ISSUE 3
YEAR: 2023 VOLUME: 4

ARCHIVES OF CURRENT MEDICAL RESEARCH

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https://dergipark.org.tr/tr/pub/acmr

ARCHIVES OF CURRENT MEDICAL RESEARCH (ACMR)

Volume: 4

Number: 3

September 2023

Publishing Language
English

E-ISSN
2717-9788

Type of Publication
Peer Reviewed Academic Journal

Publishing Period
Three Times a Year (January, May, September)

Journal Name
Archives of Current Medical Research
Arch Curr Med Res

Owner
14th March Medical Association

General Publication Director
Mehmet Ali Tokgöz

Management Location - Content Advisor
Alban Tanıtım Ltd. Şti.
Tunalı Hilmi Cad. Büklüm Sokak No: 45/3
Kavaklıdere/Ankara Tel: 0.312 430 13 15
E-mail: info@acmronline.org
editor@albantanitim.com.tr

Graphic Design
Alban Tanıtım Ltd. Şti.

Proofreading
S. Bahar Alban

Prepress
Alban Tanıtım Ltd. Şti.

ARCHIVES OF CURRENT MEDICAL RESEARCH

Archives of Current Medical Research is an international refereed journal. Authors bear responsibility for the content of their published articles.

EDITORIAL TEAM

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Archives of Current Medical Research
Arch Curr Med Res 2023;4(3):113-122

Received: 8 August 2023
Revised: 15 August 2023
Accepted: 18 August 2023
DOI: 10.47482/acmr.1339401

ORIGINAL ARTICLE

A cost-based comparative analysis of diabetic hand ulcers and diabetic foot ulcers

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Abstract

Background: In 2021, the Social Insurance Institution (SII) of Turkey reported that there were approximately 12 million patients with diabetes under universal health insurance and the expenditure was incurred for the treatment of complications was 2.6 billion Turkish Liras (₺). Although several previous studies have analyzed the cost of diabetic foot ulcers, no study from Turkey has compared the costs of diabetic hand ulcers and foot ulcers together and analyzed the relationship between the cost and demographic characteristics of patients, yet.

Methods: In this study, the data of 49 patients with diabetic hand ulcers and 44 patients with diabetic foot ulcers, from January to June, in 2022, have been analyzed retrospectively based upon the demographic datas and costs. In order to analyze the correlations, cross tables, chi-square statistics, and partial correlation analysis have been used. The groups in the study have been compared by using t-test for independent groups and covariance analysis.

Results: The calculated average cost of the patients who were followed up and treated for diabetic hand and foot ulcers between January and June, in 2022 was 257.01 US dollars ($) and 462.54 $, respectively. There has been no statistically significant difference between the patients with diabetic hand and diabetic foot ulcers in terms of mean age, the length of hospital stay, or hemoglobin A1c and C-reactive protein levels at admission. It is seen that the mean cost of the patients with diabetic hand ulcer has been lower than that of the patients with diabetic foot ulcer, and this difference is statistically significant.

Conclusions: Although diabetic hand infections are less costly and cause fewer major amputations, it is a clinical condition that should be given at least as much attention as diabetic foot ulcer due to its atypical localized onset and the reproductive potential of different microorganisms.

Keywords: Cost Analyze, Diabetic Foot Ulcer, Diabetic Hand Ulcer, Tropical Hand Infection.

Cite this article as: *Çiçek Ç. A cost-based comparative analysis of diabetic hand ulcers and diabetic foot ulcers. Arch Curr Med Res. 2023;4(3):113-122*

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INTRODUCTION

According to the data taken from the Turkish Statistical Institute, private sector and general government health expenditure in Turkey increased by 41.6% in 2021 when it is compared to the previous year, reaching 353.941 billion (1)". An analysis of the distribution of total health expenditure by health service providers has showed that the top three health service providers are hospitals (49.5%), retailers and other medical equipment providers (22.8%), and ambulatory care providers (9.4%) (1). By the year 2025, the number of people with diabetes is expected to increase in developed countries by 41%, from 51 million to 72, and by 170% in developing countries, from 84 million to 228 (2). Increases in diabetes-related complications have resulted in a situation where most related health expenditures are incurred for the treatment of complications rather than for the treatment of diabetes itself (3). While carrying out an analysis, not only the direct costs arising from the follow-up and the treatment of diabetes and related diseases, but also the indirect costs arising from reduced productivity at work, shorter life expectancy, and the loss of productivity of caretakers should also be taken into account. A study conducted in 2016 reported that the annual direct cost of diabetes worldwide was 825 billion $. The same study reported that China, the United States of America (USA), India, and Japan were some of the countries with the highest diabetes-related direct costs and that approximately 60% of the global cost of diabetes originated from low and middle-income countries (4). In 2021, the Social Insurance Institution (SII) of Turkey reported that there were approximately 12 million patients with diabetes under universal health insurance whose diabetes care was covered by the SII. The expenditure incurred by the SII for the treatment of these patients in 2021 was 8.6 billion ₺, and 2.6 billion ₺ of it was for the treatment and the complications (5). Although several previous studies have analyzed the cost of diabetic foot ulcers, no study from Turkey has compared the costs of diabetic hand ulcers and foot ulcers together and analyzed the relationship between the cost and demographic characteristics of the patients, yet. Therefore, our study is the first cost-based comparative analysis on the subject.

MATERIALS AND METHODS

In this study, the data of 49 patients with diabetic hand ulcers and 44 patients with diabetic foot ulcers, all of whom were treated as inpatients in the wound care clinic from January to June, in 2022, have been analyzed retrospectively based upon the demographic datas and costs. The data that belongs to the patients have been retrieved from the online hospital records. This study was approved by the clinical research Ethics Committee of the Kartal Dr. Lütfi Kırdar Training and Research Hospital (Date: 29.05.2023, Number: 2023/514/250/23). Recorded data includes demographic characteristics of the patients (age, gender, education status, income percentile, and the distance between their residence and the health care facility), as well as ulcer site, hemoglobin A1c (HbA1c) levels at time of admission, presence or absence of chronic renal failure (CRF), microbial wound culture result (if positive, the isolated agent), levels of C-reactive protein (CRP) at time of diagnosis, antibiotherapies used, treatment administered, and the length of hospital stay. For diabetic hand, the upper limb has been divided into anatomical subregions consisting of the phalanx, thenar, and hypothenar region, palmar region, dorsum of the hand, and forearm, and the foot has been divided into anatomical subregions consisting of the phalanx, dorsum of the foot, plantar region, heel, ankle, and cruris. Phalanx amputations for the extremity are considered as minor, and amputations proximal to the phalanx are considered as major. Besides, in this study, a household has been defined as a group of one or more peeople, relatives or non-relatives, who reside in the same domicile and who provide financial support to each other. Also, per capita income has been calculated as the annual disposable income of the household and divided equally between the household. The distribution of annual equivalized household disposable income has been divided into quintiles. Thus, percentile 1 represents the lowest income group, and 5 represents the highest. The distance between the residence of the patient and the nearest healthcare facility has been divided into three subgroups as <1 km, between 1 and 3 km, and >3 km. The report of costs for each patient covered by the SII has been taken from the income accrual unit of our hospital. Total costs include preoperative diagnostic tests, emergency room costs, operating room charges, hospital accommodation, medication, surgical instruments, anesthesia, and facility care charges. While analysing the cost, the patients who received conventional wound dressing as part of the follow-up and treatment are included and the patients who received specialized wound care products (topical/injectable growth factor,

stem cell, PRP (platelet rich plasma) and SVF (stromal vascular fraction), etc.) are excluded because the cost of patients without conventional wound dressing is thought to cause confusion for basic patient cost. The study has also excluded the patients with ulcers in both limbs (hand and foot) to avoid confusion during the analysis. The costs are calculated in Turkish Liras (₺) and converted into USD ($) using the currency exchange rate applicable at the time of discharge between January and June, in 2022 (1$ = 18.75₺/January, 1$ = 16.63₺/June). In this study, the data have been analyzed by using SPSS 22.0. Descriptive statistics and quantitative variables are provided as mean ± standard deviation. After the data have been checked for the normality of distribution, the correlations are analyzed by using cross tables, chi-square statistics, and partial correlation analysis, and groups are compared by using t-test for independent groups and covariance analysis. Statistical significance is set at $p < 0.05$ for all tests.

RESULTS

In this study, the mean age is 60.8 years old (21-84) for patients with diabetic foot ulcers and 60.5 years old (28-82) for patients with diabetic hand ulcers. When the data is analysed, it is observed that men are affected in 74% and 72% of diabetic foot ulcers and hand ulcers, respectively. The mean HbA1c level measured at the time of admission was 9.3 (7.1-12.8) for the patients with diabetic foot ulcers and 9.8 (5.5-14.8) for the patients with diabetic hand ulcers. CRF was present in 31% of the patients with diabetic hand ulcers and in 16% of the patients with diabetic foot ulcers. The site of onset of symptoms was the phalanx in 73% of the patients with diabetic hand ulcers, and the dorsum of the foot and heel in 54% of the patients with diabetic foot ulcers (Figure 1 and 2). Mean CRP levels recorded at the admission were 110 and 111 mg/L for the patients with diabetic hand and foot ulcers, respectively. The patients with diabetic hand ulcers stayed at the hospital for an average of 18.3 days and those with diabetic foot ulcers stayed for an average of 20.5 days. Major amputation was performed in 0.04% of the patients with diabetic hand ulcers, while 34% of the patients with diabetic foot ulcers underwent major amputation. When the demographic data have been analysed, it can be seen that 52% of the patients with diabetic hand ulcers had only a primary school education and 36% were in a low income group (first or second quintile). In addition, 78% of them had their residence at a distance of less than 3 km from the nearest healthcare facility. 45% of the patients with diabetic foot ulcers had only a primary school education and 29% were in a low income group (first or second quintile). Besides, 66% of them had their residence at less than 3 km from the nearest healthcare facility. While no growth has been detected in 47% of the patients with diabetic hand ulcers, the most common microorganisms that grew in the isolated agents are staph. aureus, strep agalactia, and candida. Enterococcus Faecalis and Pseudomonas Aureginosa are the agents most frequently isolated from tissue cultures at hospitalizations of the patients with diabetic foot ulcers. The demographic data of the patients is summarized in Table 1. The calculated average cost of the patients who have been followed up and treated for diabetic hand and foot ulcers is 257.01 $ and 462.54 $, respectively. It is determined that, there is no statistically significant difference between the patients with diabetic hand and diabetic foot ulcers in terms of mean age, the length of hospital stay, or HBA1C and CRP levels at the admission ($p > 0.05$). The mean cost for the patients with diabetic hand is lower than the mean cost for the patients with diabetic foot, and it can be concluded that this difference is statistically significant ($t = -2.11$, $p < 0.05$). The analysis using diabetic hand or foot status as a covariate has demonstrated that variables such as the presence or absence of CRF, the presence or absence of microbial growth in wound culture, the distance between the residence and the hospital, the previous use of antibiotherapy, the history of surgery, the educational status, and income quintile ($p > 0.05$) do not have a significant effect on the cost of the ulcers. The analysis of the relationship between variables and ulcer development has also indicated that there is no statistically significant difference between the diabetic hand and diabetic foot groups in terms of mean age, the length of hospital stay, or HBA1C and CRP levels at the admission ($p > 0.05$). Moreover, CRF is not statistically related with ulcers in the patients with diabetic hand or foot ulcers ($p > 0.05$). Furthermore, it is also seen that the education level, income status and the distance between the residence and the nearest healthcare facility have no statistically significant relation with the development of hand or foot ulcers ($p > 0.05$). (Table 2 and 9)

Figure 1: The presentation of diabetic hand infection - volar aspect

Figure 2: The presentation of diabetic hand infection - dorsal aspect

Table 1. The demographic data of the patients

		Diabetic Hand Ulcer %(n)		Diabetic Foot Ulcer %(n)	
Education Status	None	4 (2)		2 (1)	
	Primary School	52 (25)		45 (20)	
	Secondary School	33 (16)		27 (12)	
	High School	10 (5)		16 (6)	
	University and Postgraduate	5 (3)		12 (5)	
Income Status	Percentile 1	8 (4)		7 (3)	
	Percentile 2	28 (14)		22 (10)	
	Percentile 3	34 (17)		37 (16)	
	Percentile 4	19 (9)		21 (9)	
	Percentile 5	11 (5)		13 (6)	
The Distance Between the Residence and the Nearest Healthcare Facility	<1 km	26 (13)		30 (13)	
	1-3 km	52 (25)		36 (16)	
	>3 km	22 (11)		34 (15)	
Ulcer Site		Phalanx	73 (36)	Phalanx	21 (9)
		Hypothenar region	4 (2)	Dorsum of the foot	27 (12)
		Thenar region	4 (2)	Plantar of foot	12 (5)
		Palmar region	6 (3)	Heel	27 (12)
		Dorsum of the hand	10 (5)	Ankle	9 (4)
		Forearm	2 (1)	Cruris	4 (2)
CRF*	Absent	69 (34)		84 (37)	
	Present	31 (15)		16 (7)	
Treatment	None	36 (18)		36 (16)	
	Minor Amputation	60 (29)		30 (13)	
	Major Amputation	4 (2)		34 (15)	

** CRF: Chronic Renal Failure*

Table 2. The difference between the costs of diabetic hand ulcer and diabetic foot ulcer

	Diabetic Ulcer	N	Mean	Std. Deviation	t	p
Cost	Diabetic Hand Ulcer	49	4950.67	2736.19	-2.11	0.04
	Diabetic Foot Ulcer	44	8909.57	8634.76		

Std. Deviation: Standart Deviation

Table 3. The relation between Diabetic hand/foot ulcer and the Length of Hospitalization, Age, Hemoglobin A1c and C-Reactive Protein Levels

	Diabetic Ulcer	N	Mean	Std. Deviation	t	p
The Length of Hospitalization	Diabetic Hand Ulcer	49	18.3158	10.36046	-0.59	0.55
	Diabetic Foot Ulcer	44	20.5833	13.81215		
Age	Diabetic Hand Ulcer	49	60.5263	13.18403	-,0.06	0.94
	Diabetic Foot Ulcer	44	60.7917	13.38389		
HBA1c*	Diabetic Hand Ulcer	49	9.8000	2.52477	0.72	0.47
	Diabetic Foot Ulcer	44	9.3333	1.69158		
CRP**	Diabetic Hand Ulcer	49	110.0000	96.33160	-0.03	0.97
	Diabetic Foot Ulcer	44	111.0417	100.24166		

Std. Deviation: Standart Deviation

t: t-value

**HBA1c: Hemoglobin A1c*

***CRP: C-Reactive Protein*

Table 4. The Relation Between the Costs of Chronic Renal Failure and Diabetic Ulcer

Dependent Variable: Cost					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	188574551.798[a]	2	94287275.899	2.064	0.140
Intercept	3434132.908	1	3434132.908	0.075	0.785
Diabetic Ulcer	140739333.499	1	140739333.499	3.081	0.087
CRF*	22369312.580	1	22369312.580	0.490	0.488
Error	1827252696.330	90	45681317.408		
Total	4220427194.967	93			
Corrected Total	2015827248.128	92			

R Squared = 0.094 (Adjusted R Squared = 0.048)

Sig.: Significance

df: Difference of Freedom

f: f-value

**CRF: Chronic Renal Failure*

Table 5. The Relation Between the Tissue Culture and Diabetic Ulcer Cost

Dependent Variable: Cost					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	179161850.973[a]	2	89580925.486	1.951	0.155
Intercept	7565719.610	1	7565719.610	0.165	0.687
Diabetic Ulcer	110313957.769	1	110313957.769	2.402	0.129
Tissue Culture	12956611.755	1	12956611.755	0.282	*0.598*
Error	1836665397.155	90	45916634.929		
Total	4220427194.967	93			
Corrected Total	2015827248.128	92			

R Squared = 0.089 (Adjusted R Squared = 0.043)

Sig.: Significance

df: Difference of Freedom

f: f-value

Table 6. The Relation Between the Distance to the Nearest Health Center and the Cost of Diabetic Ulcer

Dependent Variable: Cost					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	228666341.764[a]	3	76222113.921	1.663	0.191
Intercept	6730997.057	1	6730997.057	0.147	0.704
Diabetic Ulcer	164972727.989	1	164972727.989	3.600	0.065
The distance between the residence of the patient and the nearest healthcare facility	62461102.547	2	31230551.273	0.682	*0.512*
Error	1787160906.363	89	45824638.625		
Total	4220427194.967	93			
Corrected Total	2015827248.128	92			

R Squared = 0.113 (Adjusted R Squared = 0.045)

Sig.: Significance

df: Difference of Freedom

f: f-value

Table 7. The Relation Between the Costs of Surgery and Diabetic Ulcer

Dependent Variable: Cost					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	167953426.603[a]	2	83976713.302	1.818	0.176
Intercept	3576573.853	1	3576573.853	0.077	0.782
Diabetic Ulcer	166878503.157	1	166878503.157	3.612	0.065
Surgery	1748187.386	1	1748187.386	0.038	*0.847*
Error	1847873821.524	90	46196845.538		
Total	4220427194.967	93			
Corrected Total	2015827248.128	92			

R Squared = 0.083 (Adjusted R Squared = 0.037)

Sig.: Significance

df: Difference of Freedom

f: f-value

Table 8. The Relation Between the Education Status and the Cost of Diabetic Ulcer

Dependent Variable: Cost					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	327211290.199[a]	4	81802822.550	1.841	0.141
Intercept	550976.431	1	550976.431	0.012	0.912
Diabetic Ulcer	154470925.342	1	154470925.342	3.476	0.070
Education Status	161006050.982	3	53668683.661	1.208	*0.320*
Error	1688615957.928	88	44437262.051		
Total	4220427194.967	93			
Corrected Total	2015827248.128	92			

R Squared = 0.162 (Adjusted R Squared = 0.074)

Sig.: Significance

df: Difference of Freedom

f: f-value

Table 9. The Relation Between the Income Status and the Cost of Diabetic Ulcer

Dependent Variable: Cost					
Source	**Type III Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Corrected Model	238232712.924[a]	3	79410904.308	1.742	0.174
Intercept	1977995.097	1	1977995.097	0.043	0.836
Diabetic Ulcer	174476016.259	1	174476016.259	3.828	0.058
Income Status	72027473.706	2	36013736.853	0.790	*0.461*
Error	1777594535.204	89	45579347.057		
Total	4220427194.967	94			
Corrected Total	2015827248.128	92			

R Squared = 0.118 (Adjusted R Squared = 0.050)

Sig.: Significance

df: Difference of Freedom

f: f-value

DISCUSSION

The number of people with diabetes and diabetes-related complications has been rapidly increasing worldwide despite the advances in medical science. The World Health Organization estimates that diabetes, which is likely to increase in prevalence in the future, will impose a substantial economic burden on states due to both the treatment of diabetes itself and its long-term complications, including renal, ocular, cardiac, and nervous system problems (1). While calculating the cost of diabetes, there are two components to take into account; direct costs (the follow-up, the treatment of diabetes, and the medication) and indirect costs (work-related absenteeism, presenteeism, and diabetes-related disability) (2). The data from the SII in 2021, in Turkey has showed that there have been approximately 12 million patients with diabetes under universal health coverage whose diabetes care has been covered by the SII. The SII has reported to incur 8.6 billion ₺ in expenditures for the treatment of these patients in 2021. 2.6 ₺ billion of this total cost was for the treatment and complications and 5.4 billion ₺ was for the medications. 550 million ₺ was for glucometers and insulin pen needles, and 14 million ₺ was for insulin pumps, pump sets, and reservoirs (3). Given this economic burden, resources are limited in the face of this increase in expenditures. In 2019, the International Diabetes Federation (IDF) published the

ninth edition of its diabetes atlas. The atlas, which analyzes the current status of diabetes and projects future trends and estimates that, by 2045, Turkey will be one of the top ten countries in terms of the population with diabetes (4). According to the atlas, in 2019, diabetes-related health expenditure for the European region, including Turkey was approximately 161.4 billion $, and the region had the third largest expenditure on diabetes of all IDF regions. As a result of the intensity of the treatmet for diabetes in the European region, diabetes has become responsible for a large share of total health expenditure, ranging from 4.2% in Ireland to 23.8% in Turkey (5). In the world, the age group with the largest diabetes-related health expenditure, which is 177.7 billion $, has been those aged between 60 and 69 years. This group is followed by those aged between 50 and 59 years and between 70 and 79 years at an amount of 173.0 billion $ and 171.5 billion $, respectively (4). The reason behind this large expenditure that has been observed in older age groups is due to almost certainly the higher frequency of diabetes-related complications in later stages of life. In 2019, a slightly higher diabetes-related health expenditure was seen in women than in men, at an amount of 382.6 billion $ versus 377.6 billion $, respectively. Although some studies have suggested that diabetes and related complications are more common in women, our study has not found any relation between gender and ulcers or the cost of ulcers. In our study, most of the patients in the diabetic hand and foot ulcer groups are male and obese individuals. This might be explained by insufficient physical exercise and non-adherence to diet suggestions. Also, in general, the male population has higher economic and social interactions than woman in our country, which might be the cause of this result. According to our findings, the overall frequency of regular physical exercise is low in both the diabetic hand and foot ulcer groups, which are consisted mostly of the patients with non-regular physical exercise. Furthermore, it is determined that the majority of the patients has not received any information about diabetes within the previous year. It is suggested that an efficient education process for the patients about diabetes might have a positive impact on the cost-effective control of the disease. Diabetes-related chronic kidney disease is associated with significant additional health expenditure. In a study conducted in the USA between 1999 and 2002, mean annual healthcare costs were 49% higher among people with diabetes and clinical nephropathy than among those with no nephropathy. For people with diabetes and who were undergoing dialysis, the mean annual healthcare cost increased 2.8 times when it is compared with the end-stage renal disease patients who were not on dialysis (6,7). In this study, the presence of renal failure is not found to be related with the development of diabetic hand and foot ulcers or with the cost of existing ulcers. Moreover, although the presence of CRF is known to contribute to mortality in patients with diabetic ulcers, it is seen that it hasn't been resulted in mortality in any patient included in this study. People with diabetes who have foot ulcers bear health expenditures five times higher than those without foot ulcers. When it is compared to people with diabetes without foot ulcers, the cost of care for people with diabetes and foot ulcers is 5.4 times higher in the year of the first episode (8). A single-center study conducted in 2014, by Gençalioğlu, has reported that the cost of the treatment for the patients hospitalized with diabetic foot ulcers was 2203 $ per person on average (1$: 2.18 ₺) (9). A study titled "Problems in Diabetic Foot Infections and Cost Analysis for 2012" by Gönen has reported that the cost for per patient has been 2144.6 ± 2046.6 $, which is consistent with our study (1$: 1.8 ₺, based on the exchange rate for 2012) (10). Until the 90s, complications in diabetic patients were mostly related to the lower limbs. However, during the last two decades, several reports have demonstrated an increasing prevalence of diabetic hand ulcers, which are mostly observed in tropical countries and can be quite dangerous. Thus, the effect of diabetes on upper limbs is no longer limited to decreased joint mobilization, Dupuytren's contracture, neuropathy, nerve entrapment, and trigger finger (11). The condition, first described by Gill et al. and named as 'tropical diabetic hand syndrome,' typically affects women with type 2 diabetes and the patients in the fifth or sixth decade of their lives (12,13,14). Turkey is also located in a tropical region and is humid due to the effect of the Mediterranean climate. It can be concluded that it makes diabetic hand complications inevitable in our country. This study, unlike previous reports, has found that most of the patients presenting with a diabetic hand are male, but the age of onset is usually the sixth decade, which is consistent with the results in the literature. This might be attributed to the overrepresentation of men in Turkey in both social life and employment, making the upper limbs in men more vulnerable to pathogens when they are compared to women. Other risk factors for tropical hand infections

include poor control of diabetes or poor compliance, low socioeconomic status, minor trauma, and delayed treatment (13,15). In this study, the patients with diabetic hand ulcers have been checked for glucose levels for the past three months in order to determine their diabetes control status. Mean HbA1c levels are found to be higher in patients with diabetic hand ulcers, which supports previous reports that poor diabetes control is correlated with the development of hand infections. Although delayed treatment and low socioeconomic status are known to complicate hand infections, 64% of the patients with hand infections in our study are in a middle or high income group (quintiles 3-5). Moreover, 78% of them had their residence at a distance of less than 3 km from the nearest healthcare facility. This seems to point at low awareness of diabetic hand infections and delayed treatment in Turkey. Our experience also indicates that due to the low awareness of the diagnosis of diabetic hand ulcers among healthcare professionals, the initiation of an appropriate treatment for patients is usually preceded by a number of different treatments prescribed by other healthcare professionals, resulting in delayed referral to our clinic. Moreover, tropical diabetic hand infections have been claimed to be more common among patients with end-stage renal failure (15). In our study, the relation between the presence of CRF and diabetic hand ulcers is not statistically significant. However, in 86% of the patients with diabetic hand ulcers, the ulcer started in the limb with fistula. This might be explained by the steal phenomenon occurring in the limb with fistula, which reduces the blood flow distally. In their study, Bajaj et al. have reported that diabetic hand infections might be fatal (16). In this study, the clinical course ended with mortality in two patients with diabetic hand infection. In these patients, the site of onset was at the proximal level of the limb, and they had no glycemic control. Poor glycemic control leading to peripheral neuropathy might play a more significant role in the pathogenesis of hand sepsis (17). In addition to peripheral neuropathy, peripheral vascular disease also acts as a risk factor for diabetic foot infections (18,19). However, in this study, it has been found that diabetic hand ulcers might develop without vascular pathology in the affected limb. It might be explained by the fact that the hand plays a more active role in social activities and thus has less tolerance to neuropathy. Indeed, reduced sensation in the hand can complicate common and otherwise harmless hand injuries. In the present study, 72% of the patients who presented with a diabetic hand did not report a history of trauma. In 1977, a study with a limited number of patients (20) conducted by Mann et al. has reported that hand infections are more associated with type 2 diabetes. Francel et al., on the other hand, have suggested that diabetic hand infections are associated with type 1 diabetes (21). In our study, it is seen that there has been no relation between the type of diabetes and costs or ulcer development. Thus, the role of the type of diabetes in the pathogenesis of hand ulcers remains equivocal. Diabetic hand infections usually involve a polymicrobial infection, but a monomicrobial one is also possible. The bacterial isolates can be both Gram-positive and Gram-negative with Klebsiella, Pseudomonas, and Staphylococcus species being the most common (22). In this study, unlike the literature, candida species have been identified in patients with diabetic hand infection. Candida thrive in a warm, humid environment, and a reduced immune response or other conditions can allow an infection to develop. Since the hands and fingers are more involved with water, fungal infections should also be considered in diabetic hand infections. S. aureus is one of the most prominent pathogens in diabetic foot ulcers, warranting targeted empiric therapy in all patients. P. aeruginosa is becoming one of the most prominent Gram-negative pathogens in diabetic foot ulcers and is the second-most common pathogen behind S. aureus (23,24). In this study, the growths in tissue cultures of patients with foot ulcers have been compatible with the literature. The main limitation of the present study is the absence of analysis on the direct and indirect costs of diabetes. Moreover, in an attempt to understand the basic economic burden of diabetes, the study has excluded the patients who received specialized wound care products. It is known that complications of diabetes are more costly than diabetes itself. Thus, hand ulcers, like foot ulcers, should be recognized as a serious and costly complication of diabetes, and measures should be taken to develop preventive strategies. In addition to its impact characterized by premature mortality and lower quality of life due to related complications, diabetes imposes a significant economic impact on countries, health systems and, when healthcare needs to be funded 'out-of-pocket,' for individuals and their families. Although diabetic hand infections are less costly and cause fewer major amputations, it is a clinical condition that should be given at least as much attention as diabetic foot ulcer due to its atypical localized onset and the reproductive potential of different microorganisms.

Acknowledgment: The statistical analysis of the data has been evaluated professionally by Ece Türker, Mersin Toros University

Declarations

The authors have no conflicts of interest to declare. The authors declared that this study has received no financial support.

This study was approved by the clinical research Ethics Committee of the Kartal Dr. Lütfi Kırdar Training and Research Hospital (Date: 29.05.2023, Number: 2023/514/250/23).

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Archives of Current Medical Research
Arch Curr Med Res 2023;4(3):123-130

Received: 13 April 2023
Revised: 17 May 2023
Accepted: 15 August 2023
DOI: 10.47482/acmr.1282407

ORIGINAL ARTICLE

Retrospective analysis of traffic accidents related injuries in a tourism region

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Abstract

Background: The number of applications to the emergency service after a traffic accident is quite high. In this study it is aimed to provide up to date data to the literature by making a detailed analysis of the patients who applied to the emergency department after an accident.

Methods: This study was carried out by retrospectively scanning the patients who applied to the emergency department between 01.01.2022 and 31.12.2022 after a traffic accident in a secondary level hospital through the hospital electronic data. The patient's admission date and time, age, gender, accident mechanisms, being a vehicle driver and ethanol positivity above the legal limit in the driver, as well as laboratory and imaging methods performed in the emergency department were examined. The injuries and outcomes seen in the patients were analyzed.

Results: 1596 patients were evaluated within the scope of the study. The mean age of the patients was 32.93±19.26 years old and 66.7% were male. Among the accident mechanisms, 71.1% were found to be in vehicle traffic accidents. Head and neck tomography and extremity imaging were performed most frequently in the patients. Soft tissue trauma and extremity fractures were the most common cases. The discharge rate was 89.2%. It was concluded that hospitalized cases were most frequently made in neurosurgery, orthopedics and thoracic surgery clinics.

Conclusions: The fact that vehicle drivers are drunk increases the risk of traffic accidents. The most common cause of fatal traffic accidents is cerebral hemorrhage. Increasing the safety measures that can be taken to prevent traffic accidents will reduce morbidity and mortality.

Keywords: Emergency Department, Traffic Accidents, Traumatology, Multiple Injuries.

Cite this article as: *Alpaslan M, Baykan N. Retrospective analysis of traffic accidents related injuries in a tourism region. Arch Curr Med Res. 2023;4(3):123-130*

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INTRODUCTION

A traffic accident is defined as an event in which vehicles or people present on the highway are exposed to, resulting in damage and in which injuries and deaths occur (1). Traffic accidents have an important place in social life due to their negative effects on societies. Injuries, disabilities and deaths that occur after an accident are undesired negative consequences (2). About half of the deaths that occur after a traffic accident happen at the scene and shortly after the event. In these cases, the victim of the accident dies rapidly as a result of a sudden and major injury to the heart, great vessels, brain, brain stem and spinal cord (3). It is obvious that deaths and disabilities in this patient group would be prevented viaa rapid and effective intervention in the emergency departments. Reaching the accident site as quickly as possible and having well equipped health institutions for trauma patients in the centers that are closest to the regions where traffic accidents are common will be effective in immediate intervention to patients (2). In this study, it is aimed to evaluate both the demographics and the management process of the patients who applied to a secondary level emergency department with a traffic accident.

MATERIALS AND METHODS

The study has been approved by Hacıbektaş Veli University Non-Interventional Clinical Research Ethics Committee, numbered 2023/02 on 27.02.2023. It has been carried out by retrospectively scanning the hospital electronic data of the patients who applied to the emergency department in a secondary care hospital, with a traffic accident between 01.01.2022 and 31.12.2022

All patients who were diagnosed with a traffic accident in the "V01-V99" ICD diagnostic code range in the hospital electronic data and all pediatric and adult patient groups have been evaluated for the study. The admission date and time, age and gender of the patients, accident mechanisms, whether the patient is the driver of the vehicle or not, and whether the ethanol positivity of the driver is above the legal limit (>0.5 promile) or not have been examined. Moreover, laboratory and imaging methods performed in the emergency department have also been examined. When the ethanol levels in blood have been examined in patients who were the driver of the vehicle and if it has been found as positive (>0.5 promile), which means it is above the legal limit, these patients have been accepted as drunk drivers.

Injuries and outcomes seen in patients have also been analyzed. Within the scope of the study, no distinction is made between patients arriving by ambulance or outpatients. Cases that ended in death at the scene are excluded from the study. Patients who were transferred to another health institution are not followed up and their mortality rate is not included in the evaluations of the study.

RESULTS

For this study, a total of 1596 patients have been analyzed. 66.7% of the patients are male. The mean age is 32.93±19.26 years, and when it is evaluated according to the age groups, it is seen that the most frequent admissions are between the ages of 18 and 65 (70.2%) and the minimum age of 65 years (7.6%). Among the examined patients for this study, the youngest case is a four-month-old baby and the oldest patient is 99 years old. The number of unlicensed vehicle driver patients under the age of 18 who had a traffic accident is 75, which is 10% of the total number of the drivers. The number of patients over the age of 65 who had an accident as a driver is 46, which constitutes 37.7% of the patient group over the age of 65. The number of patients who applied to the emergency department as drivers is 757 (47.4%) and the number of drunk drivers is 103. When drivers are analyzed according to their genders and their alcohol intake status, it is seen that the number of male drunk drivers is 92 (89.3%). When the admission times of the patients are evaluated, it is observed that the most frequent admissions are during the summer months (32.4%) and most of the cases are seen in July. The distribution of patients by months is given in Figure 1. The analysis has been made according to the admission days of the week and it can be concluded that traffic accidents occured mostly on Friday (17.5%) and at least on Sunday (12.8%). The time of admission to the emergency department after a traffic accident have been examined in 3 periods as between 08:00 a.m. and 04:00 p.m. (600 patients, 37.6%), between 04:00 p.m. and 11:59 p.m. (814 patients, 51%), and between 12:00 a.m. and 08:00 a.m. (182 patients, 11.4%).

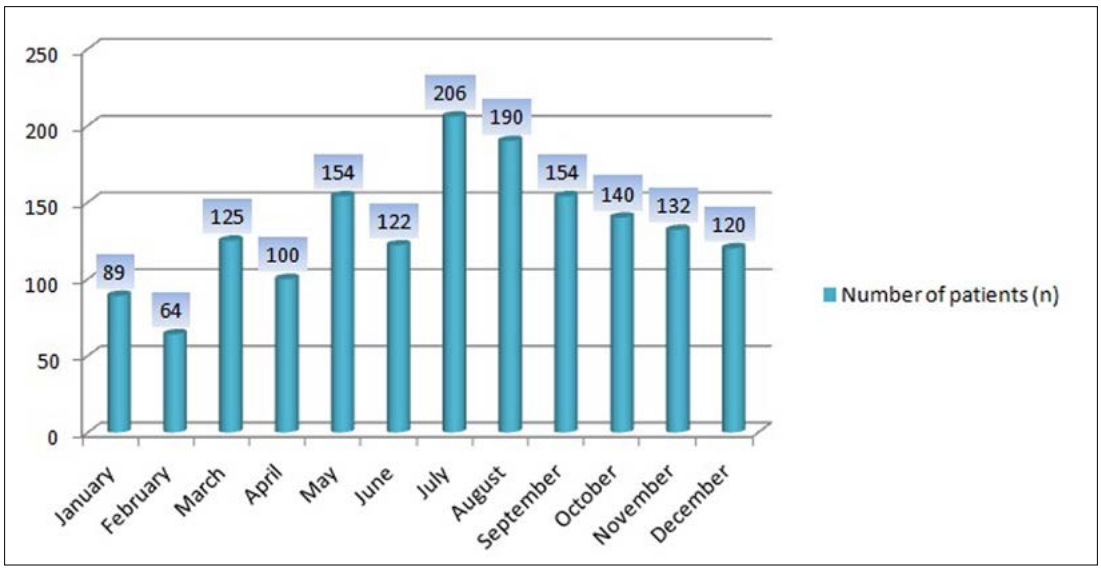

Figure 1.The analysis of the number of the patients admitted to the emergency department after a traffic accident according to the months within the year.

When the alcohol intake rates of the drivers are compared to their admission hours, some significant results are obtained (p<0.001, Chi square:164.163). According to the results, the number of drivers who are drunk and are involved in the accident during the evening and night hours of the day is higher (Table 1). The mechanisms of the accidents are classified in four categories as in vehicle traffic accident (IVTA), nonvehicle traffic accident (NVTA), motorcycle accident and other accidents (tractor accident, ATV accident, bicycle accident etc.). The most common accident type is IVTA (71.1%). The number of patients according to the accident categories is given in Table 2. When the types of accidents are compared according to age groups, it is seen that there have been important differences. The rate of IVTA is higher in all age groups (p<0.001, Chi square: 186.544). In particular, 77.9% of the patients between the ages of 18 and 65 are recorded as having under gone IVTA. When the imaging and laboratory methods performed in the emergency department are examined, it is seen that the rate of direct plain radiograph and computed tomography (CT) in patients is 92.7%, the rate of laboratory evaluation is 62.7% and the rate of the evaluation of radiographs and laboratory together is 60%. Ultrasound has been performed in 32 (2%) patients. The radiographs taken in the patients are classified as tomography and plain radiograph separately and are given in Table 3. Accordingly, it is understood that patients mostly had a head and neck tomography. According to the results, it is observed that 226 patients (14.1%) had whole body tomography (except extremities). A significant correlation is found between the whole-body CT scans and accident types and it can be seen that more shots were taken in cases with IVTA (p<0.001, Chi square: 68.523). According to the classification made according to the types of injuries in the body as a result of the accident, soft tissue trauma (37.1%) is most commonly occurred.

Table 1. Analysis of the number of patients with ethanol positivity above the legal limit in the laboratory test of drivers who had an accident at the time of the traffic accident.

Time Zone	Alcohol Test		Total
	Negative	Positive*	
08:00 a.m.-04:00 p.m.	589	11	600
04:00 p.m.-11:59 p.m.	773	41	814
11:59 p.m.-08:00 a.m.	131	51	182
Total	1493	103	1596

* Patients with positive blood ethanol values above the legal limit (>0.5 promile)

Table 2. Analysis of the number of patients injured in traffic accidents according to the way the accident occurred.

Accident Categories	Number of Patients (n)	Ratio (%)
In vehicle traffic accident*	1134	71.1
Non vehicle traffic accident**	239	15
Motorcycle accident	205	12.8
Other accidents***	18	1.1
Total	1596	100

* Patients who were in the vehicle at the time of the accident

** Patients who were out of the vehicle at the time of the accident, pedestrians etc.

***Tractor accident, bicycle accident, all train vehicle accident etc.

Table 3. Analysis of the number of radiological imaging performed to diagnose patients in the emergency department

Examination type	Number of patients	Ratio (%)*
Brain and/or cervical CT**	1021	64
Thorax CT	636	39.8
Abdomen CT	424	26.6
Pelvis CT	257	16.1
Thoracolumbar CT	287	18
Extremity CT	112	7
Brain, cervical, thorax CT	584	36.6
Brain, cervical, thorax, abdomen CT	405	25.4
Brain, cervical, thorax, abdomen, pelvis, Thoracolumbar CT	226	14.2
Posteroanterior lung graphy	441	27.6
Pelvis graphy	337	21.1
Spinal graphy	58	3.6
Upper extremity graphy	561	35.2
Lower extremity graphy	623	39

* It is the rate given according to the total number of patients.

**Computerized Tomography

Moreover, there has been statistically significant relation between the rate of soft tissue injuries (STI) and accident types. (p<0.001, Chi square: 166.573). It has been observed that STI is seen in 76% of the motorcycle accidents. Injuries such as simple skin incision, edema, hematoma and abrasion are evaluated as STI. Extremity fractures are seen as the second most common injury in patients and the lower extremity fracture rate is the highest among all injuries. Table 4 includes the list of the body parts that are injured as a result of the accident and the number of patients. Given in Table 5, it is seen that in the cases, 1423 (89.2%) patients were discharged from the emergency department, 97 (6.1%) patients were admitted to the service, 53 (3.3%) patients were admitted to the intensive care unit, 13 (0.8%) patients were referred to the upper center and 11 (0.7%) patients died in the emergency department or intensive care unit. The most frequently admitted clinical departments have been orthopedics, neurosurgery and thoracic surgery, respectively. Traumatic aortic dissection has been found in 3 of the cases that ended in death, while multi organ injury, especially cerebral hemorrhage, has been observed in other cases. Eleven of 103 patients who were found to be alcoholic have been treated in the intensive care unit. On the other hand, it is observed that there has been no statistically significant relation in the comparison made in terms of resulting in death among drunk drivers (p=0.521, Chi square: 0.128). Also, a comparison is made between accident mechanisms and resulting in death. However, it is concluded that there is no significant difference (p=0.694, Chi square: 1.451). There is no significant value in the comparison made in terms of death at the time of the accident (p=0.272, Chi square: 2.602).

Table 4. Analysis of the types of injuries detected according to the results of examination and imaging methods in patients evaluated in the emergency department after the accident.

Type of Injury	Number of Patıents	Ratio (%)*
Fracture of skull or facial bones	56	3.5
Bleeding, edema, contusion in the skull base	39	2.4
Cervical vertebral fracture	11	0.7
Thoracic vertebral fracture	11	0.7
Lumbar vertebral fracture	33	2.1
Pneumothorax / hemothorax	21	1.3
Lung contusion	43	2.7
Costal fractures	60	3.8
Intra abdominal organ injury	15	0.9
Pelvic fracture	24	1.5
Fracture of upper extremity bones	95	6
Fracture of lower extremity bones	99	6.2
Soft tissue ınjury**	601	37.7

* It is the rate given according to the total number of patients.

**Simple skin incision, edema, hematoma, abrasion etc.

Table 5. The results of the patients who were diagnosed and treated in the emergency department after the accident

Results	Number of patients	Ratio(%)
Discharge from the emergency department	1423	89.2
Admission to service	97	6.1
Intensive care hospitalization	53	3.3
Referral to higher health institution	13	0.8
Death	11	0.7

DISCUSSION

Nowadays, people have been using highways more and the number of vehicles has been increasing day by day. While it affects the increase in accident rates, it is also clear that alcohol use, sleepless driving, being non compliance with traffic rules, inadequate traffic training and inspections also cause accidents (4-6). In this study, it has been observed that traffic accident smostly happen during summer months. In accidents that occur in the evening and at night, the number of drunk drivers is higher than in other times of the day. It is also determined that the rate of IVTA (in vehicle traffic accident) is higher than the other types of accidents. In addition, it is seen that soft tissue injuries, mainly; extremity fractures; chest, head and neck injuries are the most common types of injuries as a result of the accidents

In this study 66.7% of the traffic accident cases admitted to the emergency department are male. In studies conducted in our country and in different parts of the world, similarly, it is observed that the cases who had traffic accidents are predominantly male (1-3,5,7,8). It is thought that these results occur due to the fact that men spend more time in traffic and the drivers of vehicles in many countries are predominantly male.

When the age group is examined in the study, it is seen that the most frequent traffic accidents are in the age group between 18 and 65. The mean age is 32.93±19.26 years. In similar studies conducted in our country, the results are obtained with an average age of between 30 and 35 (1,3,5,9) and between 20 and 30 (2,4). The average age is found to be 28 by Sawe et al. (7), 29±13,549 by Honelg et al. (8), and between 25 and 35 by Lenjani et al. (10).

Although the average values vary according to the demographic structures of the regions where the studies are conducted, it seen that similar results are obtained. One of the striking values in this study is that the drivers who drive without a license against the rules are found to be 4.7%. In addition, the drivers over the age of 65 have been involved in an accident with a rate of 37.7% in their age group. Considering these values, it can be concluded that the rules should not be violated, up to date inspections should be carried out at regular intervals, especially in the driver group over the age of 65, and the ability of the person to drive with chronic diseases should also be evaluated.

It is determined that 13.6% of the drivers, who have been included in the study, were alcoholic. Most of the patients who had an accident especially between 11:59 p.m. and 08:00 a.m. are alcoholics. When several other studies have been exmined it is seen that in a study conducted in Edirne, the rate of the drunk drivers has been determined as 18.9% (4). In another study conducted in Antalya it has been 22.1% (11) and in a study conducted in Trabzon it has been 40.2% (12). Although it can be assumed that the rates vary according to the regions and the patient group in the center of the cities where the study is conducted, it is obvious that alcohol use causes serious traffic accidents. Similar to the study conducted in Trabzon, in this study, one of the most important causes of night time accidents is also alcohol use (12).

When the seasonal analysis of the accidents is made, it is seen that the accidents increase in the summer months. In similar studies in the literature, it has been reported that the accident rate increases in summer (2-4,9,11). However Armagan et al. (5) have reported that the increase is seen in October. Besides, Ozdemir et al.(13) have observed that traffic accidents occur more frequently in the winter months. However, it cannot be ignored that there are seasonal differences in weather conditions according to the study centers. Active presence of people in traffic and adverse weather conditions will also affect the results. Although it is seen that the analysis of the days of the accidents is not very frequent in the studies, it has been stated that the most frequent accident rate is on Saturday (4,14). In this study, it has come to the fore on Friday. When the admission hours after the accident have been examined, it is determined that the most frequent admission time is between 04:00 p.m. and 11:59 p.m., with a rate of 51%. In several other studies conducted in our country, admission hours are generally between 04:00 p.m. and 11:59 p.m., too (2,4,11). However, in a study conducted on NVTA in the pediatric age group, it is observed that the most frequent admission is between 08:00 a.m. and 04:00 p.m. (15). Due to the different age groups, it is thought that daytime hours come to the fore in this study. In a study conducted in Korea on pedestrian accidents experienced by elderly patients, it has been observed that there are more frequent accidents between 11:59 p.m. and 08:00 a.m. with a rate of 44.5% (16). Considering the demographic difference of the study groups and the time difference between countries, different results are expected to emerge.

There have been some factors such as types of accidents, seasonal factors, cultural differences and the use of different vehicle types that are affecting the results between regions. In similar studies conducted in our country various results have been reported. In our study, it is observed that the highest rate of IVTA is 71.1%. In the study of Aydeniz et al.(2), 56.6%of the cases are seen as IVTA. However, in other studies that belong to Ozdemir et al.(13) and Atik et al., (17) the rates of NVTA are found to be higher. In a study conducted in Tanzania, more than two thirds of the cases are found to be motorcycle accidents (7). In another study conducted in Ethiopia, 85.5% of the injuries are found to be IVTA and 14.6% of them are pedestrian injuries (8).

Traffic accidents are considered as high energy trauma, and laboratory and imaging methods are widely evaluated in the diagnosis and the treatment process of patients. In this study, the rate of direct radiography and computed tomography (CT) is 92.7%, the rate of laboratory evaluation is 62.7% and the rate of evaluation of radiographs and laboratory together is 60.5%. Also, the rate of ultrasound is 2%. In the study performed by Ozdemir et al.(13) the rates belonging to the diagnosis and the treatment process are as following; 53.6% blood examination, 72.5% direct radiography, 52.3% CT, and 11.4% ultrasound. In the study performed by Varlık et al. (1) the imaging rates are 65% for head and neck CT, 24% for thorax CT, 45% for spinal CT, 15% for abdominal CT, 19% for extremity CT and 8% for ultrasound. When the rates of plain radiographs performed in patients in similar studies are evaluated, similar to our study, plain radiographs of the head, neck, thorax and extremities come to the fore most frequently. Although more specific injuries are seen in different parts of the body according to the types of the accidents and the severity of the accident, head, neck and extremity injuries are more common in the studies available in the literature (1-5,13,16,18). Uzun et al.(19) have reported that the most common lower extremity injury is seen in motorcycle accidents. As in this study, the rate of STI is found to be more frequent in motorcycle accidents than in other accident types (4,19). It can be thought that motorcycle accidents are caused by the body's direct contact with the external environment and there is a problem of the in adequate use of protective equipment. In this study, the results are similar to the literature.

When the literature is reviewed, it seen that there have been several studies examining the way in which the

treatment of the patients in the emergency department is terminated and similar results have been reported. Although the discharge from the emergency department is the highest in the vast majority of the cases, hospitalization, referral to another center, and death rates have resulted in close numbers (1-5,15,16). In the literature, it is seen that mortality rates are higher in some studies than others.

In the study conducted by Lee et al.(16) in Korea, the death rate is 5% and, in the study, conducted by Kocak et al.(18) on motorcycle accidents, it is reported that the death rateis 14%. It can be thought that this difference between studies is due to the limited number of patients included. In these studies, the orthopedics and neurosurgery clinics are the most frequently hospitalized clinics due to injuries after a traffic accident (1,3,5,13). In this study patients are admitted to orthopedics, neurosurgery and thoracic surgery clinics most frequently. In a study conducted in the Thrace region, 57.8% lung and 48.5% brain damage are observed in traffic accidents (4).

In a study it has been found that the most common causes of death among forensic cases seen in emergency departments are IVTA and NVTA, respectively (20). Deaths in accidents occur most frequently at the scene and as a matter of fact, transportation to the nearest health institution is also important for the survival rate. In a study conducted in the United States of America, it is reported that the death rate of motorcycle accidents occurring in the country side is higher than the ones in the city center (21). Among the causes of death by traffic accidents, brain hemorrhages due to head trauma are the most common. (4,8,20). In this study, it is seen that most of the patients who have been admitted to the intensive care unit and died are significantly associated with intracranial hemorrhage (p<0.001, Chi-square: 674.552). The alcohol consumption of the drivers can also affect the severity of the accident and affect both the intensive care hospitalization process and death. While Goksu et al.(11) have stated that there has been no relationship between alcohol positivity and hospitalization rates in their study, Kesen et al.(12) have found a significant relationship between low Glasgow Coma Score (GCS) and alcohol positivity. In our study, while alcohol positivity has affected the intensive care hospitalization rates, no significant correlation is observed in the cases that resulted in death.

It is known that traffic accidents are mostly due to negligence. Besides, alcohol use increases the accident rates. Most of the deaths in traffic accidents occur at the scene and in the emergency departments within the first hour. We think that the data obtained from this study will be useful in evaluating the measures that can be taken to prevent the occurrence of traffic accidents. In addition, we anticipate that there will be more effective diagnosis and treatment admissions with current data in the evaluation of patients admitted to emergency departments after a traffic accident. We think that it would be beneficial to establish trauma centers in regions where traffic accidents are intense.

Declarations

The authors have no conflicts of interest to declare. The authors declared that this study has received no financial support.

This study was approved by the Hacıbektaş Veli University Non-Interventional Clinical Research Ethics Committee (Date: 27.02.2023, Number: 2023/02)

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Archives of Current Medical Research
Arch Curr Med Res 2023;4(3):131-136

Received: 5 April 2023
Revised: 24 April 2023
Acccepted: 16 May 2023
DOI: 10.47482/acmr.1277981

ORIGINAL ARTICLE

Evaluation of patients admitted to the hematology outpatient clinic for spontaneous ecchymosis: Does it suggest bleeding diathesis?

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Abstract

Background: Spontaneous ecchymosis is a common reason for referral to the hematology outpatient clinic. It is important to determine the underlying bleeding is benign or a symptom of diathesis.

Methods: The sample of this retrospective study consisted of 119 patients with normal platelet counts who presented to the adult hematology outpatient clinic with spontaneous ecchymosis between September 2021 and August 2022. The site of the ecchymosis, patients' familial and bleeding histories, and the drugs they have been using were queried. Hemogram and coagulation parameters and peripheral smear findings of the patients were recorded, and their ISTH-SSC (International Society on Thrombosis and Haemostasis Scientific and Standardization Committee) Bleeding Assessment Tool scores were calculated.

Results: The median age of the patients, of whom 113 (95%) were female and 6 (5%) were male, was 30 (18-85) years. The ecchymosis was in the extremities and the trunk in 110 (92.4%) and 9 (7.6%) patients, respectively. There was no significant difference between the patients with and without bleeding history in terms of the site of spontaneous ecchymosis, the hemogram parameters and peripheral smear findings. Similarly, the patients with and without factor deficiency have not differed significantly in terms of hemogram parameters and peripheral smear findings. Patients with any factor deficiency had significantly higher ISTH-SSC Bleeding Assessment Tool scores compared to the patients without factor deficiency.

Conclusions: The findings of the study revealed that the site of ecchymosis and hemogram and coagulation parameters cannot be used as markers in the general sense, except for the ISTH-SSC Bleeding Assessment Tool scores, which predicted factor deficiency. Another finding of the study worth mentioning is the fact that the number of patients with ecchymosis on the trunk among the patients presenting with the complaint of ecchymosis was significantly lower than that of patients with ecchymosis on the extremities.

Keywords: Ecchymosis, Factor Deficiency, Platelet.

Cite this article as: *Yılmaz S, Çiftçiler R, Dağ M. Evaluation of patients admitted to the hematology outpatient clinic for spontaneous ecchymosis: Does it suggest bleeding diathesis?. Arch Curr Med Res. 2023;4(3):62-69*

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INTRODUCTION

Ecchymosis is a subcutaneous hemorrhage that concerns the skin and subcutaneous structure, platelet count and function, and coagulation cascade (1). The incidence of spontaneous ecchymosis in healthy individuals reported in the literature varies between 12% and 55% and it is reportedly more common among women (2-5). Bruising can easily occur in cases of physical trauma, vitamin C deficiency, conditions involving blood vessels and surrounding tissue such as connective tissue disorders, medication-related conditions, infectious diseases or platelet abnormalities such as von Willebrand disease, coagulation factor deficiencies, and coagulation defects that may develop due to conditions such as vitamin K deficiency or liver disease. Given that spontaneous ecchymosis is a common complaint, it is important to determine which cases will require further examinations.

In this context, answers were sought to the questions of the location of ecchymosis is related to the bleeding history?", "does the presence of ecchymosis suggest factor deficiency?", "is there a difference in hemogram parameters and peripheral smear findings between those with and without bleeding history?", and "are the hemogram parameters different between those with and without factor deficiency?" based on the data obtained from the patients that applied to the hematology outpatient clinic with spontaneous ecchymosis.

MATERIAL AND METHODS

The sample of this retrospective study consisted of 119 patients with normal platelet counts who presented to the adult hematology outpatient clinic with spontaneous ecchymosis between September 2021 and August 2022. The site of the ecchymosis, patients' familial and bleeding histories, and the drugs they have been using were queried. Hemogram and coagulation parameters and peripheral smear findings of the patients were recorded. Patients' spontaneous gingival bleeding, spontaneous nose bleeding, prolonged bleeding after incision, prolonged bleeding after tooth extraction, and prolonged bleeding after surgery histories were queried. In addition, in the case of female patients, prolonged postpartum bleeding history and menstrual bleeding intensity (changing pads more than once every 2 hours, no tapering in the intensity of menstrual bleeding even after 3 days, presence of clots in the menstrual blood, feeling the need to use large pads due to the high intensity of menstrual bleeding, etc.) were also investigated. Each parameter in question was scored separately. Patients' ISTH-SSC (International Society on Thrombosis and Haemostasis Scientific and Standardization Committee) Bleeding Assessment Tool scores were calculated and recorded. Factor results were evaluated according to the laboratory reference range (Factor V: 62-140%, factor VII: 70-181%, factor VIII: 56-91%, factor IX: 78-184%, factor X: 81-157%, factor XII: 58-166%, factor XIII:60-192%, von Willebrand ristocetin cofactor: 51-215 December, von Willebrand factor antigen: 52-214)

Statistical Analysis:

Statistical analyses were carried out using SPSS 26.0 (Statistical Product and Service Solutions for Windows, Version 26.0, IBM Corp., Armonk, NY, U.S., 2019) software package. The normal distribution characteristics of the variables investigated within the scope of the study were analyzed by visual (histograms, probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's tests). Comparisons featuring categorical variables were made using Pearson's chi-squared test. Comparisons featuring continuous numerical variables were made using student's t-test (for two independent samples). The probability (p) statistics of ≤ 0.05 were deemed to indicate statistical significance. The study protocol was approved by the Ethics Committee of Karatay University Faculty of Medicine (Approval No. 2022/026, Approval Date: 21.09.2022).

RESULTS

General Characteristics of the Patients

The study sample included 119 patients who presented with spontaneous ecchymosis to the adult hematology outpatient clinic where this study was conducted. The median age of the patients, of whom 113 (95%) were female and 6 (5%) were male, was 30 (min. 18, max. 85) years. The ecchymosis was in the extremities and the trunk in 110 (92.4%) and 9 (7.6%) patients, respectively. The general characteristics of the patients with spontaneous ecchymosis are shown in Table 1.

Table 1. General characteristics of the patients presented with spontaneous ecchymosis

Number of patients (n)	119
Gender (Female/Male)	113 (95%)/6 (5%)
Age (median, years)	30 (8-85)
ISTH-SSC Bleeding Assessment Tool score	1 (1-8)
Site of ecchymosis (extremities/trunk)	110 (92.4%)/9 (7.6%)
Bleeding history (yes/no)	43 (36.1%)/76 (63.9%)
Menstrual bleeding intensity complaint (yes/no)	25 (22.1%)/88 (77.9%)
Gingival bleeding (yes/no)	10 (8.4%)/109 (91.6%)
Nose bleeding (yes/no)	8 (6.7%)/111 (93.3%)
Prolonged bleeding after incision (yes/no)	6 (5%)/113 (95%)
Prolonged bleeding after surgery (yes/no)	5 (4.2%)/114 (95.8%)
Prolonged postpartum bleeding (yes/no)	4 (3.5%)/109 (96.5%)
Prolonged bleeding after tooth extraction (yes/no)	9 (7.6%)/110 (92.4%)
Familial history (yes/no)	4 (3.4%)/115 (96.4%)
Medication history (yes/no)	28 (23.5%)/91 (76.5%)

Abbreviations: ISTH-SSC, International Society on Thrombosis and Haemostasis Scientific and Standardization Committee

Evaluation of Patients According to Bleeding History

Comparison of the patients with and without bleeding history in terms of spontaneous ecchymosis site revealed that ecchymosis was located in the extremity in 41 (95.3%) and 69 (90.8%) patients with and without bleeding history, respectively. Accordingly, there was no significant difference between the two groups in spontaneous ecchymosis sites (p: 0.36).

Comparison of the patients with and without bleeding history in terms of hemogram parameters revealed no significant difference between the two groups in any hemogram parameter, i.e., hemoglobin (p=0.85), leukocyte (p=0.73), and platelet (p=0.50) levels, mean platelet volume (MPV) value (p=0.81), MPV/PLT (platelet count) ratio (p=0.45), procalcitonin (PCT) (p=0.94) level, and platelet distribution width (PDW) value (p=0.94).

Comparison of the patients with and without bleeding history in terms of presence of factor deficiency revealed no significant difference between the two groups (p=0.29). There was no significant difference between the two groups in coagulation parameters and factor levels, i.e., prothrombin time (PT) (p=0.63), international normalized ratio (INR) (p=0.64), activated partial thromboplastin clotting time (aPTT) (p=0.81), fibrinogen (p=0.83), d-dimer (p=0.15), von Willebrand factor (p=0.52), factor VIII (p=0.61) and factor 7 (p=0.89) levels.

Additionally, peripheral smears of patients with and without bleeding history were evaluated according to whether the platelets were large or small or whether they formed aggregates or not. Accordingly, there was no significant difference between the two groups in terms of peripheral smear characteristics (p=0.53) (Table 2).

Table 2. Comparison of general characteristics and laboratory findings of patients with and without bleeding history

Parameters	Patients with Bleeding History	Patients without Bleeding History	*p* value
Number of patients (n)	43 (36.1%)	76 (63.9%)	
Gender (Female/Male)	42/1 (97.7%/2.3%)	71/5 (93.4%/6.6%)	0.30
Age (median, years)	29 (18-70)	30 (18-85)	0.52
ISTH-SSC Bleeding Assessment Tool score	2 (1-8)	1 (1-1)	<0.001
WBC ($10^3/\mu L$)	6.4 (0-19.5)	5.8 (0-14.8)	0.73
Hemoglobin (g/dl)	12.8 (4.9-15.8)	13.1 (3.2-17.5)	0.85
Platelet ($10^3/\mu L$)	236 (5-742)	234 (12-379)	0.50
MPV (fL)	11.1 (8.8-410)	10.7 (8.5-428)	0.81
MPV/PLT	0.04 (0-11.7)	0.04(0.02-12.6)	0.45
PCT (ng/mL)	0.28 (0.07-13.7)	0.29 (0.08-28)	0.94
PDW	11.8 (9.6-49)	12.5(8.5-16.7)	0.94
INR	1.0 (0.93-4.8)	1.0 (0.92-10.8)	0.64
aPTT (sec.)	26 (19-36)	26.0 (20-57)	0.81
Fibrinogen (mg/dL)	2.98 (0.83-479)	2.94 (1.96-548)	0.83
D-dimer (ng/mL)	0.25 (0.19-0.76)	0.25 (0.1-3.6)	0.15
Factor deficiency Yes/No (%)	14/29 (32.6%/67.4%)	18/58 (23.7%/76.3%)	0.29
Factor VIII	66.0 (31.8-108)	48.5 (27.9-97.2)	0.61
von Willebrand Factor	100 (75-201)	121 (31.2-256.8)	0.52
Factor XIII	134 (134-149)	102 (73-145)	0.02
PT (sec.)	17.10	16.4	0.36
Factor IX	72.05	123	0.01
Factor V	74 (62-85)	63 (63-63)	0.69
Factor X	71 (68-73)	89 (89-89)	0.15
Factor XII	102 (96-108)	106 (106-106)	0.75
Factor VII	96 (61-132)	86 (86-86)	0.89

Abbreviations: ISTH-SSC: International Society on Thrombosis and Haemostasis Scientific and Standardization Committee, WBC: White Blood Cell Count, MPV: mean platelet volume, MPV/PLT: mean platelet volume/platelet count ratio, PCT: procalcitonin, PDW: platelet distribution width, PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin clotting time

Evaluation of Patients According to Factor Deficiency

No factor deficiency was detected in 87 (73%) of the patients who applied to the hematology outpatient clinic with spontaneous ecchymosis. The remaining 32 (27%) patients had a factor deficiency. Factor deficiency defined based on laboratory reference range. Factor levels were re-studied in patients with factor deficiencies. For von Willebrand disease, von Willebrand antigen, von Willebrand ristocetin cofactor and factor VII levels were requested. Of these patients, 8 (7%) had von Willebrand deficiency (type 1), 11 (9%) had factor VII deficiency, 12 (10%) had factor VIII deficiency and 1 (1%) had both factor VIII and von Willebrand deficiencies. The distribution of patients by factor deficiency is shown in Figure 1. Factor deficiency was detected in 29 (26.4%) patients who had ecchymosis in extremities and 2 (22.2%) patients who had ecchymosis in the trunk. Accordingly, there was no significant relationship between the site of ecchymosis and factor deficiency (p=0.78).

Comparison of the patients with and without factor deficiency in terms of hemogram parameters revealed no significant difference between the two groups in any hemogram parameter, i.e., hemoglobin (p=0.57), leukocyte (p:0.80), and platelet (p=0.66) levels, MPV value (p=0.48), MPV/PLT ratio (p=0.49), PCT (p=0.21) level, and PDW value (p=0.81).

In addition, there was no significant difference between the patients with and without factor deficiency in terms of peripheral smear characteristics (p=0.17).

Evaluation of Patients According to ISTH-SSC Bleeding Assessment Tool Scores

Distribution of the ISTH-SSC Bleeding Assessment Tool scores by factor deficiency is shown in Table 3. Of the 6 male patients, five (83.3%) had a bleeding score of 1, and one (16.7%) had a bleeding score of 3. Of the 113 female patients, two (1.6%) had a bleeding score of 6, one (0.8%) had a bleeding score of 8, and the remaining 110 (97.6%) had a bleeding score of three and below. There was a significant correlation between the patients with and without factor deficiency and the ISTH-SSC Bleeding Assessment Tool scores (p=0.004). Accordingly, patients with any factor deficiency had significantly higher ISTH-SSC Bleeding Assessment Tool scores than patients without factor deficiency.

Table 3. Distribution of the ISTH-SSC Bleeding Assessment Tool scores by factor deficiency

ISTH-SSC Bleeding Assessment Tool Scores *p*: 0.004	Patients without Factor Deficiency	Patients with any Factor Deficiency
Score 1	59 (67.8%)	18 (56.3%)
Score 2	26 (29.9%)	6 (18.8%)
Score 3	1 (1.1%)	5 (15.6%)
Score 4	0	0
Score 5	0	1 (3.1%)
Score 6	1 (1.1%)	1 (3.1%)
Score 7	0	0
Score 8	0	1 (3.1%)

Abbreviations: ISTH-SSC, International Society on Thrombosis and Hemostasis Scientific and Standardization Committee

DISCUSSION

As in other studies in the literature, 95% of the patients presenting with spontaneous ecchymosis included in this study were female (2). The ecchymosis was in the extremities in 92.4% of the patients. The fact that the ecchymosis was in the extremities could be attributed to the presence of physical traumas (6). Then again, patients without a history of trauma were included in this study. 23.5% of the patients had a history of antiaggregant, non-steroidal anti-inflammatory and selective serotonin reuptake inhibitors group drug use. These medications are known to be effective on primary hemostasis (7). Therefore, it is critical to query the medications patients have used and have been using. In addition, given that the diets with low protein content and vitamin C and K deficiencies may also predispose to ecchymosis, patients' dietary habits should also be queried. Patients' alcohol intake was queried in this study, yet a detailed inquiry about nutrition was not made, which can be considered one of its limitations. It is important to query the presence of hemorrhagic diathesis in the family (8). 3.4% of the patients included in the study had a familial history of hemorrhagic diathesis. However, they did not have detailed information about their familial history. 75% of these patients had factor 7 deficiency, a finding which suggests that patients with a familial history of hemorrhagic diathesis should be further analyzed, even if no abnormality is detected in the initial laboratory tests.

The site of ecchymosis may be important in terms of bleeding diathesis, but there are no studies on ecchymosis unrelated to trauma in adult patients. The analysis of patients in terms of ecchymosis site revealed that 92.4% and 7.6% of the patients had ecchymosis in the extremities and in the trunk, respectively. Factor deficiency was detected in 26.9% of the patients. There was no significant relationship between the presence of factor deficiency and the ecchymosis site. Further large-scale studies are needed to shed more light on this subject.

Patients' spontaneous gingival bleeding, spontaneous nose bleeding, prolonged bleeding after incision, prolonged bleeding after tooth extraction, and prolonged bleeding after surgery histories were queried. In addition, in the case of female patients, prolonged postpartum bleeding history and menstrual bleeding intensity were also investigated. Analysis of the patients with and without bleeding history in terms of whether they had

factor deficiency did not reveal any significant difference between the two groups.

Querying the menstrual cycle of female patients can provide key information in terms of bleeding diathesis. Studies conducted on this subject demonstrated that changing pads more than once every 2 hours, no tapering in the intensity of menstrual bleeding even after 3 days, presence of clots in the menstrual blood, and the need to use large pads due to high intensity of menstrual bleeding were associated with excessive menstrual bleeding (9,10). The actual prevalence of hemophilia carriage is unknown. The diagnosis of women with mild factor deficiency and female hemophilia carriers may be overlooked (11). In this study, 22.1% of the patients described excessive menstrual bleeding. A factor deficiency was detected in 32% of these patients. Of these patients, 75% had factor VIII deficiency and 25% had factor 7 deficiency.

The ISTH-SSC Bleeding Assessment Tool is used to detect abnormal bleeding and determine the severity of bleeding (8). Each type of bleeding is scored according to its severity, whether it requires medical intervention, and the method used in its treatment. ISTH-SSC Bleeding Assessment Tool scoring has been shown to be effective in determining bleeding severity and screening for hereditary bleeding disorders (12-18). In parallel, in this study, patients with a factor deficiency had a significantly higher ISTH-SSC Bleeding Evaluation Tool score compared to the patients without a factor deficiency.

The findings of the study revealed that the site of ecchymosis and hemogram and coagulation parameters cannot be used as markers in the general sense, except for the ISTH-SSC Bleeding Assessment Tool scores, which predicted factor deficiency. Another finding of the study worth mentioning is the fact that number of the patients with ecchymosis on the trunk among the patients presenting with the complaint of ecchymosis was significantly lower than that of patients with ecchymosis on the extremities.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

The study protocol was approved by the Ethics Committee of Karatay University Faculty of Medicine (Approval No. 2022/026, Approval Date: 21.09.2022).

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Archives of Current Medical Research
Arch Curr Med Res 2023;4(3):137-145

Received: 29 November 2022
Revised: 21 February 2023
Acccepted: 11 May 2023
DOI: 10.47482/acmr.1211570

ORIGINAL ARTICLE

Investigation of the knowledge, attitudes and behaviors on active aging of people between 30-40 years: A multi-central cross-sectional study

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Abstract

Background: Aging is a physiological process in every human and causes a decrease in all functions. It is essential to prepare the elderly population for the future as individuals who can care for themselves, have a rare incidence of chronic diseases, and have economic competence. Primary prevention is essential and cost-effective for healthy aging. This study aims to analyze the knowledge, attitudes, and behaviors of people aged 30-40, who are the elderly of the future, about healthy aging.

Methods: This study was conducted face-to-face and over the call with people aged 30-40 who applied to Family Health Centers randomly selected across Turkey between March 2019 and January 2020 for any reason. A questionnaire prepared by researchers, including sociodemographic information, health control, vaccinations, smoking and other addictions, nutrition, sports habits, and hobbies questions prepared by the researchers, was applied to the participants.

Results: 300 people were included in the study. When the medical precautions taken by the participants regarding their health were questioned. 68.0% of participants had their blood pressure measured, 69.3% had their blood sugar levels measured, 65.0% had their blood fats measured, and 70.7% had their vision measured, 79.0% got their teeth examined, 31.7% had their hearing measured, and it was observed that 11.0% of them had stool examinations for occult blood.

Conclusions: The results of our study were for individuals between the ages of 30 and 40; revealed that they do not plan for healthy aging. However preparing for a healthy aging period while still young is extremely important in transforming the protections to be taken into a lifestyle.

Keywords: Family Health Center, Aging, Healthy Aging, Lifestyle.

Cite this article as: *Yeltekin Yılmaz S, Görpelioğlu S. Investigation of the knowledge, attitudes and behaviors on active aging of people between 30-40 years: A multi-central cross-sectional study. Arch Curr Med Res. 2023;4(3):137-145*

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INTRODUCTION

Old age is a definition WHO uses for those aged 65 and over. The aging period includes physiological changes as decreasing all physical and mental functions (1). All over the world, with the decrease in infectious diseases and developments in acute and chronic disease treatments, life expectancy is prolonged, and the elderly population is increasing numerically (2). By 2050, the number of older adults worldwide will be twice that of children (3).

Along with the world, the proportion of the elderly population in our country is increasing rapidly. According to 2022 data, life expectancy at birth in Turkey is generally calculated as 75.6 years for men and 81.2 years for women. According to statistical projections, Turkey is a rapidly aging country and ranks second in the aging rate after South Korea. Between 2008 and 2040, an increase of 201% is expected in the elderly population in Turkey. It is predicted that the proportion of the population aged 65 and over, defined as the elderly population, was 8.7% in 2018 and will be 10.2% in 2023, 16.3% in 2040, 22.6% in 2060, and 25.6% in 2080 (4). 43.9% of the elderly population is male, and 56.1% is female. This rate is approximately the same for almost all provinces (5).

The number of years a person expects to live without a health problem that would limit their activities in daily life is called 'healthy life expectancy' (6). Due to chronic degeneration, diseases, and social status changes, as they get older, individuals may become financially and morally dependent on others. Health policies aim at productive, successful, and independent aging (7). Longevity, biological and mental health, cognitive competence, social competence and productivity, personal control, and enjoyment of life are the most basic indicators of successful aging (8). The successful aging of individuals is closely related to their characteristics and the psychosocial, economic, and physiological support services to be provided to them socially (9).

In the concept of successful aging, one of the essential tasks of the individual is to foresee some processes that will be experienced in old age and to prepare mentally, economically, and physically. Therefore, this study reveals the knowledge, attitudes, and behaviors of individuals aged 30-40 about healthy aging.

MATERIALS AND METHODS

The study type, location, and duration

Our study was planned and conducted as a cross-sectional field study to determine knowledge, attitudes, and behaviors about healthy aging in individuals aged 30-40. Our research was carried out at The Health Sciences University Dışkapı Yıldırım Beyazıt Health Application and Research Center, and the data were collected from Family Health Centers in 20 randomly selected provinces from each geographical region between August 1, 2018 and January 31, 2019. As the criteria for inclusion in the study, the conditions of speaking and understanding Turkish between the ages of 30 and 40 were sought. Individuals with cognitive, neurological, and psychiatric disabilities who could not continue to work were excluded from the study. This study was approved by the clinical research Ethics Committee of the University of Health Sciences Turkey, Dışkapı Education and Research Hospital (Date: 07.01.2019, Number: 58/13).

Universe and sample

The population of the study consisted of 12.681.788 individuals between the ages of 30 and 40 who were registered to the population in Turkey as of 06.07.2022 (4). The sample size was 385, with a 95% confidence level and a 5% margin of error. Assuming that the genders are approximately evenly distributed and considering the possible data loss, 400 people, approximately 200 men and 200 women, registered to family health centers, which were selected by simple random sampling method from the provinces selected by simple random sampling method after geographical stratification, formed the sample group. After the geographical stratification, 20 provinces were selected (Adana, Adıyaman, Aksaray, Ankara, Antalya, Bitlis, Bursa, Denizli, Erzincan, Gümüşhane, İstanbul, Kocaeli, Mardin, Mersin, Muğla, Niğde, Şırnak, Trabzon, Urfa, Van). Therefore, the total population of the provinces where the research was 42.318.727, covering 51% of Turkey. However, our research had to be terminated with 300 participants because the responses were not at the expected rate during the data collection period.

Data sources and application of the research

The research data was created by the researchers using a form containing 45 questions created by examining the current literature. The participants in the study questioned

the following: sociodemographic data, chronic illness, drug use, regular health checks, vaccination, economic capabilities, whether they can save, whether they have social security, driving status, social relations, hobbies, sociocultural activities, daily living habits, nutrition and water, their drinking status, whether they do sports or not, whether they live with a family member or not, their perception of the elderly, whether there is an elder in need of care, whether they will have income in old age and whether this income will be sufficient, and where they want to spend their old age. A face-to-face or telephone interview technique was used in the implementation of the questionnaire.

Statistical analysis

In the evaluation of the study findings, it was decided to limit the situations that may affect the preparation for old age by the region of residence, gender, marital status, education level, economic situation, and whether there was social security, and it was accepted that these factors should be independent variables. In the questioning of the dependent variables, it was focused on the extent to which the individuals participating in the study fulfilled the biological, psychological, and socioeconomic conditions that will ensure successful aging.

The data were analyzed with IBM SPSS ver. the package program 21 (Statistical Package for Social Sciences). Continuous variables were expressed as mean±standard deviation, median (minimum and maximum values), and categorical variables were expressed as numbers and percentages. The conformity of the data to the normal distribution was examined with the Kolmogorov-Smirnov test. Differences between categorical variables were examined with chi-square analysis, and Fischer's exact test was used where necessary. In all analyses, $p<0.05$ was considered statistically significant. Since the study was concluded with 300 participants, the G Power 3.1.9.7 program was used for the post hoc power analysis. Type 1 (α) error= 0.05 in the post hoc power analysis performed with the sample number obtained; When Type 2 (1-β) error = 0.2, the power of the research analyzes was found to be 0.99.

RESULTS

The distribution of the people included in the study according to some demographic characteristics is given in Table 1.

Table 1. Some demographic characteristics of the people included in the study (n=300).

Distribution of participants by region (n, %)	Marmara	20(6.7)
	Aegean	22 (7.3)
	Mediterranean	25 (8.3)
	Inner Anatolia	156 (52.0)
	Blacksea	41 (13.7)
	Eastern Anatolia	18 (6.0)
	Southeastern Anatolia	18 (6.0)
Gender (n, %)	Female	167 (55.7)
	Male	133 (44.3)
Age (Mean±SD)	Female	35.32 ± 3.45
	Male	35.12 ± 3.47
	Total	35.23 ± 3.45
Educational status (n, %)	Illiterate	10 (3.3)
	Primary / secondary school	57 (19.0)
	High school	62 (20.7)
	College	171 (57.0)
Number of children (n, %)	None	29 (9.7)
	1	122 (40.7)
	2	104 (34.7)
	3	32 (10.7)
	4	5 (1.7)
	5+	8 (2.6)
Marital status (n, %)	Married	199 (66.3)
	Single	101 (33.7)
Social security (n, %)	There is.	281 (93.7)
	None	19 (6.3)
Economic situation (n, %)	Financial support	47 (15.7)
	Self-sufficient	150 (50.0)
	Accumulation	103 (34.3)

Analysis was done with the chi-square test.

The biological readiness of the people included in the study was evaluated according to the regions they lived in, and it was observed that there was a statistical difference between regions in blood glucose measurement (p=0.008), fat blood measurement (p=0.021), and visual examination (0.035). The most frequent control was a visual examination (70.7%), and the least frequent control

was fecal blood analysis (FBA) (89.0%). The social and economic preparation of the people included in the study were evaluated according to the regions they lived in, and significant differences were found only in the parameters of having an income of one's own in old age (p=0.017), driving a vehicle (p=0.032), and using the internet (p=<0.001). It has been observed that the difference in all three variables is due to the high number of participants in the Central Anatolia region.

The biological readiness of the people included in the study was evaluated according to their genders; it was seen that the rate of having FBA was significantly lower in both genders and that women had FBA significantly more than men among the genders (p=0.010). In addition, the social and economic preparation of the people included in the study was evaluated according to their gender, and it was found that men used more vehicles (p=<0.001), women went to the cinema and theater more (p=0.049), and regularly read books, magazines, and newspapers (p=0.048).

The biological readiness of the subjects included in the study was evaluated according to their marital status, and it was determined that the single subjects used significantly less medication (p=0.030) and had a smear (p=0.035); they did more sports (p=0.002) and received adult vaccines (p=0.031). In addition, the social and economic preparation of the participants was evaluated according to their marital status. No significant difference was found, except that the participation in activities such as puzzle solving and cinema/theatre was higher in married people (both p=<0.001).

The biological readiness of the subjects included in the study was evaluated according to their educational status. As the education level increased, it was determined that the frequency of regular drug use (p=0.017), blood pressure monitoring (p=0.006), blood sugar and blood lipids (p=0.002), vision and oral-dental medical examinations (p=<0.001), and the number of vaccinations increased significantly (p=<0.001) in table 2.

Table 2. The distribution of the biological readiness of the people included in the study according to their educational status

		Educational Status				Total (n, %)	p
		Illiterate (n, %)	Primary/secondary school (n, %)	High school (n, %)	College (n, %)		
Is there any medication you use regularly?	Yes	2 (0.7)	25 (8.3)	12 (4.0)	44 (14.7)	83 (27.7)	**0.017**
	No	8 (2.7)	32 (10.7)	50 (16.7)	157 (52.3)	217 (72.3)	
Have you ever had your blood pressure measured?	Yes	3 (1.0)	32 (10.7)	46 (15.3)	123 (41.0)	204 (68.0)	**0.006**
	No	7 (1.7)	25 (8.3)	16 (5.3)	48 (12.0)	96 (32.0)	
Have you ever had your blood sugar measured?	Yes	3 (1.0)	34 (11.3)	40 (13.3)	131 (43.7)	208 (69.3)	**0.002**
	No	7 (1.7)	23 (7.7)	22 (7.3)	40 (13.3)	92 (30.7)	
Have you ever had your blood fats measured?	Yes	3 (1.0)	29 (9.7)	39 (13.0)	124 (41.3)	195 (65.0)	**0.002**
	No	7 (1.7)	28 (9.3)	23 (7.7)	47 (9.7)	105 (35)	
Have you ever had a vision exam?	Yes	2 (0.7)	29 (9.7)	42 (14)	139 (39.67)	212 (70.7)	**<0.001**
	No	8 (2.7)	28 (9.3)	20 (6.7)	32 (10.7)	88 (29.3)	
Have you ever had a hearing test?	Yes	2 (0.7)	13 (4.3)	17 (5.7)	63 (21)	95 (31.7)	0.149
	No	8 (2.7)	44 (14.7)	45 (15)	108 (36)	205 (683)	
Have you ever had a fecal blood analysis (FBA)?	Yes	1 (0.3)	6 (2.0)	5 (0.7)	21 (7.0)	33 (11.0)	0.236
	No	9 (3.0)	51 (17.0)	57 (19.0)	150 (50.0)	267 (89.0)	
Do you have regular dental check-ups?	Yes	2 (0.7)	36 (12.0)	50 (16.7)	149 (49.7)	237 (79.0)	**<0.001**
	No	8 (2.7)	21 (7.0)	12 (3.0)	22 (7.3)	63 (21.0)	
Have you ever done or had a breast exam? (n=167)	Yes	1 (0.6)	13 (7.8)	7 (4.2)	22 (13.2)	43 (25.7)	0.520
	No	6 (3.6)	26 (15.6)	28 (16.8)	64 (38.3)	124 (74.3)	
Have you ever had a swab taken from your cervix? (n=167)	Yes	0	18 (10.8)	12 (7.2)	37 (22.2)	67 (40.1)	0.108
	No	7 (4.2)	21 (12.6)	23 (13.8)	49 (29.3)	100 (59.9)	
Have you ever had a prostate exam? (n=133)	Yes	0	3 (2.3)	2 (1.5)	3 (2.3)	8 (6.0)	0.185
	No	3 (2.3)	15 (11.3)	25 (18.8)	82 (61.7)	125 (94.0)	
Have you had any vaccinations in the last 5 years?	Yes	3 (1.0)	33 (11.0)	34 (11.3)	122 (40.7)	192 (64.0)	**<0.001**
	No	7 (1.7)	24 (8.0)	28 (9.3)	49 (16.3)	108 (36.0)	
Do you exercise/sport regularly?	Yes	7 (2.3)	31 (10.3)	37 (12.3)	113 (37.7)	188 (62.7)	0.449
	No	3 (1.0)	26 (8.7)	25 (8.3)	58 (19.3)	112 (37.3)	

Analysis was done with the chi-square test and Fischer exact test.

The social and economic readiness of the people included in the study was evaluated according to their educational status; as the level of education increased, a statistically significant increase was observed in having an income of their own in old age (p=<0.001), making an economic investment for old age (p=<0.001), driving a vehicle (p=<0.001), solving puzzles (p=<0.001), and participation in activities such as cinema/theatre (p=<0.001), using the internet (p=<0.001), regularly reading books, magazines, newspapers, etc. (p=<0.001) and having a hobby (p=<0.001) in table 3.

The biological readiness of the people included in the study was evaluated according to their economic status; a statistically significant increase was observed that their economic status as 'I am self-sufficient' showed in terms of visual examination (p=0.037) and FBA analysis (p=0.045) positively; it was determined that there was no significant difference in other parameters. Furthermore, the social and economic preparation of the people included in the study was evaluated according to their economic status, and a significant positive difference was found in the parameters of driving (p=0.006), participating in activities such as weddings/engagement (p=0.028), and having a hobby (p=0.002).

The biological readiness of the people included in the study was evaluated according to their social security status; participants with social security had significantly more measuring blood pressure (p=0.003), blood sugar (p=0.008), blood lipids (p=0.031), visual (p=0.005), oral and dental health examinations (p=<0.001). Furthermore, the social and economic preparation of the people included in the study was evaluated according to their social security status; participants with social security had significantly more income in old age (p=<0.001), driving a vehicle (p=0.012), using the internet (p=<0.001), newspapers, books, and journals regularly, etc. (p=0.026) and having a hobby (p=0.002).

Table 3. Distribution of social and economic readiness of the people included in education status.

		Educational Status				Total (n, %)	p
		Illiterate (n, %)	Primary/secondary school (n, %)	High school (n, %)	College (n, %)		
Will you have your own income in old age?	Yes	4 (1.3)	39 (13.0)	41 (13.3)	154(51.3)	238(79.3)	**<0.001**
	No	6 (2.0)	12 (4.0)	11 (3.7)	6 (2.0)	35 (11.7)	
	May be	0	6 (2.0)	10 (3.3)	11 (3.7)	27 (9.0)	
Are you making an economic investment for your old age?	Yes	6 (2.0)	9 (3.0)	22 (7.3)	104(34.7)	141(47.0)	**<0.001**
	No	4 (1.3)	48 (16.0)	40 (13.3)	67 (22.3)	159(53.0)	
Can you drive?	Yes	4 (1.3)	21 (7.0)	41 (13.7)	156(52.0)	222(74.0)	**<0.001**
	No	6 (2.0)	36 (9.0)	21 (7.0)	15 (3.0)	78 (26.0)	
Can you solve the puzzle?	Yes	4 (1.3)	34 (11.3)	57 (19.0)	147(49.0)	242(80.7)	**<0.001**
	No	6 (2.0)	23 (7.7)	5 (1.7)	24 (8.0)	58 (19.3)	
Do you have friends/friend groups?	Yes	10 (3.3)	52 (17.3)	61 (20.3)	168(56.0)	291(97.0)	0.079
	No	0	5 (1.7)	1 (0.3)	3 (1.0)	9 (3.0)	
Do you work in non-governmental organizations?	Yes	3 (1.0)	3 (1.0)	9 (3.0)	15 (5.0)	30 (10.0)	0.094
	No	7 (2.3)	54 (18.0)	53 (17,7)	156(52.0)	270(90.0)	
Do you go to theater, cinema etc.?	Yes	8 (2.7)	43 (14.3)	58 (19.3)	162 (54)	271(90.3)	**<0.001**
	No	2 (0.7)	14 (4.7)	4 (1.3)	9 (3.0)	29 (9.7)	
Would you attend a wedding/engagement etc.?	Yes	9 (3.0)	52 (17.3)	61 (20.3)	155(51.7)	277(92.3)	0.253
	No	1 (0.3)	5 (2.7)	1 (0.3)	16 (5.3)	23 (7.7)	
Do you use internet?	Yes	6 (2.0)	43 (14.3)	60 (20)	166(55.3)	275(91.7)	**<0.001**
	No	4 (1.3)	14 (4.7)	2 (0.7)	5 (1.7)	25 (8.3)	
Do you regularly read books, magazines, newspapers, etc.?	Yes	0	33 (11.0)	49 (16.3)	151(50.3)	233(77.7)	**<0.001**
	No	10 (3.3)	24 (8.0)	13 (4.3)	20(6.7)	67 (22.3)	
Do you have a hobby?	Yes	4 (1.3)	37 (12.3)	58 (19.3)	160(53.3)	259(86.3)	**<0.001**
	No	6 (2.0)	20 (6.7)	4 (1.3)	11 (3.7)	41 (13.7)	
Do you watch TV regularly?	Yes	8 (2.7)	48 (16,0)	51 (17.0)	119(39.7)	226(75.3)	0.067
	No	2 (0.7)	9 (3.0)	11 (3.7)	52 (17.3)	74 (24.7)	
Where do you plan to spend your old age?	nursing home	0	2 (0.7)	2 (0.7)	11 (3.7)	15 (5.0)	0.238
	my own home	1 (0.3)	8 (2.7)	6 (2.0)	35 (11.7)	50 (16.7)	
	my children's house	7 (2.3)	37 (12.3)	38 (12.7)	79 (26.3)	161(53.7)	
	Others	2 (0.7)	10 (3.3)	16 (5.3)	46 (15.3)	74 (24.7)	

Analysis was done with the chi-square test and Fischer exact test

DISCUSSION

When the results of the study are evaluated in general, individuals between the ages of 30 and 40; revealed that they do not plan for healthy aging. However, considering the statistical significance of readiness for old age, it was observed that women, married people, those with a high level of education, those who are economically self-sufficient, and those with have social security are more biologically, socially, and economically prepared for old age.

Healthy aging is a process that includes biopsychosocial and economic preparation. This process includes the environment in which individuals live, their diet, chronic diseases (10), BMI, drugs used, regular health checks and vaccinations if necessary, drug and alcohol addictions, education levels, regular sports habits, hobbies and leisure activities, marital status, and a healthy aging philosophy. In order to be able to spend this process independently, with the least amount of chronic diseases, with economic competence and preserving a social life, it is necessary to start preparations in the youth years. The process of preparing for old age should begin at the age of 30-40. This study investigated the knowledge, attitudes, behaviors, and preparations of individuals between the ages of 30 and 40 about healthy aging.

As our study data is examined in general, the rate of those who stated that they went to the cinema/theatre among the people included in our study was found to be 90.3%. In a study conducted with individuals over the age of 60 in Mersin, the preference rate of cinema as a leisure time activity in this age group was determined as 14.6% (11). We concluded that this significant difference in our study is due to the age difference between the sample groups and that individuals are less willing to go to the movies as they get older. Likewise, although there are studies suggesting that the habit of reading books decreases as we get older, we thought that more detailed studies should be conducted to reveal the reasons for this (12).

Hypertension awareness in Turkey is 58.1% according to TURDEP-II data (13). In this study, it was determined that 68.0% of the participants had their blood pressure measured. With these results, it was thought that society had a similar sensitivity to the prevention of hypertension in all age groups. The fact that hypertension is a common disease in our society and its diagnosis and treatment are possible in family health centers (14) may explain the reason for the high awareness of hypertension.

According to cancer statistics in Turkey, the rate of breast cancer specific to 30-34 and 35-39 age groups in women is 26.1% and 47.8%, respectively (15). In our study, the rate of self-examination by a physician, which is one of the most important steps in preventing breast cancer, was found to be 25.4%. Tent et al. found the rate of breast self-examination (BSE) to be 66% (16). In a study conducted in Gaziantep, 48.5% of the women included in the study did not know how to do BSE; 21.5% of those who do BSE once a month; 13.7% of them performed BSE at the right time; 25.3% of them believed in the necessity of BSE (17). We think that the low rate in our rates is because our case group is relatively young and does not care enough about BSE.

In our study, the rate of cervical swab applied was found to be 47.3%. In another study conducted in Kütahya, the rate of having pap smears in women was found to be 36.0% (18). In a study conducted in Istanbul, women between 31-40 were the group with the highest awareness of Pappanicolaou test screening compared to women in other age ranges: It has been interpreted that awareness of the pap smear screening is associated with physician information (19). According to these, family physicians could take an active role in the healthy aging by increasing the participation of people in screening programs.

Regular physical exercise protects health in advancing age. The secreted serotonin hormone prevents the depression. Chronic diseases are less common in those who do sports regularly (20). In our study, the rate of those who answered yes to the question "Do you exercise/sports regularly?" was found to be 62.7%. According to the Chronic Diseases Risk Factors study conducted in 2011, it was seen that 87% of women and 77% of men in Turkey do not do enough physical activity (21). It has been determined that 14% of the participants in a group with an average age of 40 in Turkey perform regular physical activity (22). Some differences, such as education levels and occupations of the population in which the study was conducted may explain the difference in the results of the study.

In our study, the rate of internet users was found to be 91.7%. According to the Household Information Technologies Usage Survey conducted by the Turkish Statistical Institute, computer and internet use among individuals aged 16-74 increased from 54.9% and 61.2% in 2016 to 56.6% and 66.8% in 2017 (23). In recent years, the fact that individuals meet in socialization areas such as shopping, education, reading news, reading books, and magazines through the internet explains the high internet

usage. Access to the Internet is associated with economic level and education level (24), which explains the fact that more than 50% of our study population has a bachelor's degree.

When the sociodemographic characteristics of the people included in the study were analyzed according to the regions where they lived, it was observed that there was a statistically significant difference between regions in terms of the number of children, education level, and having social security. In a society, education and social security are two important elements that show well-being and are directly related to healthy aging. As shown in other studies, interregional development disparities remain an important structural problem in Turkey, despite partial and limited improvements (25). For this reason, it is seen that healthy aging is closely related to the regional development of the country in its relationship with sociodemographic characteristics.

According to our study, when the number of children was analyzed by region, a significant difference was found in Southeastern Anatolia. Our result agrees with the fact that the Turkish Demographic and Health Survey found the fertility rate to be quite high in Southeastern Anatolia in 2018 (26). According to the 2016 results of the Family Structure Research conducted by the Turkish Statistical Institute, the rate of those who want to spend their old age with their children was found to be 37.6% (27). Traditionally, having more children in old age is seen as a guaranty of economic security and care in Turkey.

In terms of biological readiness for healthy aging, there were differences between geographical regions in terms of blood sugar and blood fat measurement, visual examination, oral-dental control, and regular exercise. According to this difference, the biological preparation for healthy aging is lower in the Eastern and Southeastern Anatolia regions than in other regions. The low participation, the low health literacy, the low level of education, and the low awareness of periodic health examinations may explain this result in the study in these two regions. In relation to the consistency of the data in our study, it has been observed that as the education level increases, the biological readiness for healthy aging also increases.

Our results were evaluated in terms of gender, and one of our biological preparation questions was 'Have you ever had an FBA analysis?'. Although there is a statistically significant difference in female gender, FBA for both genders was very low (11.0%). In a study conducted with individuals aged 50-70 years in Erzurum, 20.6% of the participants had a FBA test before, 49.3% had a FBA test because the doctor wanted it, and 57.7% had no information about having it done. It was found that 60.9% of the patients without an FBA test for the disease were considering having an FBA test (28). This difference between the two studies was because FBA analysis was performed between the ages of 50 and 70 according to the colorectal cancer screening program, and our study group included individuals aged 30 and 40 (29).

By evaluating their biological readiness according to their marital status, it was determined that being single meant they used significantly less medication, did more sports, were more sensitive about adult vaccination, but less sensitive about having smears taken. According to a study, it was determined that married people aged 70-79 showed more physical activity (30). According to a study conducted in 2021, single people do more physical activity than married people (31). As can be seen from our own study results and literature data, married elderly, and single adults exercise because they have free time, but adult married couples do not exercise because they have more responsibilities. The same was true for solving puzzles and participating in activities such as cinema/theatre. According to our research results, single people are more active in both activities than married ones.

The use of health services is determined by factors such as the purchasing power of the person who will use the service and the possibility of obtaining the services (32). Health insurance of individuals provides this opportunity. It is not expected that the elderly, who have economic problems and are not covered by social security, find solutions to their health problems on their own and meet their health and care expenses (33). Therefore, an important component of healthy aging is having social security in old age. In our study, the fact that people with social security are more ready for old age biologically, socially, and economically is compatible with other studies in the literature (34,35). Consistent with health insurance, increasing income level and its positive effects on health are consistent with other studies in the literature (23-31). In our study, similar results were obtained with other studies, and more positive responses were received from the group receiving support for living in the "I am self-sufficient" and "I am saving" groups in the questions about the biological and socioeconomic preparation processes for old age.

The small population and the fact that the regions of Turkey were not homogeneously included in the study constitute our limitations. The other is that FBA screening is not routine in the 30-40 age group, so low results, and a small number of cases are the limitations of the study.

As a conclusion, being ready for old age biologically, socially, and economically will reduce the frequency of neurodegenerative diseases and the need for care in society by determining how active the aging process will be. In this case, it is especially important to raise awareness of health policies and to raise the education.

Declarations

The authors have no conflicts of interest to declare. The authors declared that this study has received no financial support.

This study was approved by the clinical research Ethics Committee of the University of Health Sciences Turkey, Dışkapı Education and Research Hospital (Date: 07.01.2019, Number: 58/13).

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Archives of Current Medical Research
Arch Curr Med Res 2023;4(3):146-152

Received: 5 June 2023
Revised: 1 July 2023
Accepted: 28 July 2023
DOI: 10.47482/acmr.1309737

ORIGINAL ARTICLE

Retrospective investigation of the relationship between clinical and laboratory parameters and allergy tests in children with allergic rhinitis

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Abstract

Background: It was aimed to investigate the relationship between neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), eosinophil-lymphocyte ratio (ELR), serum total immunoglobulin E (IgE) values and allergy test positivity in patients with allergic rhinitis (AR).

Methods: The study is a descriptive study with a retrospective design. Data on patients aged 10-18 years with a diagnosis of AR were investigated retrospectively. Age, gender, hemogram parameters (leukocyte, eosinophil, lymphocyte, platelet), total IgE values, allergy history and allergy test positivity were evaluated. A p value of less than 0.05 was considered as a statistically significant result.

Results: In the study, the data of 230 pediatric patients with AR were analyzed. The median age of the children was 13 years (10-18). Of the patients 57.4% (n=132) were male, 42.6% (n=98) were female. All laboratory values, except PLR, of the patients with positive allergy test were higher than the patients with negative allergy test. This elevation in WBC, neutrophil, absolute eosinophil, eosinophil percentage, total IgE and ELR values was statistically significant ($p<0.05$). When the cut-off point for ELR was 0.066; sensitivity was 78.8% and specificity was 70.4%. When the cut-off point for total IgE is 134.5; sensitivity was 75.8%, specificity was 74.1% ($p<0.001$)

Conclusions: According to study results, 3 out of every 4 patients with positive allergy test can be detected by ELR and total IgE values. Since allergy tests cannot be performed in every clinic, it is extremely important to evaluate the success of more practical and accessible blood tests in predicting allergy test positivity.

Keywords: Allergic Rhinitis, Children, Allergy Test, Laboratory Parameters.

Cite this article as: *Altaş U, Tunce E, Altaş ZM, Çiçek F, Özkars MY. Retrospective investigation of the relationship between clinical and laboratory parameters and allergy tests in children with allergic rhinitis. Arch Curr Med Res. 2023;4(3):146-152*

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INTRODUCTION

Rhinitis is presented with symptoms such as nasal congestion, runny nose, sneezing, and itching, arising from an underlying inflammatory process and/or a dysfunctional nasal mucosa (1). Allergic rhinitis (AR) causes a significant burden of disease worldwide (2, 3). For this reason; diagnosis, treatment, and follow-up of allergic rhinitis with laboratory parameters are extremely important for the control of the disease.

Allergic rhinitis refers to an immunoglobulin E (IgE)-mediated reaction against allergens that starts clinically from the nasal mucosa (4, 5). In addition to the nasal inflammation observed in allergic rhinitis, there is also a systemic inflammation (6). In patients with AR, early and late allergic responses triggered by allergens are mediated by a number of inflammatory cells. Within minutes of contact with the allergen, IgE-dependent mast cells degranulate and release synthesized inflammatory mediators. TH2 lymphocytes and eosinophils play a role in immunological processes in both nasal and bronchial tissue. Eosinophils are the dominant cells in the chronic inflammation that is the typical feature of the late-phase allergic response (7).

Neutrophils, lymphocytes, and platelets are important blood parameters that play a role in inflammation. Today, these laboratory parameters are used to evaluate many infectious and inflammatory conditions and are easy to apply and accessible (8). There are data showing that these parameters should be evaluated for the diagnosis and follow-up process of allergic rhinitis as in other allergic diseases (9-11).

Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and eosinophil-lymphocyte ratio (ELR) values are calculated by dividing the blood lymphocyte value, respectively. Many studies in the literature have reported that NLR, PLR, and ELR parameters can be used as inflammatory markers in chronic inflammatory diseases (12-14). In a study conducted in pediatric patients diagnosed with allergic rhinitis in the literature; NLR of children with AR was found to be higher than the control group (14). In a study conducted in adult patients with a diagnosis of allergic rhinitis, ELR was reported to be significantly higher than the control group (12). In another similar study, eosinophil values were elevated in pediatric patients having AR when compared with the control group without AR (15).

In our study, we aimed to investigate the relationship between NLR, PLR, ELR, serum total immunoglobulin E (IgE) values that can be measured from peripheral blood, and allergy test positivity in patients with allergic rhinitis.

MATERIALS and METHODS

Study design, type and sample

The study is a descriptive study with a retrospective design. Data on pediatric patients aged 10-18 years with a diagnosis of allergic rhinitis who applied to the Ümraniye Training and Research Hospital Pediatric Allergy and Immunology outpatient clinic between January 2022 and December 2022 were investigated retrospectively from the hospital's database. No sample size was calculated; all patients with allergic rhinitis who applied to our clinic within a year were included in the study.

Measures

Children's sociodemographic characteristics such as age and gender, hemogram parameters (leukocyte, eosinophil, lymphocyte, and platelet), total IgE values, allergy history, and allergy test positivity were evaluated in the study.

The diagnosis of allergic rhinitis was made when at least 2 of the main symptoms of runny nose, nasal congestion, nasal itching, and sneezing were present for more than 1 hour in a day and for at least 2 consecutive days. These findings were questioned in the outpatient clinic examination of the patients, and the diagnosis of allergic rhinitis was made based on the clinical history and physical examination. Allergen-specific IgE test was performed in order to detect allergens in the patients. Skin prick test was also applied to the patients who had negative results for allergen-specific IgE. Allergy test positivity was defined as a positive allergen-specific IgE or skin prick test. Patients who were both negative were defined as the allergy test negative patient group.

Allergic rhinitis is classified according to symptom duration and severity. Patients with AR symptoms lasting less than 4 days a week or less than 4 weeks are classified as having intermittent AR; Those with symptoms lasting more than 4 days per week and longer than 4 weeks were classified as having persistent AR. While AR patients with at least one of the signs of sleep disturbance, impairment in daily activities, recreational and/or sports activities, deterioration in school or work performance, and disturbing symptoms are classified as moderate-severe AR; patients with none of these findings were classified as mild AR (16).

Statistics

The analysis and the recording of the data were performed with SPSS (Statistical Package for Social Sciences for Windows 25.0) program. Descriptive data were represented as median, minimum, maximum values, numbers (n) and percentages (%). The categorical data was analyzed with the chi-square test. Conformity of continuous variables to the normal distribution was investigated with visual (histograms and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Mann Whitney U test was used to compare continuous variables that did not have a normal distribution. The capacity of serum total IgE, ELR, NLR and PLR values in predicting test positivity (skin prick test or specific IgE positivity) analyzed using ROC (Receiver Operating Characteristics) curve analysis. When a significant cutoff value was observed, the sensitivity and specificity were presented. A p value <0.05 was accepted as the significance level.

Ethics

The study was approved by the Health Sciences University Ümraniye Education and Research Hospital Ethics Committee on 11/05/2023 with decision number 140.

RESULTS

In the study, the data of 230 pediatric patients with AR were analyzed. The median age of the children was 13 years (10-18). Of the patients 57.4% (n=132) were male, 42.6% (n=98) were female. When the AR clinic of the patients was evaluated, most of the patients were persistent moderate-severe (38.3%, n=88) (Table 1).

Table 1. Age, gender and disease clinic of the patients

Age (years), median (min-max)	13 (10-18)	
Gender, n (%)	Female	98 (42.6)
	Male	132 (57.4)
Disease clinic, n (%)	Intermittent Mild	58 (25.2)
	Intermittent Moderate-Severe	18 (7.8)
	Persistent Mild	66 (28.7)
	Persistent Moderate-Severe	88 (38.3)

When the allergy test positivity of the patients was evaluated, house dust mite allergy was the most common, followed by cat and pollen allergies, respectively. House dust mite allergy was positive in 66.1% (n=152) of the patients. The percentage of patients with positive cat and pollen allergy tests were 22.6% (n=52) and 13.0% (n=30), respectively. Two patients had cow's milk allergies and 6 had peanut allergies. Inhalant allergen sensitivity was accompanied by all eight food allergy cases. There was no patient with egg allergy. The number of monosensitized cases was 92 (59.7%), and the number of polysensitized cases was 62 (40.3%). The patient's allergy test positivity and laboratory values such as WBC, neutrophil, and eosinophil are shown in Table 2.

Table 2. Laboratory parameters and allergy test positivity of the patients

Laboratory parameters	*Median (min-max)*
WBC (10^3 mm^3)	7600.0 (4600.0-19510.0)
Neutrophil (10^3/uL)	3920.0 (1800.0-14960.0)
Eosinophil (10^3/uL)	260.0 (31.0-2930.0)
Eosinophil (%)	3.4 (0.2-24.1)
Lymphocyte (10^3/uL)	2670.0 (1000.0-5270.0)
Platelet (10^3 mm^3)	298000.0 (209.0-566000.0)
Total IgE (IU/mL)	178.0 (3.0-2472.0)
*Allergy test positivity**	*n (%)*
House dust mite	152 (66.1)
Cat	52 (22.6)
Pollen	30 (13.0)
Cow's milk	2 (0.9)
Peanut	6 (2.6)
Egg	0 (0)
Monosensitized cases	92 (59.7)
Polysensitized cases	62 (40.3)

** Percentages were proportioned to the total number of patients (n=230). WBC:White blood cell, IgE: Immunoglobulin E*

There were 154 (67.0%) patients with positive allergy tests. Of the 154 patients with positive allergy tests, 120 (77.9%) had positive specific IgE test and 34 (22.1%) had a positive skin prick test. Allergy test was negative in 76 patients (33.0%). In the study, AR patients with positive allergy test (allergen specific IgE or skin prick test positive) and allergy test negative test (specific IgE and skin prick test negative) were compared. All laboratory values, except PLR, of the

patients with positive allergy tests were higher than the patients with negative allergy tests. The elevation in WBC, neutrophil, absolute eosinophil, eosinophil percentage, total IgE and ELR values in patients with test positive AR was statistically significant (p<0.05) (Table 3).

Table 3. Laboratory values of patients with and without allergy test positivity

	Test Positive AR (n=154)	Test Negative AR (n=76)	P value
	Median (min-max)	Median (min-max)	
WBC (10^3 mm^3)	7995.0 (4600.0-19510.0)	7270.0 (5040.0-11100.0)	0.009
Neutrophil (10^3/uL)	4075.0 (1800.0-14960.0)	3780.0 (2430.0-7840.0)	0.048
Eosinophil (10^3/uL)	330.0 (40.0-2930.0)	140.0 (31.0-870.0)	<0.001
Eosinophil (%)	4.2 (0.3-24.1)	2.0 (0.2-10.6)	<0.001
Lymphocyte (10^3/uL)	2700.0 (1000.0-5270.0)	2560.0 (1340.0-3980.0)	0.981
Platelet (10^3 mm^3)	302000.0 (209.0-474000.0)	283000.00 (216000.0-566000.0)	0.475
Total IgE (IU/mL)	248.0 (15.0-2472.0)	31.0 (3.0-882.0)	<0.001
NLR	1.5 (0.7-6.1)	1.3 (0.9-3.3)	0.068
PLR	110.8 (0.08-220.5)	110.9 (62.3-191.0)	0.806
ELR	0.13 (0.02-0.81)	0.05 (0.01-0.49)	<0.001

WBC:White blood cell, AR:Allergic rhinitis, IgE: Immunoglobulin E, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ELR:Eosinophil-lymphocyte ratio

When the relationship between disease severity and laboratory parameters was examined, absolute eosinophil, eosinophil (%) and ELR values were significantly lower in patients with moderate-severe AR (p=0.023, p=0.006, p=0.008, respectively) (Table 4).

Table 4. Relationship between disease severity and laboratory parameters

	Mild AR (n=124)	Moderate-Severe AR (n=106)	P value
	Median (min-max)	Median (min-max)	
WBC (10^3 mm^3)	7550,0 (4680.0-16230.0)	7895.0 (4600.0-19510.0)	0.208
Neutrophil (10^3/uL)	3800.0 (2220.0-12700.0)	4200.0 (1800.0-14960.0)	0.216
Eosinophil (10^3/uL)	300.0 (31.0-2930.0)	200.0 (50.0-2930.0)	0.023
Eosinophil (%)	3.9 (0.3-12.5)	2.3 (0.2-24.1)	0.006
Lymphocyte (10^3/uL)	2520.0 (1000.0-5270.0)	2710.0 (1550.0-4400.0)	0.066
Platelet (10^3 mm^3)	295000.0 (209.0-474000.0)	304500.00 (212000.0-566000.0)	0.121
Total IgE (IU/mL)	223.0 (11.0-1802.0)	148.5 (3.0-2472.0)	0.065
NLR	1.5 (0.8-6.1)	1.5 (0.7-4.6)	0.907
PLR	110.8 (0.08-220.5)	110.0 (62.3-189.3)	0.775
ELR	0.13 (0.01-0.80)	0.07 (0.02-0.81)	0.008

WBC:White blood cell, AR:Allergic rhinitis, IgE: Immunoglobulin E, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ELR:Eosinophil-lymphocyte ratio

ROC analysis was performed to evaluate the prediction of allergy test positivity by NLR, PLR, ELR and total IgE values. The area under the curve was 0.592, 0.499, 0.784 and 0.794 for NLR, PLR, ELR and total IgE values, respectively (Table 5).

Table 5. ROC analysis of NLR, PLR, ELR and total IgE values

Parameters	Area Under Curve	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
NLR	0.592	0.049	0.503	0.681
PLR	0.499	0.990	0.410	0.589
ELR	0.784	<0.001	0.709	0.858
Total IgE	0.794	<0.001	0.715	0.872

ROC: Receiver Operating Characteristics, IgE: Immunoglobulin E, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ELR:Eosinophil-lymphocyte ratio

Since the area under the curve is sufficient for ELR and total IgE; the cut-off point for predicting allergy test positivity of ELR and total IgE values was analyzed by ROC analysis. When the cut-off point for ELR is 0.066; sensitivity was 78.8% and specificity was 70.4%. When the cut-off point for total IgE is 134.5; sensitivity was 75.8%, specificity was 74.1% (p<0.001) (Figure 1).

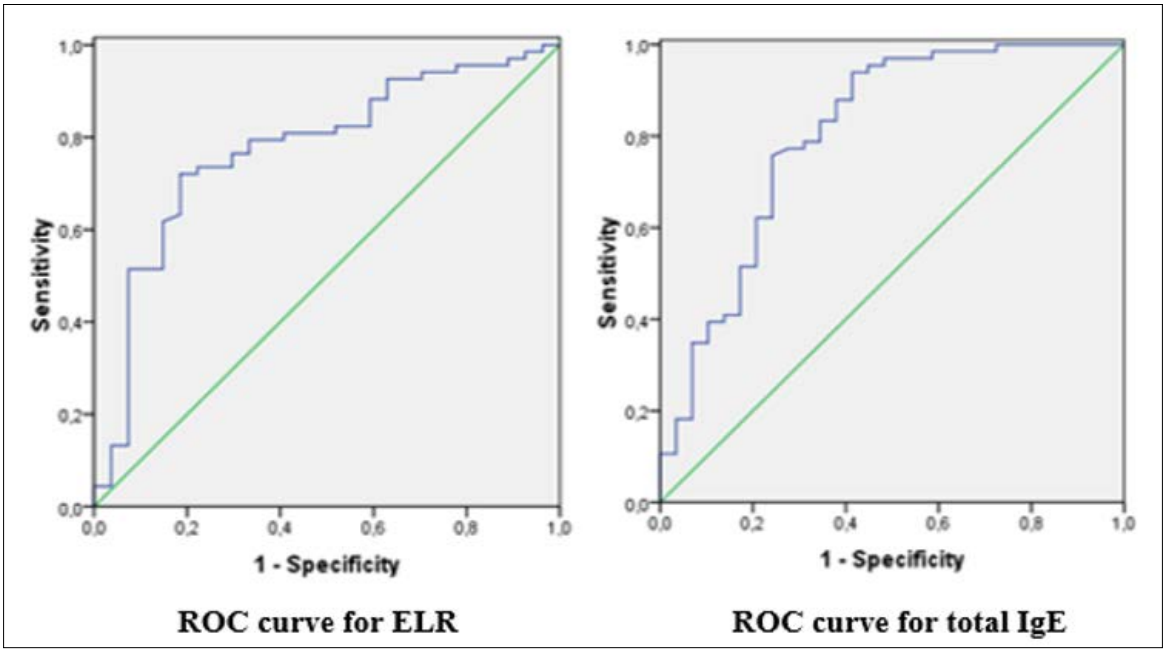

Figure 1. ROC curve for ELR and total IgE

DISCUSSION

In cases where inflammation accompanies chronic diseases, an increase in laboratory parameters indicating inflammation in the blood can be observed in patients. Easily accessible and practical tests such as complete blood count are used in the follow-up of many diseases. Evaluation of complete blood count parameters in AR patients and the level of NLR, ELR, and PLR parameters that can be evaluated with these parameters will provide practicality in disease management. In the study carried out in this context; the relationship between laboratory parameters and allergy test positivity was evaluated in AR, which is one of the allergic diseases accompanied by inflammation.

Environmental allergens enter the body through the upper respiratory tract. For this reason, the nasal mucosa is exposed to many environmental allergens. Aeroallergens such as house dust mites and pollens are often responsible for the pathogenesis of allergic respiratory diseases such as asthma and allergic rhinitis (17). When allergy test positivity was evaluated in AR patients in our study, house dust mite tests was the most common, followed by cat and pollen allergy tests, respectively. Similarly, in the literature, house dust mite allergy sensitivity has been observed most frequently in pediatric patients with allergic rhinitis (18). In studies conducted in our country, sensitivity to house dust mite was found most frequently in children (19-21).

In a study conducted in our country, the eosinophil levels were significantly increased in AR patients, and lymphocyte levels were low in children with AR. In the same study, it was reported that ELR could be used in the diagnosis and follow-up of pediatric AR patients (22). In our study, all laboratory values of patients with positive allergy test were higher than those with negative allergy test, except PLR. This elevation in WBC, neutrophil, absolute eosinophil, eosinophil percentage, total IgE and ELR values were statistically significant. In the literature, it has been reported that blood eosinophil and total IgE values are high in AR patients (23). Eosinophils are the most dominant cells in the pathogenesis of allergic inflammation. Eosinophils are elevated in blood and nasal secretions of atopic individuals (12). IgE release is also seen during inflammatory processes in allergic diseases (24). For these reasons, higher eosinophils and total IgE are expected in patients with a positive allergy test.

Studies in the literature have shown that eosinophilia is associated with allergen sensitivity and can be used as a sensitivity marker (12, 25). The number of studies that set a cut-off point for predicting allergen sensitivity is limited in the literature. In this context, in our study, ROC analysis was used to determine the cut-off point in predicting allergy test positivity for ELR and total IgE values. In our study, when the cut-off point for ELR was 0.066; sensitivity was 78.8% and specificity was 70.4%. For Total IgE, when the cut-off point was 134.5; sensitivity was 75.8% and specificity was 74.1%. These results can be interpreted as the ELR and total IgE values of approximately 3 out of every 4 patients with positive allergy tests are above the cut-off points of 0.066 and 134.5, respectively. In a study conducted in our country, when the ELR was over 0.09 in predicting allergen sensitivity, the sensitivity was reported as 61.8% and the specificity as 73.3% (26). In a study conducted in our country in adult AR patients, sensitivity and specificity were reported as 76.6% and 69.4%, respectively, when ELR was above 0.067 (12). The fact that the ELR cut-off point, which we found in predicting allergen sensitivity in our study, was similar to the literature shows that ELR can be used as a marker to predict allergy test positivity.

Strengths and limitations

Studies evaluating the relationship between complete blood count parameters and total IgE values, as well as NLR, PLR, ELR parameters, and allergy test positivity in pediatric patients with a diagnosis of allergic rhinitis are limited in the literature. One of the strengths of our study is that it makes an important contribution to the literature in this field. Another strength of our study is that we present data with our ROC analysis showing that eosinophil and total IgE values can be evaluated with a cutoff value in predicting allergy test positivity. In addition to the strengths of our study, it was conducted in a single center creating a limitation in terms of the generalizability of the results. Besides, the absence of a healthy control group in the study also creates a limitation.

Conclusions

Evaluation of laboratory parameters is extremely important in the diagnosis and follow-up of AR patients. In our study, laboratory parameters of pediatric patients with AR were evaluated. WBC, neutrophil, absolute eosinophil, eosinophil percentage, total IgE and ELR values were statistically significantly higher in patients with positive allergy tests. In addition, in the ROC analysis performed to evaluate the prediction of allergy test positivity by laboratory values; at a cut-off value of 0.066 for ELR,

the sensitivity was 78.8% and the specificity was 70.4%. When the cut-off point for Total IgE is 134.5; sensitivity was 75.8% and specificity was 74.1%. According to these results, 3 out of every 4 patients with positive allergy tests can be detected by ELR and total IgE values. Since allergy tests cannot be performed in every clinical center, it is extremely important to evaluate the success of more practical and accessible blood tests in predicting allergy test positivity. It may be beneficial for risky patients to take general allergen precautions against possible allergens until they have an allergy test. In light of our study results, large-sample and multicenter studies should be planned to evaluate the prediction of inflammatory markers for allergy test positivity in AR patients.

Declarations

The authors have no conflicts of interest to declare. The authors declared that this study has received no financial support.

This study was approved by the University of Health Sciences Turkey, Ümraniye Education and Research Hospital Ethics Committee (Date: 11/05/2023, Number: 140)

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Archives of Current Medical Research
Arch Curr Med Res 2023;4(3):153-177

Received: 28 July 2023
Revised: 26 August 2023
Acccepted: 25 September 2023
DOI: 10.47482/acmr.1333906

ORIGINAL ARTICLE

Determining the turnaround time in a newly established biochemistry laboratory

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Abstract

Background: The aim of our study was to compare the turnaround times at the central biochemistry laboratory of Etlik City Hospital in terms of time and between clinics and to reveal the reasons for the variations in these times.

Methods: The time of acceptance of the samples to Etlik City Hospital Central Biochemistry Laboratory and the time of confirmation of the results were noted and the difference between these two times was calculated.

Results: Delay rates were significantly different between patients hospitalized in October, November and December 2022 (P<0.001). Delay rates for troponin tubes were significantly different between patients hospitalized in October, November and December (P<0.001). In the emergency department, the highest delay rate was 73.8% for troponin and the lowest was 12.1% for hormone, regardless of time. The highest and the lowest delay rate in the outpatient clinic was observed for biochemistry (43.2%) and complete blood count (3.7%), respectively. When the tubes were compared for inpatient clinic, the highest delay rate in the emergency department was observed for troponin.

Conclusions: The expected benefits of our study are to clearly demonstrate the rapid turnaround times of newly established biochemistry laboratories in large hospitals and centers, to show the variations of these times between clinics, to increase clinicians' satisfaction with the laboratory, to reduce costs by shortening hospital stays and to develop measures that can be adopted.

Keywords: Turnaround Time, City Hospital, Laboratory, Efficiency.

Cite this article as: *Öztürk A, Demirci G. Determining the turnaround time in a newly established biochemistry laboratory. Arch Curr Med Res. 2023;4(3):153-177*

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INTRODUCTION

Laboratory turnaround time (LRT) is the time between the acceptance of a sample in the laboratory and the availability of an approved report. However, the definition of TAT is different between various studies and scientific institutions. The clinician considers TAT as the time between an order and approval of the specialist. On the other hand, laboratory specialists consider TAT as the time between the acceptance of the sample and the opinion of the specialist (1). Clinicians often use TAT when evaluating laboratory performance. The reason for this is that clinicians need fast turnaround times to diagnose their patients quickly, administer the right treatment within the shortest possible time and discharge their inpatient clinic as soon as possible. Another benefit of faster TAT times is to reduce costs by shortening hospitalization and length of stay. Prolonged turnaround times also increase the laboratory workload. For patient satisfaction and laboratory quality, it is important to frequently evaluate TAT times and implement appropriate measures (2-4).

There are many parameters that affect TAT and are beyond the authority of the laboratory. Such non-analytical delays can be responsible for up to 96% of total TAT (5-7). Clinical laboratories classically have limited analytical and technical quality debates and focus on uncertainty and inaccuracy targets. At the same time, clinicians evaluate the "quality of the laboratory" for fast, reliable and efficient service delivered at low cost. To illustrate this, timeliness is one of the key attributes prepared to be assessed as one of the key quality steps. The TAT times described above are also one of the most important indicators (8-11).

TAT is a laboratory service that is used by many clinicians to assess the quality of the laboratory. According to Lundberg, which evaluates the total testing cycle, the following steps need to be completed for a test to be performed in the laboratory: ordering, identification, processing, preparation, analysis, reporting, interpretation and action (12-15). Due to the limitations and difficulties of controlling all the steps mentioned above, most laboratories assess TAT with in-laboratory activities.

Delays in turnaround times and complaints of patients and clinicians increase the workload of the laboratory and the work stress of laboratory staff. However, identifying the causes of these delays can lead to problem solving and efficient workflow, ultimately increasing the satisfaction and motivation of patients, clinicians and laboratory staff.

The aim of our study was to compare the turnaround times on a daily, weekly and monthly basis and between clinics (emergency department, inpatient, outpatient) in the newly established central biochemistry laboratory of Etlik City Hospital, which was recently opened and serves as a large center, and to reveal the reasons for the variations between these times. We also believe that our study will contribute to the development of solutions that can further shorten TAT times.

MATERIALS AND METHODS

Patients

No specific disease group was included in our study. All samples for which test order and result times were determined were included in the study. The acceptance times and the approval times of the results of the samples that were accepted to the Central Biochemistry Laboratory of Etlik City Hospital were noted and the difference between these two times was calculated. These times were evaluated separately according to time and clinics. The TAT of the samples studied in October, November and December 2022 were calculated. The reason for choosing these first 3 months is that our laboratory is in its early stages of establishment and we want to be able to clearly observe both positive and negative rapid changes in TAT. No test results were analyzed except for the timing of the samples. Our study is a retrospective observational study.

Laboratory analysis

Tests for biochemistry, hormones and troponin tubes are performed on the Roche Cobas c 702 (Roche Diagnostics GmbH, Mannheim, Germany) (up to 2,000 tests/hour) and Roche Cobas c 801 (Roche Diagnostics GmbH, Mannheim, Germany) (up to 300 tests/hour), complete blood count analysis on the XN-1000 (Sysmex corp. Kobe, Japan) (up to 100 tests/hour) and urinalysis studies are performed on the Roche cobas 6500 (Roche Diagnostics GmbH, Mannheim, Germany) urine analyzer series (cobas u 601 urine analyzer system cobas u 701 microscopy) (up to 240 samples per hour). Table 1 shows the target times used in our laboratory.

Table 1. Our target times according to type of tubes and clinics

Tube type	Emergency (minutes)	Outpatient-Inpatient (minutes)
Biochemistry	90	180
Complete blood count	45	120
Hormone	120	240
Coagulation	60	120
Urınalysis	45	90
Troponin	60	120

Inclusion criteria

Inclusion criteria include that the test is requested by the clinician at Etlik City Hospital, accepted by our laboratory and confirmed by the biochemist after performing the test. Therefore, we do not have a specific age range or gender criteria.

Exclusion criteria

Samples that were requested by the clinician but not accepted, samples that were not analysed even if accepted and samples that were not approved by the biochemist even if analysed were excluded from our study.

Statistical analysis

Statistical analyses of the data obtained in the study were performed using the SPSS (Version 22.0, Spss Inc, Chicago, IL, USA) package program. Descriptive statistics of categorical variables were reported using number (n) and percentage (%). Descriptive statistics of numerical data were reported using mean, standard deviation (SD), median and quartiles: first quarter (Q1) and third quarter (Q3). The chi-square test was used to compare proportions of categorical variables between study groups and to investigate associations based on sample sizes in cross-tabulations. The level of statistical significance was set at $P<0.05$.

RESULTS

The statistical analyses were performed according to months (October, November, December), service type (emergency, outpatient, inpatient) and tube types (biochemistry, complete blood count, hormone, coagulation, complete urinalysis, troponin) and the rates of deviation from the target values were compared according to months, service type and tube types.

Table 2, Table 3 and Table 4 present the descriptive statistics of turnaround times according to tube types in the emergency department, outpatient clinic and inpatient clinic in October, November and December, respectively. For each procedure, all turnaround times were subtracted from the target times to determine if there were delays, and the rates were statistically compared according to months, service type and tube types.

Table 2. Descriptive statistics of turnaround times according to the types of tubes in the Emergency, İnpatient clinic and Outpatient clinic in October

Service type	Tube	N	Mean (minutes)	SD	Q1	Median	Q3
Emergency	**Biochemistry**	6767	96.05	525.55	48	66	99
	Complete blood count	6473	32.96	517.09	11	19	31
	Hormone	739	76.96	40.47	52	66	90
	Coagulation	2347	62.92	420.07	36	47	64
	Urinalysis	3184	54.36	62.97	28	44	66
	Troponin	391	184.50	1833.9	55	71	94
Outpatient	**Biochemistry**	23073	248.73	1104.4	121	169	233
	Complete blood count	17274	77.46	782.75	30	47	73
	Hormone	16699	465.79	1804.8	153	223	341
	Coagulation	4703	105.73	645.65	62	84	113
	Urinalysis	6667	121.32	653.03	63	92	127
	Troponin	5165	142.56	514.37	92	119	159
Inpatient	**Biochemistry**	10340	240.83	1369.8	69	109	188
	Complete blood count	9335	68.26	1149.1	20	32	52
	Hormone	1729	770.85	3154.6	146.5	274	556.5
	Coagulation	4198	74.89	51.77	47	63	90
	Urinalysis	1479	113.42	1323	32	54	86
	Troponin	1368	115.75	167.22	64	87.5	129

Table 3. Descriptive statistics of turnaround times according to the types of tubes in the Emergency, İnpatient clinic and Outpatient clinic in November

Service type	Tube	N	Mean (minutes)	SD	Q1	Median	Q3
Emergency	Biochemistry	13178	98.75	102.62	58	82	117
	Complete blood count	12238	36.61	275.94	15	26	42
	Hormone	1999	85.76	51.62	57	74	102
	Coagulation	5345	60.51	47.11	36	50	71
	Urinalysis	5759	56.54	161.17	29	44	68
	Troponin	1001	170.25	863.21	63	84	116
Outpatient	Biochemistry	44309	240.19	690.45	119	168	240
	Complete blood count	35902	48.90	222.83	25	37	57
	Hormone	32998	448.25	1260.2	132	188	277
	Coagulation	9065	93.88	282.91	57	74	99
	Urinalysis	14043	75.68	279.09	44	61	85
	Troponin	10151	125.79	294.26	86	108	135
Inpatient	Biochemistry	23509	239.55	947.75	86	130	202
	Complete blood count	21519	57.60	277.04	27	44	67
	Hormone	3909	760.04	1902.1	124	220	425.5
	Coagulation	9573	80.24	77.83	49	68	94
	Urinalysis	2991	62.88	225.42	31	49	75
	Troponin	2877	176.18	858.30	85	110	148

Table 4. Descriptive statistics of turnaround times according to the types of tubes in the Emergency, İnpatient clinic and Outpatient clinic in December

Service type	Tube	N	Mean (minutes)	SD	Q1	Median	Q3
Emergency	Biochemistry	14653	89.84	346.9	51	67	94
	Complete blood count	14527	35.98	239.88	17	28	43
	Hormone	2218	79.55	65.35	56	70	90
	Coagulation	6874	59.23	48.82	36	48	67
	Urinalysis	6520	47.58	28.84	27	41	62
	Troponin	1233	116.64	742.86	60	80	107
Outpatient	Biochemistry	50866	213.12	448.96	119	164	225
	Complete blood count	42946	43.84	72.91	23	33	52
	Hormone	39550	402.5	1148.8	128	172	241
	Coagulation	10763	76.72	68.29	55	68	90
	Urinalysis	15925	63	143.74	41	55	75
	Troponin	12073	101.85	94.14	73	91	115
Inpatient	Biochemistry	26518	194.04	654.08	73	110	180
	Complete blood count	26625	53.16	153.2	28	41	63
	Hormone	4911	431.2	1537.6	86	138	231
	Coagulation	12508	84.55	101.67	50	66	95
	Urinalysis	3321	53.36	74.32	30	46	67
	Troponin	3659	138.04	520.66	82	103	132

Statistical findings regarding the comparison of delay rates in the emergency, outpatient and inpatient clinics in October, November and December for all tubes are presented in Table 5. Delay rates differed significantly among inpatient clinic in October, November and December (P<0.001). In October, the highest delay rate was observed in samples from outpatient clinics and the lowest delay rate was observed in samples from inpatient clinic. In November, the highest delay rate was observed in samples from emergency departments and the lowest delay rate was observed in samples from inpatient clinic. In December, the highest delay rate was observed in samples from emergency departments and the lowest delay rate was observed in samples from inpatient clinic.

Table 5. Statistical findings on the comparison of the delay rates experienced in the Emergency Department, Outpatient clinic and İnpatient clinic in October, November and December for all departments

			Delay		Total	*P*
			No	Yes		
October	**Emergency**	n	14592	5309	19901	<0.001
		%	73.3	26.7	100	
	Outpatient Clinic	n	47807	25774	73581	
		%	65,0	35.0	100	
	Inpatient	n	23214	5235	28449	
		%	81.6	18.4	100	
	Total	n	85613	36318	121931	-
		%	70.2	29.8	100	
November	**Emergency**	n	25639	13881	39520	<0.001
		%	64.9	35.1	100	
	Outpatient Clinic	n	106598	39870	146468	
		%	72.8	27.2	100	
	Inpatient	n	51518	12860	64378	
		%	80.0	20.0	100	
	Total	n	183755	66611	250366	-
		%	73.4	26.6	100	
December	**Emergency**	n	32677	13348	46025	<0.001
		%	71.0	29.0	100	
	Outpatient Clinic	n	134223	37900	172123	
		%	78.0	22.0	100	
	Inpatient	n	65270	12272	77542	
		%	84.2	15.8	100	
	Total	n	232170	63520	295690	-
		%	78.5	21.5	100	

Statistical findings that compare the delay rates in October, November and December for all inpatient clinic are presented in Table 6. The delay rates in October, November and December are significantly different according to tube types (P<0.001). In October, the highest delay rate was observed for Complete Urinalysis and the lowest delay rate was observed for Complete Blood Count. In November, the highest delay rate was found for biochemistry and troponin, while the lowest delay rate was for complete blood count. In December, the highest delay rate was for biochemistry and the lowest for complete blood count.

Table 6. Statistical findings for the comparison of delay rates in October, November and December for all tubes

			Delay		Total	*P*
			No	Yes		
October	Biochemistry	n	25236	14944	40180	<0.001
		%	62.8	37.2	100	
	Complete blood count	n	30869	2213	33082	
		%	93.3	6.7	100	
	Hormone	n	10603	8564	19167	
		%	55.3	44.7	100	
	Coagulation	n	9100	2148	11248	
		%	80.9	19.1	100	
	Urinalysis	n	6077	5253	11330	
		%	53.6	46.4	100	
	Troponin	n	3728	3196	6924	
		%	53.8	46.2	100	
	Total	n	85613	36318	121931	-
		%	70.2	29.8	100	
November	Biochemistry	n	48644	32352	80996	<0.001
		%	60.1	39.9	100	
	Complete blood count	n	64796	4863	69659	
		%	93.0	7.0	100	
	Hormone	n	25714	13192	38906	
		%	66.1	33.9	100	
	Coagulation	n	19585	4398	23983	
		%	81.7	18.3	100	
	Urinalysis	n	16581	6212	22793	
		%	72.7	27.3	100	
	Troponin	n	8435	5594	14029	
		%	60.1	39.9	100	
	Total	n	183755	66611	250366	-
		%	73.4	26.6	100	
December	Biochemistry	n	60090	31947	92037	<0.001
		%	65.3	34.7	100	
	Complete blood count	n	78707	5391	84098	
		%	93.6	6.4	100	
	Hormone	n	35374	11305	46679	
		%	75.8	24.2	100	
	Coagulation	n	25120	5025	30145	
		%	83.3	16.7	100	
	Urinalysis	n	20621	5145	25766	
		%	80.0	20.0	100	
	Troponin	n	12258	4707	16965	
		%	72.3	27.7	100	
	Total	n	232170	63520	295690	-
		%	78.5	21.5	100	

Statistical findings regarding the comparison of delay rates according to tube types in October, November and December at the emergency department are presented in Table 7. Delay rates according to tube types were significantly different in October, November and December at the emergency department (P<0.001). In October, the highest delay rate was observed for troponin and the lowest delay rate was observed for complete blood count. In November, the highest delay rate was seen for troponin and the lowest delay rate was seen for hormone. In December, the highest delay rate was seen for troponin and the lowest delay rate was seen for hormones.

Table 7. Statistical findings for the comparison of delay rates according to the type tubes in October, November and December for the emergency department

			Delay		Total	*P*
			No	Yes		
October	Biochemistry	n	4747	2020	6767	<0.001
		%	70.1	29.9	100	
	Complete blood count	n	5725	748	6473	
		%	88.4	11.6	100	
	Hormone	n	652	87	739	
		%	88.2	11.8	100	
	Coagulation	n	1651	696	2347	
		%	70.3	29.7	100	
	Urinalysis	n	1684	1500	3184	
		%	52.9	47.1	100	
	Troponin	n	133	258	391	
		%	34.0	66.0	100	
	Total	n	14592	5309	19901	-
		%	73.3	26.7	100	
November	Biochemistry	n	7654	5524	13178	<0.001
		%	58.1	41.9	100	
	Complete blood count	n	9577	2661	12238	
		%	78.3	21.7	100	
	Hormone	n	1710	289	1999	
		%	85.5	14.5	100	
	Coagulation	n	3479	1866	5345	
		%	65.1	34.9	100	
	Urinalysis	n	2987	2772	5759	
		%	51.9	48.1	100	
	Troponin	n	232	769	1001	
		%	23.2	76.8	100	
	Total	n	25639	13881	39520	-
		%	64.9	35.1	100	
December	Biochemistry	n	10613	4040	14653	<0.001
		%	72.4	27.6	100	
	Complete blood count	n	11433	3094	14527	
		%	78.7	21.3	100	
	Hormone	n	1995	223	2218	
		%	89.9	10.1	100	
	Coagulation	n	4665	2209	6874	
		%	67.9	32.1	100	
	Urinalysis	n	3648	2872	6520	
		%	56.0	44.0	100	
	Troponin	n	323	910	1233	
		%	26.2	73.8	100	
	Total	n	32677	13348	46025	-
		%	71.0	29.0	100	

Statistical findings regarding the comparison of delay rates according to tube types in October, November and December for outpatient clinic are presented in Table 8. For the outpatient clinic, the delay rates according to tube types in October, November and December were significantly different (P<0.001). In October, the highest delay rate was for complete urinalysis and the lowest delay rate was for complete blood count. In November, the highest delay rate was for biochemistry and the lowest for complete blood count. In December, the highest delay rate was for biochemistry and the lowest for complete blood count.

Table 8. Statistical findings for the comparison of delay rates for outpatient clinic in October, November and December according to types of tubes

			Delay		Total	*P*
			No	Yes		
October	Biochemistry	n	12914	10159	23073	<0.001
		%	56.0	44.0	100	
	Complete blood count	n	16113	1161	17274	
		%	93.3	6.7	100	
	Hormone	n	9182	7517	16699	
		%	55.0	45.0	100	
	Coagulation	n	3723	980	4703	
		%	79.2	20.8	100	
	Urinalysis	n	3247	3420	6667	
		%	48.7	51.3	100	
	Troponin	n	2628	2537	5165	
		%	50.9	49.1	100	
	Total	n	47807	25774	73581	-
		%	65.0	35.0	100	
November	Biochemistry	n	24660	19649	44309	<0.001
		%	55.7	44.3	100	
	Complete blood count	n	34805	1097	35902	
		%	96.9	3.1	100	
	Hormone	n	21911	11087	32998	
		%	66.4	33.6	100	
	Coagulation	n	7695	1370	9065	
		%	84.9	15.1	100	
	Urinalysis	n	11062	2981	14043	
		%	78.8	21.2	100	
	Troponin	n	6465	3686	10151	
		%	63.7	36.3	100	
	Total	n	106598	39870	146468	-
		%	72.8	27.2	100	
December	Biochemistry	n	29554	21312	50866	<0.001
		%	58.1	41.9	100	
	Complete blood count	n	41687	1259	42946	
		%	97.1	2.9	100	
	Hormone	n	29601	9949	39550	
		%	74.8	25.2	100	
	Coagulation	n	9901	862	10763	
		%	92.0	8.0	100	
	Urinalysis	n	13981	1944	15925	
		%	87.8	12.2	100	
	Troponin	n	9499	2574	12073	
		%	78.7	21.3	100	
	Total	n	134223	37900	172123	-
		%	78.0	22.0	100	

Statistical findings regarding the comparison of delay rates for inpatient clinic in October, November and December according to tube types are presented in Table 9. The delay rates for inpatient clinic according to tube types in October, November and December were significantly different (P<0.001). In October and November, the highest delay rate was hormone and the lowest delay rate was complete blood count. In December, the highest and lowest delay rates were found for troponin and complete blood count, respectively.

Table 9. Statistical findings for the comparison of delay rates for inpatient clinic in October, November and December according to types of tubes

			Delay		Total	*P*
			No	Yes		
October	Biochemistry	n	7575	2765	10340	<0.001
		%	73.3	26.7	100	
	Complete blood count	n	9031	304	9335	
		%	96.7	3.3	100	
	Hormone	n	769	960	1729	
		%	44.5	55.5	100	
	Coagulation	n	3726	472	4198	
		%	88.8	11.2	100	
	Urinalysis	n	1146	333	1479	
		%	77.5	22.5	100	
	Troponin	n	967	401	1368	
		%	70.7	29.3	100	
	Total	n	23214	5235	28449	-
		%	81.6	18.4	100	
November	Biochemistry	n	16330	7179	23509	<0.001
		%	69.5	30.5	100	
	Complete blood count	n	20414	1105	21519	
		%	94.9	5.1	100	
	Hormone	n	2093	1816	3909	
		%	53.5	46.5	100	
	Coagulation	n	8411	1162	9573	
		%	87.9	12.1	100	
	Urinalysis	n	2532	459	2991	
		%	84.7	15.3	100	
	Troponin	n	1738	1139	2877	
		%	60.4	39.6	100	
	Total	n	51518	12860	64378	-
		%	80.0	20.0	100	
December	Biochemistry	n	19923	6595	26518	<0.001
		%	75.1	24.9	100	
	Complete blood count	n	25587	1038	26625	
		%	96.1	3.9	100	
	Hormone	n	3778	1133	4911	
		%	76.9	23.1	100	
	Coagulation	n	10554	1954	12508	
		%	84.4	15.6	100	
	Urinalysis	n	2992	329	3321	
		%	90.1	9.9	100	
	Troponin	n	2436	1223	3659	
		%	66.6	33.4	100	
	Total	n	65270	12272	77542	-
		%	84.2	15.8	100	

Statistical findings regarding the comparison of the delay rates for biochemistry tubes in October, November and December according to the services are presented in Table 10. The delay rates for biochemistry tubes in October, November and December were significantly different among inpatient clinic (P<0.001). In October, November and December, the highest delay rate was observed in outpatient blood count and the lowest delay rate was observed in inpatient blood count.

Table 10. Statistical findings for the comparison of delay rates in biochemistry tubes in October, November and December according to services

			Delay		Total	*P*
			No	Yes		
October	**Emergency**	n	4747	2020	6767	<0.001
		%	70.1	29.9	100	
	Outpatient	n	12914	10159	23073	
		%	56.0	44.0	100	
	Inpatient	n	7575	2765	10340	
		%	73.3	26.7	100	
	Total	n	25236	14944	40180	-
		%	62.8	37.2	100	
November	**Emergency**	n	7654	5524	13178	<0.001
		%	58.1	41.9	100	
	Outpatient	n	24660	19649	44309	
		%	55.7	44.3	100	
	Inpatient	n	16330	7179	23509	
		%	69.5	30.5	100	
	Total	n	48644	32352	80996	-
		%	60.1	39.9	100	
December	**Emergency**	n	10613	4040	14653	<0.001
		%	72.4	27.6	100	
	Outpatient	n	29554	21312	50866	
		%	58.1	41.9	100	
	Inpatient	n	19923	6595	26518	
		%	75.1	24.9	100	
	Total	n	60090	31947	92037	-
		%	65.3	34.7	100	

Statistical findings regarding the comparison of delay rates for complete blood count tubes of patients hospitalized in October, November and December are presented in Table 11. The delay rates for complete blood count tubes were significantly different among inpatient clinic in October, November and December (P<0.001). The highest delay rate was seen in emergency samples in October, November and December, while the lowest delay rate was seen in inpatient clinic in October and outpatients in November and December.

Table 11. Statistical findings for the comparison of delay rates in complete blood count tubes in October, November and December according to services

			Delay		Total	*P*
			No	Yes		
October	**Emergency**	n	5725	748	6473	<0.001
		%	88.4	11.6	100	
	Outpatient	n	16113	1161	17274	
		%	93.3	6.7	100	
	Inpatient	n	9031	304	9335	
		%	96.7	3.3	100	
	Total	n	30869	2213	33082	-
		%	93.3	6.7	100	
November	**Emergency**	n	9577	2661	12238	<0.001
		%	78.3	21.7	100	
	Outpatient	n	34805	1097	35902	
		%	96.9	3.1	100	
	Inpatient	n	20414	1105	21519	
		%	94.9	5.1	100	
	Total	n	64796	4863	69659	-
		%	93.0	7.0	100	
December	**Emergency**	n	11433	3094	14527	<0.001
		%	78.7	21.3	100	
	Outpatient	n	41687	1259	42946	
		%	97.1	2.9	100	
	Inpatient	n	25587	1038	26625	
		%	96.1	3.9	100	
	Total	n	78707	5391	84098	-
		%	93.6	6.4	100	

Statistical findings regarding the comparison of the delay rates for hormone tubes according to the services in which the samples were taken in October, November and December are presented in Table 12. The delay rates for hormone tubes showed a significant difference among inpatient clinic in October, November and December (P<0.001). In October and November, the highest delay rate was observed in the inpatient clinic and the lowest delay rate was observed in the emergency department. In December, the highest delay rate was observed in outpatient clinic and the lowest delay rate was observed in emergency department.

Table 12. Statistical findings for the comparison of delay rates in hormone tubes in October, November and December according to services

			Delay		Total	*P*
			No	Yes		
October	**Emergency**	n	652	87	739	<0.001
		%	88.2	11.8	100	
	Outpatient	n	9182	7517	16699	
		%	55.0	45.0	100	
	Inpatient	n	769	960	1729	
		%	44.5	55.5	100	
	Total	n	10603	8564	19167	-
		%	55.3	44.7	100	
November	**Emergency**	n	1710	289	1999	<0.001
		%	85.5	14.5	100	
	Outpatient	n	21911	11087	32998	
		%	66.4	33.6	100	
	Inpatient	n	2093	1816	3909	
		%	53.5	46.5	100	
	Total	n	25714	13192	38906	-
		%	66.1	33.9	100	
December	**Emergency**	n	1995	223	2218	<0.001
		%	89.9	10.1	100	
	Outpatient	n	29601	9949	39550	
		%	74.8	25.2	100	
	Inpatient	n	3778	1133	4911	
		%	76.9	23.1	100	
	Total	n	35374	11305	46679	-
		%	75.8	24.2	100	

Statistical findings regarding the comparison of delay rates in coagulation tubes according to the services in October, November and December are presented in Table 13. In October, November and December, the delay rates of coagulation tubes showed a significant difference among inpatient clinic (P<0.001). The highest delay rate was observed in the emergency department in October, November and December, while the lowest delay rate was observed in inpatient clinic in October and November and in outpatients in December.

Table 13. Statistical findings for the comparison of delay rates in coagulation tubes in October, November and December according to services

			Delay		Total	*P*
			No	Yes		
October	**Emergency**	n	1651	696	2347	<0.001
		%	70.3	29.7	100	
	Outpatient	n	3723	980	4703	
		%	79.2	20.8	100	
	Inpatient	n	3726	472	4198	
		%	88.8	11.2	100	
	Total	n	9100	2148	11248	-
		%	80.9	19.1	100	
November	**Emergency**	n	3479	1866	5345	<0.001
		%	65.1	34.9	100	
	Outpatient	n	7695	1370	9065	
		%	84.9	15.1	100	
	Inpatient	n	8411	1162	9573	
		%	87.9	12.1	100	
	Total	n	19585	4398	23983	-
		%	81.7	18.3	100	
December	**Emergency**	n	4665	2209	6874	<0.001
		%	67.9	32.1	100	
	Outpatient	n	9901	862	10763	
		%	92.0	8.0	100	
	Inpatient	n	10554	1954	12508	
		%	84.4	15.6	100	
	Total	n	25120	5025	30145	-
		%	83.3	16.7	100	

Statistical findings regarding the comparison of delay rates for complete urinalysis tubes according to the services in October, November and December are presented in Table 14. The delay rates for these samples were significantly different among inpatient clinic in October, November and December (P<0.001). In October, the highest delay rate was observed in the outpatient clinic, and the highest delay rate was observed in the emergency department in November and December. The lowest delay rate was seen for samples collected from inpatient clinic in October, November and December.

Table 14. Statistical findings for the comparison of delay rates in urinalysis tubes in October, November and December according to services

			Delay		Total	*P*
			No	Yes		
October	**Emergency**	n	1684	1500	3184	<0.001
		%	52.9	47.1	100	
	Outpatient	n	3247	3420	6667	
		%	48.7	51.3	100	
	Inpatient	n	1146	333	1479	
		%	77.5	22.5	100	
	Total	n	6077	5253	11330	-
		%	53.6	46.4	100	
November	**Emergency**	n	2987	2772	5759	<0.001
		%	51.9	48.1	100	
	Outpatient	n	11062	2981	14043	
		%	78.8	21.2	100	
	Inpatient	n	2532	459	2991	
		%	84.7	15.3	100	
	Total	n	16581	6212	22793	-
		%	72.7	27.3	100	
December	**Emergency**	n	3648	2872	6520	<0.001
		%	56.0	44.0	100	
	Outpatient	n	13981	1944	15925	
		%	87.8	12.2	100	
	Inpatient	n	2992	329	3321	
		%	90.1	9.9	100	
	Total	n	20621	5145	25766	-
		%	80.0	20.0	100	

Statistical findings regarding the comparison of the delay rates for troponin tubes in October, November and December according to services are shown in Table 15. The delay rates for troponin tubes were significantly different among inpatient clinic in October, November and December (P<0.001). The highest delay rate was observed in the emergency department in October, November and December. The lowest delay rate was seen in inpatient clinic in October and in outpatients in November and December.

Table 15. Statistical findings for the comparison of delay rates in troponin tubes in October, November and December according to services

			Delay		Total	*P*
			No	Yes		
October	**Emergency**	n	133	258	391	<0.001
		%	34.0	66.0	100	
	Outpatient	n	2628	2537	5165	
		%	50.9	49.1	100	
	Inpatient	n	967	401	1368	
		%	70.7	29.3	100	
	Total	n	3728	3196	6924	-
		%	53.8	46.2	100	
November	**Emergency**	n	232	769	1001	<0.001
		%	23.2	76.8	100	
	Outpatient	n	6465	3686	10151	
		%	63.7	36.3	100	
	Inpatient	n	1738	1139	2877	
		%	60.4	39.6	100	
	Total	n	8435	5594	14029	-
		%	60.1	39.9	100	
December	**Emergency**	n	323	910	1233	<0.001
		%	26.2	73.8	100	
	Outpatient	n	9499	2574	12073	
		%	78.7	21.3	100	
	Inpatient	n	2436	1223	3659	
		%	66.6	33.4	100	
	Total	n	12258	4707	16965	-
		%	72.3	27.7	100	

Statistical findings regarding the comparison of the delay rates for all tubes in the emergency department, outpatient clinic and inpatient clinic in October, November and December are presented in Table 16. The delay rates for all tubes in the emergency department, outpatient clinic and inpatient clinic were significantly different (P<0.001).

The highest delay rate in the emergency department was observed in November and the lowest delay rate was observed in October. In outpatient clinic, the highest delay rate was observed in October and the lowest in December. In inpatient clinic, the highest delay rate was seen in November and the lowest in December.

Table 16. Statistical findings for the comparison of the delay rates experienced in the Emergency, Outpatient Clinic and İnpatient clinic for all tubes between October, November and December

			Result		Total	*P*
			No	Yes		
Emergency	**October**	n	14592	5309	19901	<0.001
		%	73.3	26.7	100	
	November	n	25639	13881	39520	
		%	64.9	35.1	100	
	December	n	32677	13348	46025	
		%	71.0	29.0	100	
	Total	n	72908	32538	105446	-
		%	100.0	100.0	100	
Outpatient	**October**	n	47807	25774	73581	<0.001
		%	65.0	35.0	100	
	November	n	106598	39870	146468	
		%	72.8	27.2	100	
	December	n	134223	37900	172123	
		%	78.0	22.0	100	
	Total	n	288628	103544	392172	-
		%	100.0	100.0	100	
Inpatient	**October**	n	23214	5235	28449	<0.001
		%	81.6	18.4	100	
	November	n	51518	12860	64378	
		%	80.0	20.0	100	
	December	n	65270	12272	77542	
		%	84.2	15.8	100	
	Total	n	140002	30367	170369	-
		%	100.0	100.0	100	

Statistical findings regarding the comparison of delay rates at the Emergency department in October, November and December according to types of tubes are presented in Table 17. Statistical findings regarding the comparison of delay rates at outpatient clinic in October, November and December according to types of tubes are presented in Table 18. Statistical findings regarding the comparison of delay rates of inpatient clinic in October, November and December according to types of tubes are presented in Table 19.

Table 17. Statistical findings for the comparison of delay rates experienced in the emergency department between October, November and December according to types of tubes

			Result		Total	*P*
			No	Yes		
Biochemistry	**October**	n	4747	2020	6767	<0.001
		%	70.1	29.9	100	
	November	n	7654	5524	13178	
		%	58.1	41.9	100	
	December	n	10613	4040	14653	
		%	72.4	27.6	100	
Complete blood count	**October**	n	5725	748	6473	<0.001
		%	88.4	11.6	100	
	November	n	9577	2661	12238	
		%	78.3	21.7	100	
	December	n	11433	3094	14527	
		%	78.7	21.3	100	
Hormone	**October**	n	652	87	739	<0.001
		%	88.2	11.8	100	
	November	n	1710	289	1999	
		%	85.5	14.5	100	
	December	n	1995	223	2218	
		%	89.9	10.1	100	
Coagulation	**October**	n	1651	696	2347	<0.001
		%	70.3	29.7	100	
	November	n	3479	1866	5345	
		%	65.1	34.9	100	
	December	n	4665	2209	6874	
		%	67.9	32.1	100	
Urinalysis	**October**	n	1684	1500	3184	<0.001
		%	52.9	47.1	100	
	November	n	2987	2772	5759	
		%	51.9	48.1	100	
	December	n	3648	2872	6520	
		%	56.0	44.0	100	
Troponin	**October**	n	133	258	391	<0.001
		%	34.0	66.0	100	
	November	n	232	769	1001	
		%	23.2	76.8	100	
	December	n	323	910	1233	
		%	26.2	73.8	100	

Table 18. Statistical findings for the comparison of delay rates experienced in the outpatient clinic between October, November and December according to types of tubes

			Result		Total	*P*
			No	Yes		
Biochemistry	**October**	n	12914	10159	23073	<0.001
		%	56.0	44.0	100	
	November	n	24660	19649	44309	
		%	55.7	44.3	100	
	December	n	29554	21312	50866	
		%	58.1	41.9	100	
Complete blood count	**October**	n	16113	1161	17274	<0.001
		%	93.3	6.7	100	
	November	n	34805	1097	35902	
		%	96.9	3.1	100	
	December	n	41687	1259	42946	
		%	97.1	2.9	100	
Hormone	**October**	n	9182	7517	16699	<0.001
		%	55.0	45.0	100	
	November	n	21911	11087	32998	
		%	66.4	33.6	100	
	December	n	29601	9949	39550	
		%	74.8	25.2	100	
Coagulation	**October**	n	3723	980	4703	<0.001
		%	79.2	20.8	100	
	November	n	7695	1370	9065	
		%	84.9	15.1	100	
	December	n	9901	862	10763	
		%	92.0	8.0	100	
Urinalysis	**October**	n	3247	3420	6667	<0.001
		%	48.7	51.3	100	
	November	n	11062	2981	14043	
		%	78.8	21.2	100	
	December	n	13981	1944	15925	
		%	87.8	12.2	100	
Troponin	**October**	n	2628	2537	5165	<0.001
		%	50.9	49.1	100	
	November	n	6465	3686	10151	
		%	63.7	36.3	100	
	December	n	9499	2574	12073	
		%	78.7	21.3	100	

Table 19. Statistical findings for the comparison of delay rates experienced in the inpatient clinic between October, November and December according to types of tubes

			Result		Total	*P*
			No	Yes		
Biochemistry	**October**	n	7575	2765	10340	<0.001
		%	73.3	26.7	100	
	November	n	16330	7179	23509	
		%	69.5	30.5	100	
	December	n	19923	6595	26518	
		%	75.1	24.9	100	
Complete blood count	**October**	n	9031	304	9335	<0.001
		%	96.7	3.3	100	
	November	n	20414	1105	21519	
		%	94.9	5.1	100	
	December	n	25587	1038	26625	
		%	96.1	3.9	100	
Hormone	**October**	n	769	960	1729	<0.001
		%	44.5	55.5	100	
	November	n	2093	1816	3909	
		%	53.5	46.5	100	
	December	n	3778	1133	4911	
		%	76.9	23.1	100	
Coagulation	**October**	n	3726	472	4198	<0.001
		%	88.8	11.2	100	
	November	n	8411	1162	9573	
		%	87.9	12.1	100	
	December	n	10554	1954	12508	
		%	84.4	15.6	100	
Urinalysis	**October**	n	1146	333	1479	<0.001
		%	77.5	22.5	100	
	November	n	2532	459	2991	
		%	84.7	15.3	100	
	December	n	2992	329	3321	
		%	90.1	9.9	100	
Troponin	**October**	n	967	401	1368	<0.001
		%	70.7	29.3	100	
	November	n	1738	1139	2877	
		%	60.4	39.6	100	
	December	n	2436	1223	3659	
		%	66.6	33.4	100	

Statistical findings regarding the comparison of delay rates according to types of tubes independent of time and services are presented in Table 20. Delay rates are significantly different according to the types of tubes (P<0.001). The highest delay rate was found in Biochemistry tubes and the lowest delay rate was found in complete blood count tubes.

Table 20. Statistical findings for the comparison of delay rates independent of time and services according to types of tubes

			Result		Total	*P*
			No	Yes		
Tube types	**Biochemistry**	n	133970	79243	213213	<0.001
		%	62.8	37.2	100	
	Complete blood count	n	174372	12467	186839	
		%	93.3	6.7	100	
	Hormone	n	71691	33061	104752	
		%	68.4	31.6	100	
	Coagulation	n	53805	11571	65376	
		%	82.3	17.7	100	
	Urinalysis	n	43279	16610	59889	
		%	72.3	27.7	100	
	Troponin	n	24421	13497	37918	
		%	64.4	35.6	100	
Total		n	501538	166449	667987	-
		%	75,1	24.9	100.0	

Statistical findings regarding the comparison of time-independent delay rates according to types of tubes are presented in Table 21. Delay rates were significantly different in Emergency, Outpatient and Inpatient according to the types of tubes (P<0.001). Regardless of the types of tubes, the delay rates were, from lowest to highest, in inpatient (17.8%), outpatient (26.4%) and emergency departments (30.9%), respectively.The highest delay rate in emergency departments was seen for troponin (73%). In outpatient clinics, the highest delay rate was found for biochemistry (43.2%) and the lowest delay rate was found for complete blood count (3.7%). In inpatient clinic, the highest and lowest delay rates were found in hormones (37.1%) and complete blood count (4.3%), respectively.

Table 21. Statistical findings for the comparison of time-independent delay rates according to types of tubes

Service type				Result		Total	*P*
				No	Yes		
Emergency	Tube	Biochemistry	n	23014	11584	34598	<0.001
			%	66.5	33.5	100	
		Complete blood count	n	26735	6503	33238	
			%	80.4	19.6	100	
		Hormone	n	4357	599	4956	
			%	87.9	12.1	100	
		Coagulation	n	9795	4771	14566	
			%	67.2	32.8	100	
		Urinalysis	n	8319	7144	15463	
			%	53.8	46.2	100	
		Troponin	n	688	1937	2625	
			%	26.2	73.8	100	
	Total		n	72908	32538	105446	-
			%	69.1	30.9	100.0	
Outpatient clinic	Tube	Biochemistry	n	67128	51120	118248	<0.001
			%	56.8	43.2	100	
		Complete blood count	n	92605	3517	96122	
			%	96.3	3.7	100	
		Hormone	n	60694	28553	89247	
			%	68.0	32.0	100	
		Coagulation	n	21319	3212	24531	
			%	86.9	13.1	100	
		Urinalysis	n	28290	8345	36635	
			%	77.2	22.8	100	
		Troponin	n	18592	8797	27389	
			%	67.9	32.1	100	
	Total		n	288628	103544	392172	-
			%	73.6	26.4	100.0	
Inpatient clinic	Tube	Biochemistry	n	43828	16539	60367	<0.001
			%	72.6	27.4	100	
		Complete blood count	n	55032	2447	57479	
			%	95.7	4.3	100	
		Hormone	n	6640	3909	10549	
			%	62.9	37.1	100	
		Coagulation	n	22691	3588	26279	
			%	86.3	13.7	100	
		Urinalysis	n	6670	1121	7791	
			%	85.6	14.4	100	
		Troponin	n	5141	2763	7904	
			%	65.0	35.0	100	
	Total		n	140002	30367	170369	-
			%	82.2	17.8	100.0	

The bar graph showing the number of delays experienced by emergency, outpatient and inpatient patients according to the types of tubes in October, November and December is shown in Figure 1. The other bar graph showing the rate of delay in emergency, outpatient and inpatient patients according to the types of tubes in October, November and December is presented in Figure 2.

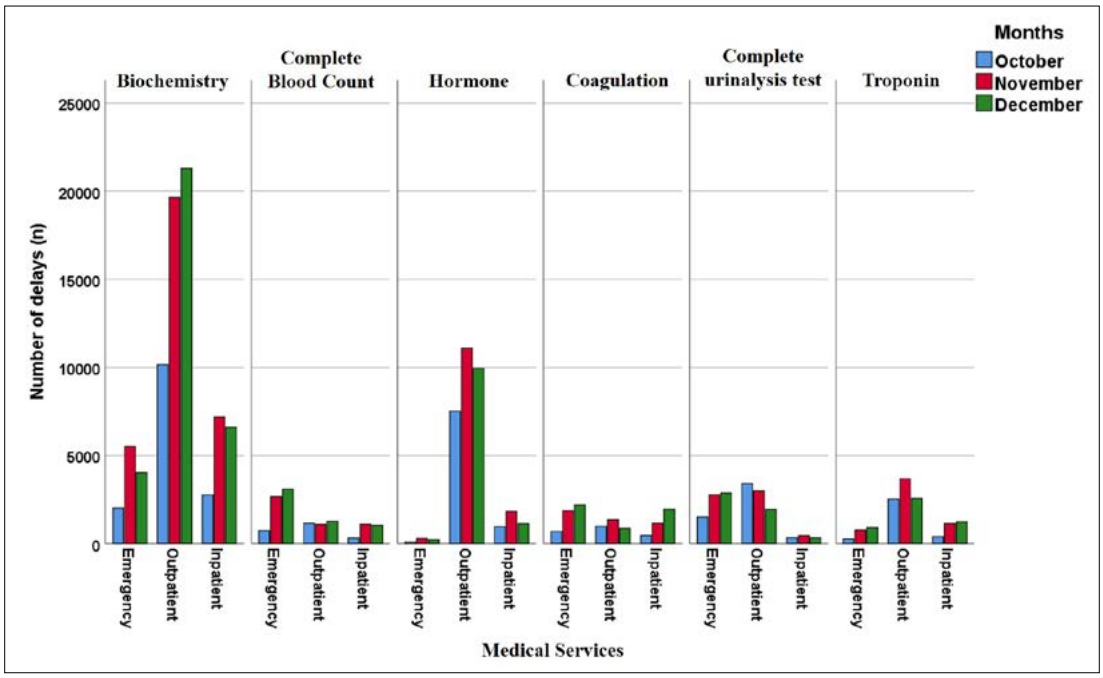

Figure 1. Box plot showing the number of delays in the Emergency, Outpatient Clinic and Inpatient Clinic according to types of tubes in October, November and December by time

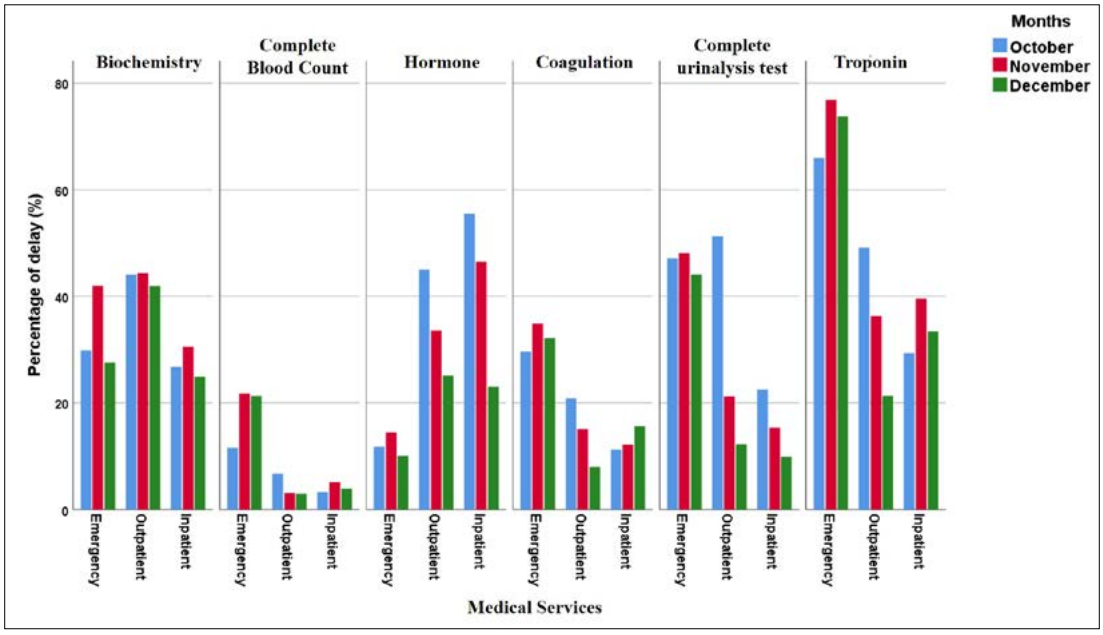

Figure 2. Box plot showing the rate of delays in the Emergency, Outpatient Clinic and Inpatient Clinic according to types of tubes in October, November and December by time

When only inpatient clinic were compared regardless of time and tubes, the delay rates were 17.8% in inpatient clinic, 26.4% in outpatient clinic and 30.9% in emergency department. When only tubes were evaluated regardless of time and inpatient clinic, the highest and lowest delay rates were observed for biochemistry tubes (37.2%) and complete blood count tubes (6.7%), respectively.

Regardless of time, the highest and lowest delay rates in the emergency department was observed for troponin (73.8%) and hormone (12.1%), respectively: In the outpatient clinic, the highest delay rate was for biochemistry (43.2%) and the lowest for complete blood count (3.7%). In inpatient clinic, the highest and lowest delay rates were found for hormones (37.1%) and complete blood count (4.3%), respectively. When tubes were compared according to inpatient clinic, it was observed that the highest delay rate in the emergency department was for troponin.

Considering time, there was no significant difference in the delay rates at the emergency department. In the outpatient clinic, delay rates for hormone, coagulation, complete urinalysis and troponin have decreased from October to December. In inpatient clinic, the delay rates for hormone and complete urinalysis have decreased from October to December.

DISCUSSION

The turnaround time is one of the important indicators of quality as well as the accuracy and reliability of the test results of laboratories (2-4). The longer turnaround time of the laboratory means the longer the patients' access to diagnosis and treatment and the longer the hospital stay (8-10).

Delays in reaching diagnosis and treatment and prolonged hospitalization lead to an increased risk of medical complications. It also significantly reduces the satisfaction of clinicians and patients about the laboratory (11,12).

The analysis and adjustments required for laboratories to achieve the 'ideal timeliness' target involve a multi-stage process. First of all, the target TAT for each test should be determined and the TAT should be monitored. For samples that exceed the target time, the preanalytical, analytical and postanalytical process should be thoroughly reviewed. Adjustments should be made to address modifiable factors that cause time delays.

In our study, when the three-month period of our laboratory's establishment period was examined, it was observed that the highest delay rate in the first month was observed for samples from outpatient clinics. In our laboratory, emergency samples and routine samples are analyzed on different devices.

Considering the high number of samples from outpatient clinics in the evaluations made regarding the process, the number of devices for routine analyzes was increased. As a result of this adjustment, it has been observed that the delay rate in outpatient clinics has decreased over the months.

The delay rate in the emergency department increased in the second month in parallel with the rapid increase in the number of samples and decreased again in the following month. It was observed that the most important factor for the delay in emergency samples was the delay in the delivery of samples to the device due to the insufficient number of technical personnel in charge of emergency devices, and therefore the number of personnel was increased. Thus, in newly established laboratories, delays in result delivery times can be reduced when the rapid increase in the number of samples in the first months is intervened with appropriate adjustments.

In our study, when the delay rates for different tests for all inpatient clinic were compared on a monthly basis, it was observed that the highest delay rate in the first month was for complete urinalysis. When the reason for this delay in urinalysis in the first month was analyzed, it was observed that the insufficient number of personnel allocated for the urine device in the on-call teams played a role.

This delay rate decreased in the second month when the number of urine device personnel was increased. As the waiting time at room temperature increases in urine samples, changes such as pH increase and decrease in the number of leukocytes may occur.

Therefore, the waiting time after sample collection should be maximum 4 hours (16). During the establishment phase of newly established laboratories, urine samples may remain in the background when the personnel in the on-call teams are directed to more critical and urgent tests and air devices. However, complete urinalysis is the first-line test in the diagnosis of urinary system diseases. Therefore, attempts to reduce the number of waiting specimens and provide accurate results are important.

In our study, the highest delay rate was observed in biochemistry and troponin tests in October. In December, the highest delay rate was observed in biochemistry tests.

It is also noteworthy that troponin was the most delayed test in the emergency department in all three months. In the first months, troponin and biochemistry samples were delivered to the laboratory in the same tube, which played an important role in this delay.

In the following period, troponin and biochemistry tubes were separated. Since troponin is a critical test used in the diagnosis of acute coronary syndrome, the target TAT is recommended as <60 minutes in clinical and laboratory guidelines. It has also been reported that the length of stay of patients in the emergency department is shortened when the target value is reached in troponin TAT (17). The increase in the number and capacity of patients in emergency departments has also been shown to play an important role in the increase in troponin TAT (18).

When the delay rates were compared according to the types of tubes, regardless of time and services, the highest delay rate was observed for biochemistry tubes, while the lowest delay rate was observed for complete blood count tubes. The higher number of biochemistry samples compared to other samples plays an important role in the delay.

Because high sample volume is an important factor in TAT delay. In order to prevent this delay, an increase in both the number of personnel and the number of devices is planned.

In a large cohort study that examined TAT values for biochemistry tests, it was reported that TAT delays were mostly caused by the preanalytical and analytical process. In the same study, it was reported that laboratories prefer to monitor part of the preanalytical process (the part after the sample arrives at the laboratory) and the analytical process, which are mostly under their control, when monitoring TAT (19). Therefore, the part of the preanalytical process before the sample reaches the laboratory is not adequately monitored by many laboratories.

Achieving the desired target value in TAT is a multi-stage process. Patient triage, keeping the laboratory at a capacity to respond to patient volume, sufficient number of personnel responsible for sample collection-transfer-acceptance and analysis, number and capacity of devices, sufficient number of specialists in the postanalytical process and quality management are some of the issues that should be considered in the management of the process. Some of the important results of our study include a decrease in the frequency of device malfunctions, full operation of the pneumatic system throughout the hospital, installation of preanalytical rail systems, and shorter TAT after the increase in the number of biochemistry specialists and laboratory technicians. Since the approval support system (automatic approval) was not in place at the time of the study, we could not measure its impact on TAT.

In conclusion, we found that analyzing TAT and delays in our newly established laboratory was useful in several areas. First of all, it allowed us to discover areas where we were understaffed and under-equipped despite the increased number of samples. We closely examined the process for problems in these areas and took various measures for improvement. Therefore, TAT monitoring and early detection of existing delays are important for improving quality in the laboratory. Reduced TAT approaching the target value lead to increased clinician and patient satisfaction.

TAT is one of the most important parameters used by clinicians to assess the quality of a laboratory. It is therefore an important service feature that all laboratories should pay attention to. We attribute the shortening of TAT for all samples as time progresses to the increasing number of technicians working in the laboratory and their experience, more organized sample transportation system, slightly more biochemistry specialists, and more efficient hospital and laboratory information management systems. The benefits of our study include clearly demonstrating the rapid turnaround times of newly established biochemistry laboratories in large hospitals and centers, showing the variations in these times between clinics, increasing clinicians' satisfaction with the laboratory, reducing costs by shortening hospital stays, and developing measures that can be considered.

There are some limitations and situations that may cause bias in our study, such as the use of only 3 months of data, frequent technical malfunctions in autoanalyzers due to the new establishment of our laboratory, prolonged TAT due to inexperience of some personnel, insufficient number of laboratory technicians, and the pneumatic system not yet fully functioning regularly.

Declerations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the Ankara Bilkent City Hospital Ethics Committee (Dated: 30.11.2022; Approval Number: E1/3060/2022)

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Archives of Current Medical Research
Arch Curr Med Res 2023;4(3):178-185

Received: 19 April 2023
Revised: 30 June 2023
Accepted: 21 August 2023
DOI: 10.47482/acmr.1285642

ORIGINAL ARTICLE

Wet cupping therapy removes oxidative stress related miRNAs

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Abstract

Background: Wet cupping therapy is commonly used in conditions such as hypertension, diabetes, and inflammatory and infectious diseases. The mechanism of action of wet cupping therapy is not yet precise; however, several studies have demonstrated that it has a role in limiting oxidative stress. This study aimed to investigate the effect of wet cupping therapy on oxidative stress-related miRNAs miRNA-34a, miRNA-200a, miRNA-21 levels and oxidant-antioxidant status markers malondialdehyde (MDA) and glutathione (GSH) levels.

Methods: 60 healthy volunteer women aged 20-75 years (n=30, 20-45 years; n=30, 45-75 years) who had wet cupping at Necmettin Erbakan University Meram Medical Faculty Traditional and Complementary Medicine Center were included in this study. Plasma miRNA-34a, miRNA-200a, and miRNA-21 levels were analyzed using real-time quantitative PCR (RT-PCR) analysis. MDA and GSH levels were measured using commercial ELISA kits.

Results: MDA levels [2003.10 (1810.17-7392.15) vs. 1884.04 (1800.10-4488.05), p=0.027] of wet cupping blood samples were higher than venous blood samples, while GSH levels [125.97 (90.65-219.43) vs. 131.77 (88.77-246.42), p=0.037] were lower. miRNA-34a [(0.94±0.74) vs. (0.53±0.28), p<0.001], miRNA-21 [0.058 (0.01-0.54) vs. 0.033 (0.01±0.18), p=0.001] and miRNA-200a [24.42 (7.46-103.97) vs. 20.32 (4.32-56.49), p=0.037] levels of wet cupping blood samples were significantly higher than venous blood samples.

Conclusions: Wet cupping therapy eliminates oxidative stress-related miRNAs from the body. Therefore, it is seen as a promising method for the welfare of reactive oxygen species (ROS)-related diseases by limiting oxidative damage.

Keywords: Cupping Therapy, miRNAs, Oxidative Stress, Reactive Oxygen Species.

Cite this article as: *Unat B, Yerlikaya FH, Alp H, Eryavuz Onmaz D. Wet cupping therapy removes oxidative stress related miRNAs. Arch Curr Med Res. 2023;4(3):178-185*

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INTRODUCTION

Cupping therapy is a traditional therapy method that has been practiced for nearly 2000 years (1). Eber's papyrus (1550 BC) is one of the earliest medical texts to mention cupping therapy (2). Cupping therapy is applied by creating localized pressure through a glass, plastic, or bamboo cup on patients' skin over acupuncture points, painful areas, or a reflex zone (3). In general, there are two main classes of cupping therapy, wet cupping (bleeding cupping) and dry cupping (4). However, the former is one of the most widely preferred types of cupping therapy (5). Other types include needle, retained, flash, and medicinal (herbal) cupping (6). Dry cupping is performed by stimulating the skin through the application of cups with a vacuum pressure without allowing blood to flow (7). In wet cupping therapy, also known as Hijama, the skin is incised with a needle, and then the blood is removed from the body by creating a vacuum with a cup (8). The reported effects of cupping therapy include increasing cutaneous blood flow, altering the biomechanical characteristics of the skin, raising the pain threshold, improving local anaerobic metabolism, restriction of inflammation, and regulating the immune system (9). Cupping therapy is applied for preventive and therapeutic purposes in various disorders such as back, neck, shoulder, and knee pain, migraine and headache, acne, asthma, inflammatory and infectious diseases, immune system disorders, diabetes mellitus, hypertension, anxiety, depression, and sleep disorders (10). Wet cupping is believed to remove toxins, heavy metals, metabolic wastes, and free radicals from the body (8). An imbalance between the generation of reactive oxygen species (ROS) and the enzymatic or non-enzymatic antioxidant defense system leads to oxidative stress (11). Excess free radicals attack cellular proteins, lipids, and DNA, inhibiting everyday functions (12). Therefore, oxidative stress is involved in the pathogenesis of various diseases, including cancer, diabetes, cardiovascular diseases, neurodegenerative diseases, and aging (13). miRNAs are 21-23 nucleotides long, small non-coding RNAs that affect gene expression at the translational or posttranslational level through mRNA degradation or repression (14). Although evaluated separately, microRNA (miRNA) networks and oxidative stress are tightly linked. Oxidative stress affects the expression level of various miRNAs, while miRNAs affect the expression levels of essential genes that play a vital role in the oxidative stress response (15). Abnormal expression of miRNAs has been related to various diseases, including cancer, cardiovascular, and neurodegenerative diseases, diabetes, and viral infections (16). Although various studies investigated the impact of cupping therapy on heavy metal concentrations, oxidative stress, and antioxidant status markers, no studies have been reached to determine the effects on miRNA levels (5, 17-19). The study aimed to investigate the effect of wet cupping therapy on oxidative stress-related miRNAs miRNA-34a, miRNA-200a, miRNA-21 levels and oxidant-antioxidant status markers malondialdehyde (MDA) and glutathione (GSH) levels.

MATERIALS AND METHODS

Study design

Subjects

This study included a total of 60 healthy volunteer women aged 20-75 years (n=30, 20-45 years; n=30, 45-75 years) who had wet cupping at Necmettin Erbakan University Meram Medical Faculty Traditional and Complementary Medicine Center. Enrollment criteria of the study were hemoglobin levels above 9.5 mg / dL, being over 18 years old and healthy, and attending Traditional and Complementary Medicine Center of Necmettin Erbakan University Meram Medical Faculty for wet cupping therapy to preserve health. Exclusion criteria were antioxidant, vitamin, mineral supplements, diabetes, cardiovascular diseases, chronic liver or kidney disease, infectious diseases, use of any blood thinning drug (antiaggregant, salicylic acid, coumadin), pregnancy, alcohol, or smoking. Within the scope of the study, 107 volunteers who wanted to have wet cupping therapy could be reached. Of these, 15 were smokers, 18 individuals had comorbidities such as diabetes and hypertension, 7 individuals were taking supplements, and 7 participants were men. Males were excluded from the study due to the limited number of male participants, and only female participants were included. Thus, the study was carried out with 60 volunteer participants. The participants' 5 mL venous blood samples were drawn into serum separator gel tubes after 12 hours of fasting and just before the first wet cup application. 2 mL wet cupping blood samples were transferred from the cup to serum separator gel tubes during application. Serum samples were separated at 2000 g for 10 min; then, serum samples were aliquoted and kept at -80 ° C until analysis. For miRNA, blood samples were drawn into EDTA tubes and centrifuged at 1300 g for 10 min, and plasma samples were separated and stored at -80°C until analysis. The Necmettin Erbakan University Faculty of Medicine ethics committee approved the study (Number: 2017/1110, Date: 01/12/2017).

Wet Cupping

Wet-cupping therapy was carried out using sterile vacuum cups on acupuncture point locations; Du-14(Dazhui) point on the posterior median line, in the depression below the processus spinosus of the 7th cervical vertebra; Ub-42 (Pohu) points bilaterally on the back 3.0 cun lateral to the lower border of spinosus process of the 3rd thoracic vertebra; Ub-46(Geguan) points bilaterally on the back, 3.0 cun lateral to the lower border of spinosus process of the 7th thoracic vertebra, and interscapular region; on the posterior median line between 3rd and 7th thoracic vertebra. BL-12-15 is near the interscapular site for wet cupping. Furthermore, according to Chinese medicine, several important back-shu points, including the heart back-shu point, are known to stimulate the whole body in the area. Points BL-13 through 15 are associated with the lungs, pericardium, and heart, respectively, and are used in acupuncture theory to support these organs (20).

Laboratory tests

The serum levels of urea, creatinine, total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-C), very low-density lipoprotein (VLDL-C), glucose, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were analyzed with an Architect C 8000 Auto Analyzer (Abbott Laboratories, Abbott Park, IL, USA) according to the manufacturer's instructions. Low-density lipoprotein (LDL-C) was calculated using Friedewald's formula.

Serum MDA (Cat.No E-BC-K025-S) and GSH (Cat.No E-EL-0026) levels were analyzed using commercial human ELISA kits (Elabscience, Wuhan, China) according to the manufacturer's instructions. The absorbance of all wells was measured at 450 nm in an ELx800 Absorbance Microplate Reader (Biotek, Winooski, VT, USA).

miRNA expression profiling

Total RNA was extracted from plasma samples via High Pure miRNA Isolation Kit (Roche Life Science, Mannheim, Germany). Total RNA was reversely transcribed to cDNA using miScript II RT Kit (Qiagen, Hilden, Germany). Obtained cDNA samples are PreAmplified via miScript Microfluidics PreAMP Kit (Qiagen, Hilden, Germany). Quantitative real-time PCR (qRT-PCR) analysis was carried out using miScript miRNA Assays (Qiagen, Hilden, Germany) with Dynamic Array (Fluidigm, South San Francisco, CA, USA) on BioMark System (Fluidigm, South San Francisco, CA, USA) according to manufacturer's protocol. miRNA expressions were normalized to β-actin. β-actin (forward, 5′-GGCACCCAGCACAATGAAG-3′, and reverse, 5′-CGTCATACTCCTGCTTGCTG-3′) was used as the internal control. The relative gene expression was calculated by comparing cycle times for target PCR using this equation: relative gene expression = $2^{-(\Delta Ctsample - \Delta Ctcontrol)}$.

Statistical analysis

Statistical evaluation was carried out using SPSS statistical software package version 21.0. One-Sample Kolmogorov-Smirnov test was used to determine the distribution of data. The mean and median values between the two groups were compared using Student's t and Mann-Whitney U tests, respectively. Kruskal – Wallis test (post-hoc analysis Mann-Whitney U) also compared multiple groups. Correlation analyses were performed using Spearman's correlation test. $p < 0.05$ was considered to be statistically significant.

RESULTS

The study was completed with 60 volunteer women aged 20 to 75 years. The mean age of the participants was 45.5 years, and the mean BMI was 26.91±4.20 kg/m^2. All participants were female. The demographic properties of the participants are expressed in Table 1.

Table 1. Demographic characteristics of the participants.

Variable	Subjects (n=60)
Age (years)	45.5 (20-75)
Gender (n, %)	Female (60, %100)
Education (n, %)	Primary (6, 10%)
	Secondary (42, 70%)
	University (12, 20%)
Length (m)	1.62±0.57
Weight (kg)	71.59±11.71
BMI (kg/m^2)	26.91±4.20
BMI: body mass index.	

As a result of our study, it was shown that there was a significant difference between the cupping blood samples and venous blood samples of the participants in terms of MDA, GSH, and circulating miRNA levels. MDA levels [2003.10 (1810.17-7392.15) vs. 1884.04 (1800.10-4488.05) ng/mL, p=0.027] were higher in wet cupping blood samples compared to venous blood samples, while GSH levels [125.97 (90.65-219.43) vs. 131.77 (88.77-246.42) µg/mL, p=0.037] were lower. Circulating miRNA-34a [(0.94±0.74) vs. (0.53±0.28), p<0.001], miRNA-21 [0.058 (0.01-0.54)

vs. 0.033 (0.01±0.18), p=0.001] and miRNA-200a [24.42 (7.46-103.97) vs. 20.32 (4.32-56.49), p=0.037] levels of wet cupping samples were significantly higher than venous blood samples. The miRNA-34a, miRNA-21, miRNA-200a, MDA, and GSH levels of the blood samples are expressed in Table 2.

Table 2. The miRNA-34a, miRNA-21, miRNA-200a, MDA and GSH levels of the blood samples.

Parameters	Venous blood (n=60)	Wet cupping blood (n=60)	p
miRNA-34a	0.53±0.28	0.94±0.74	**<0.001**
miRNA-21	0.033 (0.01±0.18)	0.058 (0.01-0.54)	**0.001**
miRNA-200a	20.32 (4.32-56.49)	24.42 (7.46-103.97)	**0.037**
MDA (ng/mL)	1884.0 (1800.1-4488.1)	2003.1 (1810.2-7392.2)	**0.027**
GSH (μg/mL)	131.77 (88.77-246.42)	125.97 (90.65-219.43)	**0.037**

Moreover, the participants were divided into groups according to age and biochemical findings; miRNA-34a, miRNA-21, miRNA-200a, MDA, and GSH levels were compared. The biochemical findings of the participants were summarized in Table 3.

Table 3. Biochemical findings of the participants.

Biochemial Parameters	Group 1 (n=30)	Group 2 (n=30)	p
Glucose (mg/dL)	94.48 ± 11.15	106.74 ± 16.23	**0.002**
Cholesterol (mg/dL)	202.23 ± 38.10	206.77 ± 33.33	0.626
LDL (mg/dL)	115.57 ± 32.58	119.97 ± 25.26	0.561
HDL (mg/dL)	53.99 ± 11.49	51.18 ± 11.10	0.340
VLDL (mg/dL)	28.83 ± 12.64	30.83 ± 14.66	0.574
TG (mg/dL)	146.23 ± 62.85	156.07 ± 73.36	0.579
Urea (mg/dL)	26.87 ± 6.94	30.71 ± 10.03	0.091
Creatinine (mg/dL)	0.79 ± 0.08	0.78 ± 0.08	0.610
ALT (IU/L)	16.36 ± 6.26	19.50 ± 10.12	0.156
AST (IU/L)	16.73 ± 5.05	18.34 ± 4.21	0.189
Hemoglobin (mg/dL)	13.08 ± 0.92	13.15 ± 1.17	0.818

Group 1: women between the ages of 20-45, n = 30; Group 2: women between the ages of 45-75, n = 30.

When the blood samples of the participants are classified according to their age, they are divided into the following four groups: Group 1, venous blood samples of women between the ages of 20-45; Group 2, venous blood samples of women between the ages of 45-75; Group 3, wet cupping blood samples of women between the ages of 20-45; Group 4, wet cupping blood samples of women aged 45-75. In addition, the comparison of Group 1 and Group 3 showed that miRNA-200a, miRNA-34a, miRNA-21, and MDA levels were higher, and GSH levels were lower in Group 3 compared to Group 1. However, only the difference between miRNA-200a, miRNA-34a, and miRNA-21 levels was statistically significant ($p<0.05$). Similarly, the statistical comparison of Group 2 and Group 4 revealed that miRNA-200a, miRNA-34a, miRNA-21, and MDA levels were higher, and GSH levels were lower in Group 4 compared to Group 2. However, only the difference between MDA and GSH levels was statistically significant ($p<0.05$). The miRNA-34a, miRNA-21, miRNA-200a, MDA, and GSH levels of blood samples according to age groups are expressed in Table 4.

Table 4. The miRNA-34a, miRNA-21, miRNA-200a, MDA and GSH levels of blood samples according to age groups.

Parameters	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	Group 4 (n=30)	p
miRNA-34a	0.54±0.33	0.52±0.23	0.70±0.31	1.17±0.95	a:0.789
					b:0.015 **c:0.049** **d:0.001**
miRNA-21	0.022 (0.01-0.12)	0.053 (0.01-0.54)	0.062 (0.01-0.18)	0.055 (0.02-0.18)	a:0.193
					b:0.003 **c:<0.001** d:0.900
miRNA-200a	17.04 (4.32-49.52)	25.63 (4.79-56.49)	24.42 (7.46-84.45)	27.99 (9.13-103.97)	**a:0.001**
					b:0.905 **c:0.005** d:0.888
MDA (ng/mL)	1908.7 (1800.1-4069.1)	1861.6 (1800.2-4488.1)	2350 (1810.2-6432.9)	1924.0 (1826.5-7392.2)	a:0.650
					b:0.905 c:0.334 **d:0.030**
GSH (μg/mL)	132.89 (103.34-246.42)	131.76 (88.77-236.52)	131.37 (94-188.49)	117.92 (90.65-219.43)	a:0.633
					b:0.078
					c:0.279 **d:0.047**

Group 1: venous blood samples of women between the ages of 20-45; Group 2: venous blood samples of women between the ages of 45-75; Group 3: wet cupping blood samples of women between the ages of 20-45; Group 4: wet cupping blood samples of women aged 45-75. a: Comparison of Group 1 and Group 2, b: Comparison of Group 3 and Group 4, c: Comparison of Group 1 and Group 3, d: Comparison of Group 2 and Group 4.

Comparison of venous blood samples according to age groups showed that there was no significant difference between miRNA-34a (p=0.789), miRNA-21 (p=0.193), MDA (p=0.650), and GSH (p=0.701) levels of Group 1 and Group 2 while miRNA-200a (p=0.001) levels of Group 1 were lower than the Group 2. A comparison of cupping blood samples showed that miRNA-34a (p=0.031) and miRNA-21 (p=0.003) levels of Group 3 were lower than Group 4.

DISCUSSION

Wet cupping therapy is one of the traditional therapies used for centuries. Although it is commonly used to treat inflammatory, infectious, and immune disorders, its mechanism of action is still unknown (10). Previous studies have reported that wet cupping therapy affects oxidative balance (18, 19). In this study, we hypothesized that wet cupping therapy might also affect oxidative stress-related-miRNA levels and therefore be involved in limiting oxidative stress via the non-coding transcriptome. Tagil et al. implemented wet cupping therapy on 31 healthy volunteers. Wet cupping blood and venous blood samples were collected simultaneously from the participants. The nitric oxide (NO), MDA levels, superoxide dismutase (SOD), and myeloperoxidase (MPO) activities of participants were evaluated. As a result of the study MPO activity, MDA, and NO levels were higher, and SOD activity was lower in wet cup blood compared to venous blood (18). Twenty-four participants were enrolled in the study conducted by Ersoy et al., and wet cupping therapy was carried out on participants every month for 3 months. Venous blood samples of the participants were taken before the application (Venous 1) and after the last application (Venous 2). Wet cupping blood samples were taken during the first and last applications. The oxidant status markers MDA, total oxidant status (TOS), and antioxidant status markers GSH, SOD, total antioxidant status (TAS), and catalase (CAT) activities were measured in the collected blood samples. As a result of the study, it was reported that the highest MDA and TOS levels

and the lowest TAS, GSH, SOD, and CAT levels were detected in the initial cup of blood. At the same time, these parameters improved in the second cupping blood samples compared to the first cupping blood samples. In addition, MDA and TOS levels, as well as TAS, GSH, SOD, and CAT, have been shown to change favorably in Venous 2 compared to Venous 1 (19). Our findings were consistent with previous studies. Similarly, MDA levels, which is an indicator of oxidative damage, were higher ($p=0.027$) in wet cupping samples compared to venous blood. In comparison, GSH levels, one of the antioxidant indicators, were lower ($p=0.037$) (Table 2). Unlike other studies, our study investigated the influence of wet cupping therapy on oxidative stress-related miRNAs. To our best knowledge, this is the first study to investigate the effect of wet cupping therapy on oxidative stress-related miRNAs. Studies have shown that ROS generated under oxidative stress is involved in the pathogenesis of various diseases such as cancer, cardiovascular diseases, and neurodegenerative diseases and modulates miRNAs' expression (20-22). These alterations in miRNA expression levels mainly occur through the modulation of nuclear factor erythroid 2-related factor 2 (Nrf2), sirtuins (SIRT1), calcineurin / nuclear factor of activated T cell (NFAT), or nuclear factor kappa B (NF-κB). Therefore, various miRNAs can be identified as potential biomarkers for ROS-related diseases. Increasing evidence suggests that SIRT1 is involved in cellular responses to oxidative stress. SIRT1 is the target of a variety of redox-sensitive mechanisms. Various miRNAs have been revealed to affect oxidative stress via SIRT1. One of these is miRNA-34a. Downregulation of SIRT1 by miRNA-34a has been shown to promote aging and inflammation of vascular smooth muscle cells in aged mouse aortas by mechanisms mediated by oxidative stress (23). NADPH oxidases (NOXs) are a family of membrane-bound enzymes that oxidize NADPH to generate ROS through the catalytic metabolism of oxygen during host defense. Increased expression of the NOX2 isoform has been demonstrated due to the overexpression of miR-34a in glioma cells (24). In addition, miRNA-34a has been shown to regulate various genes and pathways involved in cancer initiation, progression, and metastasis (25). miRNA-21 is one of the miRNAs reported to be a potential biomarker for oxidative stress related-cardiovascular diseases, similar to miRNA-34a (23). NF-κB transcriptionally modulates various miRNAs. NF-κB is an important modulator of pro-inflammatory / stress-like responses that play important roles in DNA damage response and apoptosis in various cell types. ROS-induced NF-κB upregulates miRNA-21 and promotes cancer progression and fibrogenesis (24). Recently, miRNA-21 has been shown to play a role in the pathogenesis of diabetes, and studies aimed at elucidating the role of miRNA-21 in diabetes pathogenesis have drawn attention to miRNA's role in ROS homeostasis (26). Sala et al. demonstrated that miRNA-21 could support the suppression of homeostatic signaling, which limits ROS damage (27). Their subsequent study showed that circulating miRNA-21 could be an early marker of ROS-mediated damage in people at high risk of developing diabetes and in type 2 diabetic individuals who were not on medication (28). Under oxidative stress conditions, Nrf2 / Keap1 complexes disrupt, and Nrf2 transfers to the nucleus. This change increases the expression and activity of several antioxidant genes that inhibit cell apoptosis and support the survival and tumorigenesis of cancer cells. Previous studies have reported that one of the miRNAs targeting the Nrf2 signaling pathway is miRNA-200a (29). Eades et al. and Yang et al. revealed that miR-200a and miR-28 might modulate Nrf2 expression levels by directly targeting Keap1 mRNA in breast cancer cells (30, 31). Mateescu et al. reported that miRNA-200a modulates ROS production by targeting p38a under oxidative stress and potentiates tumor growth and progression (32). The primary aim of our study was to demonstrate that wet cupping therapy provides excretion of markers associated with oxidative stress. As a result of our study, the presence of these markers in wet cup blood has been demonstrated. The second important finding of our study was that the levels of miRNA-200a, miRNA-34a, and miRNA-21, which are markers associated with oxidative stress, were higher in wet cupping blood samples compared to venous blood samples when both age groups were evaluated among themselves and when a general comparison was performed. GSH levels were higher in the venous blood sample than in the wet cup blood sample. These findings show that wet cupping therapy may significantly remove oxidant markers from the body while contributing to an increase in the antioxidant defense. The mechanism of action of wet cupping therapy is not fully known despite its common use. Wet cupping therapy might act through a lot of different mechanisms. We hypothesize that one of the mechanisms of action of wet cupping may be through oxidative balance, and our findings support our hypothesis. This study showed that venous blood and wet cupping blood did not have the same characteristics. Wet cupping blood had higher oxidants compared to venous samples. The therapeutic effects of wet cupping in various conditions might be due to the excretion of these oxidants from the body.

In conclusion, our findings show that miRNA-34a, miRNA-21, and miRNA-200a, which are involved in the pathogenesis of diabetes, cardiovascular diseases, or cancer through oxidative stress-mediated mechanisms in previous studies, are significantly removed from the body by cupping therapy. In addition, our findings indicate that MDA levels, which can cause oxidant damage, are reduced by cupping therapy, and antioxidant defense is improved. However, to prove the effects of cupping treatment on oxidant damage and these markers, further studies are needed in a larger population, especially involving the measurement of these markers before and after cupping therapy. We hope that the relationships between wet cupping and other harmful substances in the body will be investigated in the future and this preliminary study would be a guide for these studies.

Declarations

The authors have no conflicts of interest to declare.

This study was supported by the Necmettin Erbakan University Scientific Research Projects Office [Grant Number 181318002]. The authors would like to thank the Necmettin Erbakan University for funding this project.

This study was approved by the clinical research Ethics Committee of the Necmettin Erbakan University Faculty of Medicine (Date: 01.12.2017, Number: 2017/1110).

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Archives of Current Medical Research
Arch Curr Med Res 2023;4(3):186-191

Received: 10 August 2023
Revised: 23 August 2023
Acccepted: 12 September 2023
DOI: 10.47482/acmr.1340949

ORIGINAL ARTICLE

Primary epiploic appendagitis: A retrospective analysis of clinical and tomographic findings in 14 patients

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Abstract

Background: The aim of this study is to describe the clinical features and imaging findings of 14 patients diagnosed with primary epiploic appendagitis on computed tomography (CT).

Methods: Between January 2019 and August 2022, the hospital records of 14 patients were retrospectively reviewed. We recorded patients' age, gender, fever presence, blood leukocyte count (WBC), C-reactive protein (CRP) level, localization of abdominal pain, the presence of nausea or vomiting, the involved part of the colon on CT, whether they received treatment or not, and whether they underwent surgery.

Results: This study included 14 patients, 8 male and 6 female. Their ages ranged from 27 to 63. All patients presented with acute abdominal pain without an elevation in body temperature or a significant increase in inflammation markers. CT scan images showed a fat oval lesion corresponding to the inflamed epiploic appendix with a peripheral hyper-attenuated frame and a central "dot" in some cases referring to the thrombosed vessel. The patients were successfully treated with conservative methods.

Conclusions: Epiploic appendagitis can mimic surgical diseases such as appendicitis and diverticulitis due to its non-specific clinical presentation. CT scan is essential in diagnosing this disease, which can be managed with more conservative treatment methods.

Keywords: Primary Appendagitis Epiploica, Acute Abdomen, Computed Tomography.

Cite this article as: *Çevik B, Kasapoğlu B. Primary epiploic appendagitis: A retrospective analysis of clinical and tomographic findings in 14 patients. Arch Curr Med Res. 2023;4(3):186-191*

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INTRODUCTION

Appendices epiploica are pedicled formations rich in adipose tissue located on the colon wall. They are often found in the transverse and sigmoid colons. They can easily undergo torsion and infarction due to the weakness of their arterial supply and the freely movable pedicle (1).

Primary epiploic appendagitis (PEA) is an acute condition in which the surrounding tissues become inflamed after torsion or ischemia. Secondary epiploic appendagitis is defined as the inflammation that develops due to the spreading of infections from other intra-abdominal organs. PEA can mimic some surgical pathologies, such as appendicitis and diverticulitis, depending on its localization in the colon (2). PEA usually responds to conservative treatment. However, it may lead to unnecessary laparotomies in undiagnosed cases.

PEA is a rare disease, and the exact prevalence is unknown. However, the estimated frequency of PEA in patients with abdominal pain is reported as 1.1-1.3% (3). However, developments in imaging methods in recent years have facilitated the diagnosis of the disease and caused it to be recognized more frequently. Nowadays, the best diagnostic method for PEA is regarded as abdominal computed tomography. In general, computed tomography (CT) scans reveal an ovoid mass lesion with a fat-density appearance, encapsulated by a dense rim in all cases (4-6).

This study aimed to evaluate the clinical and tomographical findings in patients who presented to the emergency department with the complaint of abdominal pain and were diagnosed with PEA and to increase awareness about this disease, which is likely to be overlooked, especially in emergency services.

MATERIALS AND METHODS

In this study, it was retrospectively analyzed the CT scans of the patients who were admitted to the Lokman Hekim Akay Hospital emergency department with abdominal pain between January 2019 and August 2022. The study was conducted in accordance with the Declaration of Helsinki. The ethical approval was obtained from the Lokman Hekim University Ethics Committee (Date: 08.08.2023, No: 2023/143).

Approximately 780 CT scans of the patients, admitted to the emergency department with abdominal pain were retrospectively analyzed. We assessed the reports and included the patients who had the diagnosis of appendagitis epiploicae in the study. All other patients, with the diagnosis of any other causes of abdominal pain and/or malignancy were excluded from the study. A total of 14 patients who were diagnosed with appendices epiploica by computed tomography were included in this study.

The medical records of the patients were evaluated, and their age, gender, presence of fever, localization of abdominal pain, presence of nausea or vomiting, blood leukocyte count (WBC), C-reactive protein (CRP) level, the affected colon segment on CT, whether they received treatment, and if they underwent surgery were recorded.

Statistical Analysis Statistical analysis was performed with SPSS (Windows version 21.0, SPSS Inc., Chicago, IL, USA), using descriptive statistics tests.

RESULTS

This study included 14 patients, 8 males and 6 females, ranging in age from 27 to 63. Two patients presented with high fever. The WBC counts in 3 patients and the CRP levels in 7 patients were higher than normal. Pain localization was in the right lower quadrant for 2 patients, in the left upper quadrant for 1 patient, and in the left lower quadrant for 11 patients. The pain was accompanied by vomiting in 2 patients and nausea in 4 patients. The most common site of involvement on CT was the sigmoid colon (n=6). Other sites of involvement were the descending colon (n=5), cecum (n=2), and splenic flexure (n=1) (Table 1).

Table 1. Clinical examination and radiologic findings

Patient (n=14)	Sex	Age	Temperature	Nausea or vomiting	Site of pain	Segment of colon	WBC (4490-12680) /μL	CRP (0-5) mg/l	Clinical resolution delay (days)
1	M	32	37	nausea	left lower quadrant	sigmoid colon	7940	7.5	3
2	M	30	38.4	vomiting	left lower quadrant	sigmoid colon	12500	9.3	8
3	F	54	37.5	absent	right lower quadrant	caecum	9200	7.7	7
4	F	33	37.8	nausea	left lower quadrant	decending colon	13550	9.9	7
5	M	41	37	absent	left lower quadrant	decending colon	8470	8.58	5
6	M	51	37.4	absent	left lower quadrant	sigmoid colon	8860	20.03	10
7	M	27	36.8	absent	left lower quadrant	sigmoid colon	7770	3.31	4
8	M	43	37	nausea	right lower quadrant	caecum	7990	8.2	5
9	M	63	37	absent	left upper quadrant	splenic flexura	7580	5	3
10	F	43	36.9	absent	left lower quadrant	decending colon	7810	2.17	4
11	M	45	37.3	absent	left lower quadrant	sigmoid colon	7300	3.6	5
12	F	37	37	absent	left lower quadrant	decending colon	7900	6.2	3
13	F	41	37.8	nausea	left lower quadrant	sigmoid colon	8400	10.8	7
14	M	40	38.6	vomiting	left lower quadrant	decending colon	14700	13	11

CT scans consistently revealed an ovoid mass lesion with a fat-density appearance, encapsulated by a dense rim in all cases (Figure 1). Accompanying findings included a thickened lining of the peritoneum (Figure 2 A) and fat stranding around the appendage (Figure 1-2). In a subset of four cases, a prominently attenuated central dot was observed within the inflamed appendage (Figure 2 B). Table 1 presents a summary of the clinical examination and radiologic findings for each patient.

Figure 1. The contrast-enhanced CT image shows a central, heterogeneous, fat mass lesion with a peripheral hyperdense rim, situated anterior to the descending colon.

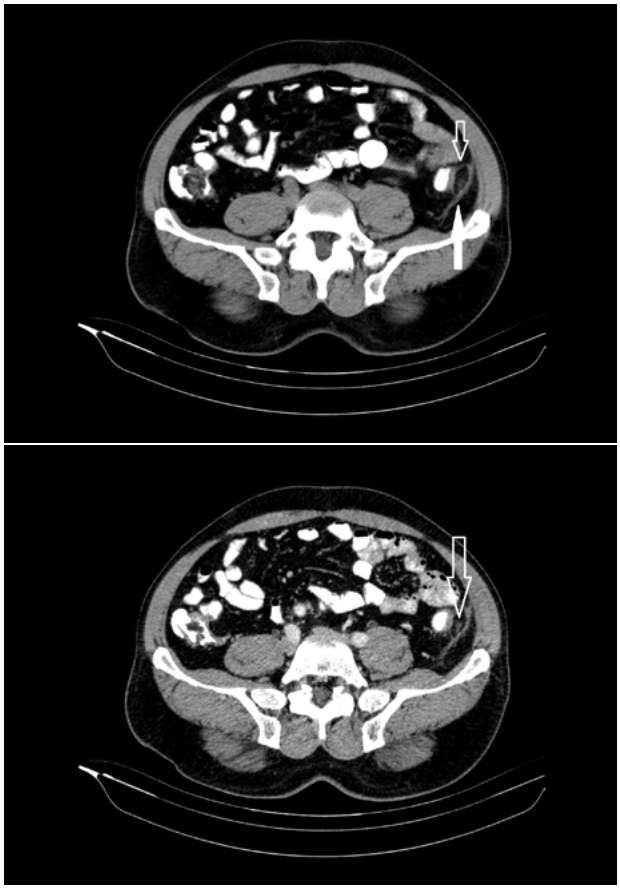

Figure 2 (A-B): The axial contrast-enhanced CT images show an oval fat lesion characterized by a hyper-attenuated peripheral border (A), and an associated localized thickening of the peritoneum (A, white arrow). Additionally, the CT images depict severe fat stranding, along with a fatty ovoid mass featuring a hyperattenuated rim and a central dot (B).

Figure 3. The contrast-enhanced CT image shows a central, heterogeneous, fat mass lesion with a peripheral hyperdense rim, situated anterior to the ceacum.

All patients recovered within 3-11 days with conservative treatment without complications. Surgery is not required for any of the patients.

DISCUSSION

Appendices epiploicae, rich in fat and with one or two small arteries and veins on its pedicle, was first described by the anatomist Vesalius in 1543. Torsion or vascular thrombosis from the pedicle of the appendices epiploicae can cause PEA due to inflammation (7). Lynn et al. first coined the term "epiploic appendagitis" in 1956, while CT characteristics of this condition were initially detailed by Danielson et al. in 1986 (8,9).

As a rare clinical pathology, PEA is most common in adults in their second to fifth decades and in obese individuals, and the incidence is four times higher in males than females (10,11). In our study, the mean age of the patients was 41.4 years. However, none of the patients were obese and, males outnumbered females. It often presents with acute-onset, non-migrating abdominal pain,with localized tenderness on abdominal palpation and rebound tenderness on some occasions. Fever, nausea, and vomiting may accompany abdominal pain.

With the more widespread use of imaging methods in recent years, PEA has been diagnosed more frequently. Although abdominal ultrasound is beneficial in diagnosing AE, it may not show any abnormality in some cases (12,13). In the abdominal ultrasound an oval or rounded, noncompressible, hyperechoic mass adjacent to the colonic surface, without internal vascularity surrounded by a hypoechoic line is the most common finding. Doppler images divulge the absence of central blood flow (14,15).

In a recent study, the diagnostic efficacy of ultrasound (US) was compared to CT in 92 patients with PEA and it was reported that the US was also highly sufficient for the diagnosis of PEA (16).

Ultrasound is a rapid, non-invasive imaging diagnostic test that may be helpful in the diagnosis of PEA in non-obese patients. However, CT is currently considered the gold standard for definitive diagnosis (17,18). The following CT findings can be observed in PEA: an oval mass with a hyperdense ring, thickening of the parietal peritoneum, a hyper-dense thrombosed drainage vessel (the "central point" sign), intestinal wall thickening, mass localization in front of the colon wall, and adjacent mesenteric inflammation, which appears on imaging as a characteristic "fat stranding" sign (19-22). In our study, CT scans consistently revealed an ovoid mass lesion with a fat-density appearance, encapsulated by a dense rim in all cases. Accompanying findings included a thickened lining of the peritoneum and fat stranding around the appendage. In a subset of four cases, a prominently attenuated central dot was observed within the inflamed appendage. The first and most important point in the diagnosis of PEA is the awareness and suspicion of the clinicians and radiologists. Since there is not a specific pathognomonic clinical or laboratory finding, imaging modalities gain more importance in the diagnosis.

Although PEA can occur in any segment of the colon, the sigmoid colon is most commonly affected (19). This was also the most common site of involvement in our cases, followed by the descending colon.

Appendagitis epiploica is typically a self-resolving condition with the majority of patients experiencing relief from symptoms within 1-14 days following treatment with analgesic drugs (23, 24). In the cases we examined, recovery was observed within a period of 3 to 11 days under conservative management. However, in instances where symptoms fail to improve, exacerbate, or when complications like abscesses or intestinal obstruction arise, consideration for antibiotics or surgical intervention might be necessary (23). The most common differential diagnoses of PEA include acute diverticulitis, acute appendicitis, ovarian torsion, acute cholecystitis, omental infarction, neoplasms, diverticulitis, and mesenteric panniculitis, depending on the site of involvement (24,25). Unfortunately, most of those diseases may require long-term treatments and surgery. To avoid unnecessary hospitalizations and invasive treatments, clinicians should be aware of this more harmless condition in the differential diagnosis of acute abdominal pain.

There are some limitations of this study that should be mentioned. First, the number of patients included in the study is not large; but since this is a rare disease, we tried to include all cases diagnosed with PEA in the emergency department. Second, the follow-ups, or the ultrasound findings were not present in the hospital records of all patients.

In conclusion, epiploic appendagitis is a self-limiting disease that responds well to conservative treatment. In our experience, many clinicians can manage the disease with the support of a radiologist. It should be kept in mind in the differential diagnosis of patients with acute abdominal pain since recognizing PEA, which is a relatively rare cause of acute abdomen, can prevent unnecessary hospitalizations, treatments, and surgeries.

Declarations

The authors have no conflicts of interest to declare. The authors declared that this study has received no financial support.

The study was conducted in accordance with the Declaration of Helsinki. The ethical approval was obtained from the Lokman Hekim University Ethics Committee (Date: 08.08.2023, No: 2023/143).

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Archives of Current Medical Research
Arch Curr Med Res 2023;4(3):192-197

Received: 20 August 2023
Revised: 25 August 2023
Acccepted: 1 September 2023
DOI: 10.47482/acmr.1346676

ORIGINAL ARTICLE

The effect of SGLT2 inhibitors on cardio-electrophysiological balance index in diabetic patients with preserved ejection heart failure

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Abstract

Background: Heart failure with preserved ejection fraction (HFpEF) is a syndrome commonly associated with type 2 diabetes mellitus (DM). The use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors, which have been shown to have cardioprotective effects in HFpEF, has increased in frequency. The index of cardio-electrophysiological balance (iCEB) is a marker that can be calculated for electrocardiography (ECG) and has been proven to be a good predictor of ventricular arrhythmia. This study aimed to investigate the effects of SGLT-2 inhibitors on the iCEB and the iCEBc in HFpEF patients with type 2 DM.

Methods: We retrospectively analyzed the data of 76 patients with type 2 DM with HFpEF who were started on SGLT-2 inhibitors. We compared the ECG parameters obtained at baseline and six-month follow-up.

Results: The mean age of the patients included in the study was 64.7±8.9 years. When ECG parameters before and after treatment were compared, iCEB (4.33±1.95 vs. 4.24±1.50, p=0.006) and iCEBc (4.67±1.35 vs. 4.59±1.36, p<0.001) values were found to be lower compared to before treatment.

Conclusions: The iCEB and iCEBc values of patients decreased considerably with the use of SGLT-2 inhibitors. These results suggest that SGLT-2 inhibitors may reduce the risk of ventricular arrhythmia in patients with HFpEF.

Keywords: Diabetes Mellitus, Index of Cardio-Electrophysiological Balance, Sodium-Glucose Co-Transporter-2 Inhibitors, Preserved Ejection Fraction Heart Failure.

Cite this article as: *Gökalp G, Özbeyaz NB. The effect of SGLT2 inhibitors on cardio-electrophysiological balance index in diabetic patients with preserved ejection heart failure. Arch Curr Med Res. 2023;4(3):192-197*

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INTRODUCTION

Diabetes mellitus (DM), with its rampant prevalence and various adverse cardiovascular consequences, is a chronic disease that needs to be understood in all its aspects (1). With increasing sedentary life and obesity, type 2 DM, which constitutes nearly 90% of the diabetic group in recent years, poses a higher risk of adverse cardiovascular disease compared to type 1 (2). Among the adverse cardiovascular outcomes in patients with type 2 DM, heart failure (HF) is important in terms of morbidity and mortality (3, 4). Epidemiologic and clinical data over the past 20 years have shown that the prevalence of HF in type 2 DM is very high and that the prognosis in patients with HF with type 2 DM is worse than in patients without type 2 DM (5). In antidiabetic drug studies, the rate of HF is reported to be up to 30% in the diabetic population (6). Type 2 DM causes unique adverse changes in the myocardium independent of traditional risk factors, such as coronary artery disease, hypertension (HT), and valvular heart disease, increasing the risk of all three phenotypes of HF, i.e., preserved, reduced, and midrange ejection fraction (HFpEF, HFrEF, and HFmrEF, respectively) (7). However, the most common type of HF in type 2 DM is HFpEF, which accounts for approximately half of the population (8, 9).

HFpEF is a phenotype of HF associated with type 2 DM, advanced age, female gender, HT, obesity, and atrial fibrillation, with normal systolic function (EF≥50%) and impaired diastolic function (7). It is a syndrome characterized by left ventricular (LV) diastolic dysfunction, increased LV filling pressure, decreased LV volume, and coronary microvascular dysfunction (10). The mechanisms for explaining these pathologies are not yet precise. However, increased oxidative and metabolic stress, systemic inflammation, and myocardial fibrosis with type 2 DM are thought to be involved in the development of HFpEF (7).

Until recently, conventional HF drugs were not effective in treating HFpEF. However, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, an antidiabetic drug group, have revitalized treatment with favorable results for HFpEF (11). In the EMPEROR-Preserved study of nearly 6,000 patients, empagliflozin reduced the risk of cardiovascular death and hospitalization with HFpEF, independent of type 2 DM (12). Another large cohort study of HFpEF and HFmrEF patients treated with another SGLT-2 inhibitor, dapagliflozin, found that it reduced the risk of worsening HF and cardiovascular death (13). Increasing evidence has elevated SGLT-2 inhibitors to the preferred option for the treatment of all types of HF.

SGLT-2 inhibitors are antidiabetic agents that reduce glucose reuptake from the renal proximal tubules, leading to increased urinary glucose excretion (5). In addition to providing glycemic control, primarily through glucosuria with their renal effect, these inhibitors reduce the number of major cardiovascular events and hospitalizations due to HF, independent of type 2 DM, thanks to their positive systemic effects (12, 13). Although the mechanisms of their beneficial cardiac effects are unclear, the standard views are that they improve myocardial remodeling, myocardial fibrosis and hypertrophy, and increase cardiac energy production (14, 15). In addition, their effect on arrhythmia has also been studied. Although the direct effects of SGLT-2 inhibitors on sodium and calcium (L-type) ion channels have been demonstrated in animal studies, their effects on other stages of cardiac action potential still need to be determined (16).

As in many cardiovascular diseases, the risk of malignant arrhythmias increases in the presence of HF (17). One of the most important baseline tests for predicting the development of malignant arrhythmias is 12-lead surface electrocardiography (ECG). QT and heart rate-corrected (QTc) distances, which indicate ventricular repolarization for ECG, are classic electrocardiac parameters used to predict ventricular arrhythmias (18). In addition, a somewhat newer parameter, the Tp-e (Tpeak-Tend) distance and the ratio of Tp-e to QT and QTc are predictive markers of ventricular arrhythmia (19). Increases in all of these electrocardiac parameters and rates have previously been shown to be associated with ventricular arrhythmogenesis (20). The index of cardio-electrophysiological balance (iCEB), calculated as the QT distance divided by the QRS distance in ECG, is a new and popular marker for predicting ventricular arrhythmia. Noninvasive and enabling the simple measurement of iCEB, it is used as a surrogate of cardiac wavelength, which indicates susceptibility to ventricular arrhythmia and can only be measured by an invasive electrophysiological study (21, 22). Our study aimed to evaluate the effect of SGLT-2 inhibitors on the iCEB and the iCEBc in HFpEF patients with type 2 DM.

MATERIALS AND METHODS

All of the procedures performed in our study comply with the ethical standards of the corporate committee. Our study also complies with the ethical standards of the Declaration of Helsinki. This study was approved by the clinical research Ethics Committee of the Etlik City Training and Research Hospital (Date: 14.06.2023, Number: AEŞH-EK1-2023-272).

Study population

Our single-center observational study was conducted retrospectively by examining patients with type 2 DM with a diagnosis of HFpEF who had been started on SGLT-2 inhibitors (dapagliflozin or empagliflozin) in the internal medicine outpatient clinic between November 2022 and June 2023. Data were obtained from 98 of 147 patients.

Patients with acute HF, low EF (<50%), advanced valvular heart disease, prosthetic valvular heart disease, complete bundle branch block, atrial fibrillation, advanced renal failure (grade 4–5), hepatic failure, active infection, electrolyte abnormalities, malignancy, and patients taking antiarrhythmic drugs at baseline or throughout treatment were excluded. The study was conducted with a total of 76 patients, minus 22 due to exclusion criteria. The participants' baseline demographic, laboratory, and echocardiographic data were recorded by reviewing the hospital records system. The 12-lead surface ECG data obtained from the hospital registry system were evaluated at baseline and six months after SGLT-2 inhibitors were administered.

Electrocardiography

The recording speed of 12-lead ECG data for all patients was 25 mm/sec and the amplitude was 10 mm/mV. To ensure adequate amplification when measuring ECG parameters, the recordings were computerized and evaluated by two different cardiologists. The intraobserver and interobserver coefficients of variation were <5%. In the case of differing results, mean measurements were taken as the basis. In ECG recordings, heart rate, QRS duration, QT interval, and Tp-e interval were measured manually. The distance from the beginning to the end of the QRS wave was defined as the QRS duration. The QT interval was defined as the time from the beginning of the QRS to the end of the T wave. The QTc was calculated by Bazett's formula (QTc=QT/√RR). The Tp-e interval was determined by measuring the distance from the peak of the T wave to the end of the T wave in lead V5 (23). Using these measurements, the Tp-e/QT and Tp-e/QTc ratios were calculated. The iCEB was obtained by dividing the QT interval, and the iCEBc was obtained by dividing the QTc interval by QRS duration (D2 or V5) (22).

Statistical analysis

Statistical analyses were conducted using the IBM SPSS 23.0 statistical software package. Before performing significance tests, the Levene test was used to determine the homogeneity of variances and the Kolmogorov–Smirnov test was used to evaluate whether continuous variables were normally distributed. The dependent groups t-test was used to compare the ECG data of patients at admission and six months after admission. The significance level was set to $p<0.05$ for all statistical analyses.

RESULTS

A total of 76 patients were included in the study. The mean age of the patients was 64.7±8.9 years; 44 (58.2%) of the patients were female. Empagliflozin was started in 47 (61.8%) patients and dapagliflozin in 29 (38.2%). Table 1 shows the baseline demographic and clinical characteristics of the patients who participated in the study.

Table 1. Baseline characteristics of the study population

Demographic characteristics	N=76
Age (years)	64.7±8.9
Male, n(%)	32(41.8)
Hypertension, n(%)	48(63.5)
Hyperlipidemia, n(%)	20(26.1)
Coronary artery disease, n(%)	12(15.3)
BMI, kg/m^2	29.6±2.7
Echocardiographic findings	
LVEF %	62.8±4.3
LV diastolic diameter, mm	46.4±5.1
LV systolic diameter, mm	28.5±3.8
LA diameter, mm	39±2.7
IVS, mm	1.28±0.4
Laboratory characteristics	
Hemoglobin, g/dl	12.7±5.3
Glucose, mg/dl	148±29
Creatinine, mg/dl	1.1±0.3
Platelet, 10^9/l	275±44
Na, meq/L	136±18
K, meq/L	4.1±1.3
HbA1c, %	7.9±0.9
Medications	
Beta-blocker	70(92)
Renin-angiotensin-aldosterone inhibitors	73(96)
Calcium channel blockers	33(43)
Diuretic (hydrochlorothiazide-indapamide)	72(95)
Metformin	74(98)
Sulfonylureas	8(11)
Dipeptidyl dipeptidase-4 inhibitors	27(35)
Thiazolidinediones	5(7.1)
Glucagon-like peptide-1 receptor agonist	3(3.4)
Insulin	49(65)

BMI: body mass index, LV: left ventricle, EF: ejection fraction, IVS: interventricular septum diameter, WBC: white blood cell, HbA1c: glycosylated hemoglobin

When ECG data at admission and six months were compared, the QT interval (368.2±31.3 vs. 361.4±22.6, p=0.008), the QTc interval (397±37.6 vs. 390.8±35.5, p=0.002), the Tp-e interval (101±19 vs. 92±17, p=0.012), the Tp-e/QT (0.28±0.09 vs. 0.23±0.06, p<0.001), the Tp-e/QTc (0.26±0.08 vs. 0.22±0.07, p=0.001), the iCEB (4.33±1.95 vs. 4.24±1.50, p=0.006), and the iCEBc (4.67±1.35 vs. 4.59±1.36, p<0.001) had decreased compared to pretreatment. No significant difference was found between heart rate and QRS duration (Table 2).

Table 2. Pretreatment and posttreatment electrocardiographic changes in the study population

Parameters	Pretreatment	Post-treatment	P
Heart rate, beat/min	87±11	86±10	**0.013**
QT interval, ms	368.2±31.3	361.4±22.6	**0.008**
QTc interval, ms	397±37.6	390.8±35.5	**0.002**
QRS duration, ms	85±16	85±15	**0.198**
Tp-e interval, ms	101±19	92±17	**0.012**
Tp-e/QT	0.28±0.09	0.23±0.06	**<0.001**
Tp-e/QTc	0.26±0.08	0.22±0.07	**0.001**
iCEB	4.33±1.95	4.24±1.50	**0.006**
iCEBc	4.67±1.35	4.59±1.36	**<0.001**

iCEB: index of cardio-electrophysiological balance, ms: milliseconds

DISCUSSION

Our study investigated the effect of SGLT-2 inhibitors on different electrocardiographic parameters and cardiac electrical activity in type 2 DM patients with HFpEF. In these patients, iCEB and iCEBc values were found to have been reduced by SGLT-2 inhibitors. In addition, QT, QTc, Tp-e distances, and Tp-e/QT and Tp-e/QTc ratios had also been considerably decreased. To our knowledge, our study is the first to show the effect of SGLT-2 inhibitors on the iCEB in HFpEF patients with type 2 DM.

The frequency of ventricular arrhythmias can lead to an increase in sudden death with HFpEF. The mechanisms of ventricular arrhythmias in this patient group were multifaceted. These mechanisms comprised i) decreased conduction velocity with ventricular hypertrophy, ii) increased re-entry circuits with ventricular fibrosis, and iii) delayed repolarization caused by the upregulation of potassium channels (17). It was previously shown that the

frequency of ventricular arrhythmias due to repolarization abnormalities, independent of HF, increased in type 2 DM (24). In addition, the role of SGLT-2 inhibitors (which have shown mortality benefits in HF patients) in terms of cardiac arrhythmias has aroused curiosity and guided studies. For these reasons, we formulated our study population from type 2 DM patients with HFpEF who had an increased risk of ventricular arrhythmia. We evaluated the ventricular arrhythmia risk markers of SGLT-2 inhibitors using ECG parameters, a noninvasive, accessible, and simple test.

Our study used a newer ECG parameter, the iCEB, in addition to the classic repolarization parameters used as ventricular arrhythmia risk markers. The iCEB is an ECG parameter that estimates the invasively measurable cardiac wavelength, which is associated with both the repolarization and depolarization of cardiac electrical activity. The iCEB was previously shown to be associated with ventricular arrhythmias, independent of torsade de pointes (21, 22). A recent study showed that SGLT-2 inhibitors reduced iCEB and iCEBc values within physiological limits in diabetic patients without HF (25). Our study evaluated patients with HFpEF in whom SGLT-2 inhibitors have achieved breakthroughs in treating HFpEF. Our study found that SGLT-2 inhibitors also lowered the iCEB and iCEBc in patients with HFpEF. This decrease in iCEB values was related to the shortened QT distance, as there was no significant change in QRS duration compared to the baseline.

In ECG, the classic ventricular repolarization and torsadogenicity parameter is the QT interval. The duration of the QT interval depends on heart rate; accordingly, the QTc value is more commonly used (26). Modern computer-based ECG devices can calculate QTc automatically. However, the use of different correction formulas is less sensitive to identifying individuals at high risk of ventricular arrhythmias (27). Therefore, we manually calculated QTc using Bazett's formula in the current study. Although different results were obtained in previous studies that evaluated the effect of SGLT-2 inhibitors on QT and QTc distances, the common conclusion is that they do not prolong QT and QTc (25, 28, 29). In our study, QT and QTc distances, among the ventricular repolarization parameters, were significantly decreased with the use of SGLT-2 inhibitors.

In our study, the changes that SGLT-2 inhibitors caused on Tp-e distance, a proarrhythmogenic marker for ECG, were also evaluated. The Tp-e distance is a parameter showing the distribution of transmural repolarization. An increase in this distance has been associated with malignant arrhythmias and sudden cardiac death (30). Previous studies provided evidence that SGLT-2 inhibitors favorably modified the Tp-e distance in diabetic patients (25, 28). Our study supports existing research, as it was observed that Tp-e distances lessened with the use of SGLT-2 inhibitors. In addition, since both Tp-e distance and QT, as well as QTc distances may vary according to body weight, Tp-e/QT and Tp-e/QTc ratios were recently used to increase the sensitivity of these parameters in predicting arrhythmogenicity (20). In our study, Tp-e/QT and Tp-e/QTc ratios decreased with SGLT-2 inhibitor treatments, as did QT, QTc, and Tp-e distances.

Previous studies suggested that SGLT-2 inhibitors reduced the risk of arrhythmias through cardioprotective mechanisms, such as having direct effects on myocyte ion channels, lowering blood pressure, reducing afterload and preload, improving myocardial fibrosis and hypertrophy, and sympathetic nervous system blockade (15, 31). Since our study was retrospective, it is impossible to explain the causality of the favorable effects of SGLT-2 inhibitors on the iCEB and other proarrhythmic predictive parameters. However, our results suggest that SGLT-2 inhibitors contribute to lowering the risk of ventricular arrhythmia in type 2 DM patients with HFpEF in addition to enabling glycemic control.

In conclusion, in type 2 DM patients with HFpEF, SGLT-2 inhibitors meaningfully reduced QT, QTc, Tp-e, Tp-e/QT, Tp-e/QT, Tp-e/QTc, iCEB, and iCEBc parameters. Prospective and comprehensive cohort studies are needed to prove the association of the results in our study with a reduced risk of malignant arrhythmias.

The primary limitation of this study is that it was single-center focused and included a small sample. The patients in the sample group had no data on the severity of HF. Another major limitation was that arrhythmias or sudden cardiac deaths that may develop in patients could not be followed up due to the retrospective study design.

Declarations

The authors have no conflicts of interest to declare. The authors declared that this study has received no financial support.

This study was approved by the clinical research Ethics Committee of the Etlik City Training and Research Hospital (Date: 14.06.2023, Number: AEŞH-EK1-2023-272).

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