2.1 arasındaki duyarlılık ve özgüllük karşılaştırıldı. V2'den v2.1'in kullanımında yükseltilmiş ve indirgenmiş lezyonlarda klinik olarak anlamlı prostat kanserlerinin tespit oranları değerlendirildi. Gözlemciler arası uyum κ istatistikleri kullanılarak değerlendirildi.
Bulgular: PI-RADS v2.1 ve v2, csPCA tespitinde kategori ≥4 lezyonlar için periferik zonda yüksek duyarlılık ve düşük özgüllük (%100, %52,38) ve transizyonel zonda yüksek duyarlılık ve özgüllük (%92,86, %98,79) gösterdi, iki versiyon arasında anlamlı bir fark bulunamadı. Her iki sınıflandırmaya göre de gözlemciler arası uyum istatistiksel olarak anlamlı ve transizyonel zonda çok zayıf (sırasıyla κ=0,383, κ=0,279), periferik zonda çok güçlü (κ=0,869) ve benzerdi.
Sonuç: PI-RADS v2 ve v2.1'in tanısal performansı, klinik olarak anlamlı kanserlerin ve her iki bölgedeki tüm kanserlerin tespitinde benzer bulundu. Geçiş bölgesindeki kategori 2+1 lezyonlarda klinik olarak anlamlı kanser tespit oranı, kategori 2 lezyonlara göre daha yüksekti ancak istatistiksel olarak anlamlı değildi. Her iki versiyonda da gözlemciler arası uyum transizyonel zonda düşük, periferik zonda ise çok güçlüydü.

Anahtar Kelimeler: PI-RADS V2.1, klinik olarak anlamlı prostat kanseri, gözlemciler arası uyum

Introduction

The main purpose of multiparametric prostate magnetic resonance imaging (mpMRI) is to identify and situate abnormalities corresponding to clinically significant prostate cancer (csPCa) (1,2). PI-RADS is a guideline created to advance the identification, localization, qualification, and risk classification of PC and to provide international standardization in the acquirement, explication and evaluation of mpMRI examinations (3). In order to determine the minimum and optimal parameters for early diagnosis, staging, and LN/bone evaluation of PC, a guideline containing T1WI, T2WI, DWI, DCI, and MRSI examinations was published and defined as PI-RADS v1 in 2012, by the ESUR (4,5). In 2015, an advanced version of PI-RADS v2 was defined by AJR, ESUR, and AdMeTech Foundation (6). Although PI-RADS v2 is widely supported by many clinical studies, due to a lack of experience in scoring and differences among readers, without changing the general scope or principles of version 2, it has been made with a few minor adjustments to simplify and standardized evaluation and reduce interobserver agreement, the v2.1 version has been created (7). T2WI imaging also maintains the dominant sequence position in the current version, especially in the evaluation of TZ lesions and tumor staging. BPH nodules, which are very common in TZ, especially in

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old age, and are mixed with PC, are detailed in the T2WI in the new version. In the new version, normal-appearing (rare) or round encapsulated nodules on T2W images in TZ are classified as "typical nodules" in the score 1 category. Generally, encapsulated nodules or non-encapsulated homogeneous nodules with smooth borders are defined as "atypical nodules" and evaluated in the score 2 category. Nodules in category 2 in TZ and with a DWI score of ≥ 4 are considered as category 3 in the new classification. In addition, homogeneous slightly hypointense areas between the nodules were also included in the score 2 category. In PZ, the diffusion score of linear-wedge-shaped focal diffusion restricting areas in DWI is reported as 2 (8).

In this retrospective study, lesions at risk of PC according to two versions were compared with their histopathological findings after cognitive fusion biopsy and/or radical prostatectomy (RP). The purpose of the study is the comparison of diagnostic performances of both versions by calculating sensitivity, specificity, PPV, NPV, and diagnostic accuracy parameters. In addition, the interobserver agreement was appraised in two versions.

Material And Methods

Patient selection

In our study, 326 patients with mpMRI, cognitive fusion biopsy, and/or RP in the radiology clinic with the suspicion of PC between June 2018 and May 2021 were evaluated. 68 patients were excluded from the study due to criteria, the rest 258 patients and their 394 nodules were analyzed. More than 1 nodule was present in 102 patients. The study population flowchart is shown in Figure 1.

Imaging Protocol

The mpMRI images included in the study were obtained on 3T Siemens MR (Skyra, Siemens Healthcare, Erlangen, Germany) devices with 24-channel pelvic phase array coils in such a way that all prostate glands and seminal vesicles (SV) enter the imaging field. Routine antispasmodic and antiperistaltic agents were not used in patients who were recommended bowel cleaning before the examination. High-resolution T2WI was taken in three plans corresponding to the position of the prostate gland. Moreover, the axial DWI was obtained with 3 different b values (b: 50, 1000, and 1500 sec/mm2), and ADC maps were created. When artifactual DWI was obtained due to gas distension in the rectum, the examination was terminated and repeated after being given antispasmodic and antiperistaltic agents. In addition, before, during, and after IV administration of contrast agent (with a concentration of 0.1–0.2 mmol/kg and an injection rate of 2-4 mL/sec) appropriate for the weight of the patients, axial fat-suppressed T1WI of the entire prostate gland was taken 3 times in 7 seconds for 240-300 seconds with a slice thickness of 0.5 mm. For the determination of pelvic metastases and lymph nodes, the area from the bifurcation of the aorta level to the pubic tubercules was evaluated on T1WI with wide FOV.

Imaging analysis

Before the start of the image analysis, significant changes in PI-RADS v2 and v2.1 were discussed with self-learning materials and representative cases between two readers. A more experienced reader (15 years of experience with>500 prostate MRIs a year) marked both zones' lesions on the PACS workstations with the basis of a PI-RADS sector map. Marked lesions were then scored by the more experienced reader and by the second reader (5 years of experience with>250 prostate MRIs a year) at different times according to both versions of PIRADS. T2WI was used about the morphological and signal characteristics of the lesions in PI-RADS category 1 lesions (downgrade 2-1) and category 2 lesions (downgrade 3-1) with PI-RADS v2.1. For PI-RADS 3 lesions in both versions and PI-RADS 2 lesions in PI-RADS v2.1, the DWI was used to figure out the final score. PI-RADS category 2 + 1 or 3 + 1 lesions enhanced to the final category proportional to the DWI criteria. In PIRADS 4 and above lesions, action was taken according to the size, extension and diffusion signal characteristics according to the guideline. Then final scores of two readers in both versions were compared with histopathological results. In this way, both the diagnostic performance and the interobserver agreement in both versions were evaluated. In addition, sensitivity, specificity, PPV, NPV and accuracy values between the two versions were compared.

Histopathologic analysis for reference standard

Specimens were prepared according to the International Society of Urological Pathology Consensus (9). A radiologist signed all suspicious lesions with a urologic pathologist to mate the pathologic outcomes. More than one nodule was detected in 102 patients. Benign prostatic hyperplasia (BPH) nodules, calcifications, and anatomic landmarks such as verumontanum and urethra were used to compare images and specimens. Cancers with a Gleason score of 7 and above and/or tumor volume of 0.5 cc and above and/or extraprostatic extension were considered clinically significant while tumors with a Gleason score of 6 were considered to be in the benign group, including non-tumor pathologies covering clinically insignificant cancer and precancerous lesions.

Statistical analysis

Analysis of the data was performed in the IBM SPSS Statistics 21.0 package program (IBM Corporation, Armonk, NY, USA). Figurative statistics were presented as mean ± standard deviation or median (width between quarters) for continuous numerical variables while categorical variables were shown as number of cases and symbol (%).

Age, PSA, free PSA, prostate volume, and PSA density in terms of the difference in importance were examined with students' t-tests in binary groups.

In PI-RADS v2 and PI-RADS v2.1, the levels of interobserver agreement were analyzed by ascertaining the Kappa coefficient. A Kappa coefficient in the range of 0.00-0.20 indicates that there is no agreement among the observers, the range of 0.21-0.39 is a very weak agreement between the observers, the range of 0.40-0.59 is poor agreement between the observers, the range of 0.60-0.79 is a moderate agreement, the range 0.80-0.90 is strong agreement and above 0.90 indicates a very strong agreement. The statistical significance of PI-RADS v2.0 and PI-RADS v2.1 in detecting clinically significant prostate cancer was investigated by calculating the area under the ROC curve and with 95% confidence intervals. Diagnostic performance indicators for different threshold values of two versions were evaluated by calculating sensitivity, specificity, PPV, NPV, and diagnostic accuracy rates.

Unless otherwise stated, results for $p<0.05$ were noted as statistically significant.

Results

The study included 258 patients who underwent cognitive fusion biopsy or radical prostatectomy. The mean ± standard deviation values of age, PSA, free PSA, prostate volume and PSA densities of all patients are presented in Table 1. Mean age, PSA, free PSA and PSA density values were statistically significantly higher, and volume was lower in clinically significant prostate cancer ($p<0.05$). Sixty-one (18.7%) of the lesions were in the PZ; 262 (80.4%) were located in the TZ.

Forty PZ lesions (65.5%) were defined as clinically significant prostate cancer and 21 lesions (34.5%) were defined as clinically insignificant prostate cancer or benign. No scoring difference was found between the two PI-RADS versions in both readers in PZ lesions. 14 of TZ lesions (5.3%) were diagnosed as clinically significant prostate cancer and 248 lesions (94.7%) were diagnosed as clinically insignificant prostate cancer or benign. According to the first reader, there were no diagnostic differences between both versions in clinically significant cancer detection. According to the second reader, only 1 lesion reported as PI-RADS 2+1 was identified as clinically significant cancer. 39 lesions defined as PI-RADS 2 according to v2 by both readers were evaluated as PI-RADS1 according to v2.1 due to their total encapsulation appearance and all were benign. In addition, clinically significant cancer was not detected between 16 lesions evaluated as 2+1 in PIRADS v2 by radiologist 1 and 30 lesions evaluated by radiologist 2 as 2+1 in PI-RADS v2 (Table 3). All of the lesions that we classified as category 2 (downgrade 3-1) about v2.1 were benign (Figure 2).

Both versions showed the same diagnostic effectiveness in the recognition of clinically significant prostate cancers and all cancers in PZ. The diagnostic effectiveness of the two versions was similar in TZ (Figure 3, Table 3).

In our study, when the cut off ≥3 was taken due to 16 lesions according to the 1st reader and 30 according to the 2nd user, a decrease in the specificity, PPD and accuracy rates was noted. When cut-off ≥4 was taken, no difference was found between the two versions in other parameters. According to the second reader, the sensitivity and NPV increased in PI-RADS v2.1 when the cut-off ≥3 was taken in the recognition of clinically significant cancer in TZ, while the specificity, PPV, NPV, and accuracy rates increased when the cut-off was ≥4. When all cancers in the TZ were evaluated and the cut off ≥3 was taken, sensitivity and NPV values increased in PI-RADS v2.1 compared to the first reader, and sensitivity, NPV, and PPV values increased compared to the second reader. When the cut off ≥4 was taken, no significant difference was found between the parameters specified in both versions in both readers.

Interobserver agreement was statistically significant and very strong according to the two classification systems in the PZ. The interobserver agreement was statistically significant and very weak according to the two classification systems in the TZ (Table 4).

Table 1. Comparison of age, PSA value, prostate volume, and PSA density values according to clinical significance and frequency distributions of pathology, ISUP grade, and Gleason scores according to lesion location in patients

	csPCa (n = 54)	ciPCa (n=272)	p*
	Value	Value	
Age*	68.44 ±8.98	64.08±7.32	0.001
PSA*	17.44±16.77	11.56±12.23	0.017
Free PSA*	3.35±3.45	2.53±2.65	0.05
Prostate Volume*	60.05±39.44	84.80±53.59	0.001
PSA density*	0.37±0.44	0.15±0.16	<0.001
	PZ (n=61)	TZ (n=262)	
Pathology Groups**			
Benign	14 (23)	223 (85.1)	
csPCa	7 (11.5)	25 (9.5)	
ciPCa	40 (65.6)	14 (5.3)	
ISUP grade or Gleason score**			
ISUP 1 or ≤ 6	7 (14.9)	25 (64.1)	
ISUP 2 or 3+4 = 7	13 (27.6)	8 (20.5)	
ISUP 3 or 4+3 = 7	12 (25.5)	4 (10.2)	
ISUP 4 or 4+4 = 8	7 (14.9)	-	
ISUP 5 or 9-10	8 (17)	2 (5.1)	
Pathology**			
Prostatitis	3 (4.9)	79 (30.2)	
Adenomatous hyperplasia	4 (6.5)	118 (45)	
HGPIN	1 (1.6)	4 (1.5)	
PIN	1 (1.6)	3 (1.1)	
ASAP	2 (3.3)	18 (6.9)	
Adenocancer	46 (75.4)	39 (14.9)	
Intraductal cancer	4 (6.5)	-	
Insitu cancer	-	1 (0.4)	

*Data values are presented as a mean ± standard deviation. **Data values are presented as a count and percentages. ISUP = International Society of Urological Pathology; PZ= Peripheral zone, TZ = Transition zone, csPCa = Clinically significant prostate cancer, ciPCa = Clinically insignificant prostate cancer and benign.

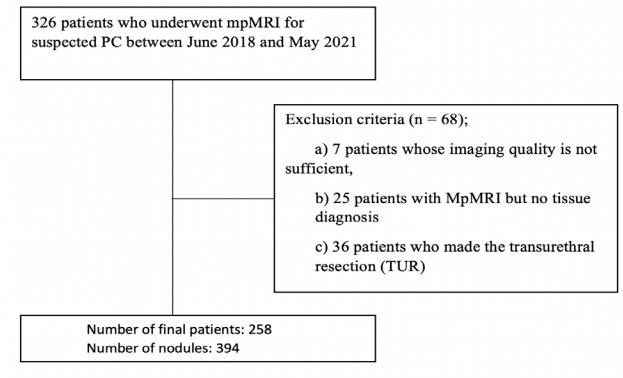

Figure 1. Study population flowchart.

Table 2. Distribution of lesions located in the PZ and TZ according to PI-RADS 2 and PI-RADS 2.1

	Reader 1		Reader 2	
	csPCa	ciPCa	csPCa	ciPCa
PZ				
PI-RADS v2				
PI-RADS 1	-	-	-	-
PI-RADS 2	-	-	-	-
PI-RADS 3	-	11 (52.4)	1 (2.5)	9 (42.9)
PI-RADS 4	17 (42.5)	8 (38.1)	16 (40)	10 (47.6)
PI-RADS 5	23 (57.5)	2 (9.5)	23 (57.5)	2 (9.5)
PI-RADS v2.1				
PI-RADS 1	-	-	-	-
PI-RADS 2	-	-	-	-
PI-RADS 3	-	11 (52.4)	1 (2.5)	9 (42.9)
PI-RADS 4	17 (42.5)	8 (38.1)	16 (40)	10 (47.6)
PI-RADS 5	23 (57.5)	2 (9.5)	23 (57.5)	2 (9.5)
TZ				
PI-RADS v2				
PI-RADS 1	-	-	-	-
PI-RADS 2	-	215 (86.7)	1 (7.1)	127 (51.2)
PI-RADS 3	1 (7.1)	30 (12.1)	4 (28.6)	88 (35.5)
PI-RADS 4	10 (71.4)	3 (1.2)	6 (42.9)	32 (12.5)
PI-RADS 5	3 (21.4)	-	3 (21.4)	1 (0.4)
PI-RADS v2.1				
PI-RADS 1	-	39 (15.7)	-	39 (15.7)
PI-RADS 2	-	160 (64.5)	-	58 (23.4)
PI-RADS 3	1 (7.1)	46 (18.5)	5 (35.7)	118 (47.6)
PI-RADS 4	10 (71.4)	3 (1.2)	6 (42.9)	32 (12.9)
PI-RADS 5	3 (21.4)	-	3 (21.4)	1 (0.4)

Data in parentheses are percentages. PI-RADS = Prostate Imaging Reporting and Data System; csPCa = clinically significant prostate cancer, ciPCa = clinically insignificant prostate cancer, PZ = Peripheral zone, TZ = Transition zone

Table 3. Diagnostic performance of PI-RADS v2 and v2. 1 in PZ and TZ cancers

	p-value	Cut-off	PI-RADS V2	PI-RADS V2.1
Peripheral zone				
csPCa				
Sensitivity (%)	<0.001	≥4	100 (91.19-100)	100 (91.19-100)
Specificity (%)	<0.001	≥4	52.38 (29.78-74.29)	52.38 (29.78-74.29)
PPV (%)	<0.001	≥4	80 (71.86-86.23)	80 (71.86-86.23)
NPV (%)	<0.001	≥4	100	100
Accuracy (%)	<0.001	≥4	83.61 (71.91-91.85)	83.61 (71.91-91.85)
AUC (%95 GA)	-	-	0.851 (0.744-0.959)	0.851 (0.744-0.959)
All Cancers				
Sensitivity (%)	<0.001	≥4	95.74 (85.46-99.48)	95.74 (85.46-99.48)
Specificity (%)	<0.001	≥4	64.29 (35.14-87.24)	64.29 (35.14-87.24)
PPV (%)	<0.001	≥4	90 (81.64-94.8)	90 (81.64-94.8)
NPV (%)	<0.001	≥4	81.82 (52.32-94.86)	81.82 (52.32-94.86)
Accuracy (%)	<0.001	≥4	88.52 (77.7-95.3)	88.52 (77.7-95.3)
AUC (%95 GA)	-	-	0.819 (0,671-0.968)	0.819 (0,671-0.968)
Transition zone				
csPCa				
Sensitivity (%)	<0.001	≥4	92.86 (66.13-99.82)	92.86 (66.13-99.82)
Specificity (%)	<0.001	≥4	98.79 (96.51-99.75)	98.79 (96.51-99.75)
PPV (%)	<0.001	≥4	81.25 (58.23-93.09)	81.25 (58.23-93.09)
NPV (%)	<0.001	≥4	99.59 (97.37-99.94)	99.59 (97.37-99.94)
Accuracy (%)	<0.001	≥4	98.47 (96.14-99.58)	98.47 (96.14-99.58)
AUC (%95 GA)	-	-	0.988 (0.971-1.00)	0.988 (0.971-1.00)
All Cancers				
Sensitivity (%)	<0.001	≥4	38.46 (23.36-55.38)	38.46 (23.36-55.38)
Specificity (%)	<0.001	≥4	99.55 (97.53-99.99)	99.55 (97.53-99.99)
PPV (%)	<0.001	≥4	93.75 (67.1-99.1)	93.75 (67.1-99.1)
NPV (%)	<0.001	≥4	90.24 (87.83-92.22)	90.24 (87.83-92.22)
Accuracy (%)	<0.001	≥4	90.46 (86.24-93.73)	90.46 (86.24-93.73)
AUC (%95 GA)	-	-	0.690 (0.583-0.797)	0.690 (0.583-0.797)

Data are percentages, with the 95% confidence interval shown in parentheses. PI-RADS = Prostate Imaging Reporting and Data System. PZ= Peripheral zone, TZ = Transition zone. PPV= Positive predictive value, NPV= Negative predictive value, csPCa= clinically significant prostate cancer

Table 4. Interobserver agreement scores according to PI-RADS v2.0 and v2.1 classifications for the PZ and TZ.

PI-RADS category	Zone	Kappa coefficient	p-value
PI-RADS V2	PZ	0.869	<0.001
PI-RADS V2	TZ	0.279	<0.001
PI-RADS V2.1	PZ	0.869	<0.001
PI-RADS V2.1	TZ	0.400	<0.001

The levels of interobserver agreement were evaluated by calculating the Kappa coefficient.

PI-RADS = Prostate Imaging Reporting and Data System, PZ= Peripheral zone, TZ = Transition zone.

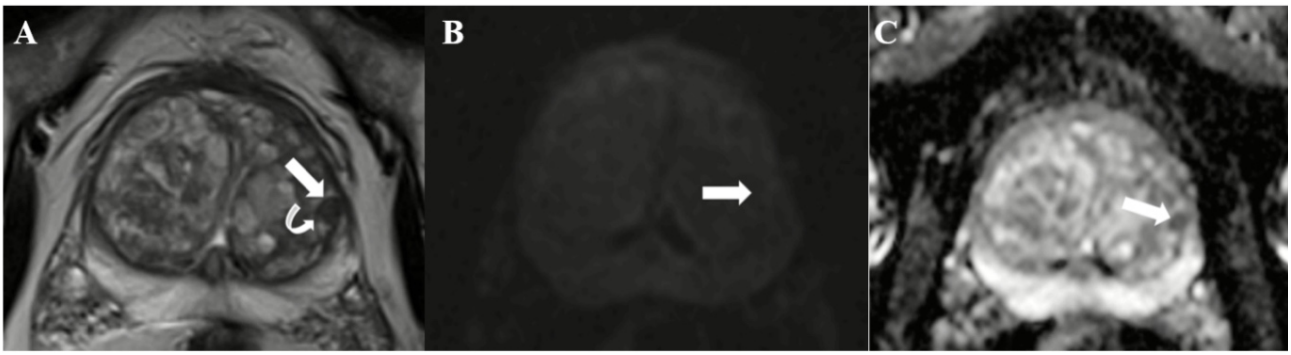

Figure 2. Multiparametric MRI of a 68-year-old patient with PSA 14,82 who underwent radical prostatectomy. Axial T2-weighted image (A) showed a mostly encapsulated nodule (arrow) with a slightly obscured margin (curved arrow) in the left TZ, which was categorized as category 3 by PI-RADS v2 but downgraded to category 2 by v2.1. A focal mildly hyperintense nodule was evident on DWI (B) and mildly hypointensity was observed on an ADC map (C), which was a DWI score of 3. The histopathology of the lesion was reported as benign tissue.

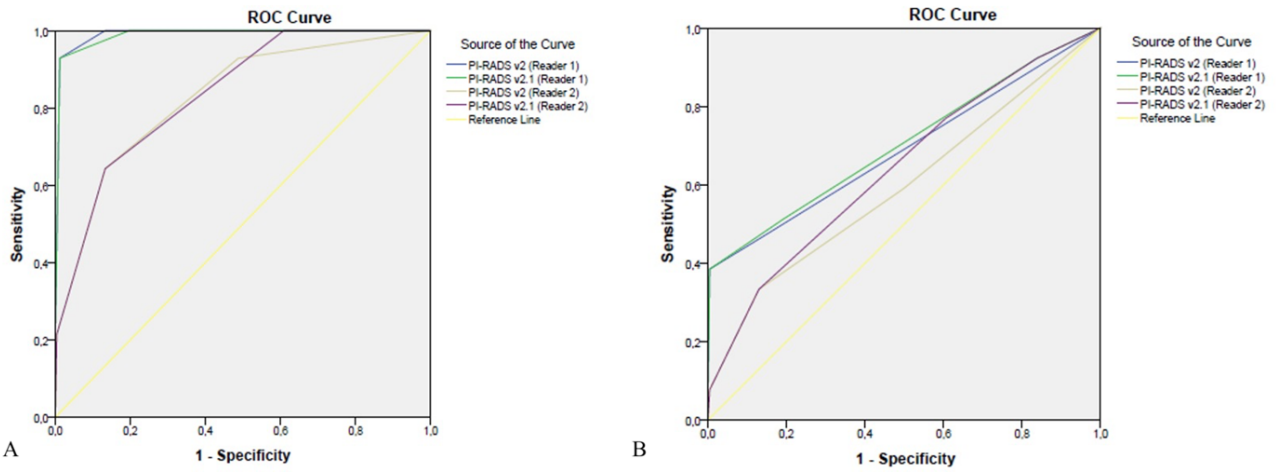

Figure 3. Curves of PI-RADS v2 and v2.1 relative to both readers in the PZ (A) and TZ (B).

Discussion

In this study, the diagnostic effectiveness of PI-RADS v2 and PI-RADS v2.1 and the interobserver agreement in both versions were compared using mpMRI in both PZ and TZ cancers. In our analyses, we identified that the diagnostic performance of PI-RADS v2 and v2.1 was similar in both csPCa and all cancers in PZ and TZ.

Moreira et al. have stated that the most important difference between the two versions is that the lesions, which were classified in category 2 in the previous version due to the typical benign prostatic hyperplasia nodules in TZ, are in category 1 in the current version (9, 10). The results of our study were similar to this study. Chao-gang Wei et al. published a study reporting that sensitivity, specificity, and accuracy in the evaluation of TZ lesions were lower in PIRADS v2.1 than in PIRADS V1 among all readers. In the same study, they argued that PI-RADS v2.1 had a better interobserver agreement than PI-RADS v2 for analyzing TZ lesions (11). Jieun Byun et al. reported that the sensitivity and specificity of v2.1 (94.5% and 60.9%) was higher than v2 (91.8% and 56.3%) for category ≥3 lesions in the detection of csPCa in TZ, although not significantly (12).

The targeted biopsy is frequently performed for ≥3 lesions with PI-RADS v2 because of its high specificity (2,13,14). However, in the presence of high PSA values and supportive clinical findings, some urologists may request a targeted biopsy for PIRADS <3 lesions. Clinically significant cancer detection rates in category ≥3 lesions vary between 3.8-30% in studies (15-17). It is thought that this difference arises from definitions such as "ambiguity of borders" or "moderate hypointensity" defined in PI-RADS v2, which may cause different interpretations from reader to reader (18,19,20). In this context, there are also studies stating that the cut-off value should be ≥4, especially in TZ lesions, to increase the specificity in targeted biopsies (21,22,23).

As a result of the clear and understandable definitions of the 'atypical nodule' concept that came with the current version in TWI, all of the lesions that we classified as category 2 (downgrade 3-1) were benign. This enhanced the sensitivity and specificity of category ≥3 lesions to determine csPCa. One of the major changes that came with PIRADS v2.1 is the definition of 'typical nodule', downgrading category 2 lesions to category 1. In our study, there was no clinically significant cancer in any of the total encapsulated lesions defined as

"typical BPH nodules" downgraded from category 2 to 1 according to v2.1. In previous studies, clinically insignificant cancers with low volume and Gleason score ≤ 6 have been detected in some category 1 lesions. (12). However, this can be ignored because the most important target of PI-RADS classification is to detect csPCa.

Many studies have been done about the importance of DWI in v2 before (24). One of the most important changes in PIRADS v2.1 is that the DWI score of ≥4 in atypical nodules in the TZ upgrades the lesion from category 2 to category 3. According to PI-RADS v2.1, clinically significant cancer was detected in only 1 case whose DWI score was ≥4 in TZ and upgraded from category 2 to 3. In our study, the detection level of csPCa and all cancers in category 2+1 lesions was higher in the current version, but it was not significant. Also, we understood that especially in PI-RADS 3 lesions, which are frequently confused with BPH nodules in TZ, increasing the agreement interobserver and preventing unnecessary biopsies is the main purpose of v2.1. However, in our study, the number of lesions that were upgraded (2+1) due to DWI score in TZ compared to v2.1 was higher than the number of lesions downgraded with the definition of ''atypical nodule'' (3-1=2), and there was an increase contrary to the decrease in the number of targeted biopsies.

In our analyses; the interobserver agreement was statistically significant and very strong according to the PI-RADS v2.0 and v2.1 classifications in the PZ and very weak according to the two classifications in the TZ. Rajesh Bhayana et al. claimed that agreement between interobservers enhanced using PI-RADS v2.1 in the PZ but there were no similar findings in TZ (25). This study yielded similar results to our study. Jieun Byun et al. stated that interreader agreement at category ≥3 lesions in the TZ, v2.1 showed better performance than v2 (12). Hotker AM et al. found that the diagnostic performance and inter-reader agreement of v2.1 were higher than v2.0 but the changes in the new version applied to a small group of patients (26).

In our study, there were some limitations the first of which was a single-center retrospective study. Non-targeted systematic biopsy in MR-negative patients was a limitation. The low number of PI-RADS category 2+1 lesions was another limitation and reduced the effect of statistical analysis. In addition, the fact that not all pathological results were obtained from RP material, radiologists, and urologists who did not have sufficient experience in targeted fusion biopsies, was another limitation.

Conclusion

PI-RADS v2.1 and v2 showed higher sensitivity and lower specificity in PZ and showed higher sensitivity and specificity in TZ in the detection of csPCa, and there was no significant difference between the two versions. On the other hand, in our study; the interobserver agreement was statistically significant and very weak according to the two classifications in the TZ and very strong according to the two classifications in the PZ. PI-RADS category 2 + 1 lesions upgraded by DWI from category 2 identified on T2WI showed a higher detection rate of csPCa than category 2 lesions, but it was not significant. Although clinically significant cancer was detected in only one of the lesions whose category was evaluated as 2+1 according to PI-RADS v2.1 in our study, the rate of csPCa detection can increase in 2+1 category lesions compared to category 2 lesions in larger and multicenter studies. Although there was no statistically significant difference in csPCa detection between the two versions, it can be determined that v2.1 is superior to v2.0, especially in the diagnostic performance of TZ cancers, in studies with a larger number of patients. With the updated versions, more detailed descriptions of especially difficult to score TZ lesions can make the difference in lesion character clearer and the agreement of evaluation among readers can be increased. With each updated version of the MpMRI and PI-RADS scoring system, it has made progress in creating a common interpretation language and strengthens its place in the diagnosis and follow-up of PC day by day.

Abbreviation: PI-RADS = Prostate Imaging Reporting and Data System, ISUP = International Society of Urological Pathology; PZ= Peripheral zone, TZ = Transition zone, csPCa = Clinically significant prostate cancer, ciPCa = Clinically insignificant prostate cancer, PPV= Positive predictive value, NPV= Negative predictive value, RP = Radical prostatectomy, ESUR = European Association of Urogenital Radiology, AJR = American Journal of Roentgenology

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Availability of data, code and materials: The datasets used and/or analyzedduring the current study are available from the corresponding author on reasonable request.

Ethics approval: Our institutional review board approved this retrospective study with a waiver of informed consent.

Authors' contributions: Ahmet Baytok manuscript writing/editing. Mustafa Koplay: manuscript writing/ editing. Halil Özer: statistical analysis. Ömer Faruk Topaloğlu: manuscript editing. Mehmet Kaynar: collecting data. Serdar Göktaş: collecting data. Ali Furkan Batur: contributed to data interpretation.

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ORIGINAL ARTICLE

Evaluation of the Presentation of Newly Diagnosed Type 1 Diabetes Mellitus in Children During and After the COVID-19 Pandemic

Türkiye'nin Güneyindeki İkinci Basamak Bir Sağlık Merkezinde, COVİD-19 Salgını Sırasında ve Sonrasında Tip 1 Diyabet Tanısı Alan Çocukların Tanı Özelliklerinin Değerlendirilmesi

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ABSTRACT

Background: The COVID-19 pandemic has been a global health problem with high morbidity and mortality. In this study, it was aimed to compare the clinical and laboratory findings of patients diagnosed with type 1 diabetes mellitus (T1D) during the pandemic and after the pandemic.
Method: This is a 30-month-single-center, cross-sectional study. The time between October 2020 and December 2021 was defined as the pandemic period, and between January 2022 and March 2023 as the post-pandemic period. During these periods, clinical and laboratory parameters of pediatric patients diagnosed with T1D were compared at the time of admission.
Results: While 87 patients were diagnosed during the pandemic period, 86 patients were diagnosed during the post-pandemic period. The rate of male patients diagnosed during the pandemic period was significantly higher (56%, 36%, respectively, p=0.007). Anti-islet Cell antibody (ICA) positivity was statistically significantly higher in those diagnosed during the pandemic period. (52.6%, 18.6%, respectively, p<0.001). There was no difference between the groups in terms of hemoglobin A1C, thyroid autoantibodies and tissue transglutaminase antibodies (p>0.05). C peptide levels were significantly lower in those diagnosed during the pandemic period (0.39±0.4, 0.63±0.6, respectively, p=0.021). Admissions with severe acidosis were more common during the pandemic than those admitted after the pandemic (29.9%, 16.3%, respectively, p=0.151).
Conclusion: The numbers of children with T1D newly diagnosed in a secondary health center were similar during and after the pandemic. In the pandemic period, admissions with autoantibody positivity, low C-peptide and severe acidosis were more common.

Keywords: COVID 19, diabetes mellitus type 1, newly diagnosed

ÖZ

Amaç: COVİD-19 salgını yüksek morbidite ve mortaliteye sahip küresel bir sağlık sorunu olmuştur. Bu çalışmada pandemi sırasında ve pandemi sonrasında tip 1 diyabet (T1D) tanısı alan hastaların klinik ve laboratuvar bulgularının karşılaştırılması amaçlandı.
Yöntem: 30 aylık, tek merkezli, kesitsel bir çalışma şeklinde dizayne edilen bu çalışmada Ekim 2020 ile Aralık 2021 arası pandemi dönemi, Ocak 2022 ile Mart 2023 arası ise pandemi sonrası dönem olarak tanımlandı. Bu iki dönemde başvuran yeni tanı alan T1DM hastalarının klinik ve laboratuvar parametreleri karşılaştırıldı.
Bulgular: Pandemi döneminde 87 hastaya tanı konulurken, pandemi sonrası dönemde 86 hastaya tanı konuldu. Pandemi döneminde tanı alan erkek hasta oranı anlamlı olarak daha yüksekti (sırasıyla %56, %36, p=0,007). Pandemi döneminde tanı konulanlarda Anti-Adacık Hücre Antikoru (ICA) pozitifliği istatistiksel olarak anlamlı derecede yüksekti. (sırasıyla %52,6, %18,6, p<0,001). Gruplar arasında hemoglobin A1C, tiroid otoantikorları ve doku transglutaminaz antikorları açısından fark yoktu (p>0,05). Pandemi döneminde tanı konulanlarda C peptid düzeyleri anlamlı derecede düşüktü (sırasıyla 0,39±0,4, 0,63±0,6, p) =0,021). Pandemi sırasında şiddetli asidoz nedeniyle başvurular, pandemi sonrasına göre daha sık görüldü (sırasıyla %29,9, %16,3, p=0,151).
Sonuç: İkinci basamak sağlık merkezimizde yeni tnaı koyulan T1D hastası çocukların sayısı pandemi sırasında ve sonrasında benzerdi. Pandemi döneminde otoantikor pozitifliği, C-peptid düşüklüğü ve ciddi asidoz şikayetleriyle başvurular daha sıktı.

Anahtar Kelimeler: covid 19, diabetes mellitus type 1, yeni tanı

Introduction

The World Health Organization declared COVID-19 a pandemic on March 24, 2020, as it caused high morbidity and mortality in a short time and turned into a global health problem (1). The first case was seen in Türkiye on March 11, 2020 (2). COVID-19 disease can affect the health of children directly or indirectly, and this situation can cause many social, biological and economic negativities. Many studies have revealed interesting findings related to the increase in the prevalence of newly diagnosed type 1 diabetes during the pandemic period and the effect of COVID-19 on the clinical severity of the symptoms at the time of first admission (3,4). During the pandemic period, some studies showed that there was a significant decrease in vitamin D levels in children and it was associated with decreased sun exposure during confinement (5). In this study, the clinical and laboratory characteristics of the newly diagnosed type 1 diabetes mellitus (T1D) patients during and after the pandemic were compared at the time of diagnosis.

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Material and Methods

This descriptive cross-sectional study was approved by the Gaziantep University Faculty of Medicine Clinical Research Ethics Committee (Number:01/2023). All patients younger than 18 years of age who were diagnosed with T1D at Gaziantep Gynecology and Children's Hospital between October 2020 and March 2023 were included in the study. We diagnosed patients with type 1 diabetes according to the International Society for Pediatric and Adolescent Diabetes 2018 criteria (6). All diabetic ketoacidosis (DKA) and non-DKA (non-DKA) patients (venous pH>7.3 or bicarbonate >15 mmol) diagnosed as T1D with plasma glucose >200 mg/dl and ketonemia or ketonuria were included in this study. DKA was classified as plasma glucose >200 mg/dl, presence of ketonemia or ketonuria, venous pH <7.3 or bicarbonate <15 mmol/L (mild DKA); pH<7.2 or bicarbonate <10 mmol/L (moderate DKA); pH<7.1 or bicarbonate <5 mmol/L (severe DKA). At the time of diagnosis, HbA1C (%), C-peptide, islet cell antibody (ICA), glutamic acid decarboxylase antibody (GAD), anti-insulin antibody (Anti IA), anti-thyroid peroxidase antibody (Anti TPO) and celiac antibodies (tissue transglutaminase IGA, IGG) were evaluated. At the time of the study, the same micro enzyme-linked immunosorbent assay (ELISA) was used to measure autoantibody positivity. We also evaluated the 25(OH) D3, Vitamin B12 and anti-HBS levels of the patients.

According to the data of the Turkish Statistical Institute (TUİK) dated 31 December 2021, the population of Türkiye was 84 million 580 thousand 273 people (7). As of January 2022, covid 19 vaccine (Sinovac or BioNTech) has been applied for 1 year in Türkiye, and approximately 138 million doses of vaccine have been applied to individuals over the age of 18 years (8). For this reason, the period between October 2020 and December 2021 was defined as the pandemic period, and the period between January 2022 and March 2023 was defined as the post-pandemic period. Based on these data, we divided the patients into two groups as those diagnosed during and after the pandemic.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 23.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and min-max where appropriate). Chi-square test was used to compare categorical expressions. Shapiro-Wilk test was employed to determine whether the parameters in the study showed normal distribution. Mann Whitney U test was used for the parameters that did not show normal distribution. Statistical significance level was taken as 0.05 in all tests.

Results

Of the 173 patients included in the study, 80 (46.2%) were male and 93 (53.9%) were female. Their mean age was 15.7 (±3.8) years. Only 38 patients (22%) were refugees. 57 patients (32.9%) were in pubertal period. Anti-HBs was positive in only 69 patients (39.9%). The numbers of Anti-HBs positive patients were similar in the groups (p=0.59). The mean level of 156 patients whose vitamin D levels were checked was 14.1±7.8 ng/ml. Of the patients, 130 (83.3%) whose vitamin D values were checked had a vitamin D level below 20 ng/ml and had vitamin deficiency. Vitamin D value was higher in male patients than in female patients (p=0.029). Also, Vitamin D levels of pandemic and post-pandemic patients were similar (p=0.59).

Of the patients, 87 (50.3%) were diagnosed during the pandemic period (group 1), and 86 (49.7%) were diagnosed during the post-pandemic period (group 2). The presence of anti-ICA was found higher in group 1 (p<0.001). The co-positivity of Anti GAD and ICA antibodies was higher in group 1 (39/87 [%44.8] and 16/86 [%18.6], respectively) (p<0.001). Again, in group 1, the positivity of 3 antibodies together (Anti-Gad, ICA and Anti insulin) was statistically higher (7/87 [%8], 2/86 [%2.3], respectively) (p=0.001). There was no difference between the groups in terms of hemoglobin A1c, thyroid autoantibodies and tissue transglutaminase antibodies (p>0.05). Potassium and C-peptide values were higher in group 2 compared to group 1 (p=0.037; p=0.021, respectively); Vitamin B12 value was observed low (p=0.011). The low potassium in group 1 was considered due to the high number of patients presenting with DKA. The comparison of other values between the groups is shown in Table 1.

When male and female patients were compared, the presence of Anti-GAD was higher in female patients than in male patients (p=0.046). No significant finding was found between the other parameters in Table 2 and the groups (p>0.05). Height SD and HbA1c values of Turkish patients were higher than those of refugee patients (p=0.020).

The number of people diagnosed with non-DKA was higher in the post-pandemic period than in the pandemic period, but it was not statistically significant (47 [54.7%], 37 [42.5%], respectively) (p=0.15). Similarly, the number of admissions with severe acidosis was higher during the pandemic period than in the post-pandemic period. (respectively 26 [29.9%], 14 [16.3%]) (p=0.15). Among the patients diagnosed during the pandemic period, 49(56.3%) male patients were significantly more than female patients (p=0.007).

While patients in the pandemic period were most diagnosed in November (19 cases) and March (11 cases), the most diagnosed months were January (12 cases) and October (9 cases) in the post-pandemic period. While 11 patients were diagnosed during the pandemic period in the summer season, only 4 patients were diagnosed during the post-pandemic period.

In terms of HbA1c levels, there was no significant difference between the pandemic and post-pandemic periods. During the pandemic period, SARS-CoV-2 PCR test was performed and only 2 patients were positive with resistant severe acidosis and respiratory distress and significantly higher infection indicators.

Table 1 Evaluation of laboratory and clinical characteristics of 2 groups

Related parameters	Group 1 (n=87)	Group 2 (n=86)	p†
	n(%)	n(%)	
Sex			
Male	49 (56.3)	31 (36)	0.007**
Female	38 (43.7)	55 (64)	
Puberty	27 (31)	30 (34.9)	0.590
Nationality			
Immigrant	21 (24,1)	17 (19.8)	0.488
Turkish	66 (75.9)	69 (80.2)	
DM in the family	7 (8)	5 (5.8)	0.563
Anti GAD	50 (64.1)	50 (58.1)	0.434
Anti ICA	41 (52.6)	16 (18.6)	<0.001**
Anti insulin	6 (7.7)	3 (3.5)	0.238
Celiac antibody	10 (11.5)	9 (10.5)	0.829
Anti TPO	18 (20.7)	16 (18.6)	0.730
Anti HBs	33 (37.9)	36 (41.9)	0.598
Acidosis severity			
none	37 (42.5)	47 (54.7)	0.151
1	13 (14.9)	16 (18.6)	
2	11 (12.6)	9 (10.5)	
3	26 (29.9)	14 (16.3)	
	Mean ± SD	Mean ± SD	p‡
Age (years)	12.,2±3.8	9.75±3.81	0.519
Height (cm)	138.2±22.6	134.1±23.4	0.181
Height SD	0.023±1.1	-0.11±1.2	0.415
Weight (kg)	35.6±15.9	33.9±19.4	0.199
Weight SD	-0.16±1.2	-0.45±1.1	0.075
Laboratory values (at diagnosis) Glucose (mg/dl)	456.5±106.9	478.4±15.0	0.685
Sodium (mmol/L)	133.2±3,8	145.1±107.3	0.447
Potassium (mmol/L)	3.60±0.5	3.74±0.4	0.037*
C peptide (ng/ml)	0.39±0,4	0.63±0.6	0.021*
HbA1c (%)	12.9±1.6	12.5±2.0	0.265
Insulin (µIU/mL)	2.91±2.8	3.58±2.9	0.079
Vitamin D (ng/ml)	13.7±7.1	14.5±8.4	0.598
Vitamin B12 (pg/ml)	465.4±224.1	386.9±188.1	0.011*
			-

** p<0,05, **p<0,001, †: chi-square, ‡: Mann Whitney U*

GAD: Glutamic acid decarboxylase, ICA: islet cell antibody, TPO: thyroid peroxidase

Table 2 Laboratory and clinical characteristics of the patients by gender

Related parameters	Male (n=80)	Female (n=93)	p†
	n(%)	n(%)	
Puberty	27 (33.8)	30 (32.3)	0.835
Nationality			
Immigrant	18 (22.5)	20 (21.5)	0.875
Turkish	62 (77.5)	73 (78.5)	
DM in the family	6 (7.5)	6 (6.5)	0.787
Anti GAD	40 (53.3)	60 (67.4)	0.046*
Anti ICA	29 (38.7)	28 (31.5)	0.334
Anti insulin	6 (8)	3 (3.4)	0.195
Celiac antibody	5 (6.3)	14 (15.1)	0.065
Anti TPO	14 (17.5)	20 (21.5)	0.509
Anti HBs	36 (45)	33 (35.5)	0.202
Acidosis severity			
none	40 (50)	44 (47.3)	0.417
1	13 (16.3)	16 (17.2)	
2	12 (15)	8 (8.6)	
3	15 (18.8)	25 (26.9)	
	Mean ± SD	**Mean ± SD**	p‡
Age (years)	10.40±3.90	9.40±3.65	0.151
Height (cm)	140.2±21.3	132.7±24.0	0.097
Height SD	0.05±1.1	-0.13±1.1	0.313
Weight (kg)	36.6±16.7	33.2±18.5	0.100
Weight SD	-0.19±1.2	-0.41±1.2	0.255
Laboratory values (at diagnosis) Glucose (mg/dl)	478.8±131.3	457.6±30.2	0.364
Sodium (mmol/L)	145.3±111.4	133.8±3.8	0.208
Potassium (mmol/L)	3.67±0.5	3.68±0.4	0.890
C-peptide (ng/ml)	0.45±0.4	0.58±0.6	0.534
HbA1c (%)	12.4±1.9	12.9±1.7	0.105
Insulin (µIU/mL)	2.88±2.5	3.57±3.2	0.231
Vitamin D (ng/ml)	15.2±7.1	13.2±8.3	0.029*
Vitamin B12 (pg/ml)	441.6±205.3	409.9±212.5	0.234

** p<0,05, **p<0,001, †: chi-square, ‡: Mann Whitney U*

GAD: Glutamic acid decarboxylase, ICA: islet cell antibody, TPO: thyroid peroxidase

Discussion

In this study, the clinical and laboratory characteristics of newly diagnosed patients were evaluated during and after the COVID-19 epidemic for a total of 30 months. Similar to the publications reported from our country, no difference was found in the frequency of patients diagnosed between the two periods (9). However, it has been shown that applications with severe diabetic ketoacidosis are more common during the pandemic period. Additionally, in our study, we found significantly higher antibody positivity and low C-peptide levels in patients diagnosed during the pandemic period.

Although its etiology is not clear, type 1 diabetes mellitus is a multifactorial disease. Especially in individuals with genetic predisposition, exposure to infectious agents (especially viruses) at an early age is affected by environmental factors such as toxins, food, chemicals, as well as triggering factors such as psychosocial stress (10,11).

The relationship between SARS-CoV-2 infection and incipient T1D development is unclear. A population-based study conducted in Germany between January 2020 and June 2021 among individuals younger than 18 years old showed that the observed incidence was significantly higher than the expected incidence of the new type of T1D (12). However, this study did not provide evidence to prove that the COVID-19 pandemic has had a direct impact on this increased incidence. In a study of 92 centers worldwide, no increase in pediatric new-onset T1DM was observed during the COVID-19 pandemic (13). In our study, the prevalence of newly diagnosed T1D patients during the active pandemic and post-pandemic periods was similar. Our results are in line with two large cohort studies that found no evidence of a direct link between SARS-CoV-2 infection and incipient T1D development (14,15)

A recent international multicenter study based on data from 13 national diabetes registries reported a higher prevalence of diabetic ketoacidosis (DKA)

at diagnosis of T1D among people younger than 18 years of age than the estimated prevalence in 2020 and 2021. However, the observed prevalence was not significant in all countries included in this study (16). In our study, although the number of patients with severe DKA was moderately high in the pandemic period, there was no statistically significant difference.

SARS-CoV-2 causes effects not only in the lungs but also in many organs in the body, including endocrine organs. Viral tropism in these tissues is mediated by receptors for the coronavirus spike protein such as angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2). It is known that SARS-CoV-2 can multiply by infecting the cells of the exocrine pancreas and pancreatic islets through these pathways (17).

Many studies have shown that COVID-19 is a risk factor for autoimmune disease (18,19). The studies by Chang et al. (20) and Tesch et al. (21) have comprehensively demonstrated the existence of various new-onset autoimmune conditions (rheumatoid arthritis, systemic lupus erythematosus, celiac disease, etc.) after COVID-19. Again, in some studies, the relationship between endocrine autoimmune diseases such as thyrotoxicosis and hashimoto thyroiditis and COVID-19 was discussed (22,23). Although there are different debates on the relationship between diabetes autoimmunity and Covid 19, Schiaffini et al. (24) reported in their study that COVID-19 infection would not cause diabetes autoimmunity even if it had an effect on the T1D clinic. During the echovirus 16 epidemic in Cuba, an increase in the co-occurrence of ICA and anti-GAD positivity was observed in children (25). It has been shown that having more than one antibody positivity increases the risk of developing type 1 diabetes compared to a single diabetes autoantibody positivity (26,27). In our study, ICA antibody positivity and other diabetes antibodies co-existent were found significantly higher in patients diagnosed during the pandemic period.

In another study, Sepa et al. (28) reported a high anti-GAD positivity among children participating in their study, and also noted that exposure to psychosocial stressors in children, with or without a family history of diabetes, may be considered as a risk factor for autoimmune type 1 diabetes. Accordingly, it can be thought that the reason for the high antibody positivity in patients diagnosed during the pandemic period in our study can be attributed to the psychosocial stress created by the pandemic.

It has been reported that the new diagnosis season of patients in Türkiye is mainly in winter and autumn months (29). However, in our study, there was no decrease in the number of patients diagnosed during the summer season, especially during the pandemic, and 11 patients were diagnosed with T1D, while the number of patients after the pandemic was only 4 patients. We thought that this may be due to the fact that the pandemic period Covid 19 infections continued in the summer period.

C-peptide, a molecule produced in insulin equimolar concentration, has become an established biomarker of insulin secretion in diabetic patients. Measurement of the C-peptide level can be helpful in clinical practice, particularly in patients currently scheduled to receive exogenous insulin therapy, to assess the residual function of insulin-producing β-cells (30). Significantly lower C-peptide levels in the pandemic-era patients suggested that the beta-cell reserve in the pancreas was more severely affected.

Various mechanisms by which vitamin D is effective in regulating immune response support, the role of vitamin D in the pathogenesis of autoimmune diabetes, and vitamin D as a protective compound for diabetes have been suggested. The epidemiological evidence and observational studies suggesting that adequate vitamin D is associated with a reduced risk of developing type 1 diabetes further support this concept (31). We evaluated 25(OH)vitamin D levels in 156/173 (90.1%) of our patients. Severe vitamin D deficiency (<20 ng/ml) was present in 83.3% (130/156) of our patients whose vitamin D levels were checked without any difference between pandemic or post-pandemic periods. This situation underlines the need to evaluate Vitamin D levels in children with T1D diagnosed.

Type 1 diabetes (T1DM) is predicted to result in impaired immunological response to vaccines. HBV vaccine is routinely administered to every newborn child according to the national vaccination schedule. Although there are different data regarding the humoral immune response to hepatitis B vaccine in patients with type 1 diabetes, only 39% of all our newly diagnosed patients had an adequate Anti-HBs response (32).

It has been stated that SARS-CoV-2 may cause an increase in aldosterone secretion and a decrease in angiotensin II by decreasing ACE2 expression, which may lead to an increase in renal potassium loss (33). The significant low potassium in patients diagnosed during the pandemic may be explained by a COVID-19 infection that was experienced without being symptomatic. Unfortunately, we did not routinely evaluate our patients for the presence of COVID-19 infection.

Studies evaluating vitamin B12 deficiency are mostly related to type 2 diabetes mellitus and metformin treatment (34). There is no definitive information on the relationship between T1D and B12 deficiency. In our study, although there was a significant difference in vitamin B12 levels between the two groups, there was no deficiency in either group.

In conclusion, our study, in which we detected serious vitamin D deficiency in all groups, revealed the need to evaluate vitamin D, especially in extraordinary periods such as pandemics, when sunlight exposure is highly restricted. Moreover, we found significantly high antibody positivity and low levels of C-peptide in patients diagnosed during the pandemic period. Again, although it was not statistically significant, the

presence of severe acidosis was higher at the time of diagnosis during the pandemic period. In order to clearly demonstrate the relationship between Covid 19 and T1D, larger series of reports are needed.

Limitations of the study

Covid 19 PCR test was not performed on the patients who did not have any signs.

As it was a single center study, we could not include all newly diagnosed T1D children in Gaziantep in our study. However, since our hospital is a state hospital, it is a hospital that is easily accessible and preferred by the public, and it also accepts patients from neighboring provinces when necessary. Therefore, our findings may represent Southern Türkiye with different ethnicities and cosmopolitan population structure.

Declarations

Funding and/or Conflicts of interests

The authors declare that they have no conflict of interest

Data availability

Data are available from the corresponding author upon reasonable request.

Ethical Statement

Approval for the study was received from Gaziantep University Faculty of Medicine ethics committee unit.

Author Contributions

Concept- Fatma Özgüç Çömlek, Design- Fatma Özgüç Çömlek Supervision- Fatma Özgüç Çömlek Materials, Fatma Özgüç Çömlek, data Collection and /or Processing- Fatma Özgüç Çömlek, Semine Özdemir Dilek, Analysis and /or interpretation- Fatma Özgüç Çömlek Literature Review Fatma Özgüç Çömlek; Writer- Fatma Özgüç Çömlek ;Critical Review- Fatma Özgüç Çömlek, Semine Özdemir Dilek

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ORIGINAL ARTICLE

Evaluation of Skin Prick Test Results Performed for the Diagnosis of Inhaled Allergens in Konya

Konya ilinde Solunum Alerjenleri Tanısı İçin Yapılan Deri Prick Testi Sonuçlarının Değerlendirilmesi

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ABSTRACT

Objective: We aimed to determine the distribution of inhaled allergens by evaluating the results of skin prick tests performed on patients with allergic complaints in Konya.
Material and Methods: The study included 2351 patients aged 2-18 years who underwent skin prick tests for the diagnosis of inhaled allergens at the Selçuk University Medical Faculty Pediatric Allergy and Immunology Outpatient Clinic between June 1, 2022, and May 31, 2023. The demographic characteristics and skin prick test results of 696 patients with sensitivity to at least one inhaled allergen were retrospectively evaluated.
Results: Sensitivity to at least one inhaled allergen was detected in 696 (29.6%) of 2351 patients who underwent skin prick testing for allergic symptoms. The mean age of patients with inhaled allergen sensitivity was 10.37 ± 4.14 years. 278 (39.9%) of the patients were girls, and 418 (60.1%) were boys. Considering the distribution of inhaled allergens detected by the skin prick test, the most frequent allergens were pollen allergens (78.2%), cat epithelium (38.8%), and dog epithelium (33.8%). The most common allergens detected in girls were pollen allergens (77.3%), cat epithelium (38.1%) and house dust mites (37.1%). The most common allergens detected in males were pollen allergens (78.7%), cat epithelium (39.2%), and dog epithelium (34.7%). Sensitivity to house dust mites was more prevalent in girls than boys. Sensitivity to pollen allergens was most frequently detected in all seasons. Significant differences were detected between house dust mites, pollen allergens, rye, and cat epithelium sensitivities according to seasons.
Conclusion: Our study shows the distribution of inhaled allergens in Konya province. Therefore, we assume that it can contribute to the implementation of environmental measures that can be taken to protect against allergens and, thus, to the treatment of patients.

Keywords: Allergen, Skin prick test, Sensitivity.

ÖZ

Amaç: Konya ilinde alerjik şikayetleri olan hastalara uygulanan deri prick testi sonuçlarını değerlendirerek inhaler alerjenlerin dağılımını tespit etmeyi amaçladık.
Gereç ve Yöntem: Çalışmaya Selçuk Üniversitesi Tıp Fakültesi Hastanesi Çocuk Alerji ve İmmünoloji polikliniğine 1 Haziran 2022-31 Mayıs 2023 tarihleri arasında solunum alerjenleri tanısı için deri prick testi yapılan 2-18 yaş arası 2351 hasta dahil edildi. Bu hastalardan en az bir inhaler alerjene duyarlılık saptanan 696 hastanın demografik özellikleri ve deri prick testi sonuçları retrospektif olarak değerlendirildi.
Bulgular: Alerjik şikayetler nedeniyle deri prick testi uygulanan 2351 hastanın 696'sında (%29.6) en az bir inhaler alerjene karşı duyarlılık saptanmıştır. İnhaler alerjen duyarlılığı saptanan hastaların yaş ortalaması 10.37 ± 4.14 olup hastaların 278'i (%39.9) kız, 418'i (%60.1) erkektir. Deri prick testi ile saptanan inhaler alerjenlerin dağılımına bakıldığında en sık polen alerjenleri (%78.2), kedi epiteli (%38.8) ve köpek epiteli duyarlılığı (%33.8) gözlendi. Kızlarda en sık saptanan alerjenler polen alerjenleri (%77.3), kedi epiteli (% 38.1), ev tozu akarları (%37.1) olarak tespit edildi. Erkeklerde en sık saptanan alerjenler polen alerjenleri (%78.7), kedi epiteli (%39.2) ve köpek epiteli (%34.7) olarak tespit edildi. Saptanan alerjen duyarlılıkları cinsiyete göre değerlendirildiğinde; kızlarda ev tozu akarlarına karşı duyarlılık saptanması erkeklere göre daha yüksek oranlardadır. Tüm mevsimlerde en sık polen alerjenlerine karşı duyarlılık tespit edildi. Mevsimlere göre ev tozu akarları, polen alerjenleri, çavdar, çimen ve kedi epiteli duyarlılığı arasında istatistiksel olarak anlamlı farklılık saptandı.
Sonuç: Çalışmamızın Konya ilinde inhaler alerjenlerin dağılımını göstermesi nedeniyle alerjenden korunmak için alınabilecek çevresel önlemlerin uygulanmasına ve bu sayede hastaların tedavisine katkıda bulunabileceğini düşünmekteyiz.

Anahtar Kelimeler: Alerjen, Deri prick testi, Duyarlılık

Introduction

Allergy is a hypersensitivity reaction that develops against a specific immunological trigger (1). The prevalence of allergic diseases has increased over the past decade, adversely affecting the lives of patients and their families (2). Respiratory allergies are common in all age groups, and their frequency is increasing (3). In addition to genetic factors, environmental factors also play a role in the development of allergies (4). Sensitivity to inhaled allergens may vary by geographic region (5). Geographical factors such as climate, vegetation, humidity, and sea level, as well as seasonal changes, are important in the distribution of inhaled allergen sensitivities (6).

Since their invention by Charles Harrison Blackley in 1865, skin tests have been the main method used to investigate allergies (7,8). Due to their low cost, ease of use, and rapid results in detecting allergen sensitivities in Type 1 hypersensitivity reactions such as asthma, allergic rhinitis, atopic dermatitis, anaphylaxis, and eosinophilic

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gastritis, skin prick tests are often preferred in clinical practice (9,10,11).

In our country, the distribution of inhaled allergens varies among regions. In this study, we aimed to evaluate the distribution of inhaled allergens determined by skin prick test in patients presenting with allergic complaints in Konya.

Material and Methods

Patients between the ages of 2 and 18 who underwent skin prick testing for the diagnosis of inhaled allergens at the Pediatric Allergy and Immunology Clinic of Selçuk University Medical Faculty between June 1, 2022, and May 31, 2023, were included in the study. Demographic characteristics and skin prick test results of patients with sensitivity to at least one inhaled allergen were retrospectively evaluated.

Skin prick tests were performed with solutions from Allergopharma® (Hamburg, Germany), and Lofarma® (Milan, Italy). Before the test, antihistamines were discontinued 15 days before, antidepressants were discontinued 1 week before, and medications containing montelukast were discontinued 3 days before. Histamine solution (10mg/ml) was used as a positive control and saline solution as a negative control in the skin prick test. Allergen solutions were applied to the volar surface of the forearm with a lancet. A positive reaction was considered if a wheal of 3 mm or greater, was observed 15 minutes after the application of allergen solutions, compared with the negative control (12). Inhaled allergens used in the skin prick test included house dust mites (Dermatophagoides farinea, Dermotophagoides pteronyssinus), pollen allergens (birch, rye, grass mix (orchard grass, tussac grass, blue fescue, grass), weed mix (cart-track, Xanthium strumarium, weed)), cat epithelium, dog epithelium, molds (Alternaria alternata, Aspergillus fumigatus, and Cladosporium herbarum) and cockroach.

The study was approved by the Selçuk University Faculty of Medicine Local Ethics Committee with decision No. 2023/93, dated August 1, 2023.

Statistical Analysis

Data were analyzed using the SPSS 25 statistical software package. Descriptive statistics were provided, including percentages, means and standard deviations. Categorical data were evaluated using Fisher's exact chi-squared test or Pearson's chi-squared test in contingency tables. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 2351 patients aged 2□18 years underwent skin prick testing for inhaled allergens between May 1, 2022, and June 30, 2023. Among these patients, 696 (29.6%) were sensitive to at least one inhaled allergen. Of these, 28.4% were monosensitized (sensitive to a single inhaled allergen), while 71.6% were polysensitized (sensitive to multiple inhaled allergens). The mean age of patients with inhaled allergen sensitivity was 10.37 ± 4.14 years. 278 (39.9%) of the patients were girls, and 418 (60.1%) were boys. The mean age was 11.09 ± 4.13 years for the girls, and 9.89 ± 4.09 years for the boys.

Among the inhaled allergens identified by the skin prick test, sensitivity to the pollen allergens was the most common (78.2%). The following sensitivities to pollen allergens mixes were observed: grass mix (55.2%), rye (53.9%), weed mix (48.1%) and birch (20%). The second and third most common sensitivities were cat epithelium (38.8%) and dog epithelium (33.8%). Sensitivities to house dust mites (32.3%), Alternaria alternata (28.7%) and cockroach (28%) were also observed. Sensitivity to Aspergillus fumigatus and Cladosporium herbarum was observed in 377 patients, with values of 7.5% for both. The distribution of allergen sensitization with the skin prick test is presented in Figure 1.

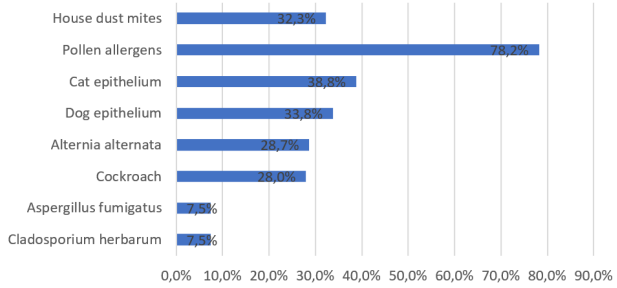

Figure 1: The distribution of allergen sensitivities identified by the skin prick test

When evaluating skin prick test results by gender, the most common allergens in girls were (77.3%), cat epithelium (38.1%) and house dust mites (37.1%). In boys, the most common allergens were pollen allergens (78.7%), cat epithelium (39.2%), and dog epithelium (34.7%). Regarding gender differences, girls exhibited a higher sensitivity to house dust mites compared to boys ($p<0.05$). Table 1 shows the distribution of skin prick test-identified allergen sensitization by gender.

When evaluating skin prick test results by season, sensitivity to was most frequently observed in all seasons of the year. In summer, sensitivity to pollen allergens (83.3%), cat epithelium (34.9%), and Alternaria alternata (27.1%) were the most common. In autumn, sensitivity to pollen allergens (81.3%), house dust mites (40.3%) and cat epithelium (39.2%) were prominent. In winter, sensitivity to pollen allergens (70.8%), house dust mites (41.5%) and cat epithelium (31%) prevailed, while in spring, sensitivity to pollen allergens (76.4%), cat epithelium (51.6%) and cockroach (35%) were prominent. The evaluation of skin prick test positivity by season is presented in Table 2. There were no statistically significant differences in sensitivity among birch, weed mix, dog epithelium, Alternaria alternata, cockroach, Aspergillus fumigatus, and Cladosporium herbarum ($p>0.05$). However, there was significant differences in sensitivity according to the season for house dust mites ($p<0.001$), pollen allergens ($p=0.021$), rye ($p<0.001$), grass mix ($p<0.001$) and cat epithelium ($p=0.001$). In pairwise comparisons, sensitivity to house

Table 1: The distribution of sensitivities to allergens identified by the skin prick test according to gender

	Total (n=696)		Girls (n=278)		Boys (n=418)		
Allergens	Number	%	Number	%	Number	%	p Value
House dust mites	225	32.3	103	37.1	122	29.2	0.030*
D. farinea	134	19.3	60	21.6	74	17.7	0.204
D. pterinus	166	23.9	78	28.1	88	21.1	0.034**
Pollen Allergens	544	78.2	215	77.3	329	78.7	0.668
Birch	139	20	50	18	89	21.3	0.285
Rye	375	53.9	140	50.4	235	56.2	0.129
Grass mix	384	55.2	155	55.8	229	54.8	0.801
Weed mix	335	48.1	129	46.4	206	49.3	0.456
Cat epithelium	270	38.8	106	38.1	164	39.2	0.770
Dog epithelium	235	33.8	90	32.4	145	34.7	0.527
Alternia alternata	200	28.7	76	27.3	124	29.7	0.506
Cockroach	195	28	69	24.8	126	30.1	0.126
Aspergillus fumigatus	52 (n=377)	7.5	19 (n=157)	6.8	33 (n=220)	7.9	0.421
Cladosporium herbarum	52 (n=377)	7.5	18 (n=157)	6.5	34 (n=220)	8.1	0.268

Note: D.pterinus: Dermatophagoides pterinus D. farinea: Dermatophagoides farinea

, Girls exhibited a higher sensitivity compared to boys (p<0.05).*

Table 2: Evaluation of skin prick test positivity by season

	Summer (n=192)		Autumn (n=176)		Winter (n=171)		Spring (n=157)		
Allergens	Number	%	Number	%	Number	%	Number	%	p Value
House dust mites	37	19.3	71	40.3	71	41.5	44	28	<0.001[1]
D. farinea	27	14.1	38	21.6	41	24	28	17.8	0.086
D. pterinus	34	17.7	54	30.7	50	29.2	28	17.8	0.002[2]
Pollen Allergens	160	83.3	143	81.3	121	70.8	120	76.4	0.021[3]
Birch	37	19.3	34	19.3	31	18.1	37	23.6	0.628
Rye	127	66.1	91	51.7	77	45	80	51	<0.001[4]
Grass mix	128	66.7	94	53.4	72	42.1	90	57.3	<0.001[5]
Weed mix	90	46.9	97	55.1	73	42.7	75	47.8	0.133
Cat epithelium	67	34.9	69	39.2	53	31	81	51.6	0.001[6]
Dog epithelium	67	34.9	61	34.7	46	26.9	61	38.9	0.133
Alternia alternata	52	27.1	56	31.8	40	23.4	52	33.1	0.177
Cockroach	43	22.4	50	28.4	47	27.5	55	35	0.076
Aspergillus fumigatus	0 (n=0)	0	5(n=49)	2.8	21	12.3	26	16.6	0.392
Cladosporium herbarum	0 (n=0)	0	7(n=49)	4	16	9.4	29	18.5	0.057

1,2 Sensitivity was higher in autumn and winter compared to spring and summer. 3 Sensitivity was higher in summer and autumn compared to winter. 4 Sensitivity was higher in the summer compared to other seasons. 5 Sensitivity was higher in the summer compared to autumn and winter, and in autumn and spring compared to winter. 6 Sensitivity was higher in spring compared to other seasons.

dust mites was higher in autumn and winter compared to spring and summer (p<0.05). Sensitivity to pollen allergens was higher in summer and autumn compared to winter (p<0.05). Rye sensitivity was higher in summer compared to other seasons (p<0.05). Grass mix sensitivity was higher in summer compared to autumn and winter, and in autumn and spring compared to winter (p<0.05). Cat epithelium sensitivity was higher in spring compared to other seasons (p<0.05). There were no statistically significant differences among the other seasons (p>0.05).

Discussion

Environmental factors are also effective in the development of allergies, as well as genetic factors (4). The development of allergic diseases in the respiratory tract can result from our environment's exposure to inhaled allergens. Exposure to these aeroallergens also leads to exacerbation of symptoms (13). Inhaled allergens can be divided into two categories as indoor and outdoor allergens. Indoor allergens include house dust mites, mold fungal spores, pet epithelium and cockroaches while pollen and some fungal spores are classified as outdoor allergens (14).

In our study, sensitization to at least one inhaled allergen was found in 29.6% of patients who underwent skin prick testing due to allergic complaints. Different rates have been reported in similar studies conducted in our country. Sensitization to at least one inhaled allergen was detected in 59% of patients with allergic complaints in Denizli (15), 59.5% in atopic children in Alanya (16), 42.3% in children with asthma and allergic rhinitis in Karaman (17) and 31.2% in atopic patients in Malatya (18). The variances in the results may be due to the differences in the distribution of allergens in the

region of residence and the patient groups included in the study.

Considering the distribution of inhaled allergens in our study, pollen allergens sensitization was the most common (78.2%). Cat epithelium sensitization (38.8%) and dog epithelium sensitization (33.8%) were observed in the second and third frequencies, respectively. Çölgeçen et al. reported that in Yozgat, the most frequently detected allergens were pine pollen 25.3%, wheat pollen 18.4% and dog epithelium 15.8% (19); Demir et al. stated that in Diyarbakır, the most frequently detected allergens were found to be meadow pollen (70%), wheat pollen (46%) and tree pollen (46%) (20). Ayçin et al. conducted a study in Erzurum in patients with allergic rhinitis and asthma, and determined that the most common sensitization was to mixed grass pollen (30.8%), followed by house dust mites (29.3%). (21). In a study conducted by Sayar on atopic children in the Alanya region, the most common sensitization was observed to mites (76.1%), molds (Alternaria alternata (51.8%) and Cladosporum herbarum (41.7%)), and pollen sensitization (39.8%) (16). In a study conducted by Havlucu et al. in Hatay, sensitization to house dust mites (48.5%) and grass mixture (39.5%) were the most common (22). The high sensitization to pollen in Konya province, which has a continental climate, is similar to that in Yozgat, Erzurum and Diyarbakır provinces, which also have a continental climate. Mites are found more in warm and humid environments. They can survive best at temperatures between 25 and 30°C and 75□80% humidity. In provinces near the sea level, such as Antalya and Hatay, susceptibility to house dust mites is more common.

Studies have reported that allergic sensitization is more common in the male gender (23,24). In our study, 60.1% of the patients with positive skin prick test results were male and 39.9% were female, compatible with the literature. When skin prick test results were evaluated according to gender, the most common allergens detected in girls were pollen allergens (77.3%), cat allergens (38.1%) and house dust mites (37.1%). The most frequently detected allergens in boys were pollen allergens (78.7%), cat allergens (39.2%) and dog allergens (34.7%). When the detected allergen sensitizations were evaluated according to gender, sensitization to house dust mites was higher in girls than in boys ($p<0.05$).

It has been reported in the literature that house dust mite sensitization is found more frequently in males (25,26). In our study, house dust mite sensitization was found more frequently in girls. In our study, it was determined that sensitivity to pollen allergens occurred most frequently in all seasons. In summer, pollen allergens (83.3%), cat epithelium (34.9%), and Alternia alternata (27.1%) were observed, and pollen allergens (81.3%), house dust mites (40.3%), and cat epithelium (39.2%) were observed in autumn., pollen allergens (70.8%), house dust mites (41.5%), and cat epithelium (31%) occurred in winter, and pollen allergens (76.4%), cat epithelium (51.6%), and cockroaches (35%) were observed in spring. There was a statistically significant difference between house dust mites, pollen allergens, rye, grass mix and cat epithelium sensitization according to the seasons. In the literature, there are very few studies evaluating the seasonal distribution of inhaled allergen sensitization. Since our study's data set is relatively high compared to other studies and similar studies are limited in the literature, we consider that our research will support the scientific contribution.

Conclusion

As a result, pollen allergens sensitization was found most frequently in Konya. Pollen allergens sensitization was observed most frequently in all seasons. Significant differences were determined among house dust mites, pollen allergens, rye, grass mix and cat epithelium sensitization according to seasons. These insights from this paper can contribute to the formation of the allergen profile of Konya province and to the establishment and evaluation of regional allergen profiles for future studies.

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

Ethical Aspects of the Research: The study was approved by the Selçuk University Faculty of Medicine Local Ethics Committee (Decision No. 2023/393, Date: 01.08.2023).

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ORIGINAL ARTICLE

Psychosocial Effect of COVID-19 Phobia in Health Workers in the Pandemic Service and Intensive Care

Pandemi Servis ve Yoğun Bakımında Çalışan Sağlık Çalışanlarında COVİD-19 Fobisinin Psikososyal Etkisi

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ABSTRACT

Objective: It was aimed to evaluate the phobia levels of COVID-19 (Coronavirus disease 2019) in medical staff working in the pandemic ward and intensive care unit and to examine its relationship with psychosocial impact levels.
Material and Method: The study included 100 people working in the pandemic ward and intensive care units in the first year of the pandemic. Sociodemographic Data Form, COVID-19 Pandemic Psychosocial Impact Scale (CPPIS) and COVID-19 Phobia Scale (CPS) were administered to all participants.
Results: The mean age of the participants was 32.5±7.4 years and 74% of them were women. Of these, 29% were doctors, 52% were nurses, 19% were allied health personnel and 66% worked in the service, 29% in the intensive care unit and 5% in both. There was very strong correlation between the CPS and the CPPIS total score, the death anxiety and anxious thoughts subscale scores. A strong positive correlation was found between the CPS and CPPIS subscales scores including close relationships, functionality and somatic symptoms. There was significant positive correlation between CPS and CPPIS scores and the duration of working in the pandemic service and intensive care unit.
Conclusion: It was considered that as choranophobia increased among medical staffs working in the pandemic service, their psychosocial effects also increased. It has been thought that reducing the working time in the service and/or intensive care unit during the pandemic, performing short-term rotations, might reduce the level of psychosocial impact and even be protective in terms of mental health of medical staff.

Keywords: COVID19, medical staff, phobia, pandemics

ÖZ

Amaç: Bu çalışmada pandemi servisi ve yoğun bakım servisinde çalışan sağlık çalışanlarında COVİD-19 (Coronavirus disease 2019, COVID-19) fobi düzeylerinin değerlendirilmesi ve psikososyal etkilenme düzeyleri ile ilişkisinin incelenmesi amaçlanmıştır.
Gereç ve Yöntem: Çalışmaya pandeminin ilk yılında pandemi servis ve yoğun bakımlarında çalışan 100 kişi alınmıştır. Tüm katılımcılara Sosyodemografik Veri Formu, COVID-19 Pandemisi Psikososyal Etkilenme Ölçeği (CPPEÖ) ve COVID-19 Fobi Ölçeği (CFÖ) uygulanmıştır.
Bulgular: Çalışmaya katılanların ortalama yaşı 32,5±7,4 ve %74'ü kadındır. Katılımcıların %29'u hekim, %52'si hemşire, %19'u yardımcı sağlık personelidir ve %66'sı servis, %29'u yoğun bakım, %5'i hem servis hem yoğun bakımda çalışmıştır. CFÖ puanı ile CPPEÖ toplam puanı arasında ve CFÖ puanı ile CPPEÖ alt ölçekleri olan ölüm kaygısı ve endişeli düşünceler boyutu puanları arasında çok güçlü; yakın ilişkiler, işlevsellik ve bedensel belirtiler boyutu puanları arasında güçlü pozitif korelasyon saptanmıştır. CFÖ ve CPPEÖ puanı ile pandemi servis ve yoğun bakımlarında çalışma süresi arasında anlamlı pozitif korelasyon saptanmıştır.
Sonuç: Pandemi servisinde çalışan sağlık çalışanlarında koronafobi artıkça psikososyal etkilenmelerinin de arttığı düşünülmüştür. Pandemide servis ve/veya yoğun bakımda çalışma süresinin azaltılması, kısa süreli rotasyonlarla yapılması, psikososyal etkilenme düzeyini azaltabileceği hatta sağlık çalışanı ruh sağlığı açısından koruyucu olabileceği düşünülmüştür.

Anahtar Kelimeler: COVID19, fobi, sağlık çalışanları, pandemik

Introduction

It has been reported that COVID-19 has a strong impact on the lives of people, and many factors such as changing social life, economic problems, and work-related risks affect situations such as anger, anxiety, stress, depression, and sleeping problems at different intensities (1). The pandemic affected individuals physically and psychologically, and the group with the highest risk of being affected was healthcare workers. Psychological negativities, as well as other mental problems, have been reported at a high rate in healthcare workers who have to work with concepts such as viruses, intensive care, pandemics and death every day (2). In this process, medical staff faces higher levels of psychological problems due to long working hours, high risk of infection, limited protective equipment, physical fatigue, loneliness and separation from their families (3). Nurses have frequently begun to provide end-of-life care and have become people who meet all the needs of patients who do not share the same environment with anyone, including their families (4). Changes in the nurse-patient ratio during the pandemic period, care for risk groups, risk of disease transmission to nurses, lack of treatment and vaccination of the disease, change in the working system, caring for patients with protective equipment for hours and the possibility of transmitting the virus to

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others or their families. Stigmatization, fear, anger, anxiety and uncertainty in nurses led to burnout (5). In a study of 1,563 healthcare professionals, more than half (50.7%) reported depressive symptoms, 44.7% reported anxiety, and 36.1% had sleeping disturbances (6). Many physicians developed depression, post-traumatic stress disorder, burnout, and anxiety after fatigue, fear, emotional disturbance, and sleep disturbances subside (7). The fear of being infected due to the risk of infecting their loved ones and families was the biggest cause of anxiety among healthcare professionals (8). In another study, it was reported that high rates of anxiety (44.6%), depression (50%), anxiety disorders (71.5%) and insomnia (34%) were observed in healthcare personnel working in COVID-19 services (9). It has been stated that COVID-19 phobia has a great impact on human psychology, and it has been shown that there is an increase in COVID-19 phobia due to psychological distress such as anxiety, panic and stress caused by the pandemic (10). Studies have shown that there is a significant relationship between COVID-19 phobia, functional impairment, psychological problems and depression levels (11).

Reasons such as increasing depression, health anxiety, loneliness, stigma and financial difficulties, changing work and working conditions, secondary traumas for medical staff, and separation from their families bring about the necessity and importance of psychological intervention (12). This study aimed to evaluate COVID-19 phobia levels in healthcare professionals working in the pandemic ward and intensive care unit and to examine its relationship with psychosocial impact levels.

The hypothesis of this is that there is a significant relationship between COVID-19 phobia levels in individuals and the psychosocial impact level of COVID-19; As the level of COVID-19 phobia increases, psychosocial effects may also increase. The evaluation of COVID-19 phobia levels in healthcare workers working in the pandemic ward and intensive care unit and its relationship with psychosocial impact levels were examined. It has been shown that there is a significant relationship between COVID-19 phobia, functional impairment, psychological problems and depression levels. It is thought that healthcare workers are affected psychosocially in all areas as the working time increases in psychosocially harsh working conditions during the pandemic. In addition, considering that the prolongation of this period increases coronaphobia and further exacerbates this psychosocial impact, it is thought that it may be a guide for the measures to be taken to protect the mental health of healthcare workers in possible processes such as pandemics. Our study is the first study to use the COVID-19 Phobia Scale, for which validity and reliability studies were conducted by Dilbaz et al. (13).

Material and Methods

The data for this study was collected between July 2022 and November 2022. It was planned to include all healthcare workers between the ages of 18 and 65 who worked in the pandemic ward and intensive care units of a university hospital in the first year of the pandemic. 300 healthcare workers were reached, but only 100 healthcare workers agreed to participate in the study. Statistical evaluation was made with 100 healthcare professionals who agreed to participate in the research. The only exclusion criterion is refusal to participate in the study.

Face-to-face interviews were held with healthcare professionals who met the inclusion and exclusion criteria and agreed to participate in the study. Informed consent was obtained from participants who agreed to participate in the study after the procedures were fully explained. Sociodemographic Data Form, Covid-19 Pandemic Psychosocial Impact Scale and Covid-19 Phobia Scale were applied to all participants.

Sociodemographic Data Form

It is a questionnaire prepared by researchers to collect sociodemographic data and clinical characteristics of participants in order to question the independent variables of the research.

Covid-19 Phobia Scale

The validity and reliability study of the COVID-19 Phobia Scale, which we used in the study, was conducted by Dilbaz et al. (13). It can be used to measure emotions such as fear and anxiety and the resulting behavioral changes that occur during the COVID-19 epidemic (13).

Covid-19 Pandemic Psychosocial Impact Scale

COVID-19 pandemic Psychosocial Impact Scale; It was developed by Sinanoğlu (14) and its validity and reliability were established (14).

The Covid-19 Pandemic Psychosocial Impact Scale employed in the study consists of a total of 33 items and five dimensions. These are anxious thoughts, death anxiety, close relationships, functionality and physical symptoms. The highest score that can be obtained from the scale is 165 and the lowest score is 33. The increase in scores indicates a high level of psychosocial impact (14).

The research report of this study complies with ethical standards and this study was given ethical approval by the decision of Pamukkale University Non-Interventional Clinical Research Ethics Committee dated 07/06/2022 and numbered 09.

Informed consent was obtained from participants who agreed to participate in the study after the procedures were fully explained. The study was conducted in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research on Human Subjects, revised in 2003.

Statistical analysis

Data were analyzed with the SPSS 25.0 (IBM SPSS Statistics 25 software, Armonk, NY: IBM Corp.) package

program. Continuous variables are given as mean ± standard deviation and categorical variables as numbers and percentages. Relationships between continuous variables were examined with Pearson correlation analyses. P<0.05 was considered statistically significant. Continuous variables between groups were examined with one-way analysis of variance. P<0.17 (0.05/3) was considered statistically significant.

Results

Of the participants, 74% were female and 26% were male in this research. The average age of the participants was 32.5±7.4. Of these participants, 29%were physicians, 52% were nurses, and 19% were allied health personnel. 66% of the participants worked in the ward, 29% in the intensive care unit, and 5% in both the ward and the intensive care unit. The average working time of the participants in pandemic wards and intensive care units was 225.78±240.345 (min: 10, max: 850) days.

A very strong positive correlation was found between the CPS score and the CPPIS total score (p<0.001; r=0.655). CPS score and CPPIS had a very strong relationship between anxious thoughts (p<0.001; r=0.730) and death anxiety (p<0.001; r=0.602), functionality (p<0.001; r=0.480), physical symptoms (p<0.001; r). =0.424), close relationships (p<0.001; r=0.530) subscale scores (Table 1).

There was a significant positive correlation between CPS score and working time in pandemic wards and intensive care units (p=0.012; r=0.278), working hours in coronavirus wards and intensive care units and CPPES total score (p=0.011; r=0.281) and close relationships (p=0.044; r=0.224), functionality (p=0.032; r=0.238), death anxiety (p=0.031). A positive correlation was found between subscale scores of; r=0.240), somatic symptoms (p=0.024; Pearson correlation coefficient=0.250), and anxious thoughts (p=0.029; r=0.243) (Table I).

No significant difference was detected between CPS, CPPIS subscale and total scores and healthcare personnel groups (physician, nurse, allied healthcare personnel) (p>0.017) (Table 2).

Table 1: Correlation of CPPIS scores with CPS score and working time

	COVID-19 Phobia Scale Score		Working time	
	R	*p**	r	*p***
Death Anxiety	.602	.000	.240	.031
Anxious Thoughts	.730	.000	.243	.029
Close Relationships	.530	.000	.224	.044
Physical Symptoms	.424	.000	.250	.024
Functionality	.480	.000	.238	.032
CPPIS Total Score	.655	.000	.281	.011

* Pearson correlation test p<0.01; ** Pearson correlation test. p< 0.05

CPPIS; COVID-19 Pandemic Psychosocial Impact Scale, CPS; COVID-19 Phobia Scale

Table 2. Comparison of CPS, CPPIS total and subscale scores between healthcare personnel groups.

	Physician	Nurse	Other Allied Health Personnel	
	n=29	**n**=52	**n**=19	
	Mean (SD)	Mean (SD)	Mean (SD)	*p**
CPS Score	68.90 (12.99)	70.83 (16.46)	71.11 (19.01)	.850
Death Anxiety	17.03 (5.93)	15.35 (6.30)	16.47 (7.83)	.511
Anxious Thoughts	19.34 (4.35)	19.87 (5.75)	22.05 (7.16)	.247
Close Relationships	14.38 (5.20)	14.00 (6.00)	16.11 (8.70)	.468
Physical Symptoms	10.83 (4.88)	10.88 (4.96)	11.58 (4.34)	.844
Functionality	14.97 (5.50)	13.63 (5.19)	14.05 (5.67)	.566
CPPIS Total Score	76.55 (21.61)	73.73 (24.66)	80.26 (28.52)	.247

*One-Way Analysis of Variance was applied. p< 0.017 (0.05/3) was considered statistically significant.

CPS; COVID-19 Phobia Scale, CPPIS; COVID-19 pandemic Psychosocial Impact Scale, SD: Standard Deviation

Discussion

When the literature is examined, the studies conducted in our country are mostly on anxiety, stress, depression, psychological health and burnout (15). In the relevant literature, no study was found using the CPS and CPPIS used in this research and investigating the relationship between psychosocial influence and coronaphobia. Research has reported that coronaphobia is higher in nurses than in the general population, and the factor that increases fear is the risk of contracting the disease and unknowingly infecting others (16,17). In a study including 310 nurses in our country, it was reported that the factors affecting the psychological dimension of coronaphobia were female gender, working in internal clinics, working during daylight hours, chronic disease, having a relative with coronavirus and vaccination (15). In this study, it was determined that as COVID-19 phobia levels increased, COVID-19 psychosocial impact levels also increased. During the pandemic, the constant fear of contamination led to obsessive thoughts, thus, causing the person to become increasingly withdrawn and less likely to engage in social relationships (9).

It has been observed that young female healthcare workers, especially those working directly in the pandemic service, experience such mental problems more (8). The study included 74% female healthcare workers. It has been reported that its level is high in nurses who are married and have children (15). Married nurses have difficulty in leading a normal life due to reasons such as working for a long time in the workplace, increased parental burden when their children stay at home, and the prolongation of the process (5,15). Therefore, in this study, it was thought that both coronaphobia levels and psychosocial effects were found higher in female healthcare workers.

During the epidemic period, changes in the nurse-patient ratio, providing care to risky groups, the risk

of transmission of the disease to nurses, uncertainty in the treatment of the disease, changes in the working system, working for hours with protective equipment and the possibility of transmitting the virus to others have caused phobic symptoms and anxiety against coronavirus (5). In this study, it was determined that the level of coronaphobia and psychosocial impact in healthcare workers increased significantly as the duration of work in the pandemic ward and/or intensive care unit increased. The prolongation of working hours has exposed people to more psychosocial work difficulties caused by the pandemic. It is thought that this may increase coronaphobia and psychosocial effects in healthcare workers.

It has been determined that the level of coronaphobia has a strong relationship with the anxious thoughts and death anxiety subscale in terms of psychosocial impact. The Death Anxiety dimension, which is the subscale of CPPIS, evaluates the concerns and thoughts experienced by the person or their relatives about death due to the epidemic. Death anxiety experienced by people has been included in many studies regarding the pandemic period (14). The high level of death anxiety among healthcare workers in terms of psychosocial impact is due to the fact that the COVID-19 pandemic causes mass deaths. The number of deaths they encounter in the pandemic is much higher than the ones they encounter during normal working days. The majority of these deaths are witnessed by healthcare workers, and the deaths they witness are caused by their anxiety that their relatives or themselves may also experience it. It was thought that it might happen. Thoughts related to concerns about COVID-19 were evaluated in the Worry Thoughts dimension, which is another subscale of the CPPIS. It is thought that the high level of anxious thoughts in psychosocial impact is due to the anxiety of themselves or their relatives getting COVID-19 due to the contagiousness of the virus.

Other subscales of CPPIS, the Close Relationships dimension; how the stress a person experiences during the pandemic affects their social relationships; The Bodily Symptoms dimension describes the problems caused by trauma in the body; The functionality dimension specifically evaluates the impairment in functionality due to anxiety. In this study, working time in the pandemic ward and/or intensive care unit was found equally related to all dimensions of psychosocial impact, including anxious thoughts, physical symptoms, death anxiety, close relationships and functionality. It is thought that healthcare workers are affected psychosocially in all areas as the working time increases under psychosocially harsh working conditions during the pandemic. In addition, it is thought that prolonging this period increases coronaphobia, further exacerbating this psychosocial impact.

Limitations of the study; Since the study is single-centered, the working conditions of the hospital where healthcare professionals work may also affect the results. Another limitation is that vaccination started during the time the study was conducted, which may have affected coronaphobia levels. After vaccination, the study can be repeated with a multicenter and larger sample.

Conclusion

It is thought that reducing the working time in the ward and/or intensive care unit during the pandemic, doing short-term rotations, may reduce the level of psychosocial impact and may even be protective for the mental health of healthcare workers. It is thought that this study may provide guidance in terms of measures to be taken and treatments to be applied to protect and improve the mental health of healthcare workers during a possible pandemic process.

Ethics Approval and Participation Approval: The research report of this study complies with ethical standards and this study was given ethical approval by the decision of Pamukkale University Non-Interventional Clinical Research Ethics Committee dated 07/06/2022 and numbered 09. Informed consent was obtained from participants who agreed to participate in the study after the procedures were fully explained. The study was conducted in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research on Human Subjects, revised in 2003.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Data Availability: The data sets generated during or analyzed during the current study are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Comparison of Radiofrequency Ablation and Steroid Injection in the Treatment of Plantar Fasciitis; Short and Medium Term Results

Plantar Fasiit Tedavisinde Radyofrekans Ablasyon ve Steroid Enjeksiyonu Etkinliğinin Karşılaştırılması; Kısa ve Orta Dönem Sonuçları

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ABSTRACT

Objective: Plantar fasciitis, commonly encountered in orthopaedic practice, can impede daily life activities and result in a loss of workforce. This study aimed to assess the short- and medium-term outcomes of radiofrequency ablation (RFA) and steroid injection treatments in patients with plantar fasciitis who did not benefit from conservative therapies, using pain and function scores.
Materials and Methods: Between July 01, 2021, and January 01, 2023, patients diagnosed with plantar fasciitis at Hakkari State Hospital were examined. Those not responding to conservative treatments and underwent RFA or steroid injection were divided into two groups. Demographic information, Visual Analog Scale (VAS), and American Orthopedic Foot and Ankle Society (AOFAS) scores were analyzed, and both groups were compared.
Results: The 6th-month post-treatment scores of 69 patients meeting inclusion criteria were examined (35 with RFA, 34 with steroid injections). Patients underwent RFA had a mean age of 43.89 ± 10.31 years, with 25 females and 10 males. Those receiving steroid injections had a mean age of 48.74 ± 5.00 years, with 23 females and 11 males. No significant difference was observed when comparing pre-intervention VAS and AOFAS values for both groups (p=0.469, p=0.244). There was no significant difference in the first-month VAS and AOFAS values between the two groups (p=0.764, p=0.466, respectively). However, a significant difference was observed in the post-6-month VAS and AOFAS values (p=0.001, p=0.001). Significant differences were found between VAS and AOFAS values in patients receiving RFA at both pre-intervention and 6 months (p=0.001, p=0.001). No significant difference was observed in pre-intervention and 6-month VAS and AOFAS values in steroid injections (p=0.512, p=0.844, respectively). No complications were observed in both groups during the follow-up period.
Conclusion: In patients who did not benefit from conservative treatment, radiofrequency ablation has been found an effective, safe, and minimally invasive method for reducing pain severity in the short to medium term and improving daily activities.

Keywords: Plantar Fasciitis, Radiofrequency Ablation, Steroid Injection, Calcaneal Spur

ÖZ

Amaç: Ortopedik uygulamalarda yaygın olarak karşılaşılan plantar fasiit, günlük yaşam aktivitelerini kısıtlayabilir ve iş gücü kaybına neden olabilir. Bu çalışma, konservatif tedavilerden fayda görmeyen plantar fasiitli hastalarda radyofrekans ablasyon (RFA) ve steroid enjeksiyon tedavilerinin kısa ve orta vadeli sonuçlarını, ağrı ve fonksiyon skorları kullanarak değerlendirmeyi amaçlamaktadır.
Materyal ve Metod: 01 Temmuz 2021 ile 01 Ocak 2023 tarihleri arasında Hakkari Devlet Hastanesi'nde plantar fasiit tanısı alan hastalar incelendi. Konservatif tedavilere yanıt vermeyen ve RFA veya steroid enjeksiyonu uygulanan hastalar iki gruba ayrıldı. Hastaların demografik bilgileri, Görsel Analog Skala (VAS) ve Amerikan Ortopedik Ayak ve Ayak Bileği Derneği (AOFAS) skorları analiz edildi ve her iki grup karşılaştırıldı.
Bulgular: Dahil etme kriterlerini karşılayan 69 hastanın 6. ay sonrası tedavi skorları incelendi (35 RFA, 34 steroid enjeksiyonu). RFA uygulanan hastaların yaş ortalaması 43.89 ± 10.31 yıl olup, 25'i kadın ve 10'u erkekti. Steroid enjeksiyonu alan hastaların yaş ortalaması ise 48.74 ± 5.00 yıl olup, 23'ü kadın ve 11'i erkekti. Her iki grup için müdahale öncesi VAS ve AOFAS değerleri karşılaştırıldığında anlamlı bir fark gözlenmedi (sırasıyla p=0.469, p=0.244). İlk ay VAS ve AOFAS değerleri arasında ise iki grup arasında anlamlı bir fark bulunmadı (sırasıyla p=0.764, p=0.466). Ancak, 6. ay sonrası VAS ve AOFAS değerleri arasında anlamlı bir fark gözlendi (sırasıyla p=0.001, p=0.001). RFA alan hastalarda, müdahale öncesi ve 6 ay sonrasında VAS ve AOFAS değerleri arasında anlamlı farklar bulundu (sırasıyla p=0.001, p=0.001). Steroid enjeksiyonu alan hastalarda ise müdahale öncesi ve 6 ay sonrasında VAS ve AOFAS değerleri arasında anlamlı bir fark gözlenmedi (sırasıyla p=0.512, p=0.844). Her iki grupta da takip süresinde komplikasyon gözlenmedi.
Sonuç: Konservatif tedaviden fayda görmeyen hastalarda, radyofrekans ablasyonunun kısa ve orta vadeli ağrı şiddetini azaltma ve günlük aktiviteleri iyileştirme konusunda etkili, güvenli ve minimal invaziv bir yöntem olduğu bulunmuştur.

Anahtar Kelimeler: Plantar Fasiit, Radyofrekans Ablasyon, Steroid Enjeksiyon, Kalkaneal Spur

Introduction

Heel pain is a common problem in society, approximately 10-15% of the adult population (1). One of the most common causes of heel pain is irritation of the plantar fascia (2). This irritation causes chronic inflammation in the proximal plantar fascia as a result of recurrent microtrauma, resulting in heels pain (3). In other words, plantar fasciitis is a pathology associated with inflammation of the plantar fascia at the site of adhesion to the calcaneus anteromedial tuberculosis (4, 5). The vast majority of patients who complain chronic heel pain are accompanied by calcaneal spur (6). Besides, every patient with calcaneal spur has not heel pain. Of these patients with calcaneal spur, 15% are asymptomatic (7). Patients' pain complaints can often change over the course of the day, but in some patients the pain can become chronic, causing

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limitation of activity and loss of workforce. Although a wide range of methods has been proposed for the treatment of plantar fasciitis, from stretch exercises to surgical intervention, there has been no consensus in choosing an effective treatment.

Recently, percutaneous procedures have been considered mini-invasive and are becoming more widely used (8). In recent years, radiofrequency ablation has been increasingly used in the treatment of many diseases (9). Good results have been achieved, especially with the help of radiological imaging in tumor surgeries and pain treatments (8). Recently, it has been used in cases of chronic inflammation, such as plantar fasciitis and lateral epicondylitis (10, 11). The general principle of radiofrequency ablation therapy is to produce heat through a low voltage, high frequency current through an electrode placed on the targeted lesion, causing thermal damage to the tissues and developing coagulation necrosis within a few days. Another effect is the disruption of covalent bonds maintaining the structure of the plantar fascia through the electrical activity generated by the RF electrode. This disruption leads to a reduction in the thickness of the plantar fascia and the elimination of sensory receptors that enable the occurrence and transmission of pain(12). However, there are no precise data and clear results on RFA treatment in patients with plantar fasciitis, the available literature has not fully clarified the issue. Our hypothesis is that the treatment of plantar fasciitis with RFA is more successful than the steroid injection, which is a conventional treatment. We conducted this study to demonstrate the effectiveness of steroid injection with RFA in patients who were treated with conservative treatments but whose symptoms did not recede.

Material and Methods

Our study began after it was approved by the ethics board of Necmettin Erbakan University resolution 2023/4625 dated 03.11.2023. Patients who applied for heel pain to the Hakkari State Hospital between 01.07.2021-01.01.2023 were scanned. The data of those who received radiofrequency ablation and steroid injection and patients with plantar fasciitis who had previously received at least six months of non-invasive conservative treatments for plantar fasciitis (NSAI, shoe modification, weight loss, lifestyle changes, etc.) but stated that they did not benefit were examined retrospectively. Patients with the body mass index over 30, patients with a history of surgical intervention in the affected limb, patients with standing fungus or other infection, people with vascular pathology in the affected limb and patients with rheumatic disease were excluded. Patients with suitable criteria were divided into radiofrequency ablation (RFA) and steroid injection (SE). The age, gender, pain score and functional score of the patients were compared. The Visual Analog Scale (VAS) and the American Orthopaedic Foot Ankle Society (AOFAS) scores were examined as pain and functional scores respectively before, 1 month and 6 months after the procedure. VAS is a scale with a numerical rating between 0 and 10.((13). 0 = no pain, 10 = very severe pain (13). The American Orthopedic Foot and Ankle Society (AOFAS) score is rated on a scale of 0 to 100 points, where values below 70 indicate poor results, values between 70 and 79 indicate average results, values between 80 and 89 indicate good results, and values between 90 and 100 are considered excellent results.

Radiofrequency Ablation Procedure

Before the procedure began, the patient was placed in a prone position. A pedal electrode was attached to the limb where the procedure would not be performed. The ankle of the limb where RFA would be applied was brought to a neutral position. A sterile local anesthesia of 2 mg/kg Priloc %2 (VEM Pharmaceuticals, Çankaya/ ANKARA) was administered to the mid-edge of the heel. As shown in Figure 1, the radiofrequency rod was advanced to the medial limit of calcaneal tuberosity. Low-energy impulses were applied at 2 Hertz(Hz), and fasciculation or toe movements were checked to rule out that the prob was near the motor nerve. After making sure we were not close to the motor nerve, we gradually raised the voltage from 0 Volt(V) at 50 Hz until the patient felt numb to find the right position. Subsequently, the voltage was reduced and the prob was thought to be close to the sensory nerve, where the sensation of numbness continued at levels of <0.5 V. At this point, ablation was applied to the sensory nerve at 90°C for 90 seconds. The treatment was terminated by wrapping the patient with an elastic bandage. RFE2-A (BNS, China) model device was used for procedure.

Steroid Injection Procedure

Patient lay in the prone position before the procedure began. The ankle of the limb to be operated was taken to a neutral position. In sterile conditions, 2 mg/kg Priloc 2% (VEM Medicine, Çankaya/ANKARA) was administered to the treatment area. After local anesthesia, steroid injection was administered to the affected area (20 mg Depo-Medrol (PFIZER PFE Medicine, Ortaköy/Istanbul).The post-operative patients were elastically bandaged and followed for at least 30 minutes for the possibility of acute complications.

Statistical Assessment

The statistical analysis of the data was carried out with the IBM SPSS 22.0 Windows (SPSS Inc, Chicago, IL, USA) application. Demographic data and defining statistics of variables were given as average ± standard deviation. Normality analysis was performed using the Shapiro-wilk test for independent variables. The Mann Whitney U test was used for independent variables that did not show normal distribution, while the Wilcoxon test for dependent variables. Values of $p<0.05$ were considered statistically significant. In the power analysis, with a predicted type 1 error of 0.05 and an efficacy power of 0.80, a minimum of 30 patients were required in both groups to achieve statistical significance.

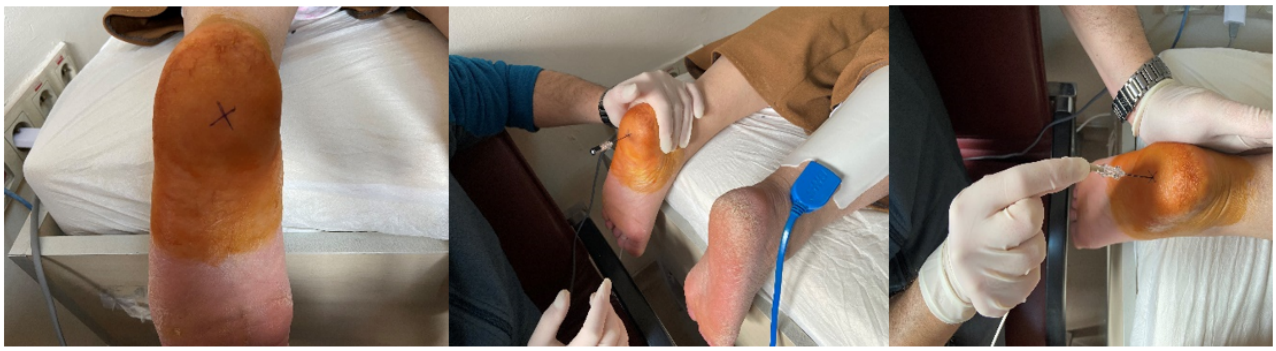

Figure 1: Application of RFA Treatment

Results

A total of 122 patients received steroid injections and/or radiofrequency ablation. Of these, 80 patients were found to meet the criteria, but 69 patients were included in the study because 11 patients did not comply with follow-up. 35 patients received radiofrequency ablation and 34 patients received steroid injections. The mean age of the patients who underwent RFA was 43.89 ± 10.31 years, 25 were female and 10 were male. The mean age of the patients who underwent steroid injection was 48.74 ± 5.00 years, 23 were female and 11 were male. Body mass index for the RFA group was 24.71 ± 3.61 while it was 24.23 ± 3.57. for the steroid group.

Preintervention VAS of the RFA group was 8.86 ± 0.77 while preintervention VAS of the steroid group was 8.70 ± 0.58, and there was no significant difference between them (p=0.469). VAS at the end of the 1st month of the RFA group was 3.00 ± 1.33 while VAS at the end of the 1st month of the steroid group was 2.94 ± 1.61, with no significant difference (p=0.764). VAS at the end of the 6th month of the RFA group was 5.71 ± 1.93 while VAS at the end of the 6th month of the steroid group was 8.52 ± 1.26, and there was significant difference between them (p=0.001). Preintervention AOFAS of the RFA group was 42.80 ± 6.13, while preintervention of the steroid group was 44.94 ± 7.35 and there was no significant difference (p=0.244). AOFAS at the end of the 1st month of the RFA group was 60.97 ± 13.67 while AOFAS at the end of the 1st month of the steroid group was 59.03 ± 12.15 and there was no significant difference between them (p=0.466). AOFAS at the end of the 6th month of the RFA group was 53.60 ± 9.49 while AOFAS at the end of the 6th month of the steroid group was 44.12 ± 7.05 and there was significant difference between them (p=0.001).

The patients were evaluated with the Wilcoxon test based on their preop state. In the RFA group, a statistically significant difference was observed between preintervention VAS value and at the end of 1st month VAS (p=0.001). In the RFA group, a statistically significant difference was observed between preintervention VAS value and at the end of 6th month VAS (p=0.001). In the steroid group, a statistically significant difference was observed between preintervention VAS and at the end of 1st month VAS (p=0.001). There was no statistically significant difference between preintervention VAS and at the end of 6th month VAS in the steroid group (p=0.512). In the RFA group, a statistically significant difference was observed between the preintervention AOFAS value and at the end of 1st month AOFAS value (p=0.001). In the RFA group, a statistically significant difference was observed between the preintervention AOFAS value and at the end of 6th month AOFAS value (p=0.001). In the steroid group, a statistically significant difference was observed between the preintervention AOFAS value and at the end of 1st month AOFAS value (p=0.001). No statistically significant difference was observed between the preintervention AOFAS and at the end of 6th month AOFAS in the steroid group (p=0.844). Means of all scores, standard deviation and p values after statistical analysis are given in Table 1.

Table 1: Scores of patients who underwent radiofrequency ablation and steroid injection

		RFA (Mean ± SD)	Steroid Injection (Mean ± SD)	p value
Preintervention VAS		8.86 ± 0.77	8.70 ± 0.58	0.469 [a]
Postintervention 1st Month VAS		3.00 ± 1.33	2.94 ± 1.61	0.764 [a]
Postintervention 6th Month VAS		5.71 ± 1.93	8.52 ± 1.26	0.001 [a]
Preintervention AOFAS		42.80 ± 6.13	44.94 ± 7.35	0.244 [a]
Postintervention 1st Month AOFAS		60.97 ± 13.67	59.03 ± 12.15	0.466 [a]
Postintervention 6th Month AOFAS		53.60 ± 9.49	44.12 ± 7.05	0.001 [a]
		Preintervention	Postintervention 1st Month	
RFA	VAS	8.86 ± 0.77	3.00 ± 1.33	0.001 [b]
	AOFAS	42.80 ± 6.13	60.97 ± 13.67	0.001 [b]
		Preintervention	Postintervention 6th Month	
RFA	VAS	8.86 ± 0.77	5.71 ± 1.93	0.001 [b]
	AOFAS	42.80 ± 6.13	53.60 ± 9.49	0.464 [b]
		Preintervention	Postintervention 1st Month	
Steroid	VAS	8.70 ± 0.58	2.94 ± 1.61	0.001 [b]
	AOFAS	44.94 ± 7.35	59.03 ± 12.15	0.001 [b]
		Preintervention	Postintervention 6th Month	
Steroid	VAS	8.70 ± 0.58	8.52 ± 1.26	0.512 [b]
	AOFAS	44.94 ± 7.35	44.12 ± 7.05	0.844 [b]

a: Mann Whitney U test, b: Wilcoxon test, SD: Standard Deviation

Discussion

The study's most significant findings indicated that patients underwent RFA had significantly lower Visual Analog Scale (VAS) scores and significantly higher American Orthopedic Foot and Ankle Society (AOFAS) scores compared to those who received steroid injections. No gold standard method has been revealed in the literature for the treatment of plantar fasciitis, which is frequently seen in patients presenting with heel pain and is frequently encountered in the routine practice of physicians of the relevant branches (Orthopaedics, physical therapy and rehabilitation, family medicine). In this study, we compared the effectiveness of RFA, A method that has been increasingly used in recent years, and steroid injection, which is a conventional method. As a result of our study, while there was no significant difference between the two groups in the first month after the procedure. A significant improvement was observed in the pain and functional scores of the patients who received RFA compared to those who received steroid injection at the end of the sixth month.

Yürük et al. evaluated the effectiveness of radiofrequency ablation in 20 patients with plantar fasciitis and stated that this method was safe and effective(12). However, the presence of patients with and without pes planus deformity in this study disrupts standardization. As it is known, the incidence of plantar fasciitis increases in pes planus deformity(7).

In symptomatic patients with plantar fasciitis who do not benefit from conservative treatments, steroid injections are usually performed in the second stage to reduce plantar fascia inflammation and edema in the adjacent area. However, the long-term effectiveness of steroid injection is limited compared to other treatments. In a randomized clinical study, Rastegar et al. revealed that steroid injection could quickly relieve plantar heel pain, but dry needling might provide more satisfactory results in the long term in patients with plantar fasciitis (14). In addition, it has been stated that platelet rich plasma (PRP) injection has more positive results in pain and function scores during the 3-month follow-up period compared to corticosteroid injections (15, 16). Some studies have also stated that steroid injection treatment has an effect similar to placebo and improves symptoms for up to 1-2 months (17). This finding correlates with the fact that in our study there was no significant difference between the two groups in the 1st month after the procedure. The scores of plantar fasciitis patients who received steroid injection in the sixth month after the procedure were close to the preoperative scores, indicating that this treatment is not a definitive treatment. Therefore, RFA treatment may be an alternative treatment in patients who do not benefit from conservative treatment.

Surgical intervention may be considered in patients with persistent plantar fasciitis who have failed at least 6 months of conservative treatment. Open plantar fascia release is the traditional operation method. According to reports, the postoperative satisfaction rate of fascia release is 50-95% (18, 19). However, the disadvantages of surgery include the larger wound, longer postoperative recovery time, and the possibility of complex regional pain syndrome occurring after surgery. We think that it is necessary to develop less invasive techniques rather than such a surgical procedure, which is prone to so many complications and has a relatively low chance of success. Since RFA treatment is a minimally invasive method compared to surgical intervention, it does not cause complications occurred in open surgery. Yapıcı et al. underscored the utility of radiofrequency ablation therapy in patients with plantar fasciitis who exhibited resistance to various treatment modalities, such as steroid injections or Extracorporeal Shock Wave Therapy, as it was evidenced by their study evaluating a substantial patient cohort of 229 individuals(20). In our study, no complications related to RFA treatment were observed in the six-month follow-up of patients who received RFA treatment. For this reason, we think that RFA can be safely applied instead of limited long-term effectiveness treatment, such as steroid injection.

Conclusion

Our study has several limiting factors. The most important of these is that it is a retrospective study. The second limiting factor is our current knowledge of patients' short- and medium-term clinical outcomes; Unfortunately, we do not have data on long-term outcomes. Another limiting factor may be that radiological evaluation of the plantar fascia cannot be performed with x-ray or tomography and requires magnetic resonance imaging. We did not use magnetic resonance imaging because it is expensive and radiological imaging for the patient who feels relieved after the treatment creates ethical concerns.

According to the results of our research, radiofrequency ablation is an effective, safe and minimally invasive method in reducing pain severity and improving daily activities in short-term (0-3 months) and medium-term (3-6 months) perspectives. Radiofrequency ablation therapy can be considered as an effective option in patients who have received conservative treatment but have not benefited from it.

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ORIGINAL ARTICLE

Maternal and Umbilical Cord Heat-Shock Protein 70 Levels in Patients with Gestational Diabetes Mellitus

Gestasyonel Diyabetes Mellituslu Gebe Hastalarda Maternal ve Umblikal Kordon Heat-Shock Protein 70 Seviyeleri

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ABSTRACT

Objectives: The objective of this investigation is to ascertain whether there is an increase in the levels of heat shock protein 70 (HSP70), a signal for cellular stress, in the maternal bloodstream and umbilical cord of pregnancies affected by gestational diabetes mellitus (GDM). Additionally, the aim is to explore whether variations in the concentrations of Hsp70 in umbilical cord serum can be indicative of the likelihood of early term delivery (between 37 0/7 and 38 6/7 weeks of gestation) in women diagnosed with GDM compared to the control group.
Methods: In this case-control study, 62 individuals diagnosed with gestational diabetes mellitus (GDM) comprised the GDM group while 22 non-diabetic, healthy women scheduled for cesarean section formed the control group. Our analysis encompassed the examination of Hsp70 serum levels in both maternal pregnancies and umbilical cord sera, alongside an evaluation of various biochemical and anthropometric markers. Additionally, the study explored the occurrence of early term delivery among all subjects.
Results: The concentration of Hsp70 in the maternal serum exhibited a notable increase among individuals diagnosed with gestational diabetes mellitus (GDM) compared to healthy pregnant women. Similarly, the levels of Hsp70 in the umbilical cord were elevated in GDM patients although the difference did not reach the commonly accepted significance threshold. Notably, cord Hsp70 levels displayed a statistically significant negative correlation with the time of delivery in women with GDM. This inverse relationship with the time of delivery was also observed in the overall study group, indicating a potential association between cord Hsp70 levels and the timing of delivery.
Conclusion: Maternal Hsp70 was significantly higher in patients with GDM. The obtained results seem to indicate that elevated umbilical cord Hsp70 values may potentially be used as indicators of risk factor for preterm delivery in pregnancies.

Keywords: Gestational Diabetes, Heat-Shock Protein 70, Preterm Birth

ÖZ

Amaç: Bu çalışmanın amacı, hücresel stresin bir belirleyicisi olan Heat shock protein 70 (Hsp-70)'in, gestasyonel diyabet mellitus (GDM) gebeliklerde maternal serum ve umbilikal kordda yüksek olup olmadığını belirlemek ve farklı serum Hsp-70 konsantrasyonlarının umbilikal kordda, GDM'li kadınlarda ve kontrol grubundaki kadınlarda erken doğumun bir göstergesi olarak ilişkilendirilip ilişkilendirilmediğini belirlemektir (37 0/7-38 6/7 hafta gebelik).
Yöntemler: Çalışma, bu durum kontrol çalışmasında sezaryen doğum olan GDM'li 62 hasta (GDM grubu) ve 22 diyabetik olmayan, sağlıklı kadını içermektedir. Hamileliklerde ve umbilikal kord serumlarında Hsp-70 düzeylerini ve tüm konulardaki erken doğumu içeren diğer biyokimyasal ve antropometrik belirteçleri analiz ettik.
Bulgular: GDM'li hastalarda maternal serum Hsp-70 düzeyleri, sağlıklı hamile kadınlardan önemli ölçüde yüksekti. GDM hastalarının umbilikal kord Hsp-70 düzeyleri de sağlıklı hamile kadınlara göre artmıştı ancak genellikle kabul edilebilir düzeyde anlam bulunamadı. Kord Hsp-70 düzeyleri, GDM'li kadınlarda doğum zamanı ile negatif anlamlı bir korelasyon gösterdi. Kord Hsp-70 düzeyleri, aynı zamanda tüm grup içinde doğum zamanı ile negatif anlamlı bir korelasyon gösterdi.
Sonuçlar: Maternal Hsp-70, GDM'li hastalarda önemli ölçüde yüksekti. Elde edilen sonuçlar, yüksek umbilikal kord Hsp-70 değerlerinin, gebeliklerde erken doğum için bir risk faktörü göstergesi olarak potansiyel olarak kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Heat-shock protein 70, Gestasyonel Diyabetes Mellitus, Erken Doğum

Introduction

Gestational diabetes mellitus (GDM) is characterized by varying degrees of glucose intolerance that emerges or is first recognized during pregnancy. This condition is linked to serious adverse perinatal outcomes, including abnormal intrauterine growth and an elevated incidence of both spontaneous and induced preterm births (1). Despite the numerous complications associated with hyperglycemia, the underlying mechanisms contributing to the physiopathology of fetal abnormalities in GDM have yet to be fully comprehended (2). Heat-shock proteins (HSPs), also known as stress proteins, serve as molecular chaperones, playing a vital role in maintaining protein homeostasis (3) and shielding cells from various forms of stress (4). Typically, under normal conditions, HSPs are regarded as intracellular proteins with anti-inflammatory effects (5). However, in situations of cellular stress, these proteins can also be expressed on the cell surface (6).

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Crucially, heat shock proteins are instrumental in the development of insulin resistance, contributing to the manifestation of hyperglycemia. This involvement underscores their significance in the physiological response to stress and the regulation of cellular processes associated with metabolic function. Heat Shock Protein 70 is a noteworthy protein in this context, acting as a cytoprotective chaperone with roles in both protein folding and degradation. The induction, transcription, and translation of Hsp70 have associations with a reduction in insulin resistance-related metabolic disorders. This impact extends to factors such as inflammation, mitochondrial function and endoplasmic reticulum (ER) stress.

Elevated levels of extracellular Hsp70 in the plasma are correlated with conditions like obesity and diabetes, both recognized as pro-inflammatory states as discussed in the current review. Conversely, a decrease in the concentration of Hsp70 may impede inflammation and mitochondrial fatty acid oxidation while concurrently enhancing the activation of SREBP-1c, a gene transcription factor intricately involved in ER stress. This intricate interplay underscores the multifaceted role of Hsp70 in regulating various cellular processes associated with metabolic health.

Moreover, increased expression of Hsp70 in brain cells holds the potential to augment insulin sensitivity and restore blood glucose levels to a normal range. This highlights the multifaceted involvement of Hsp70 in regulating diverse pathways associated with insulin resistance and other related metabolic disorders (2). The production of elevated levels of Hsp70 can be initiated by exposure to various stressors such as hyperthermia, ischemia, inflammation, and oxidative stress (1). Recent research findings have indicated that circulating Hsp70 levels were notably elevated in individuals diagnosed with type 2 diabetes mellitus when compared to those without diabetes (3). Diabetes mellitus exerts an impact on the duration of gestation and the likelihood of spontaneous preterm birth (1). The connection between preterm delivery and heat-shock protein (Hsp70) has been a subject of investigation (1, 3-7). However, findings regarding the association between Hsp70 and both preterm and term deliveries have been inconsistent. While some studies report an increased risk of early term birth (1, 4-6), international literature lacks a consensus on whether Hsp serves as an independent risk factor for spontaneous early term or preterm birth (1, 3-7). The existing body of research presents conflicting perspectives on the role of Hsp70 in influencing the timing of delivery. Nevertheless, it is crucial to acknowledge that these studies come with inherent limitations, including a retrospective design in some cases (2), the absence of umbilical cord sera in others (1, 5-7), reliance on serum from high-risk patients for preterm delivery in specific studies (5), and the lack of consideration for gestational diabetes mellitus (GDM) in certain investigations (1, 3). To the best of our knowledge, there is currently no available data regarding the changes in Hsp70 levels in both maternal and cord serum among women with GDM when compared to a carefully matched nondiabetic control group.

In the current study, we sought to address these gaps by conducting a comprehensive assessment of early term delivery. Our focus was on determining whether the levels of serum Hsp70 in umbilical cord samples could potentially serve as a reliable indicator of early term delivery in women with GDM, comparing these findings with a control group of non-diabetic individuals. This investigation aims to contribute valuable insights into the relationship between Hsp70, GDM, and early term delivery, providing a more nuanced understanding of the complex interplay involved.

Material and Methods

The current study received approval from the Ethical Committee and Institutional Review Board of Selcuk University Faculty of Medicine, where the research was conducted. Prior to participation, written informed consents were obtained from all individuals included in the study. The study comprised 62 pregnant women diagnosed with gestational diabetes mellitus (GDM) and a control group consisting of 22 individuals matched for age and body mass index (BMI), all with uncomplicated singleton pregnancies. Pregnant women were recruited from the antenatal clinic of our obstetrics department, with a history of prior cesarean section deliveries and a plan for cesarean section delivery. Exclusion criteria for all participants included the use of medication, smoking, high blood pressure, any acute or chronic diseases, fetal anomalies, and multiple gestation. Detailed clinical histories of all participants were taken and physical examinations were performed. Screening for GDM was performed using a 50 g glucose challenge test (GCT) at the 24th gestational week. This comprehensive approach to participant selection and screening aimed to ensure a detailed and representative study population, taking into account various factors that could potentially influence the study outcomes. The diagnosis of gestational diabetes mellitus (GDM) in our study followed the two-step approach proposed by Carpenter and Coustan. The 50 g glucose screening test was conducted irrespective of the time of day or preceding meals. Subsequently, an oral glucose tolerance test was recommended for all patients whose 1-hour test result equaled or exceeded 140 mg/dl. The criteria for diagnosing GDM included two or more values surpassing the established cut-off levels (95/180/155/140 mg/dl) (8). As for the age and BMI-matched control group, all individuals had negative results in the oral glucose tolerance test. This rigorous diagnostic approach ensured a clear and standardized identification of GDM cases and the selection of suitable controls for comparison. 62 patients diagnosed with gestational diabetes mellitus (GDM) underwent various treatments aimed at maintaining blood glucose levels within target ranges. The defined targets were set to be 105 mg/dl or lower before meals and 120 mg/dl or lower 2 hours after meals, with the goal of managing elevated fasting plasma glucose values (>95 mg/dl) and/or elevated

postprandial values (above 120 mg/dl for 2 hours or 140 mg/dl for 1 hour) (9, 10). If blood glucose levels remained above the specified targets despite dietary intervention, insulin therapy was implemented. The patients were categorized into three groups: Group 1 comprised 22 non-diabetic pregnancies serving as the control group, Group 2 included 28 pregnant women with GDM who underwent controlled dietary intervention, and Group 3 consisted of 34 pregnant women with GDM who received insulin therapy. In the context of this case-control study, a total of 84 pregnant women were included, with 62 in the GDM group and 22 healthy, non-diabetic women serving as controls. This comprehensive approach allowed for a thorough investigation into the impact of different treatments on blood glucose levels and their implications for both GDM and non-diabetic pregnancies. For all participants, detailed information including age, gravidity, and parity was recorded. Additionally, body mass index (BMI) was calculated before delivery as the ratio of weight divided by height squared (kg/m2). Exclusion criteria for both groups comprised multiple pregnancies, infections, chronic illnesses, smoking habits, women younger than 18 or older than 40 years, known clotting disorders, uterine or cervical abnormalities, placenta previa and placental abruption, patients with a history of previous premature delivery, and those with severe maternal diseases such as HELLP syndrome, preeclampsia, and severe chronic diseases. The inclusion of these criteria aimed to eliminate potential confounding factors and ensure a more homogeneous study population, given that these conditions are recognized risk factors in themselves for early term births (between 37 0/7 and 38 6/7 weeks of gestation). Maternal venous blood samples were obtained in the fasting state before Caesarean section, with all subjects receiving lumbar epidural analgesia for pain relief during the procedure. Simultaneously, umbilical cord blood samples were collected at the time of the Caesarean section. These blood samples were drawn into tubes and promptly centrifuged after clotting. The resulting supernatant serum was frozen at -80°C until the time of assay. The analysis of serum Hsp70 was conducted using a commercial ELISA kit from Eastbiopharm, China, with measurements performed by an ELISA reader from Rayto, India. To ensure the reliability of the results, the intra- and inter-assay coefficients of variations for Hsp70 were maintained at levels below 10% and 15%, respectively. The detection range for Hsp70 in the kit spanned from 2 to 600 ng/mL, providing a robust framework for the quantitative analysis of Hsp70 levels in the collected serum samples.

Statistical Analysis

Data analysis was conducted using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). The normality of continuous variable distributions was assessed using the Kolmogorov-Smirnov test, and the homogeneity of variances was evaluated using the Levene test. Descriptive statistics were presented as mean ± SD or median (min-max), as appropriate. For comparisons between the groups (GDM and non-diabetic group), the Independent Samples t-test and Mann–Whitney U test were employed for parametric and non-parametric numeric data, respectively. To assess mean differences among the groups (Group 1, 2, 3), One-Way ANOVA was utilized for parametric numeric data while the Kruskal-Wallis test was applied for non-parametric numeric data. In instances where the p value from the Kruskal-Wallis test statistics was statistically significant, Conover's non-parametric multiple comparison test was used to determine specific group differences. The association between continuous variables was evaluated using Spearman's Rank Correlation analyses. Nominal data were analyzed using Pearson's chi-square, Fisher's exact, or Likelihood Ratio tests, as appropriate. A p value less than 0.05 was considered statistically significant.

Results

The study encompassed 62 patients diagnosed with gestational diabetes mellitus (GDM) (GDM group), alongside 22 non-diabetic individuals. Within the GDM group, 28 received treatment with diet alone (Group 2), while 34 underwent insulin therapy (Group 3). The non-diabetic control group (Group 1) comprised 22 pregnancies. The demographic and clinical characteristics of women in the GDM and control groups are presented in Table I.

The mean maternal serum Hsp70 level in the GDM group (Group 2 + Group 3) was significantly higher than that of the non-diabetic control group, with values of 220.5 ± 96.9 ng/ml versus 166.1 ± 36.2 ng/ml, respectively (p<0.001). In contrast, the cord Hsp70 level in the GDM group (Group 2 + Group 3) was slightly elevated compared to the non-diabetic control group, but this difference did not reach statistical significance (123.2 ± 113.5 ng/ml versus 106.6 ± 71.7 ng/ml, p=0.4) (Figure 1). No significant differences were observed between the groups in terms of age, time of delivery, BMI, birth weight, maternal height, and weight (p>0.05). However, a noteworthy finding was the significantly higher incidence of a family history of gestational diabetes among women in the GDM group compared to the control group (p<0.001).

Table 1. Demographic, clinical characteristics of women with GDM and controls according to groups

	Group I (n=22) Controls	Group II (n=28) Diet	Group III (n=34) İnsulin	p-values
Age (year)	31.4±4.9	34.1±6.1	33.3±6.0	0.265
Maternal height(cm)	159.9±4.9	162.6±8.2	159.8±4.5	0.154
Maternal weight (kg)	76.3±8.8	81.6±10.5	81.7±11.1	0.121
BMI (kg/m^2)	29.9±3.5	31.0±4.2	32.0±4.2	0.172
Gestational age at birth (week)	38.6 (38.0-39.3)	38.7 (38.0-39.5)	38.4 (38.0-39.5)	0.707
Family history GDM	3 (%13.6)[a,b]	16 (%57.1)[a]	22 (%64.7)[b]	<0.001
Birth weight (g)	3237.5 (2825-3950)	3140 (2700-5100)	3150 (2700-4380)	0.785

BMI, body mass index.

[a]Significantly different from the Group 1 and Group 2 (p<0,05)

[b]Significantly different from the Group 1 and Group 3 (p<0,01)

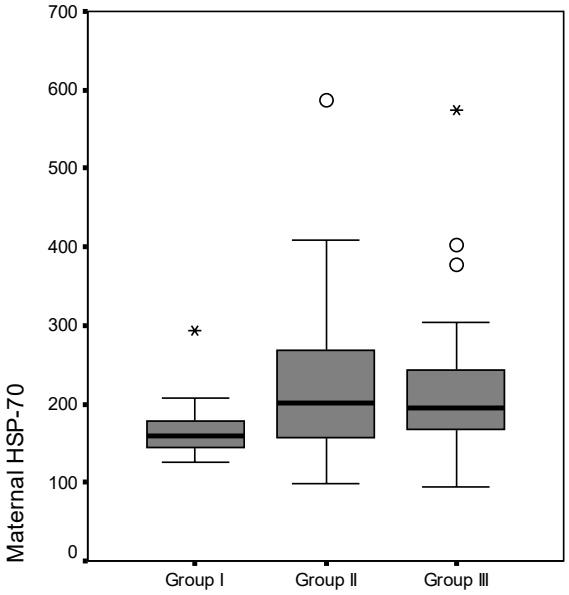

Figure 1. Maternal Hsp70 levels in women with GDM and controls according to groups.

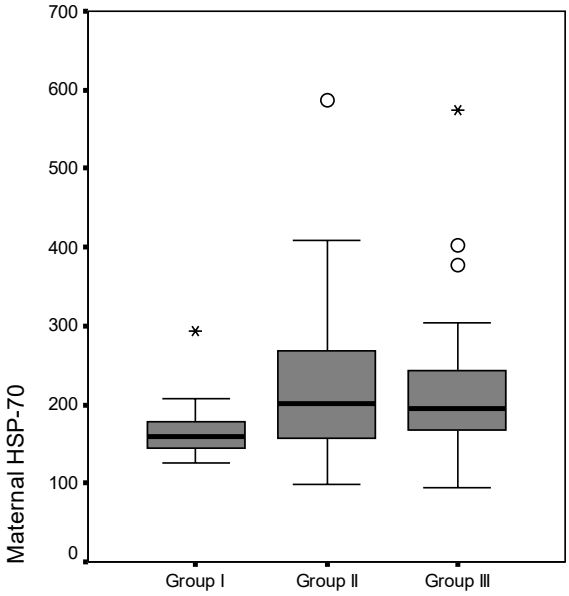

Figure 2. Maternal Hsp70 levels in women with GDM (diet and insulin group) and controls according to groups

Analyzing maternal Hsp70 levels across groups, the graphical representation uses box plots. The horizontal line within each box denotes the median, with the upper and lower boundaries indicating the 25th and 75th percentiles, respectively. The whiskers extending above and below the box represent the maximum and minimum Hsp70 levels. Open circles are used to denote outliers while asterisks specifically highlight extreme cases. This visual representation offers a clear and concise overview of the distribution and central tendency of maternal Hsp70 levels within and across the examined groups.

Maternal serum Hsp70 levels were significantly higher in group 2 than group 1 controls (201.5 [99-587] ng/ml versus 159 [126-293] ng/ml, (p=0.002). Serum Hsp70 levels were also found significantly higher in group 3 than group 1 controls (195.5 [(94-574)] ng/ml versus 159 [126-293] ng/ml, (p=0.002) (Figure 2). No significant differences were found between group 2 and group 3 in Hsp70 levels (p=0.9). Hsp70 levels in cord were not significantly different among groups. Table 2 shows maternal and cord Hsp70 levels of women with GDM (group 2, group 3) and controls according to groups.

The comparison of maternal Hsp70 levels among groups is depicted using box plots. Within each box, the horizontal line represents the median, while the upper and lower borders indicate the 25th and 75th percentiles, respectively. The whiskers extending above and below the box mark the maximum and minimum Hsp70 levels. Open circles on the plot are used to identify outliers, and asterisks highlight extreme cases. This graphical representation provides a visual summary of the central tendency, spread and presence of extreme values in maternal Hsp70 levels across the examined groups.

Table 2. Maternal and cord Hsp70 levels of women with GDM (diet and insulin group) and controls according to groups

	Group I Controls	Group II Diet	Group III İnsulin	p-value
Serum Hsp70 (ng/ml)	159 (126-293) [a,b]	201.5 (99-587)[a]	195.5 (94-574)[b]	0.008
Cord Hsp70 (ng/ml)	107.5 (5-234)	111 (5-541)	121.5 (2-389)	0.557

[a]Significantly different from the Group 1 and Group 2 (p=0,002)
[b]Significantly different from the Group 1 and Group 3 (p=0,002)

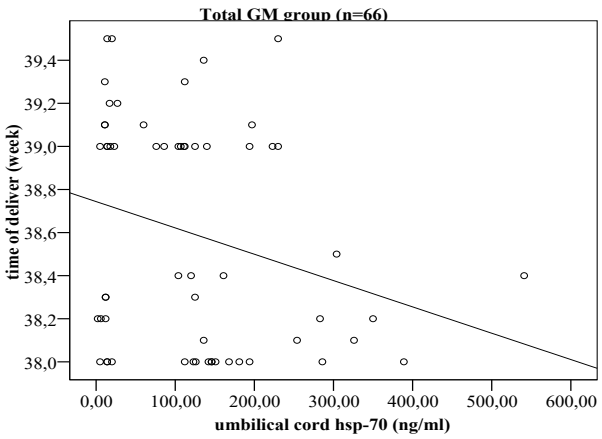

Figure 3. Cord Hsp70 levels showed a negatively significant correlation with time of delivery, (r: - 0.266, p=0.04) in women with total GDM group (diet with insulin; n=66).

Cord Hsp70 levels showed a negatively significant correlation with time of delivery, (Figure 3; r: - 0.266, p=0.04) in women with GDM group (group 2 + group 3). Cord Hsp70 levels also showed a negatively significant correlation with time of delivery, (Figure 4; r: - 0.25, p=0.02) in whole group. No correlations were found between serum and cord Hsp70 levels with age, BMI, birth weight (Table 3).

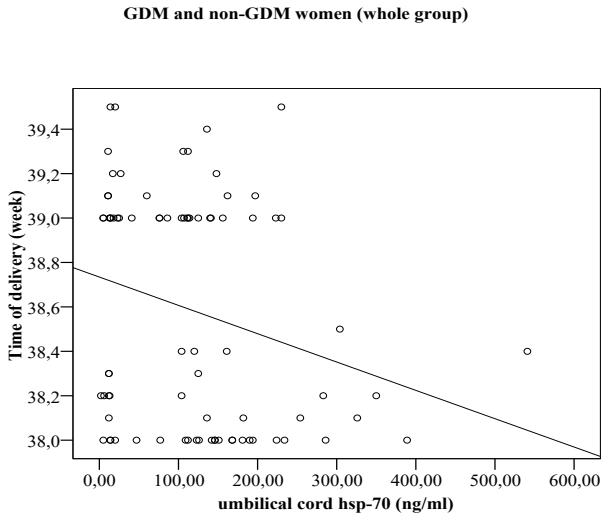

Figure 4. Cord Hsp70 levels showed a negatively significant correlation with time of delivery, (r: - 0.25, p=0.02) in whole group (n=84).

Table 3. Correlations between maternal and cord HSP70 levels and all the other parameters in whole groups

	Serum HSP70		Cord HSP70	
	r	p-values	r	p-values
Age (year)	-0.046	0.676	0.019	0.867
BMI (kg/m²)	0.120	0.278	0.158	0.160
Gestational age at birth	0.047	0.674	-0.226	0.042
Birth weight (g)	0.037	0.738	0.017	0.879
Fasting glucose (mg/dl)	0.066	0.653	0.026	0.861

Discussion

This study represents a pioneering effort, being the first to concurrently assess Hsp70 levels in both maternal and fetal compartments in the context of gestational diabetes mellitus (GDM). Our results, obtained through a meticulously matched case–control design, reveal that individuals with GDM exhibit elevated serum Hsp70 levels in comparison to those without GDM. Although umbilical cord Hsp70 levels were also higher in the GDM group, the difference did not reach statistical significance. Notably, a significant correlation was identified between umbilical cord Hsp70 levels and the time of delivery, both in women with GDM and in the entire study group. These findings shed light on the potential role of Hsp70 in GDM and its association with the timing of delivery, providing valuable insights for further exploration and understanding of the underlying mechanisms.

The molecular mechanisms implicated in the effects of hyperglycemia on inflammation and vascular complications are believed to involve the action of reactive oxygen species within the cell nucleus (11). Our study, focusing on the increase in circulating Hsp concentrations in gestational diabetes mellitus (GDM), was driven by the hypothesis that GDM might trigger a heat shock response. Our results find support from existing studies on type 2 diabetes. For instance, a previous investigation revealed higher serum Hsp70 levels in non-insulin-treated type 2 diabetes subjects compared to their insulin-treated counterparts (12). Another cross-sectional study demonstrated increased levels of Hsp70 in mononuclear cells of type 2 diabetic patients in comparison to normal subjects (13). Reports have also highlighted elevated serum Hsp70 levels in type-1 diabetic patients (14). While previous studies on pregnant patients yielded similar results, our larger-scale research further supports these findings with a more comprehensive examination involving a larger number of participants (4).

Contrastingly, some studies have reported reduced systemic Hsp70 expression in association with elevated glucose levels in non-human primates (5). In our study, participants were categorized into two groups based on treatment models. Among women with GDM (n=62), 28 were treated with diet alone (Group 2), and 34 underwent insulin therapy (Group 3). Interestingly, we observed no significant differences between Group 2 and Group 3 in Hsp70 levels. We hypothesize that the duration of glucose excursion may hold greater significance in influencing Hsp70 levels than the specific treatment model involving insulin or diet. This apparent discrepancy warrants further investigation for a comprehensive understanding of the relationship between treatment modalities, glucose levels and Hsp70 expression.

Studies focused on type 2 diabetes mellitus (DM) have played a crucial role in unveiling the functions of Hsp70 in diabetes. However, there is a notable scarcity of data concerning gestational diabetes mellitus (GDM). In a study by Katarzyna et al., it was reported that levels of Hsp70 in women with pre-pregnancy diabetes were significantly higher than those in women with GDM. These findings suggest a cellular adaptive response to oxidative stress associated with hyperglycemia, potentially linked to the elevated serum Hsp70 levels observed in non-pregnant individuals with diabetes. This strongly implies that chronic hyperglycemia over an extended period may contribute to the observed increase in serum Hsp70 levels in GDM. This underscores the importance of considering the duration and intensity of hyperglycemia in understanding the dynamics of Hsp70 levels in different forms of diabetes. (15).

Increased levels of Hsp70 expression have been detected in the placenta of women underwent conditions such as pre-eclampsia, placental vascular diseases, and other pathological pregnancies. Similarly, heightened expression of cellular stress markers has been noted in the placenta of women

with cardiovascular diseases (CVD). Earlier research has acknowledged Hsp70 as a notable angiogenic factor within the orchestrated response mechanisms in maternofetal tissues. Consequently, there appears to be a reported elevation in both angiogenesis and lymphangiogenesis in the placenta of women with CVD. These findings suggest a potential role for Hsp70 and cellular stress markers in the pathophysiology of pregnancy-related complications and cardiovascular diseases, emphasizing the intricate interplay between stress responses and vascular health during pregnancy. (16). Also, our data presented in this study demonstrate that there is a differential release of Hsp70 from umbilical cord and maternal serum obtained from normal pregnant women and women with GDM. Although no difference in Hsp70 release was observed between GDM group and non-diabetic control group in umbilical cord, it was higher in GDM group. Why Hsp70 is not increased significantly in umbilical cord is exactly remains unknown. The primary rationale for the homogeneity of our sample size can be attributed to the stringent inclusion criteria applied, coupled with the lack of significant differences in obstetric history and smoking habits among the participants. The exclusion of severe maternal diseases, such as preeclampsia and placenta previa, which are recognized risk factors for early term birth, further contributed to the uniformity of the sample. This methodological approach aimed to minimize potential confounding variables, allowing for a more focused examination of the specific factors under investigation and enhancing the internal validity of the study. Secondary explanation may be that prolonged exposure to high glucose levels may be necessary to impair Hsp responses in fetus as mentioned previous studies (17). Nakhjavani M et al. (5) showed that the acute response of serum Hsp70 levels to hyperglycemia was the indicator of average long-term serum glucose level. Therefore, it may be explained by this hypothesis that, GDM patients were much more meet with high glucose levels so that serum levels of Hsp70 were significantly higher in GDM patients than in healthy pregnant women.

Our findings of a negative association between umbilical cord Hsp70 concentrations and early term birth in pregnancies corroborate with previous studies. Increased concentrations of Hsp70 in mononuclear cells of peripheral blood obtained from women in early pregnancy were associated with subsequent miscarriages, stillbirths, and preterm births (18). The work by Ziegert M et al. has outlined the prognostic and diagnostic significance associated with the presence of Hsp60 and Hsp70 antibody complexes in the placenta, as well as the detection of antibodies to Hsp60 and Hsp70 in the blood. However, it's important to note that findings across studies are not entirely consistent. Some investigations exploring the connection between early term delivery and Hsp expression have reported no significant difference in the levels of Hsp in the placenta between full-term delivery and preterm delivery. The variability in results underscores the complexity of the relationship between heat shock proteins and the timing of delivery, indicating the need for further research to better understand these associations (19-21).

As previously noted, a strong correlation has been established between umbilical cord Hsp70 levels and early term delivery. However, it is crucial to emphasize that, as of now, maternal Hsp70 alone is not adequate for predicting early term delivery. Consequently, our ongoing efforts involve the evaluation of the potential to enhance predictive accuracy for early term delivery or assess therapeutic effects by incorporating Hsp70 with other indicators. This comprehensive approach aims to explore whether a combination of factors can provide a more precise understanding of early term delivery risks and treatment outcomes, reflecting the multifaceted nature of the underlying physiological processes. There are several limitations to our study that should be acknowledged. Firstly, the absence of data in large groups of diabetes patients limits the generalizability of our findings. This study can be considered a reasonable starting point for exploring the role of Hsp70 in gestational diabetes mellitus (GDM). Additionally, the lack of assessments such as malondialdehyde (MDA) or cytosolic reactive oxygen species (ROS) production in participants is a notable limitation, as correlating these markers with Hsp70 in women with GDM could provide valuable insights into the underlying mechanisms. This represents one of the most significant limitations of the study. Moreover, our patient cohort was drawn from a representative sample of individuals with GDM in our clinic, which may impact the generalizability of our results. Despite these limitations, our study serves as an initial exploration, and future research with larger and more diverse participant groups is warranted to further elucidate the role of Hsp70 in GDM.

The data presented in this study indicate a distinct variance in Hsp70 levels between normal pregnant women and those with gestational diabetes mellitus (GDM). Although umbilical cord Hsp70 levels were higher in the GDM group, this difference did not reach statistical significance. However, a significant correlation was identified between umbilical cord Hsp70 levels and the time of delivery in women with GDM and the overall study group.

Conclusion

Considering that many causes of early term birth remain unexplained and unknown, future studies are essential for elucidating the roles of both Hsp70 and oxidative stress in the risk of early term delivery in pregnant women. The findings from this study provide a foundation for further exploration and emphasize the need for comprehensive investigations into the complex interplay of various factors influencing the timing of delivery in the context of GDM.

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ORIGINAL ARTICLE

Preoperative Hepatitis B Seroprevalence and AntiHBs Levels in Children Consulted for Dental Procedures under Anaesthesia

Anestezi Altında Diş Girişimi İçin Konsülte Edilen Çocuklarda Preoperatif Hepatit B Seroprevalansı ve AntiHbs Antikor Düzeyleri

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ABSTRACT

Background/Aims: Hepatitis B virus infection continues to be a major global and national public health concern. The aim of this study was to examine the seroprevalence of hepatitis B virus in children who were consulted to child health and diseases before dental intervention and to share our findings with the healthcare personnel involved in this subject.
Methods: A total of 932 children 533 of whom (57.2%) were boys and 399 (42.8%) were girls were enrolled in the study. In the blood samples taken; hepatitis B virus tests were studied with the Enzyme Linked Immunosorbent Assay method. The results of blood samples and demographic data of the patients were evaluated.
Results: HBsAg positivity was not found in any of the patients (0%). AntiHBs seropositivity was found in 73.8% of the whole patient population. No statistically significant difference was detected when comparing the anti-HBs levels based on gender. The average age of children with antiHBs seropositivity was statistically significantly lower than that of those with antiHBs seronegativity. The median anti-HBS antibody levels were significantly higher in the group of children under 5 years old than in the other two age groups older than five years old in our study. When investigating the association between the level of antiHBs and age, a weak negative correlation was determined.
Conclusion: Our study showed that the antiHBs seropositivity is higher in Konya province compared to previous studies. It suggests that the national vaccination program has a positive impact on antiHBs seroprevalence. Our study revealed that children under the age of five displayed the highest levels of anti-HBs seropositivity, while the anti-HBs levels diminished with advancing age.

Keywords: Children, Consultation, Hepatitis B virus, Preoperative period, Seroprevalence

ÖZ

Arka Plan/Amaçlar: Hepatit B virüsü enfeksiyonu küresel ve ulusal düzeyde halen önemli bir halk sağlığı sorunu olmaya devam etmektedir. Bu çalışmanın amacı, diş müdahalesinden önce çocuk sağlığı ve hastalıklarına danışılan çocuklarda hepatit B virüsü seroprevalansını incelemek ve bulgularımızı konuyla ilgili sağlık personeliyle paylaşmaktır.
Yöntemler: Çalışmaya toplamda 932 çocuk katılmış olup, bunların 533'ü (%57.2) erkek ve 399'u (%42.8) kızdır. Alınan kan örneklerinde; hepatit B virüsü testleri Enzim Bağlı İmmuno Sorbent Testi yöntemiyle incelenmiştir. Kan örneklerinin sonuçları ve hastaların demografik verileri değerlendirilmiştir.
Bulgular: HBsAg pozitifliği hiçbir hastada bulunmamıştır (%0). Tüm hasta popülasyonunun %73.8'inde AntiHBs seropozitifliği bulunmuştur. Cinsiyete göre anti-HBs seviyeleri karşılaştırıldığında istatistiksel olarak anlamlı bir fark bulunmamıştır. AntiHBs seropozitif olan çocukların ortalama yaşı, antiHBs seronegatif olanlardan istatistiksel olarak anlamlı düşük bulunmuştur. Çalışmamızda, 5 yaşından küçük çocukların anti-HBS antikor seviyeleri, 5 yaşından büyük diğer iki yaş grubundakilerden anlamlı olarak daha yüksek bulunmuştur. AntiHBs seviyesi ile yaş arasındaki ilişki incelendiğinde, zayıf bir negatif korelasyon bulunmuştur.
Sonuçlar: Çalışmamız, Konya'da antiHBs seropozitifliğinin önceki çalışmalara göre daha yüksek olduğunu göstermiştir. Bu, ulusal aşılama programının antiHBs seroprevalansı üzerinde olumlu bir etkisi olduğunu düşündürmektedir. Çalışmamız, beş yaşın altındaki çocukların en yüksek anti-HBs seropozitiflik düzeylerini sergilediğini, ilerleyen yaşla birlikte anti-HBs düzeylerinin azaldığını ortaya koymuştur.

Anahtar Kelimeler: çocuklar, danışma, Hepatit B virüsü, ameliyat öncesi dönem, seroprevalans

Introduction

Hepatitis B virus (HBV) infection continues to be a major global and national public health concern (1). Chronic viral hepatitis is mostly caused by the HBV (2). It has been reported that the global prevalence of chronic HBV infection is 3-5% (1). Nearly two million children under the age of five contract the virus each year, primarily as a result of early vertical or horizontal transmission (2). Our country is a moderate-endemic region in terms of hepatitis B prevalance (3). HBV infection is a significant cause of morbidity and mortality. Although there are antiviral treatment options, there is no definitive treatment for HBV infection (1, 3). HBV infection, during the acute stage, poses a risk to an individual's life and gives rise to grave complexities such as chronic hepatitis, hepatocellular carcinoma, and cirrhosis (1).

In addition to predominantly spreading through blood and serum, HBV can also transmit vertically from mother to child. The three most typical ways that HBV is contracted are through unsafe injection practices, sexual contact and vertical transmission (4). HBV infection is one of the most important infectious diseases in dental practice (5). During dental procedures,

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HBV can be transmitted via direct contact with blood, oral fluids, or other bodily secretions. Indirect transmission of HBV can also occur through contact with contaminated tools and operator equipments. Consequently, dental professionals are susceptible to contracting hepatitis B (5, 6). Therefore, it is imperative to ascertain the results of HBV tests prior to invasive procedures, such as dental interventions. As a result, healthcare practitioners should undertake necessary precautions while performing the procedure.

Vaccination is the most reliable method of protection against the Hepatitis B virus. The number of cases of HBV infections has dropped dramatically since the vaccination were developed. Vaccinations against the HBV have been available in our country since August 1998. Accordingly, the hepatitis B vaccine is administered in three doses immediately upon birth, at the first month, and at the sixth month of life (7). In vaccinated children, antibody to hepatitis B surface antigen (anti-HBs) seroprevalence results differ. Today, a level of anti-HBs greater than 10 mIU/ml is regarded as protective (8). Clinical studies have shown that anti-HBs levels decrease as age increases in children vaccinated against hepatitis B (9). Therefore, knowing whether the children have protective antibody levels is another important issue before dental interventions in children. The findings of studies investigating at the seroprevalence of HBV in children in our country show that seroprevalence of anti-HBs differs depending on the community and region in which the study is conducted. In Konya, there are few studies on this topic in children (10, 11). In our study, we aimed to examine the HBV seroprevalence in children referred to child health and diseases before dental intervention and to share our findings with the healthcare personnel involved on this subject.

Material and Methods

This retrospective study included patients who were consulted before receiving general anaesthesia dental intervention at the Health Sciences University Konya Beyhekim Training and Research Hospital, Child Health and Diseases Outpatient Clinic, between January 2017 and December 2022. Test results for the hepatitis B virus surface antigen (HBsAg) and anti-HBs levels were reviewed in a retrospective manner. The results of blood samples and demographic data of the patients were evaluated. The study included children aged 1 to 18 who, in accordance with the family's declaration, had completed the hepatitis B vaccination schedule. In the blood samples taken; HBV tests were examined with the Enzyme Linked Immuno Sorbent Assay (ELISA) method. Anti-HBs levels more than 10 mIU/mL were considered seropositive. Ethical approval was received from Karatay University Research Ethics Board to conduct the research. This approval was granted with the decision number 2023/019, dated 17.11.2023.

Statistical analysis

The statistical analyses were conducted utilizing the Statistical Package for Social Sciences (SPSS) version 22 (IBM Corp. Armonk, NY, USA) program. The distribution of parameters was examined using the Shapiro-Wilk test. Parameters were given as mean±standard deviation if the data were normally distributed; otherwise, they were provided as median with interquartile range (IQR). Frequency and percentage values were used for categorical variables. Pearson Chi-square test was employed for the assessment of categorical data. In the comparison of parametric measurements between the groups, the Mann Whitney U test was used for the variables not conforming to the normal distribution of the groups. Kruskal-Wallis test was utilized to compare data from more than two groups that did not comply with normal distribution. Bivariate associations of continuous variables were assessed using Spearman's correlation coefficients. Significance level was accepted as $p<0.05$.

Results

A total of 932 children were enrolled in the study, 533 of whom (57.2%) were boys and 399 (42.8%) were girls. The age range of the participants varied from 1 year to 17 years 11 months, with an average age of 5.92±2.96 years (median: 5.10 years). In our study, HBsAg positivity was not detected in any of the patients (0%). The median anti-HBs level was found in the girls at 44.37 mIU/ml and in the boys at 33.01 mIU/ml. No statistically significant difference was determined when comparing the anti-HBs levels based on gender ($p= 0.212$). A presentation of the comparison of anti-HBs values based on gender and age groups is indicated in Table 1. When the participants were categorized into two groups based on anti-HBs seropositivity levels, specifically those with less than 10 mIU/ml and those with 10 mIU/ml or higher, no a statistically significant difference was found according to gender ($p= 0.181$). The average age of children with anti-HBs seropositivity was statistically significantly lower than the average age of those with anti-HBs seronegativity (5.59±2.73, 6.87±3.37 years, $p= 0.001$). Anti-HBs seropositivity was determined in 73.8% of the whole patient population. The distribution of gender, age group, and annual data based on anti-HBs levels are presented in Table 2. When investigating the association between the level of anti-HBs and age, there was a weak negative correlation ($p=0.001$, r:-0.109).

Table 1: Comparison of serum anti-HBs antibody level according to gender and age groups

		Median (IQR)	p
Gender	Boy	33.01 (113.04)	0.214
	Girl	44.37 (149.91)	
Age groups	< 4.9 years of age	60.69 (165.81)	<0.001
	5-9.9 years of age	25.20 (94.35)	
	> 10 years of age	16.91 (97.64)	
Total		36.8 (130.86)	

Table 2: Distribution of gender, age groups, and annual data based on seropositivity of anti-HBs

		Anti-HBs Negative (<10)	Anti-HBs Positive (≥10)	Total	p
Gender	Boy	133 (24.9%)	400 (75.1%)	533 (57.2%)	0.181
	Girl	111 (27.8%)	288 (72.2%)	399 (42.8%)	
Age groups	< 4.9 years of age	82[a] (19.3%)	341[b] (80.7%)	423 (45.4%)	<0.001
	5-9.9 years of age	126[a] (30.2%)	291[b] (69.8%)	417 (44.7%)	
	> 10 years of age	36[a] (39.1%)	56[b] (60.9%)	92 (9.9%))	
Years	2017	49 (22.6%)	168 (77.4%)	217 (23.3%)	0.202
	2018	56 (25.6%)	163 (74.4%)	219 (23.5%)	
	2019	66 (27.2%)	177 (72.8%)	243 (26.1%)	
	2020	7 (17.9%)	32 (82.1%)	39 (4.2%)	
	2021	16 (24.6%)	49 (75.4%)	65 (7.0%)	
	2022	50 (33.6%)	99 (66.4%)	149 (16.6%)	
Total		244 (26.18%)	688 (73.82%)	932 (100%)	

Data were presented as n (%).

Discussion

In many clinics, anti-HBs and HBsAg titers are used for the diagnosis of hepatitis B infections. HBsAg positivity is important to identify individuals infected with hepatitis B virus. Anti-HBs, on the other hand, indicates immunity after infection or vaccination (12). Therefore, the use of these screening tools to determine the sufficient antibody response in unvaccinated individuals or even in vaccinated individuals, and to detect possible hepatitis B infected individuals is particularly crucial, especially before dental procedures involving direct contact with the patient (13-15).

The seroprevalence of HBV shows variation across different countries. In the United States, the administration of the hepatitis B vaccine began in 1991, whereas in our country, it was commenced in 1998 (7, 16). Following the implementation of the hepatitis B vaccine, numerous countries have observed a notable reduction in the seroprevalence of hepatitis B (17). Hepatitis B is a viral disease that can be prevented through vaccination. Nevertheless, children who have received the hepatitis B vaccine experience a decline in the levels of anti-HBs due to several factors. It has been shown in different clinical studies that these factors include time after vaccination, gender, obesity, immunosuppression and variants of genotypes (18-22). In addition, it is suggested that the varying rates of anti-HBs positivity in clinical studies may be due to the age range of the patient group studied, socio-economic differences in the study area and different vaccination protocols (23).

In our country, the seroprevalence of HBV in children has been observed to vary in different geographic regions, and even in the same region at different times. In studies conducted in Turkiye, almost all of them show that as children grow older, the anti-HBs seroprevalence decreases. In a recent study conducted in Tokat, which included 10,175 children over an 8-year period, the rate of anti-HBs positivity was 85.8% in infants aged 1-23 months, 78.3% in children aged 2-6 years, 66.9% in children aged 7-12 years, and 61.6% in children aged 13-18 years. The study results have shown that anti-HBs levels decrease significantly with age, and when comparing genders, there is no difference in hepatitis B seroprevalence. Additionally, the seroprevalence of hepatitis B in children born before the hepatitis B vaccination is significantly lower than others. In the same study, the ages of children with anti-HBs seropositivity were significantly lower than those with anti-HBs seronegativity. HBsAg seropositivity was detected in 2% of the patients (3). Our study elucidated that individual under the age of five displayed the highest levels of anti-HBs seropositivity, while the response of anti-HBs diminished with advancing age. Moreover, we revealed that the median anti-HBs levels and the seroprevalence of Hepatitis B were not influenced by gender. Moreover, we identified a negative correlation between the levels of anti-HBs and age (p=0.001). Anti-HBs levels were significantly higher in the group of children under five years old than in the other two age groups older than five years old in our study when median anti-HBs levels were compared by age groups.

There were studies in Şanliurfa province that showed a decrease in HBsAg positivity after hepatitis B vaccination, with these rates reported as 12.5% in 1997 and 2% in 2002 (24,25). In a study including 720 children over a 2-year period in Uşak province, HBsAg positivity was found in 1 out of 720 patients, and anti-HBs seropositivity was detected in 65% of them. In comparison to other older age groups, the study indicated that the 1-3 age group had the highest levels of anti-HBs (26).

In a study involving 1332 children in Van province, the HBsAg positivity was 0.2%, while the anti-HBs seropositivity was approximately 73%, indicating that a large proportion of these individuals had been vaccinated against hepatitis B (27).

Studies conducted in Istanbul province reported that HBsAg positivity was 1% while anti-HBs seropositivity was 83.1-96.2%, indicating that these rates are better than those in Anatolian provinces (28, 29). In a study conducted on 200 infants in Antalya province, it was shown that almost all of them achieved protective levels of anti-HBs titers after vaccination (30). In these studies, the correlation of anti-HBs seropositivity with vaccination rates supports the relationship with socioeconomic levels.

In a study involving 4231 children in Ankara province, HBsAg positivity was found as 0.8% and the Anti-HBs seropositivity was approximately 75%. The study found significantly higher anti-HBs seropositivity in girls compared to boys (31). In another study involving 530

children in Ankara, HBsAg seropositivity was 0% and the anti-HBs seropositivity was approximately 66% (32).

Since there is no recent research demonstrating the seroprevalence of HBV in children in Konya province, our findings will make a valuable contribution to the existing literature by allowing for a comparison with previous studies. In two different previous studies in Konya, HBs Ag seropositivity was 0% and 1.6% respectively while the anti-HBs seropositivity was approximately 48% (10, 11). In our current study, the anti-HBs seropositivity of 74% indicates that the vaccination status in our region of Konya is better compared to previous years. Our hospital provides tertiary healthcare services and is located in an area where the population has a higher socioeconomic status, which may have contributed to these rates.

In a recent study involving 573 children who applied to the dental hospital in Eskişehir province, the anti-HBs seropositivity was 53%, and HBsAg was approximately 0.8%. This study showed that protective antibody levels were insufficient in almost half of the patients, highlighting the importance of knowing these results before dental procedures (33). This will provide an opportunity to administer booster hepatitis B vaccination to these patients. Our study revealed that the number of patients attending hospital for dental interventions has declined since 2020, which may be related to the COVID-19 pandemic.

Conclusion

The limitations of our study are that since it was planned retrospectively, we did not have information about the children's Hepatitis B vaccination status and vaccination cards. Nevertheless, we assumed that Hepatitis B vaccination had been administered.

In conclusion, we observed a complete absence of HBsAg in all patients. Our study showed that the anti-HBs seropositivity is higher in Konya compared to previous studies. It suggests that the national vaccination program has a positive impact on anti-HBs seroprevalence. Our study revealed that children under the age of five displayed the highest levels of anti-HBs seropositivity while the anti-HBs levels diminished with advancing age.

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Author contributions: SS and FK study design. SS and FK data collection. SS wrote the manuscript. All the authors have agreed to be accountable for all aspects of the study and have approved the final version of the manuscript.

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ORIGINAL ARTICLE

Correlation Between Outpatient Preliminary Diagnosis of Venous Insufficiency and Venous Doppler Ultrasound Findings: A Retrospective Cohort Study

Poliklinikte Venöz Yetmezlik Ön Tanısı ile Venöz Doppler Ultrason Bulguları Arasındaki Korelasyon: Retrospektif Kohort Çalışma

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ABSTRACT

Background: This retrospective cohort study delves into the correlation between outpatient preliminary diagnoses of venous insufficiency and venous Doppler ultrasound findings.
Methods: Conducted at our hospital from 01.0102018 to 31.12.2018, the study scrutinized patient records to gauge the concordance between clinical diagnoses and Doppler ultrasound results.
Results: Among the 92 patients included in the analysis, Doppler ultrasound confirmed venous insufficiency diagnoses in 46.74% of cases. More than half of the patients who were initially suspected to have venous insufficiency had normal radiological findings. This suggests that during outpatient treatments, physical examination may not be given enough consideration due to the high number of patients. Moreover, it can be a time-consuming and labor-intensive process. Furthermore, our findings suggest that there is a strong correlation between venous reflux in a lower extremity vein and its impact on adjacent veins.
Conclusions: The study highlights the crucial importance of Doppler ultrasonography in improving diagnostic precision, particularly for patients who have not undergone a thorough physical examination in the outpatient clinic. The study also finds that changes in flow due to venous insufficiency primarily affect adjacent veins.

Keywords: Venous insufficiency, doppler ultrasound, physical examination, varicous veins

ÖZ

Giriş: Bu retrospektif kohort çalışma, ayaktan tedavi edilen hastalarda ön tanı olarak belirlenen venöz yetersizlik ile Doppler ultrasonografi bulguları arasındaki ilişkiyi incelemektedir.
Yöntem: Kurumumuzda 01.01.2018 ile 31.12.2018 tarihleri arasında ayaktan başvuran hastalar üzerinde gerçekleştirilen bu çalışma, ön tanılar ile Doppler ultrasonografi sonuçları arasındaki uyumu değerlendirmek için hasta kayıtlarını dikkatle incelemiştir.
Bulgular: Analize dahil edilen ve poliklinik muayenesinde venöz yetmezlik ön tanısı konan 92 hastanın ancak %46,74'ünde Doppler ultrasonografi ile venöz yetersizlik tanısı doğrulandı. Başlangıçta venöz yetersizlik şüphesi bulunan hastaların yarısından fazlasının radyolojik bulguları normal bulundu. Bu durum, ayaktan tedaviler sırasında fizik muayenenin hasta sayısının fazlalığından dolayı yeterince önemsenmediğini, bu ayrıntılı fizik muayenenin zaman ve emek sarf edici olduğu fikrinin hakim olduğunu düşündürmektedir. Ek olarak, bulgularımız alt ekstremite venlerindeki venöz reflünün komşu venler üzerindeki etkisi arasında güçlü bir ilişki olduğunu da buldu.
Sonuç: Çalışma, özellikle poliklinikte, fizik muayenesi ayrıntılı yapılmayan hastalarda Doppler ultrasonografinin tanısal doğruluğu artırmadaki kilit rolünü ve venöz yetersizlikte akım değişimlerinin komşu venleri öncelikli olarak etkilediğini vurgulamaktadır.

Anahtar Kelimeler: Venöz yetersizlik, Doppler ultrasonografi, fizik muayene, varis

Introduction

Venous insufficiency, characterized by inadequate blood flow in the veins, poses a significant health concern worldwide. It often manifests with symptoms like varicose veins, leg swelling, and discomfort. While clinical examination is a primary diagnosis, doppler ultrasound is a crucial adjunct, offering detailed insights into venous hemodynamics(1). Despite its widespread acceptance, the concordance between preliminary clinical diagnoses and doppler ultrasound findings warrants exploration, especially in outpatient settings (2). This study aims to bridge this gap by scrutinizing patient data to elucidate the correlation between clinical impressions and imaging outcomes.

Material and Methods

A retrospective study was conducted with the permission of the local ethics committee. Approval was granted on 2018/428. This retrospective cohort study leveraged patient records from our hospital spanning 01.01.2018 to 31.12.2018. Patients with a preliminary

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venous insufficiency diagnosis who underwent Doppler ultrasound evaluation were eligible for inclusion (n=92). Relevant data, encompassing clinical diagnoses, Doppler ultrasound results, and demographic characteristics, were meticulously collected and analyzed. Statistical methods, including correlation analysis and lower extremity vein subgroup comparisons, were employed to discern patterns and associations within the dataset. The chi-square test was used to analyze categorical data, and Pearson Correlation analysis was used to understand the relationship between the data.

Results

A total of 92 patients met the inclusion criteria for this study. Doppler ultrasound confirmed the preliminary venous insufficiency diagnosis in 46.74% of cases. In almost half of the initial diagnoses, no radiological abnormalities were found. Based on radiological examination, there was a significant relationship ($p<0.05$) between the finding of venous reflux and lower extremity veins. These findings underscore the pivotal role of Doppler ultrasound in corroborating clinical diagnoses of venous insufficiency, thereby facilitating precise patient management.

55% of the patients were women; the average age was 51.45±14.28 years. 49 (53.26%) of the venous color Doppler US reports requested from 92 outpatient clinic patients with pre-diagnosed venous insufficiency due to their lower extremity symptoms were reported as normal. The remaining 46.74% of the patients had different degrees of pathological findings, and the difference between veins in venous insufficiency was statistically significant.

Chi-square test results of categorical data are given in Table 1. Accordingly, the difference between the data is statistically significant.

The analysis results show almost no correlation between the Saphenofemoral junction(SFJ) and the Femoral vein (FV). Similarly, no statistically significant relationship was found between the SFJ and the Small saphenous vein (SSV). However, a weak positive correlation was observed between the SFJ and the Popliteal Vein (PV).On the other hand, a negative correlation was found between the Great saphenous vein (GSV) and FV. A statistically significant and moderate negative correlation was also found between GSV and SSV. A positive relationship was observed between FV and SSV and between FV and PV. Finally, a weak positive relationship was identified between SSV and PV. These findings suggest complex relationships between deep and superficial veins (Table 2).

Discussion

Our research discovered that over half of the patients who had leg pain, swelling, and twisted veins and were diagnosed with venous insufficiency in the outpatient clinic were found to be radiologically normal, which was unexpected. We also noticed no standard protocol for reports generated when abnormal radiological findings were detected; the reports were at the discretion of the expert who conducted the Doppler US examination.

As part of the radiological diagnoses, we investigated the presence of reflux in the lower extremity veins. We determined whether reflux occurred between veins, which vein(s) were affected by reflux, and whether reflux in the lower extremity veins affected the neighboring veins. Our findings were significant and noteworthy. We identified a positive correlation between the great saphenous vein adjacent to the saphenofemoral junction and the femoral vein. As the distance between veins decreased, the correlation weakened.

The findings of this retrospective cohort study shed light on the intricate interplay between clinical diagnoses of venous insufficiency and Doppler ultrasound outcomes. Notably, the substantial concordance observed between clinical impressions and Doppler ultrasound results underscores the reliability of ultrasound imaging as a diagnostic modality for venous insufficiency. This concordance reaffirms the widespread acceptance of Doppler ultrasound in clinical practice and its pivotal role in guiding appropriate patient management decisions (2, 3). Furthermore, the study's findings provide valuable insights into the diagnostic accuracy of preliminary clinical diagnoses, emphasizing the importance of integrating ultrasound imaging into routine diagnostic protocols for venous insufficiency.

Although we expected concordance between preliminary diagnoses and Doppler ultrasound findings, we found inconsistency in almost more than 50% of the study data. These discordant cases highlight the limitations of relying solely on clinical examination to diagnose venous insufficiency. Factors such as the subjective nature of clinical assessment and variations in examiner expertise may contribute to discrepancies between clinical impressions and imaging outcomes. Therefore, a comprehensive diagnostic approach incorporating clinical judgment and imaging modalities is essential to ensure accurate diagnosis and optimal patient care (1, 3).

The study results shed light on various aspects of diagnosing and treating venous insufficiency. Doppler ultrasound played a crucial role in confirming diagnoses of venous insufficiency in nearly half of all cases, thus highlighting its importance in clinical practice. It is worth noting that several initial diagnoses did not reveal any radiological abnormalities, indicating potential limitations in traditional diagnostic methods. The significant correlation between venous reflux and lower limb veins emphasizes the importance of radiological examination in determining pathological findings. The differences in pathological findings between patients highlight the heterogeneity of this condition and the need for personalized treatment approaches. These findings contribute to a more comprehensive understanding of venous insufficiency.

Furthermore, the study underscores the need for ongoing research to refine diagnostic strategies and

address existing gaps in clinical practice. Future studies exploring novel imaging techniques, such as contrast-enhanced ultrasound or venous hemodynamic assessments, may offer additional diagnostic insights and enhance the accuracy of venous insufficiency diagnosis. Moreover, collaborative efforts between clinicians, radiologists, and vascular specialists are crucial for developing standardized diagnostic protocols and facilitating interdisciplinary approaches to venous insufficiency management (2, 34).

While this study provides valuable information on the correlation between the clinical diagnosis of venous insufficiency and Doppler ultrasound findings, it also highlights the complexities inherent in diagnosing it. This study underscores the importance of a comprehensive diagnostic approach that integrates clinical judgment with advanced imaging modalities by elucidating areas of concordance and discordance between clinical impressions and imaging outcomes. Continued research efforts to refine diagnostic strategies and foster interdisciplinary collaboration are essential for improving diagnostic accuracy and enhancing patient care in venous insufficiency management.

Conclusion

In conclusion, this retrospective cohort study elucidates the correlation between outpatient preliminary diagnoses of venous insufficiency and venous Doppler ultrasound findings. The study underscores the pivotal role of Doppler ultrasound in bolstering diagnostic accuracy, particularly in outpatient settings. By highlighting areas of concordance and discordance between clinical impressions and imaging outcomes, the study advocates for a comprehensive diagnostic approach that integrates both clinical judgment and imaging modalities. Such an approach holds promise for optimizing patient care and improving clinical outcomes in venous insufficiency management.

Table 1: Comparison of lower extremity veins using chi-square tests.

	SFJ	GSV	FV	SSV	PV
Chi-Square	88.783[a]	60.935[b]	81.478[a]	112.457[b]	40.783[c]
df	3	4	3	4	2
Asymp. Sig.	<.001	<.001	<.001	<.001	<.001

In the table, Chi-Square values, degrees of freedom (df), and p-values are presented for comparisons between different lower extremity veins. Letters (a, b, c) denote different groups, and statistically significant results are typically denoted with asterisks or other symbols. However, as all p-values are <0.001, they are highly statistically significant. SFJ= Saphenofemoral junction, GSV= Great saphenous vein, FV= Femoral vein, SSV= Small saphenous vein, and PV=Popliteal vein.

Table 2: Correlation Coefficients between deep and superficial veins of the lower extremity

		Pearson Correlation Coefficient (r)	p-value
SFJ	GSV	-0.008	0.934
	FV	0.336	0.001*
	SSV	-0.111	0.291
	PV	0.271	0.009*
GSV	FV	0.224	0.032*
	SSV	-0.463	0.000*
	PV	-0.334	0.001*
FV	SSV	0.594	0.000*
	PV	0.431	0.000*
SSV	PV	0.253	0.015*

This table provides correlation coefficients (Pearson's r) and corresponding p-values for comparisons between different veins of the lower extremity, analyzed using chi-square tests. The statistically significant results ($p < 0.05$) are indicated with asterisks. SFJ=Saphenofemoral junction, GSV= Great saphenous vein, FV= Femoral vein, SSV= Small saphenous vein, and PV=Popliteal vein.

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ORIGINAL ARTICLE

Investigation of the Frequency and Characteristic Features of De Novo Mutations in Clinical Exome Sequence Trio Samples

Klinik Ekzom Sekans Trio Örneklerinde De Novo Mutasyonların Sıklığı ve Karakteristik Özelliklerinin Araştırılması

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ABSTRACT

Advanced genome sequencing technologies have provided us with the opportunity to deeply understand the mechanisms underlying conditions associated with the genome. There has been significant interest recently in understanding the characteristics of de novo mutations, which are genetic changes that arise in reproductive cells and are not present in parents, as well as the mechanisms involved in their occurrence. These mutations can be transmitted to subsequent generations and have the potential to influence genetic diversity and susceptibility to diseases, making this topic important. Due to limited studies in this area, the formation mechanisms and characteristic features of such mutations have not yet been fully understood.
In this study, we aimed to conduct a comprehensive analysis of de novo mutations in families undergoing trio clinical exome sequencing analysis. The objectives of the study were to investigate the relationship between parental ages and the frequency of de novo mutations, the distribution, prevalence, relationships, and molecular characteristics of de novo mutations. A total of 69 families who underwent Trio Clinical Exome Sequencing (CES) analysis at the Department of Medical Genetics, Faculty of Medicine, Selçuk University, between January 1, 2017, and December 31, 2023, were included in the study. DNA samples extracted from peripheral venous blood of individuals were sequenced using the Roche CES kit and DNBSEQ-G400™ sequencing device, and a total of 3892 genes were analyzed using the Seq Platform.
Correlation analysis revealed no significant relationship between parental age and the number of de novo mutations, and regression analysis showed that age was not a significant parameter in determining the number of de novo mutations. After analysis, 407 de novo variants were identified, with the majority being variants of unknown significance (55.28%). When examining the base change profile, the most common changes were found to be C -> G, G -> A, A -> G. The most commonly mutated genes were found to be DSPP, HPS4, VCL, and BMP4 genes.

Keywords: Mutation, Exome Sequencing, Genom

ÖZ

Gelişmiş genom dizileme teknolojileri genomla ilişkili durumların temelinde yatan mekanizmaları derinlemesine anlamaıza fırsat sağladı. De novo mutasyonlar olarak adlandırılan, ebeveynlerde bulunmayan ve üreme hücrelerinde ortaya çıkan genetik değişikliklerin karakteristiklerinin ve ortaya çıkmasında rol oynayan mekanizmaların anlaşılması son dönemde büyük ilgi görmektedir. Bu tür mutasyonlar, sonraki nesillere aktarılabilir ve genetik çeşitliliği ve hastalık yatkınlığını etkileyebilme potansiyeli bu konuyu önemli hale getirmektedir. Bu konuda çalışmalar sınırlı olduğu için henüz bu tür mutasyonların oluşum mekanizmaları ve karakteristik özellikleri tam olarak anlaşılamamıştır.
Bu araştırmada, trio klinik exome dizileme analizi yapılan ailelerde de novo mutasyonların kapsamlı bir analizi gerçekleştirmeyi amaçladık. Araştırmanın amaçları olarak, ebeveynlerin yaşları ile de novo mutasyonların meydana gelme sıklığı arasındaki ilişkiyi, de novo mutasyonların dağılımını, prevalansını, birbirleriyle ilişkilerini ve moleküler karakteristiklerini araştırmak olarak belirledik.
Araştırmada, 1 Ocak 2017 ile 31 Aralık 2023 tarihleri arasında Selçuk Üniversitesi Tıp Fakültesi Tıbbi Genetik Anabilim Dalı'nda Trio Klinik Exome Dizileme (CES) analizi yapılan 69 aile incelenmiştir. Araştırmada bireylerin periferik venöz kanlardan ekstrakte edilen DNA örnekleri Roche CES kitini kullanarak ekstrakte edilmiş ve DNBSEQ-G400™ dizileme cihazıyla dizilenmiş ve Seq Platformu kullanılarak toplamda 3892 gen analiz edilmiştir.
Korelasyon analizi sonucunda, annenin ve babanın yaşının de novo mutasyon sayısı ile anlamlı bir ilişkisinin olmadığı saptanmış ve regresyon analiz sonrasında da yaşın de novo mutasyon sayısını belirlemede anlamlılık bir parametre oluşturmadığı görülmüştür
Analiz sonrası 407 de novo varyant tespit edilmiş ve bunların çoğununun anlamı bilinmeyen varyantlar (%55.28) olduğu saptanmıştır. Baz değişim profili incelendiğinde en sık rastlanan değişikliklerin C -> G, G -> A, A -> G olduğu belirlenmiştir. En sık de novo mutasyon rastlanan genlerin DSPP, HPS4, VCL, BMP4 genleri olduğu saptanmıştır.

Anahtar Kelimeler: Mutasyon, ekzom sekans, Genome, Gen

Background/Aims

Advancements in advanced genome sequencing technologies have revolutionized our understanding of genetic disorders and enabled researchers to gain deeper insights into the underlying mechanisms of hereditary conditions. One particularly intriguing area of study is the investigation of de novo mutations, which arise spontaneously in the reproductive cells of parents and are subsequently passed on to subsequent generations. Understanding the nature of de novo mutations in the human genome forms the basis for unraveling phenomena such as genetic inheritance, genetic diversity, and susceptibility to disease. While a typical human genome exhibits millions of genetic variations, a subset of these variants - rare and novel

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mutations - arises as de novo events, contributing to genetic diversity and disease susceptibility. However, the mechanisms underlying the formation and distribution of de novo mutations are not yet fully understood. DNA replication errors, particularly in CpG dinucleotides, inadequate repair mechanisms, and exposure to endogenous or exogenous mutagens, all contribute to the occurrence of de novo mutations. These mutations do not occur randomly throughout the genome; instead, specific genomic regions exhibit higher mutability due to intrinsic properties such as sequence composition, replication timing, and transcriptional activity. Additionally, recent studies have identified mutational clusters and hotspots, which denote specific genomic regions prone to de novo mutations (1, 2).

Advancements in next-generation sequencing (NGS) technologies have revolutionized studies on de novo mutations, enabling researchers to comprehensively characterize these genetic alterations. Through genome-wide studies conducted in parent-child trios, researchers have scaled the rate of de novo mutations and elucidated their parental origins, distribution, and impact on disease susceptibility (1). However, despite these advancements, many questions remain unanswered regarding the precise mechanisms of de novo mutation formation, factors influencing their distribution across the genome, and their contributions to human diseases. In this study, we conducted a comprehensive analysis of de novo mutations in families undergoing clinical Exome Sequencing (CES) analysis for various reasons. Our primary objectives in this research were to investigate the relationship between parental ages at the start of pregnancy and the occurrence of de novo mutations, the frequencies and distributions of de novo mutations, their relationships with each other, and their molecular characteristics.

Methods

In this study, a total of 69 families who underwent trio Clinical Exome Sequencing (CES) analysis at the Department of Medical Genetics, Selçuk University Faculty of Medicine, due to various complaints and suspected genetic origins between January 1, 2017, and December 31, 2023, were included. The demographic information and clinical characteristics of the patients were obtained retrospectively through data recorded during examinations and the hospital's electronic medical record system. Based on this data, the ages of the parents at the beginning of pregnancy were determined. Family trees of all cases included in the study were drawn, their histories and clinical information were collected in detail, and informed consents with wet signatures were obtained from the patients and/or legal guardians. After samples were collected in the wet laboratory, DNA extraction was performed using the Roche CES kit followed by sequencing using the DNBSEQ-G400™ sequencing platform (MGI Tech Co., Ltd.). A total of 3892 genes were analyzed using the mentioned kit. Variant classification and analysis were performed using the Seq Platform (Genomize Inc.). The Seq Platform utilized advanced artificial intelligence algorithms to expedite variant prioritization workflow and generate a variant list. FASTQ files were uploaded to the Seq Platform, and reads were aligned to the human reference genome GRCh37 (Hg19) using the Burrows-Wheeler Aligner (BWA) platform. The aligned reads were then used for variant calling with FreeBayes. The obtained variants were subsequently annotated using VEP v102. ACMG pathogenicity classification was conducted according to the guidelines published by Richards et al. Variants were filtered in various modes: exonic (coding) regions, within 20 base pairs of exon-intron junctions, and with a frequency of less than 1% in the healthy population (according to gnomAD, the 1000 Genomes Project (1000G), and the Exome Aggregation Consortium (ExAC)). Additionally, ACMG, ClinVar, and Franklin (genoox) data were used for pathogenicity determination. Trio analysis was conducted using the trio analysis tool of the Seq platform.

Statistical analysis was performed using IBM SPSS Statistics Version 26 (IBM Corp, USA). The primary dependent variable was the number of de novo mutations, and the independent variables included maternal age, paternal age, and gender. Pearson and Spearman's rank correlation coefficients were calculated to evaluate linear and monotonic relationships, respectively. Additionally, multiple linear regression was used to investigate the combined effects of maternal and paternal ages on the number of de novo mutations. The relationship between gender and the number of de novo mutations was examined using independent samples t-test and Mann-Whitney U test. While the t-test assessed mean differences, the Mann-Whitney U test provided a non-parametric perspective on distribution inequalities. These analyses aimed to provide robust findings considering both statistical and practical significance.

Results

The analyses revealed that the average age of mothers at the beginning of pregnancy was 25.95. Among them, there were 20 individuals aged 30 and above during this period, while the remaining 53 individuals were in the group under 30 years old. The average age of mothers aged 30 and above was calculated as 34.05, whereas it was 22.84 for those aged 30. The average age of fathers at the beginning of pregnancy was determined as 29.34. Among them, there were 29 individuals aged 30 and above during this period, while the remaining 44 individuals were under 30. After performing Correlation Analysis (Spearman's Rank Correlation), it was found that the mother's age had a non-significant and negligible monotonic relationship with the number of de novo mutations (rho = -0.013, p = 0.922). Similarly, it was determined that the father's age had a weak and non-significant monotonic relationship with the number of de novo mutations (rho = 0.012, p = 0.932). Regression analysis was conducted to investigate whether a regression model including maternal and paternal ages was formed to predict the number of de novo mutations. After the analysis,

it was found that the model including the age of the mother and father explained only a small portion (1.2%) of the variance in the number of de novo mutations. An ANOVA analysis was conducted to determine the overall significance level of the total model, which was found to be statistically non-significant (p = 0.724). This indicates that the combination of the mother's and father's ages does not significantly predict the number of de novo mutations. As a general conclusion from these analyses, it was concluded that the number of de novo mutations showed a weak correlation with age variables and that de novo mutations cannot be attributed solely to either maternal or paternal age.

A total of 407 de novo variants were detected in the genes included in CES in the children of the families. The distribution of these variants revealed that 225 were variants of unknown significance (VUS) (55.28%), 93 were Likely Benign (LB) (22.85%), 80 were Benign (B) (19.66%), 8 were Likely Pathogenic (LP) (1.97%), and 1 was Pathogenic (P) (0.25%) (Figure 1). The variants were distributed as 79 (19.4%) missense, 13 (3.19%) frameshift, 32 (7.86%) splicing region, 3 (0.74%) start codon loss, 3 (0.74%) start codon gain, 8 (1.97%) inframe deletion, 13 (3.19%) inframe insertion, 55 (13.5%) synonymous, 165 (40.54%) 3'UTR, and 36 (8.84%) 5'UTR variants (Figure 2). When classified as deletion, insertion, IN/DEL, and substitution, 100 deletion, 103 insertion, 11 IN/DEL, and 193 substitution type variants were found. Looking at the base change profile, the most common changes were as follows: C -> G (12.87%) (85), 68 G -> A (10.3%), 43 A -> G (6.51%), 40 T -> C (6.06%), 26 A -> C (3.9%), 26 C -> A (3.9%), 21 CT -> C (3.2%), 21 T -> TA (3.2%), and 21 TA -> T (3.2%) (Figure 3). Of these changes, 151 were transitions (C <-> T, A <-> G) (37.1%), and 256 were transversions (other changes) (62%) (Figure 4).

When looking at the most commonly observed genes for de novo mutations, they were distributed as follows: DSPP in 8 individuals (14.28571%), HPS4 in 8 individuals (14.28571%), VCL in 8 individuals (14.28571%), BMP4 in 7 individuals (12.5%), ACVR2B in 6 individuals (10.71%), TPK1 in 6 individuals (10.71429%), FLG in 5 individuals (8.92%), FYCO1 in 5 individuals (8.92%), MTPAP in 5 individuals (8.92%), PTEN in 5 individuals (8.92%), ANKRD1 in 4 individuals (7.1%), CACNB2 in 4 individuals (7.1%), EYA4 in 4 individuals (7.1%), LYZ in 4 individuals (7.1%), MUC5B in 4 individuals (7.1%), PDE4D in 4 individuals (7.14%), and RP1L1 in 4 individuals (7.1%) (Figure 5).

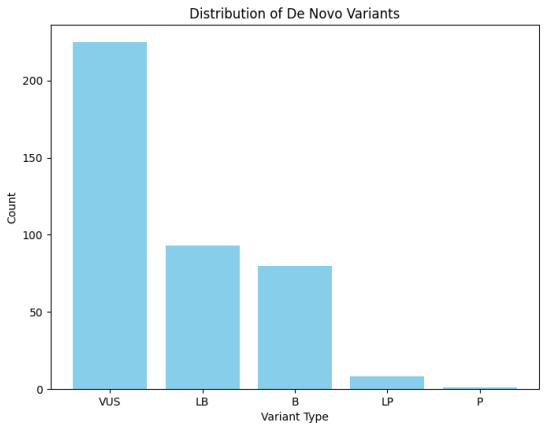

Figure 1. Clinical Significance Distribution

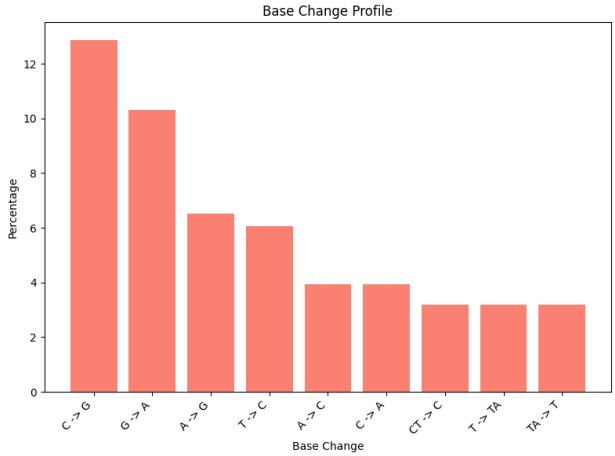

Figure 3. Base change profile of population under study

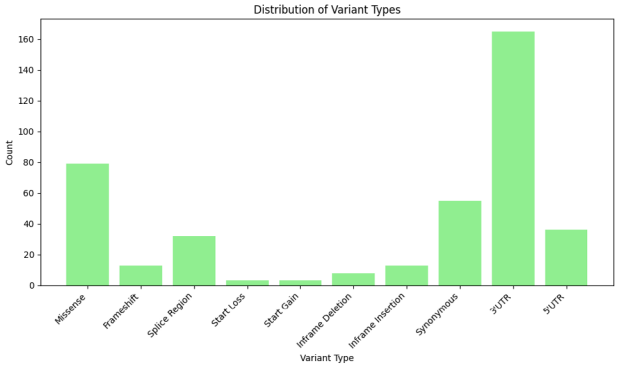

Figure 2. Mutation Type Distribution, considering the 3UTR and 5UTR classification

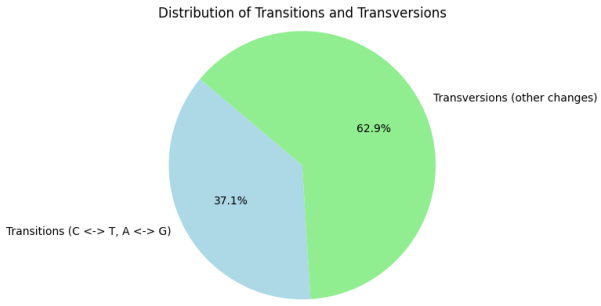

Figure 4. Distribution of transition and transversion mutations

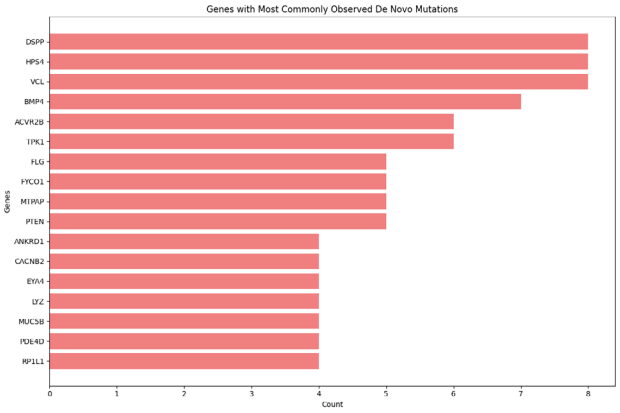

Figure 5. Genes with most commonly Observed De Novo Mutations

Conclusions

Human genome-wide Next Generation Sequencing (NGS) studies provide a range of de novo mutation rates for single nucleotide variations (SNVs) in germ cells, typically ranging from 1.0 to 1.8 × 10-8 [3, 4]. Various recent studies have been conducted to explore the reasons behind this phenomenon, leading to different interpretations. In vitro studies have shown that DNA polymerases ε and δ involved in DNA replication can perform unique base pairings during replication at rates of 10-4 to 10-5 (5, 6). Additionally, it has been observed that replication timing influences the occurrence of these errors. Regions replicating late in the cell cycle exhibit higher mutation rates compared to early replicating regions (7). This phenomenon is thought to be explained by a decrease in dNTP and protein pools contributing to replication during late replication periods [8, 9]. Furthermore, recent whole genome sequencing (WGS) studies have emphasized the clustering of mutations in specific regions of the genome, highlighting the formation of mutation hotspots in these areas (10). Currently, there is no consensus on whether de novo mutations coincide with these hotspots (10). Mutations can be found in regions ranging from 10 to 100 kb within mutation clusters (3, 10). Additionally, the analysis revealed that the rate of transition mutations is higher than that of transversion mutations. This is often associated with base changes in CpG islands abundant throughout the genome. These regions are believed to be particularly prone to errors during replication due to their repetitive nature and sensitivity to methylation during replication (11, 12). The prevalence of transversion mutations in regions harboring mutation clusters is notable. It has been suggested that this could result from dysfunctional replication forks and errors in DNA repair processes (10, 13).

Pioneering trio studies suggest that the majority of de novo mutations identified in the germline originate from the father, and the mutation rate is associated with paternal age (14). Moreover, it has been reported that approximately 80% of the de novo mutations identified in studies originate from the father, and this is correlated with paternal age (14, 15). Limited studies have been conducted to determine the relationship between maternal age and de novo mutations. While some studies suggest a mild relationship between maternal age and an increase in de novo mutations, others have not supported these findings. However, the limited number of studies on this topic complicates interpretation (16, 3, 14). Although limited studies have reported on the influence of maternal de novo mutation formation, the dominant utilization of proteins and enzymes from the mother's cytoplasm during early embryonic development, especially during initial cell divisions, suggests that this maternal factor should potentially be considered in the formation of replication errors at these early stages. Therefore, further research is needed to clarify the possible factors and origins of de novo mutation formation.

The observed distributions of variant pathogenicity in our study indicate that the majority of variants identified as de novo mutations are of unknown significance (VUS) [2]. The presence of benign (B) and likely benign (LB) mutations alongside VUSs suggests that de novo mutations may arise as new variants with no definitively established significant pathogenic importance as determined by previous clinical association studies. However, the clinical significance of these mutations should not be underestimated. Even when categorized at the lowest levels of importance, such mutations may contribute to the diversification of probands' clinical presentations or susceptibilities. Therefore, reporting and archiving these mutations should be considered for future follow-ups on evidence levels and potential revisions. Additionally, these mutations may harbor digenic or polygenic profiles and require further investigation. Indeed, the process of determining variant pathogenicity requires comprehensive evaluation of evidence from the literature, variant databases, and population studies, although these are still insufficient today. While large-scale population studies provide valuable data, the occurrence of variants in these databases should not be the sole criterion for considering variants benign. Public variant databases may contain outdated or conflicting data, underscoring the importance of primarily consulting the literature for variant classification. When assessing variant frequency in the general population for Mendelian diseases, factors such as disease inheritance models, prevalence, and penetrance should be considered. Therefore, high allele frequency in the general population does not exclude pathogenicity in variants. Although gene databases are valuable resources, they should not be the sole criterion for determining pathogenicity when it comes to de novo mutations. A comprehensive evaluation of statistical and functional evidence together is important for accurately assessing the clinical significance of a variant (2, 18).

In this study, the most commonly encountered type of mutation is 3'UTR variants, constituting 40.54% of mutations (17). In the 5'UTR region, this rate is 8.84%, and variants in this region can affect post-transcriptional regulation, mRNA stability, and translation efficiency

(18-20). Disruptions in UTRs can contribute to irregular gene expression and susceptibility or progression of diseases. Following 3'UTR variants, missense mutations account for 19.4% of the identified mutations. These variants can alter protein structure and function, leading to various phenotypic outcomes. They often play a role in Mendelian and complex diseases, highlighting the importance of such variants in disease etiology and therapeutic approaches. Synonymous variants occur with a frequency of 13.5%. Although they do not change the amino acid sequence, synonymous variants play a regulatory role in gene expression and protein function, affecting mRNA stability, splicing efficiency, and translation kinetics. Splicing site variants represent 7.86% of the identified mutations, representing disruptions in splicing consensus sequences. These variants can lead to abnormal splicing patterns and the production of dysfunctional protein isoforms, playing roles in various diseases and emphasizing their importance in understanding disease mechanisms and developing targeted therapies. Variants causing reading frame shifts have a frequency of 3.19%. These mutations often lead to early stop codon formation and subsequently short, non-functional protein products, associating frameshift variants with severe forms of diseases. Loss and gain of start codon variants are each detected at a frequency of 0.74%. These variants affect translation initiation sites and result in the complete loss of protein length. Therefore, these variants have highly destructive effects on the respective genes, resulting in an increase in disease phenotype. De novo mutations occurring in protein-coding genes are classified into three classes in the literature based on the aforementioned effects: 1) likely gene-disrupting SNVs (LGD-SNV) (stop codon, frameshift, splice donor, and acceptor), 2) missense, and 3) synonymous mutations. The impact of such mutations has been extensively studied in various types of diseases, such as neurodevelopmental disorders (NDDs); LGD and missense mutations are more frequently encountered in patients with NDDs (21). On the other hand, synonymous mutations, which play a role in regulating gene expression, are associated with both NDDs and more broadly with neuropsychiatric disorders (20, 21).

Interestingly, the frequency of de novo mutations observed in genes located on chromosomes 10 and 3 highlights a potential co-regulation or functional relationship due to their proximity. Chromosome 10 hosts a cluster of genes such as VCL (Vinculin), which is located at cytoband 10q22.2 and is involved in cell-cell adhesion and cell-matrix interactions. MTPAP, located at cytoband 10p12.31, is vital for polyadenylation of mitochondrial RNA transcripts. PTEN, located at cytoband 10q23.31, functions as a tumor suppressor gene regulating cell growth and survival. ANKRD1, located at cytoband 10q23.33, plays a role in muscle function and cardiovascular development. CACNB2, located at cytoband 10p12.33, also plays a role in calcium channel regulation. Chromosome 3 also harbors a pair of genes including ACVR2B (Activin A Receptor Type IIB) and FYCO1 (FYVE and Coiled-Coil Domain Autophagy Adaptor 1). ACVR2B functions as a receptor for activin and influences various cellular processes, while FYCO1 regulates autophagosome traffic.

Interestingly, out of the 31 DNM mutations detected in genes on chromosome 10, 28 (90%) are located in UTR regions (23 in 3'UTR and 5 in 5'UTR), and three are in splicing-associated regions. Among these, 25 are insertion/deletion and the rest are SNVs. The grouped genes on chromosome 3, all containing 3'UTR, comprise 11 mutations associated with insertion/deletion mechanisms. These two chromosome groups collectively contain 42 DNMs, the majority of which (85.7%) are of uncertain significance (VUS). Interestingly, exceptions are noted in MTPAP (5 out of 6) and CACNB2 (1 out of 6), where the density of B and LB variants stands out. Intriguingly, all 6 LB and B variants in these genes come from regions other than 3'UTR. These findings underscore the importance of 3'UTR regions in determining pathogenicity and warrant further investigation into the mechanisms of de novo mutations.

However, without considering the classification of 3'UTR and 5'UTR regions, out of 408, 203 are associated with CNV (<50bp), and 193 are associated with SNV mechanisms. These findings contrast with some other studies showing the predominance of SNVs (1 bp), but the limitations and statistical biases of these studies should be considered (21).

Nucleotide changes in DNA sequences are described as underlying molecular events, categorized as transitions and transversions; transitions occur more frequently than transversions and lead to a higher transition/transversion ratio across the genome. Transitions are often attributed to the variability of CpG dinucleotides. Methylation of cytosine in CpG dinucleotides forms 5-methylcytosine (5-mC), which is chemically unstable and prone to deamination, leading to G:T mismatches. CpG dinucleotides exhibit significantly higher mutation susceptibility compared to other dinucleotides. Interestingly, the mutation susceptibility of CpG dinucleotides varies across genomic regions. Contrary to expectations, CpG-rich regions exhibit a lower mutation rate compared to the rest of the genome. This difference is attributed to factors such as lower methylation levels, selective pressures associated with gene regulation, or physical prevention of spontaneous deamination due to stronger DNA binding. Understanding mutational signatures associated with specific mutational processes is crucial for determining the underlying mechanisms leading to genetic variations. Mutational signatures characterized by different mutation patterns have been identified in somatic cells, and correlations between these signatures and de novo mutations have been observed. Mutational signatures representing a significant portion of germline de novo mutations, signatures 1 and 5, are associated with high rates of C -> T transitions and A -> G transitions in CpG dinucleotides, respectively. Although the exact mechanisms underlying these signatures are unclear,

they likely involve processes such as deamination of methylated cytosine and spontaneous deamination of adenine. The presence of these mutational signatures has potential implications for genetic variations in both somatic and germ cells, necessitating further investigation into these mechanistic bases. However, our study indicates the predominance of transition mutations over transversion mutations. This finding may be a result of including the CNV mechanism in our population. CpG island analysis for our patients was also conducted using the UCSC online database, but no correlation was found. On the other hand, some mutations, such as those associated with HPS4, DSPP, and PTEN, were found in regions with a GC content of over 50%. This may contribute to a higher mutation rate in these regions, but the situation is different for other genes with the highest DNM counts, such as VCL, which exhibit high GC content in the mutation region.

Tandem Repeats (TRs) were also checked using the UCSC online database platform. Interestingly, some genes with a high number of DNMs were exactly located at TR sites. Genes such as CACNB2, ACVR2B, PTEN, HPS4, ANKRD1, and DSPP had variants found at TR sites. However, variants in the VCL gene were located outside of this region (22).

Overall, we identified de novo mutation (DNM) variants in a total of 242 genes. Pathway analysis for these genes was conducted using the Reactome online platform. The obtained analysis was transferred to a CSV file, filtered based on p-value < 0.05, and sorted according to the filters defined in the pathway analysis. The signaling transduction pathway (R-HSA-162582) was identified as the most common pathway among the identified genes (Figure 6). Signaling transduction is a critical cellular process where external signals lead to changes in cellular behaviors. Transmembrane receptors including receptor tyrosine kinases (RTKs) and TGF-beta receptors perceive these signals and initiate downstream cascades affecting cellular functions such as cell proliferation and survival. While RTKs activate pathways involving RAF/MAP kinases and AKT, TGF-beta receptors phosphorylate SMAD proteins, regulating gene expression. WNT receptors initially classified as G-protein coupled receptors utilize beta-catenin to regulate gene transcription. Integrins activated by extracellular matrix components influence cell adhesion and shape through cytosolic kinases. Rho GTPases respond to signals by altering cytoskeletal organization, affecting cell polarity and connections. These mechanisms enable cells to dynamically respond to their environments. Our analysis shows that our genes primarily contribute to the Hedgehog and Tumor Growth Factor Beta (TGF-BETA) families in this pathway. Studies indicate that Hedgehog signaling activates a mammalian heterochronic gene regulatory network controlling differentiation timing among cell lineages of different origins. Moreover, these genes exhibit a high tendency for de novo mutation rates, supporting our findings (23, 24, 15, 16). However, it is important to validate this hypothesis with further studies.

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Ethical aspects of the research: This study was conducted with the approval of the ethics committee of SElcuk University Medical Faculty Non-Interventional Research Ethics Committee dated 16.04.2024 and numbered 2024/198. All procedures in the study were performed according to the World Medical Association Declaration of Helsinki.

Author contributions: Conception: Nadir Kocak , Ali Torabi , Batuhan Sanlıturk , Özkan Bagcı , Ebru Marzioglu Ozdemir , Tulun Cora. Design: Nadir Kocak , Ali Torabi , Batuhan Sanlıturk. Supervision: Nadir Kocak. Resource: Ozkan Bagcı , Ebru Marzioglu Ozdemir , Tulun Cora. Materials: Nadir Kocak , Ali Torabi , Batuhan Sanlıturk. Data Collection and/or Processing: Ozkan Bagcı, Ebru Marzioglu Ozdemir , Tulun Cora. Analysis and/or Interpretation: Nadir Kocak , Ali Torabi , Batuhan Sanlıturk. Literature Review : Nadir Kocak , Ali Torabi , Batuhan Sanlıturk. Writer: Nadir Kocak Critical Review: Nadir Kocak.

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CASE REPORT

Nasopharyngeal Mucoepidermoid Carcinoma: A Rare Case Report

Nazofarengeal Mukoepidermoid Karsinom: Nadir Görülen Bir Vaka Sunumu

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ABSTRACT

Introduction: Mucoepidermoid carcinoma is one of the common malignancies of the salivary glands. Nasopharyngeal mucoepidermoid carcinoma cases are rare. The treatment of these rare cases depends on the stage of the tumor and its invasion of the surrounding tissues.
Case: The patient, who was diagnosed with thyroid papillary carcinoma in 2006 and was being followed up in medical oncology, applied to our clinic because of asymmetric thickening in the left nasopharynx, which was detected incidentally in the brain MRI. The patient had pain in the left neck area for about a month. Excisional biopsy of the lymph node with increased FDG uptake in the left jugulodigastric region on PET/CT and multiple punch biopsies from the nasopharynx were performed. The patient, whose pathology result was mucoepidermoid carcinoma, was referred to medical oncology to receive radiochemotherapy.
Discussion: It should be kept in mind that, although rare, mucoepidermoid carcinoma may be present in patients presenting with a mass in the nasopharynx. Although studies conducted to date provide information on treatment options, prospective studies are needed for prognosis and treatment selection.

Keywords: Mucoepidermoid carcinoma, nasopharynx, nasopharyngeal carcinoma

ÖZ

Giriş: Mukoepidermoid karsinom tükrük bezlerinin sık görülen malignitelerinden biridir. Nazofarengeal yerleşim gösteren mukoepidermoid karsinom vakaları nadir görülür. Nadir görülen bu olguların tedavisi tümörün evresi ve çevre dokulara invazyonuna göre şekillenir.
Olgu: 63 yaşında erkek hasta 2006 yılında tiroid papiller karsinom tanısı aldı. Bu nedenle tıbbi onkoloji takipleri yapılan hastanın beyin MR'ında insidental olarak nazofarenkste solda asimetrik kalınlaşma saptanması üzerine kliniğimize sevk edildi. Hastanın sol boyun bölgesinde yaklaşık bir aydır ağrı şikayeti mevcuttu. PET/CT de sol jugulodigastrik bölgede artmış FDG tutulumuna sahip lenf nodundan eksizyonel biyopsi ve nazofarenksten multiple punch biyopsiler yapıldı. Patoloji sonucu mukoepidermoid karsinom gelen hasta radyokemoterapi almak üzere onkolojiye sevk edildi.
Tartışma: Nazofarenkste kitle ile gelen hastalarda nadir de olsa mukoepidermoid karsinom görülebileceği akılda tutulmalıdır. Günümüze kadar yapılan çalışmalarda tedavi seçenekleri hakkında bilgiler olsa da prognoz ve tedavi seçimi için prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Mucoepidermoid karsinom, nazofarenks, nazofarengeal karsinom

Introduction

Mucoepidermoid carcinoma is the most common malignancies of the salivary glands. These cancers can also rarely be seen in the lung, nasal cavity, paranasal sinuses and nasopharynx (1). Along the sinonasal tract, it is most commonly seen in the antrum of the maxillary sinus, followed by the nasal cavity, nasopharynx and ethmoidal sinuses (2). CT and MRI, which can examine the sinonasal region in detail in suspected patients, are imaging methods used to make a diagnosis (3). In addition, endoscopic examination should be performed in suspected patients as it provides a wide field of view in the nasal region (4). According to the literature, 0.6% of salivary gland tumors and 4.8% of mucoepidermoid carcinomas are nasopharyngeal mucoepidermoid carcinomas (2).

The treatment of these rare cases depends on the stage of the tumor and its invasion into the surrounding tissues. Positron emission tomography (PET) is used for tumor staging and investigating invasion to surrounding tissues (5). While only surgery is sufficient for low-grade tumors, total resection and postoperative radiotherapy are recommended for medium and high-grade tumors (2).

In this case report, a patient diagnosed with low-grade nasopharyngeal mucoepidermoid carcinoma, who applied to our clinic due to a nasopharyngeal mass, is presented and it is emphasized that nasopharyngeal masses, although rare, can present as mucoepidermoid carcinoma.

Case

A 63-year-old male patient was diagnosed with thyroid papillary carcinoma in 2006 and underwent surgery. It was determined as a result of the pathology that the patient, who underwent neck dissection due to neck swelling in 2014, had lymph nodes with thyroid papillary carcinoma metastases. For this reason, he received doxorubicin chemotherapy. In the medical oncology follow-up, he was referred to our clinic because of the incidentally detected asymmetrical thickening of the left

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nasopharynx in the brain MRI (Figure 1-2). The patient had pain in the left neck area for a month. Physical examination revealed a 2x2 cm smooth-surfaced and limited, firm, mobile mass in the right submandibular region, and a 1x1 cm smooth-surfaced and limited, firm, mobile mass in the left upper jugulodigastric region. In the nasopharyngoscopy of the patient, a smooth surface mass of 2x2 cm was detected filling the rosenmüller fossa on the left. Multiple punch biopsy samples were taken from the patient under general anesthesia, as the results of the punch biopsy performed under local anesthesia were chronic inflammation. Excisional biopsy was performed from the lymph node with increased FDG uptake in the left jugulodigastric region in PET/CT. The pathology result of the patient was thyroglobulin (-), pancytokeratin (+), mucin (+) low grade mucoepidermoid carcinoma. Genetic analysis was not performed in our case. The patient was referred to medical oncology to receive radiochemotherapy.

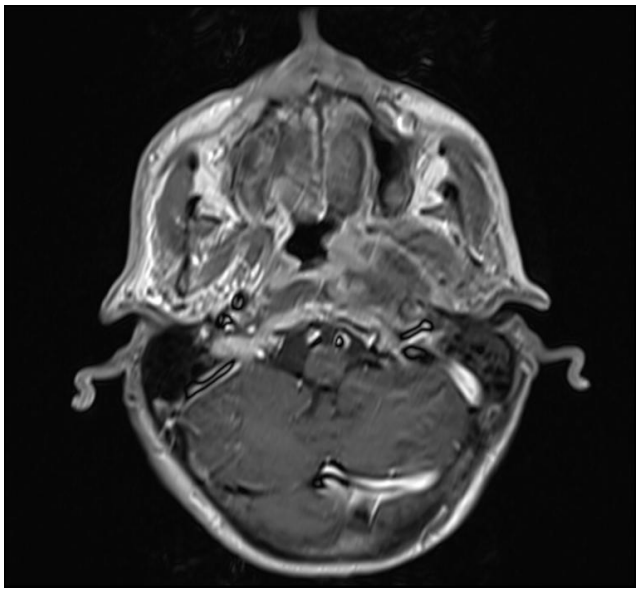

Figure 1: Asymmetry of the nasopharynx in the MRI image.

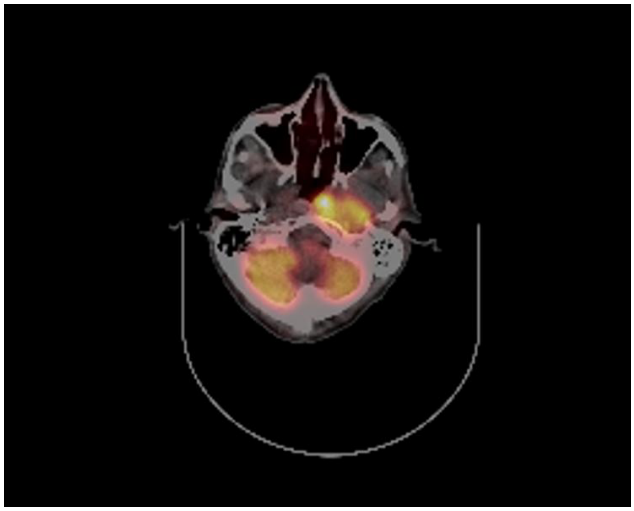

Figure 2: PET/CT images of the mass in the nasopharynx.

Discussion

Mucoepidermoid carcinoma was first defined as a rare malignancy of the major and minor salivary glands in 1945 by Stewart et al. (6). In recent studies, it is defined as the most common cancer of the parotid gland (7).

Nasopharyngeal mucoepidermoid carcinomas account for 3% of all nasopharyngeal cancers and 15% of nasopharyngeal salivary gland tumors (8).

Mucoepidermoid carcinomas occur at an average age of 50 years, and the female/male ratio is 3/1 (1). Nasal obstruction, epistaxis, and hearing loss are common symptoms, while neck mass, headache, and cranial nerve palsy are rare symptoms (9). The symptoms in our case were a neck mass and neck pain.

According to the modified mucoepidermoid carcinoma grading scheme, the degree of disease is aggressive invasion pattern if there is bone invasion and lymphovascular invasion. (7). The patient's disease grade was evaluated as high-grade because the excisional biopsy result of the lymph node with high FDG uptake on PET/CT was mucoepidermoid carcinoma.

While low-grade mucoepidermoid carcinomas respond only to surgical excision, postoperative radiotherapy should be given after total resection in intermediate and high-grade tumors (2). In our case, which was evaluated by the medical oncology council, it was deemed appropriate to apply radiochemotherapy because the disease was high-grade.

Conclusion

In conclusion, cases of mucoepidermoid carcinoma located in the nasopharynx are rare. Although there is information about treatment options in studies, prospective studies are needed on disease prognosis and treatment according to staging.

Authorship Contributions

Conception:R.Ö.E., M.A., Design: H.A., M.A.E., Supervision:M.A.D., Resource: R.Ö.E., M.A., Materials: H.A., Data Collection and/or Processing: R.Ö.E., M.A., Analysis and/or Interpretation: H.A., M.A.E., Literature Review: M.A.D., Writer: R.Ö.E., M.A., Critical Review: M.A.E., M.A.D. .

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