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Supplement

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Online article not yet published in an issue

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Book

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Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. I n: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93113.

Journal article on the Internet

Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. Am J Nurs [serial on the Internet] 2002 [cited 12 Aug 2002]; 102. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website

Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 Jul 2002]. Available from: www.cancer-pain.org

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The Intensive Care Society of Australia and New Zealand. Mechanical ventilation strategy in ARDS: Guidelines. Int Care J Aust 1996;164:282-4.

Acknowledgements

The source of financial grants and the contribution of colleagues or institutions should be acknowledged.

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Abbreviations that are used should be defined in parenthesis where the full word is first mentioned. Some common abbreviations can be used, such as iv, im, po, and sc.

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Editorial Correspondence

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Original Article / Orijinal Araştırma

The Association between Serum Soluble Klotho Level and Cardiovascular Disease and Mortality in Routine Hemodialysis Patients

Rutin Hemodiyaliz Hastalarında Serumda Soluble Klotho Seviyesi ile Kardiyovasküler Hastalıklar ve Mortalite Arasındaki İlişki

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Abstract

Aim: Serum sKlotho plays a role in identifying the risk of cardiovascular disease or death in some human populations and animal experiments. In this study, the relationship between sKlotho levels and echocardiographic parameters after 18 months of follow-up and mortality at 30 months of follow-up in routine hemodialysis patients was investigated.

Matarial and Method: Groups of patients with different sKlotho rates (≥1.24 ng/ml and <1.24 ng/ml) and ages (<54 years and ≥54 years) were compared.

Results: No significant difference was found between the left ventricular mass index and left ventricular mass parameters calculated between the sKlotho <1.24 and ≥1.24 groups. No significant difference was found between the left ventricular mass index and left ventricular mass parameters calculated between the two different age (<54 years and ≥54 years) groups. In order to determine the association between sklotho and all-reason mortality in 136 patients followed for 30 months, two groups of 34 patients who died and 102 patients who survived were compared. A significant difference was observed between these two groups in terms of age, entry creatinine, sodium bicarbonate, C-reactive protein, albumin level and existence of Diabetes Mellitus. Although there was no considerable distinction in the two groups with regards to sklotho values, the sklotho level was found to be lower in the deceased group.

Conclusion: We think that sKlotho is not an appropriate indicator to predict uremic cardiomyopathy in the long term, but sKlotho levels may be useful in predicting mortality in studies with larger patient populations.

Keywords: Cardiomyopathy, hemodialysis, sKlotho

Öz

Amaç: Serum sKlotho, bazı insan populasyonlarında ve hayvan deneylerinde kardiyovasküler hastalık veya ölüm riskini belirlemede rol oynar. Bu çalışmada rutin hemodiyaliz hastalarında 18 aylık takip sonrası sKlotho düzeyleri ile ekokardiyografik parametreler ve 30 aylık takipteki mortalite arasındaki ilişki araştırıldı.

Gereç ve Yöntem: Farklı sKlotho oranları (≥1,24 ng/ml ve <1,24 ng/ml) ve yaşları (<54 ve ≥54) olan hasta grupları karşılaştırıldı.

Bulgular: sKlotho <1,24 ve ≥1,24 grupları arasında hesaplanan sol ventrikül kütle indeksi ve sol ventrikül kütle parametreleri arasında anlamlı fark bulunmadı. İki farklı yaş (<54 yaş ve ≥54 yaş) grubu arasında hesaplanan sol ventrikül kütle indeksi ve sol ventrikül kütle parametreleri arasında anlamlı fark bulunmadı. 30 ay takip edilen 136 hastada sKlotho ile tüm nedenlere bağlı ölüm arasındaki ilişkiyi belirlemek için, ölen 34 hasta ve yaşayan 102 hastadan oluşan iki grup karşılaştırıldı. Bu iki grup arasında yaş, giriş kreatinin, sodyum bikarbonat, C-reaktif protein, albümin düzeyi ve Diabetes Mellitus varlığı açısından anlamlı fark gözlendi. Sklotho değerleri açısından iki grup arasında belirgin bir fark olmamasına rağmen, ölen grupta sKlotho düzeyi daha düşük bulundu.

Sonuç: sKlotho'nun uzun dönemde üremik kardiyomiyopatiyi öngörmede uygun bir gösterge olmadığını, ancak sKlotho düzeylerinin daha geniş hasta popülasyonlu çalışmalarda mortaliteyi öngörmede yararlı olabileceğini düşünüyoruz.

Anahtar Kelimeler: Kardiyomiyopati, hemodiyaliz, sKlotho

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INTRODUCTION

Cardiovascular disease (CVD) is one of the main causes of mortality in routine hemodialysis patients. The CVD mortality rate in patients on routine hemodialysis is 10-20 times higher than in the general population.[1] In chronic kidney disease (CKD), soluble klotho (sKlotho) has a significant role in cardiovascular disease and death.[2-4]

sKlotho is a single transition transmembrane protein with a long extracellular body and short cytoplasmic tail that seems to regulate senility process.[5] Overexpression of the Klotho gene extends lifetime, while defective Klotho proteins are related with early death.[6,7] Moreover, serum sKlotho likely plays a role in identify the risk of cardiovascular disease or death in some populations and animal experiments.[4,8]

Serum sKlotho is reduced in the early stages CKD due to the effects of uremic toxins on DNA methyltransferase protein expression, which withdraws Klotho by hypermethylation.[19 This is why CKD or dialysis patients generally are disposed to to have lower sKlotho amounts than healthy individuals.[10-12]

Serums Klotho has been related with cardiovascular diseases and mortality in the general population and several subpopulations (i.e. the geriatric or client with diabetes).[13,14] On the other hand related research in CKD patients are inconsistent. The inconsistencies between studies in patients receiving hemodialysis treatment also aroused curiosity about the role of sKlotho in this patient group.

In this study, the relationship between sKlotho levels and echocardiographic parameters after 18 months of follow-up and mortality at 30 months of follow-up in routine hemodialysis patients was investigated.

MATERİAL AND METHOD

In this study, 136 routine hemodialysis patients aged between 18-80 years who were treated in the hemodialysis unit from December 2019 to February 2020 were included. 56 of these patients with echocardiographic results at the beginning and 18 months later were included in the research to define the long-term relationship between sKlotho and uremic cardiomyopathy and echocardiographic parameters. In addition, 136 patients were included in the study to evaluate the relationship between sKlotho and all-cause mortality by being followed up from our hemodialysis center and system. Patients who did not have an echocardiography at the beginning or after 18 months, who left our hemodialysis center, who died, who have a malignancy, under the age of 18, who have an autoimmune disease, who have a mitral valve disease, who have coronary artery disease, who have severe heart failure (New York Heart Association Class III or IV), who have a history of primary cardiomyopathy and who have active infection were removed from the research.

Initial sKlotho values and echocardiographic results at the beginning and after 18 months were recorded for all patients. General information, age, time of dialysis admission, underlying CKD etiology and comorbidity status of all patients were also enrolled. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured before hemodialysis in the middle of the week were recorded. The blood results of all patients within the scope of the study were recorded, including the laboratory values at the beginning and after 18 months were simultaneously measured in 3-month periods sodium (Na), potassium (K), calcium (Ca), phosphorus (P), parathormone (PTH), hemoglobin (Hg), creatinine, albumin, C-reactive protein (CRP), ferritin, uric acid. Blood sample for sKlotho was received into standard biochemistry tubes. The peripheral venous blood samples were centrifuged at 3000g for 5 minutes, their serums were split and maintained at -20'C until the working day. Serums were melted on the day of study and all samples were analized on the same day.

The delta (Δ) difference values of the beginning and after 18-months laboratory values and echocardiography results of the patients were obtained. Values at the beginning and after 18 months were compared. Patients who died were enrolled to investigate the relationship between sKlotho and mortality based on 30-month follow-up.

Patients were separated into two groups as sKlotho value ≥1.24 ng/ml and <1.24 ng/ml according to the median value at the beginning. In addition, according to the median age at the beginning, it was separated into two groups as <54 years and ≥54 years. Initial patients were divided into two groups as deceased and surviving patients.

Echocardiographic Examination

Comprehensive echocardiography was implemented to patients in the cardiology clinic with a Philips Epiq 7G device (Philips, The Netherlands). Ventricular wall thick, ejection fractions, left atrium, M mode aorta systole and diastole diameter were measured

The left ventricular mass (LVM) was estimated through the Devereux equation: Left ventricular mass (gram)=0.8{1.04[(LVEDD+IVST+PWT)3_(LVEDD)3]}+0.6.[15] Surface area of the body was estimated with the Mosteller formula: Surface area of the body (m^2): (body weight x height/3600)1/2.[16]

Left ventricular mass index was estimated as:(LVMI)=(LVM/ body surface area) LVEDD: The end of the left ventricular end diastole diameter IVST: inter-ventricular septum thick PWT: left ventricular posterior area thick, VA: body weight, LA: Left atrial diameter, LVSF: Left ventricular systolic failure.

Echocardiographic measurements (Δ) values of the patients at baseline and after 18 months were calculated.

Statistical Analysis

Statistical analyses were made with the SPSS 22.0 (IBM) package program. Kolmogorov Smirnov and Shapiro Wilk tests were used for normality analysis. T-test was applied for determination of normally distributed parameters in pairwise comparisons and Mann-Whitney U test was used for non-normally distributed parameters. Spearman Correlation Test was used to detect correlation and cox-regression analysis to detect independent parameters. Values were given as the mean for those with regular distribution, and as the median (minimum-maximum) for those not normally distributed. Two groups with sKlotho rates ≥1.24 ng/ml and <1.24 ng/ml were compared. Statistics were made among the separated groups by separating them two groups with respect to age as <54 years and ≥54 years. In order to determine its relationship with all-cause mortality, patients were separated two groups as living and non-living patients. Parameters with P<0.05 were considered significant in paired comparisons.

RESULTS

There was no considerable distinction in the ΔSKB, ΔCa, ΔP, ΔPTH, ΔAlbumin, ΔHCO₃, ΔHgb parameters between the two groups divided with respect to the Sklotho <1.24 and ≥1.24 values of the 56 patients included in the study (**Table 1**). In the cox-regression analysis performed on parameters with P<0.1 to detect the presence of independent parameters, the presence of DM was found to be independently related with sKlotho levels. In addition, no significant difference was found between the ΔLA, ΔLVMI, ΔLVM, ΔLVEF, ΔIVST-PWT and Kt\V parameters calculated between the two groups (**Table 2**). While a significant difference was found between the two groups in terms of ΔSBP in the pairwise comparison according to age (<54 and ≥54 years), no considerable distinction was determined in the ΔCa, ΔP, ΔPTH, ΔAlbumin, ΔHCO₃, and ΔHgb parameters (**Table 1**). In addition, no significant difference was found between the ΔLA, ΔLVMI, ΔLVM, ΔLVEF, ΔIVST-PWT and Kt\V parameters calculated between the two groups (**Table 2**). According to the results of Spearman Correlation Analysis, it was determined that there is a correlation between ΔLVM and ΔCa, ΔLVEF with ΔSKB and ΔPTH, and ΔLA and ΔPTH. In order to determine the association between sklotho and all-reason mortality in 136 patients followed for 30 months, two groups of 34 patients who died and 102 patients who survived were compared (**Table 3**). A significant difference was observed between these two groups in terms of age, entry creatinine, HCO₃, CRP, albumin level and existence of DM (**Table 3**). However there was no considerable distinction in the two groups with regard to sklotho values, the sklotho level was found to be lower in the deceased group (P:0.084) (**Table 3**). In addition, P:0.057 was found to be the borderline value in terms of LVEF values between the two groups, and it was found to be lower in the deceased group. Age, CRP and HCO₃ levels were higher in the group of patients who died. Albumin, entry creatinine and sklotho were found to be lower (**Table 3**).

Table 1. Biochemical and demographic parameters

Parameters	sKlotho ≥ 1.24 ng/ml (n:30)	sKlotho < 1.24 ng/ml (n:26)	P	Age < 54 groups (n:35)	Age ≥ 54 groups (n:21)	P
Gender male female	 17 (57 %) 13 (43 %)	 13 (50 %) 13 (50 %)	0,261	 15 (42.9%) 20 (57.1%)	 9 (43 %) 12 (57 %)	0.174
Δ SBP (mm/Hg)	5.3±21.6	3.6±16.8	0.761	2.9±32.5	20.9±30.1	0.043
Δ DBP (mm/Hg)	0 (-20 - 20)	0 (-20 - 20)	0.627	0 ((-20)- 80)	10 ((-10) - 80)	0.060
Δ Kt/V urea	0.04 (-1.5-1.4)	1.70±0.26	0.331	0.08(1.52-2.0)	0 ((-1.28)-1.4)	0.175
Δ Calcium (mg/dl)	0.2±0.7	0.2±0.6	0.927	0.3±0.6	0.5±2.0	0.516
Δ Phosphorus (mg/dl)	-0.3±1.5	-0.2±1.4	0.756	-0.2±1.6	-0.1±1.7	0.859
Δ PTH (ng/ml)	-67.6±324.7	-139±444	0.506	-97.9±403	-62.8±316.8	0.735
Δ Albumin (g/dl)	0.3±0.3	0.3±0.4	0.763	0.4±0.5	0.4±0.9	0.853
Hb (g/dl)	0.5±1.5	0.2±1.6	0.404	0.4±3	0.7±1.8	0.720
Δ HCO₃ (mEq/L)	4.4±3.5	4.8±3.4	0.641	4.2±3.4	6.2±6.0	0.132

SBP: Systolic blood pressure DBP: Diastolic blood pressure Kt/V: Measure dialysis adequacy PTH: Parathroid hormone Hb:Hemoglobine HCO₃: Bicarbonate Δ:delta

Table 2. Comparison of echocardiographic parameters of sclotho and age groups

Parameters	sKlotho ≥ 1.24 ng/ml (n:30)	sKlotho < 1.24 ng/ml (n:26)	P	age < 54 groups (n:35)	age ≥ 54 groups (n:21)	P
Δ LA (cm)	0 ((-0.80)-1.2)	0.05 ((-0.6)-1.4)	0.867	0.1((-0.8)-1.4)	-0.1 ((-0.6)-1.2)	0.486
Δ LVMI (g/m²)	-14.9((-1962)-26.8)	0.02((-56)-55.9)	0.185	0 ((-119.9)-56)	-15.3((-1962)-18.8)	0.256
Δ LVEF (%)	0 ((-44.5)-25)	0 ((-5)-21)	0.560	0 ((-44.5)-25)	0 ((-22)-25)	0.696
ΔIVST/PWT	0 ((-0.11)-1.1)	0 ((-0.9)-0.20)	0.637	0 ((-0.1)-0.1)	0.01 ((-0.18)-107)	0.202

LVM: Left ventricular mass LVMI: Left ventricular mass index was IVST: inter-ventricular septum thick PWT: left ventricular posterior wall thick, LA: Left atrial caliber LVEF: Left ventricular ejection fraction

Table 3. Comparison of groups according to mortality status.

Parameters	Mortality group n:34	Living group n:102	P
sKlotho (ng/ml)	0.99 (0.7-7.5)	1.33 (0.65-21.9)	0.084
Age (year)	63.3±12.3	50.8±18.2	<0.001
BMI (g/m²)	26.9±6.2	25.5±5.9	0.295
Creatinine before dialysis (mg/dL)	6.7±2.0	7.8±2.3	0.019
Phosphorus (mg/dl)	4.5±1.5	4.9±1.6	0.270
Potassium (mmol)	5.1±0.9	5.3±0.7	0.355
HCO_3 (mEq/L)	20.2±3.1	18.8±2.9	0.016
Uric acid (mg/dl)	5.4±1.1	5.6±1.2	0.119
Gender Male Female	 18 (47.1%) 16 (52.9%)	 51 (50%) 51 (50%)	0.461
DM Yes No	 21 (61.8%) 13 (38.2%)	 29 (28.4%) 73 (71.6%)	0.001
Duration dialysis (month)	35 (3-108)	34.5 (3-271)	0.656
SBP (mmHg)	130 (90-160)	120 (90-160)	0.214
DBP (mmHg)	80 (60-100)	75 (60-100)	0.307
CRP (mg/dl)	11.3 (3.02-90.8)	4.25 (3.02-206)	<0.001
Ca (mg/dl)	8.5 (6.8-10.4)	8.6 (5.4-10.3)	0.687
Na (mEq/L)	137 (128.143)	136 (130-142)	0.360
Ferritin (ng/mL)	571.6 (6.1-1406.8)	513.7 (16.5-1922.9)	0.784
Albumin (g/dl)	3.5 (2.6-4.2)	3.8 (1.75-4.4)	<0.001
Hb (g/dl)	10.4 (5.13.3)	10.6 (6.4-14.5)	0.242
PTH (ng/mL)	300 (56.6-2000)	383.8 (4.9-2000)	0.341
LA (cm)	3.8 (2.9-5.5)	3.6 (2.2-5.3)	0.173
LVEF (%)	55 (25-65)	57 (25-69)	0.057
IVST (mm)	1.2 (0.9-1.6)	1.2 (0.8-4.7)	0.481
PWT (mm)	1.2 (0.9-1.4)	1.2 (0.8-1.7)	0.173
Kt/V urea	1.68 (1.16-2.32)	1.68 (1.16-2.36)	0.822

BMI: Body mass index HCO_3: Bicarbonate DM: Diabetes Mellitus CRP: C-reactive protein Ca: Calcium Na: Sodium IVST: inter-ventricular septum thick PWT: left ventricular posterior wall thick, LA: Left atrial caliber LVEF: Left ventricular ejection fraction

DISCUSSION

In this research, we found that sKlotho was not an appropriate indicator for predicting uremic cardiomyopathy during the 18-month follow-up period in chronic renal failure patients receiving hemodialysis treatment, and it was not significant in demonstrating all-cause mortality in the 30-month follow-up. Edip et al. and our study showed that sKlotho is neither a cardiac pathological marker nor a marker to be used in terms of cardiac protection. According to the results of the study of Edip et al. no significant correlation was found between instant Klotho and uremic cardiomyopathy and echocardiographic parameters.[17]

In this study, the similar results were found when we compared the sKlotho and echocardiographic parameters at the beginning and after 18 months surveillance. In the 30-month surveillance of 136 patients, no significant relationship was found between all-cause mortality and sKlotho, but sKlotho level was found to be lower in the group that resulted in mortality compared to the living group. There are studies supporting these results in our study. In a study by Zhang et al. in 105 patients, there was a considerable association in the sKlotho and IVST, but no considerable association was determined with LVEF, LA and LVMI.[18]

Seiler et al. noticed that sKlotho was not significantly associated with cardiovascular events and mortality in patients with CKD stages 2-4. In this study, a univariate analysis of 444 patients observed for a median of 2.6 years found that sKlotho was unable to prognosticate cardiovascular events or mortality and decompensated heart failure or mortality.[19,20]

In a late study by Buiten et al., it was found that serum sKlotho in dialysis patients was not detached related with the existence of coronary artery disease, but patients with low serum sKlotho showed a high rate of cardiovascular disease and left ventricular failure.[21] Another research by Nowak et al. also reported that sKlotho was not related in death in hemodialysis patients. In this research conducted with 239 hemodialysis patients, no correlation was found between sKlotho and all-cause mortality in cox-regression analysis.[22] In our analysis of mortality, it was found that sKlotho was not significant in showing all-cause mortality, but the sKlotho value was lower in the group of non-living (P:0.084).

In clinical studies in rodents, s-Klotho has been shown to protect for calcifications in blood vessel, while higher amounts of sKlotho in person who has not chronic kidney disease are related with fewer mortality and fewer incidence of coronary artery disease.[8,23]

In the research by Hong Cai et al. it was determined that low sKlotho was related with a higher CVD mortality rate.

It was found that lower sKlotho concentration could predict cardiovascular mortality in hemodialysis patients with no calcification or mild calcification.[24] In a study of 63 patients followed for 65 months by Naoko et al., serum Klotho levels of non-living group were numerically lower than in living group. In addition to, it showed that without cardiovascular event survival and death ratio was similar, while the cumulative survival rate was significantly lower in the low sKlotho group.[25] It is seen that these studies vary according to the numerical differences of the patients included in the study, the differences in the comorbidities of the patients and the follow-up periods. In addition, the differences in primary diseases and residual renal functions of the patients included in the study may cause these studies to yield different results. Disproportionately high sKlotho levels have been determined in recent studies of hemodialysis patients.[22,26,27] In this context, circulating sKlotho level may not necessarily reflect Klotho expression detected at the tissue level, especially in patients with late stage CKD. This may lead to different results in studies.

Studies showing that low serum albumin is related with mortality in elderly people support our results in our research.[28-30]

In the research of Lijie Ma et al. low albumin and high CRP were related with mortality.[31] In another study, high albumin/crp ratio was found to be significant in terms of mortality.[32] This study, which was conducted to determine the relationship between low albumin and mortality, supports our study.

In our study, a significant difference was found in terms of CRP and albumin when the patient group of non-living and the patient group of living were compared.[33] In the group of non-living, CRP was higher and albumin value was lower. Our study shows how important it is in terms of stabilizing the inflammation and nutritional status of hemodialysis patients and reducing the mortality risk of the patients.

From this point of view, it is necessary to seriously consider the dietary status and inflammation status of the patients. In the study conducted by Rajaa et al. it was determined that the age of the non-living group was higher in the comparison between living and non-living group in chronic hemodialysis patients.[34] These results are the same as those in our study. As age increases, comorbidity increases and patients' mortality risks increase. At the same time, as age increases, the immune system mechanism becomes more vulnerable and the risk of mortality increases.

In a meta-analysis including 220689 patients and 35 studies conducted to investigate the effect of diabetes mellitus on mortality, 33 studies showed that diabetes mellitus increased mortality.[35]

In our study, when the two groups were compared, it was significant and higher in the group of non-living. Microvascular and macrovascular complications of DM rise the risk of mortality. Microvascular and macrovascular complications of DM rise the risk of mortality. In addition, diabetes mellitus increases inflammation and immunosuppression, which increases mortality.

CONCLUSION

As a result, it has been seen that sKlotho is not an indicator to be used to determine and predict uremic cardiomyopathy both in the short and long term. At the same time, although it was not found to be a significant parameter in terms of mortality, the P value was found close to the limit value in terms of significance. It may be meaningful to use it as a mortality determining parameter in studies to be conducted with larger patient populations. In our study, it has been shown that CRP, which we have used for a long time to determine, predict and prevent mortality, and which is more cost-effective, may be more useful. This study, which we conducted in the Turkish patient population, is the first to show the long-term relationship of sKlotho with echocardiographic parameters and mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The ethics committee confirmation of the research was obtained by the Hamidiye Scientific Research Ethics Committee of the University of Health Sciences with the decision dated 31.03.2021-23746 (no: E-46418926-050.01.04—23746).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article / Orijinal Araştırma

Determination of the Relationship between the Level of Mothers' Postnatal Sense of Security and Mother-Infant Bonding

Doğum Sonrası Dönemdeki Kadınların Güvenlik Hisleri ile Anne-Bebek Bağlanması Arasındaki İlişkinin Belirlenmesi

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Abstract

Aim: This study was conducted to determine the relationship between women's postnatal sense of security and mother-infant bonding.

Material and Method: A descriptive study design was used. The sample size was determined as a minimum of 125 women, based on an effect size of 0.40 and a margin of error of 0.05. The study was completed with 130 women who were selected using the simple random sampling method. A Personal Information Form, which was created by the researcher, the Parents' Postnatal Sense of Security (PPSS), and the Mother-to-Infant Bonding Scale (MIBS) were used to collect data.

Results: The mean PPSS score was 50.42±9.79 and the mean MIBS score was 1.12±1.84. It was determined that the income level variable, which is one of the socio-demographic characteristics, was the only variable that had a significant effect on the mean PPSS score, and the family type variable had a significant effect on the mean MIBS score. The mean PPSS score of the participants was significant according to the status of receiving spousal support during pregnancy. A negative (r=-0.181), significant, and very weak correlation was found between the PPSS and MIBS ($p<0.05$).

Conclusion: It was concluded that as the level of mothers' postnatal sense of security increased, mother-infant bonding was affected positively. In line with this result, increasing the level of sense of security will be a significant step in strengthening bonding.

Keywords: Mother-infant bonding, sense of security, postnatal period, midwifery

Öz

Amaç: Araştırmada kadınların doğum sonrası dönemdeki güvenlik hisleri ve anne-bebek bağlanması arasındaki ilişkiyi belirlemek amaçlanmıştır.

Gereç ve Yöntem: Araştırma tanımlayıcı bir çalışmadır. Örneklem büyüklüğü 0.40 etki büyüklüğünde ve 0.05 yanılma payında minimum 125 kadın olarak belirlenmiş ve Basit rastgele örnekleme yöntemi kullanılarak 130 kadın ile tamamlanmıştır. Araştırmacı tarafından oluşturulan Kişisel Bilgi Formu, Annelerin Doğum Sonrası Güvenlik Hisleri Ölçeği (ADSGHÖ) ve Anne-Bebek Bağlanma Ölçeği (ABBÖ) kullanılmıştır.

Bulgular: ADSGHÖ puan ortalamasının 50.42±9.79 ve ABBÖ puan ortalaması 1.12±1.84 olarak bulunmuştur. Sosyo demografik özellikler içinde yer alan gelir düzeyi değişkeni, ADSGHÖ puan ortalaması ile anlamlı olan tek değişken olduğu, ABBÖ puan ortalamasının aile tipi değişkenine göreanlamlı olduğu belirlenmiştir.Katılımcıların gebelikte eş desteği alma durumuna göre ADSGHÖ puan ortalamalarının anlamlı olduğu saptanmıştır. ADSGHÖ ile ABBÖ arasında negatif yönlü (r=-0.181), anlamlı ve çok zayıf bir ilişki bulunmuştur($p<0.05$).

Sonuç: Annelerin doğum sonrası güvenlik his düzeyi arttıkça, anne bebek bağlanmasının da pozitif yönde etkilendiği sonucuna varılmıştır. Bu sonuç doğrultusunda güvenlik his düzeyinin artması, bağlanmanın güçlendirilmesi için önemli bir adım olacaktır.

Anahtar Kelimeler: Anne-bebek bağlanması, güvenlik hisleri, doğum sonrası dönem, ebelik

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INTRODUCTION

Successive pregnancies, birth, and postpartum periods in life bring about physical, mental, and social changes for individuals.[1,2] Possible changes may strengthen the bond of families to life with the acquisition of a new role, as well as making life more difficult.[3] The balance established between existing premises is important here. The sense of security is one of the basic needs of the individual and is considered difficult to meet both physically and psychosocially.[4] Meeting this need is based on a multifactorial dynamism.[5] It is vital to understand how people express and interpret their sense of security to adapt to the parenting role during pregnancy, birth, and the first weeks after birth.[5] Maternal feelings can be experienced more intensely, especially in the postpartum period, when the woman feels secure, the mother's interaction with her baby increases, and the mother-baby bonding occurs.[6] Bonding means that mothers express their feelings and thoughts toward their baby and a sense of trust is created in the baby.[7] Bonding is not only limited to childhood, but mother-infant bonding established after birth can be reflected in the relationships established by individuals throughout the rest of their lives.[8] There are many studies in the literature on postnatal concepts, such as postpartum anxiety, depression, role acquisition, and bonding.[9-11] Although it is known that studies on the sense of security are limited in the literature, it was determined in a study that mothers' self-efficacy was associated with the sense of security, and in another study, it was concluded that women's perception of childbirth affected their sense of security.[12,13] When the research was evaluated from this aspect, an answer was sought to the question of how the inexistence of the mother-infant bonding would affect the woman's sense of security. It was aimed to determine the relationship between these two concepts in the present study. Based on this scope, the following questions were sought to be responded in this study:

- What is the level of postnatal women's sense of security?
- What is the level of postnatal women's mother-infant bonding?
- What are the factors associated with postnatal women's sense of security and mother-infant bonding?
- Is there a relationship between the level of postnatal women's sense of security and the level of mother-infant bonding?

MATERIAL AND METHOD

A descriptive research design was used. The study population consisted of postnatal women followed in 10 family Health Centers in Amasya City Center. Women who voluntarily accepted to participate in the study, met the inclusion criteria, and presented to the family health center in the central county, and completed the first postpartum week constituted the sample. The simple random sampling method was used to select the subjects. The study group included women who were aged >18 years, did not have communication difficulties, were literate, had no diagnosed psychological disorders, had given birth to a single full-term baby, and had a healthy newborn with a birth weight of 2500-4000 g.

The sample size was calculated as at least 125 women on the G-power 3.1 software, based on an effect size of .40, a margin of error of .05, a confidence level of .95, and a representativeness power of .95. Considering some attrition, the study was completed with a total of 130 women who presented to health institutions between February and May 2021.The face-to-face interview method was used for data collection, and all the measures taken within the scope of the fight against COVID-19 were followed at every stage of the research.

Data Collection Tools

A Personal Information Form, the Parents' Postnatal Sense of Security Scale, and the Mother-to-Infant Bonding Scale were used to collect research data.

The Personal Information Form

This form, which was created by the researchers following a review of the literature, consists of a total of 27 questions.[3,14,15] The questions are intended to determine the socio-demographic and obstetric characteristics of women, such as age, family type, income level, and the status of getting information about pregnancy, birth, and postpartum.

The Parents' Postnatal Sense of Security Scale (PPSS)

This scale was developed by Persson et al. to measure mothers' sense of security in the first postpartum week.[16] The Turkish adaptation study was conducted by Geçkil et al. (2016).[17] This scale has a four-point Likert-type structure ("strongly disagree"=1, "somewhat agree"=2, "agree a lot"=3, and "strongly agree"= 4) and consists of 18 items. It has four sub-dimensions named suitably according to the original scale. The sub-dimensions and count of items are as follows:empowering behavior (items, 1, 2, 3, 4, 5, and 6); general well-being(items 7,8,9,10, and 11);affinity within the family (items 12,13,14, and 15);breastfeeding (items 16,17, and 18). Items 7, 8, 9, and 11 are reverse scored. Scoreson the scale range from 18 to 72. A high total score means a good sense of security. Cronbach'salpha value of the original scale was 0.84.[17] In this study, the alpha value was found as 0.83.

The Mother-to-Infant Bonding Scale (MIBS)

This scale, which was developed by Taylor et al. (2005), can be used in the postnatal period to reveal the relationship between the mother's feelings for her baby and the bond she establishes.[18] The validity and reliability study of the scale was carried out by Aydemir Karakulak and Alparslan (2016).[14] The scale consists of 8 items and scores vary between 0 and 24. Each item is scored on a four-point scale

with options ranging from "(0) very much" to "(3) never" ("very much" = 0, "much" = 1, "somewhat" = 2, and "never" = 3). Items 1, 4, and 6 of this scale, which consists of emotional expressions that can be classified as positive and negative, are positive and items 2, 3, 5, 7, and 8 are negative and scored in reverse. High scores are accepted as an indicator of a mother-infant bonding problem. Cronbach's alpha coefficient was reported as 0.69 on the first postnatal day and 0.68 within 8-10 weeks after birth.[14] In this study, Cronbach's alpha value of the scale was found as 0.65.

Data Analysis

Statistical analysis of the research data was conducted on the SPSS 25.0 software package. The research data were analyzed based on the suitability of the parameters to the normal distribution. Descriptive statistical methods, such as counts, percentages, mean, median, and standard deviation values, were used. In addition, the student's t-test, Mann-Whitney-U test, and Kruskal-Wallis test were used according to the data obtained. The Spearman correlation test was used to evaluate the correlation between the scales. $p<0.05$ was accepted as the level of significance.

Ethics Committee Approval

During the planning phase of the study, the permission of the authors who conducted the validity and reliability study of the scales (PPSS and MIBS) that would be used in the study was obtained. Ethical approval of Tokat Gaziosmanpaşa University Ethics Committee (Date: 13.08.2020; Number: 83116987-243 No=20-KAEK-210) and institutional permission of Amasya Provincial Health Directorate were obtained. In addition, verbal and written consent was obtained from all participants before the data collection phase was initiated. This article was produced from the master's thesis and was published in III. Presented at the International Joint Scientific and Practical Online Conference, Evidence-based Midwifery Care.

RESULTS

The findings of the research, conducted to determine the relationship between the level of women's postnatal sense of security and mother-infant bonding, are presented below. A total of 130 women participated in the study. The mean age of the women was 29.19±4.88 (min=19- max=43), the mean number of births was 1.85±0.83 (Min=1-Max=5), and 76.2% of the women had a planned pregnancy.

Table 1 shows the distribution of the findings on the socio-demographic and obstetric characteristics of the mothers included in the study. It was determined that 47.7% of the women had a university or higher education level, 66.9%worked, 88.5% had a nuclear family, and 9.2% perceived their income level as low. Considering the status of getting information about antenatal, innatal, and postnatal periods, it was determined that 61.5% of the women had received information and the source of 53.1%of those who had received information was the Internet and social media. It was found that 93.1% of the participants received spousal support, 60.0% had experienced a postpartum period before, and 44.9% of the women who had experienced a postpartum before had had mental/psychological problems during that time (**Table 1**).

Table 2 shows the mean scores of women on the total PPSS and MIBS and sub-dimensions of the PPSS. The mean scores were found as 50.42±9.79 on the total PPSS and 1.12±1.84 on the total MIBS (**Table 2**).

Table 2. Distribution of mean scores on the Parents' Postnatal Sense of Security Scale (PPSS) and the Mother-to-Infant Bonding Scale (MIBS)

Scales	Min- Max Value	$\bar{x}$±SD (Min-Max)
MIBS-Total	0-24	1.12± 1.84 (0-9)
PPSS-Total	18-72	50.42±9.79 (31-70)
PPSS Sub-Dimensions	6-24	15.55±5.42 (6-24)
Empowering behaviour	5-20	13.45±3.87 (5-20)
General well-being	4-16	12.62±3.15 (5-16)
Affinity in the family	3-12	8.81±2.39 (3-12)
Breast- feeding		

Min- Max= Minimum- Maksimum $\bar{x}$=Mean SD=Standard Deviation

Table 1. The Distribution of the Findings on Women's Socio-Demographic and Obstetric Characteristics (n=130)

Socio-demographic and obstetric characteristics		Frequency (n)	Percentage (%)	Socio-demographic and obstetric characteristics		Frequency (n)	Percentage (%)
Age (Years)*	Under 30 years	76	58.5	The status of receiving information about pregnancy, child birth and the postpartum period	Yes	80	61.5
	30 years and over	54	41.5		No	50	38.5
Educational level	Primary school	5	3.8	Source of informationacquisition (n=80)*	Medical Institution	28	35.0
	Secondary school	26	20.0		Internet /Social media	43	53.8
	High school	37	28.5		Other (TV, radio, newspaper, book, magazine, neighbor, relative)	9	11.3
	University and above	62	47.7				
Working status	Working	43	33.1	Spousal support during pregnancy	Yes	121	93.1
	Unemployed	87	66.9		No	9	6.9
Family type	Nuclear Family	115	88.5	Gravida	Primigravida	52	40
	Extended Family	15	11.5		Multigravida	78	60
Perception of income level	Low	12	9.2	Thestate of havingmentalproblems in thepreviouspuerperium (n=78)	Yes	35	44.9
	Middle	118	90.8		No	43	55.1

*More than one response has been given.

It was determined that the mean MIBS score was significant according to the family type variable (p<0.05). The income level variable, which is one of the socio-demographic characteristics, was the only variable that had a significant correlation with the mean PPSS score. It was determined that the mean PPSS score was significant according to the status of getting information about the antenatal, innatal, and postnatal periods (p<0.05). The mean PPSS scores of the participants were significant according to receiving spousal support during pregnancy (p<0.05). Only the mean general well-being sub-dimension score of the PPSS had a significant correlation with the status of experiencing mental/ psychological problems during the previous postnatal period(s) (p<0.05) (**Table 3**).

A positive and significant relationship was found between the mean PPSS score and the empowering behavior sub-dimension (r=0.814) and general well-being sub-dimension scores (r=0.459) of the scale (p<0.05). A positive and significant relationship was found between the mean PPSS score and the affinity within the family sub-dimension (r=0.619) and breastfeeding sub-dimension (r=.635) of the scale (p<0.05). A negative and significant correlation was found between the mean MIBS score and the general well-being sub-dimension (r=-0.232) of the PPSS (p<0.05). There was a negative and significant correlation between the mean PPSS and MIBS scores (r=-0.181) (p<0.05) (**Table 4**).

Table 3. Distribution of Mean Scores on the Total PPSS and MIBS According to Socio-Demographic and Obstetric Characteristics of the Women

Socio-Demographic Characteristics		PPSS Total	Empowering Behaviour	General Well-Being	Affinity İn TheFamily	Breast- Feeding	MIBS Total
				Median (Min- Max)			
Family type	Nuclearfamily	51.0 (31.0-70.0)	16.0 (6.0-24.0)	14.0 (5.0-20.0)	13.0 (5.0-16.0)	9.0 (3.0-12.0)	0.0 (0.0-9.0)
	Extendedfamily	49.0 (40.0-68.0)	18.0 (11.0-24.0)	14.0 (5.0-19.0)	12.0 (6.0-16.0)	10.0 (6.0-12.0)	1.0 (0.0-5.0)
Test andp-value*		Z=-0.324 p=0.746	Z=-1.290 p=0.197	Z=-0.135 p=0.892	Z=-0.952 p=0.341	Z=-0.820 p=0.412	Z=-2,204 p=0.027
Perception of income level	Low	38.5 (32.0-55.0)	10.0 (6.0-18.0)	13.5 (5.0-19.0)	12.0 (5.0-16.0)	7.0 (3.0-10.0)	0.0 (0.0-8.0)
	Middle	51.5 (31.0-70.0)	16.5 (6.0-24.0)	14.0 (5.0-20.0)	13.0 (6.0-16.0)	9.0 (3.0-12.0)	0.0 (0.0-9.0)
Test and p-value		Z=-3.372 p=0.001	Z=-3.352 p=0.001	Z=-0.654 p=0.513	Z=-1.779 p=0.075	Z=-2.412 p=0.016	Z=-0.981 p=0.326
Obstetric Characteristics		$\bar{x}$±SD		Median (Min- Max)			
The status of receiving information about pregnancy, child birth and the postpartum period	Yes	51.88±10.23	17.0 (6.0-24.0)	14.0 (5.0-20.0)	14.5 (6.0-16.0)	10.0 (3.0-12.0)	0.0 (0.0-9.0)
	No	48.08±8.64	14.5 (7.0-24.0)	14.0 (5.0-20.0)	12.0 (5.0-16.0)	8.0 (5.0-12.0)	0.0 (0.0-8.0)
Test andp-value		t=2.187 p=0.031	Z=-0.953 p=0.341	Z=-0.185 p=0.853	Z=-3.267 p=0.001	Z=-2.722 p=0.006	Z=-0.232 p=0.816
				Median (Min- Max)			
Spousal support during pregnancy	Yes	52.0 (31.0-70.0)	16.0 (6.0-24.0)	14.0 (5.0-20.0)	13.0 (5.0-16.0)	9.0 (3.0-12.0)	0.0 (0.0-9.0)
	No	43.0 (34.0-51.0)	16.0 (7.0-20.0)	12.0 (8.0-18.0)	8.0 (5.0-11.0)	9.0 (5.0-12.0)	1.0 (0.0-8.0)
Test andp-value		Z=-2.620 p=0.009	Z=-1.421 p=0.155	Z=-1.035 p=0.301	Z=-4.089 p=0.000	Z=-0.319 p=0.749	Z=-1.661 p=0.097
The state of having mental problems in the previous puerperium (n=78)	Yes	49.0 (31.0-68.0)	16.0 (7.0-24.0)	12.0 (5.0-18.0)	13.0 (6.0-16.0)	10.0 (4.0-12.0)	0.0 (0.0-9.0)
	No	52.0 (34.0-69.0)	17.0 (6.0-24.0)	15.0 (6.0-20.0)	12.0 (5.0-16.0)	9.0 (5.0-12.0)	0.0 (0.0-6.0)
Test andp-value		Z=-0.815 p=0.415	Z=-0.660 p=0.509	Z=-4.877 p=0.000	Z=-0.081 p=0.935	Z=-1.011 p=0.312	Z=-1.600 p=0.110

*p<0.05 $\bar{x}$=Mean SD=Standard Deviation t=t test in independent groups Z= Mann Whitney-U test

Table 4. The Relationship Between the Mean Scores on the Total PPSS and Its Sub-Dimensions and the Mean Scores on the Total MIBS

Scales	r p-value*	PPSS-Total	Empowering behaviour	General well-being	Affinity in the family	Breast- feeding
PPSS- Total	r	-				
	p-value					
Empowering behaviour	r	0.814	-			
	p-value	0.000				
General well-being	r	0.459	0.076	-		
	p-value	0.000	0.388			
Affinity in thefamily	r	0.619	0.377	0.039	-	
	p-value	0.000	0.000	0.657		
Breast- feeding	r	0.635	0.411	0.081	0.412	-0.133
	p-value	0.000	0.000	0.358	0.000	0.132
MIBS- Total	r	- 0.181	-0.074	-0.232	-0.010	
	p-value	.039	0.401	0.008	0.911	

*p<0.05, r= Spearmancorrelationcoefficient

DISCUSSION

The postnatal period is important because it is a time when new roles are added to people and new gains are made. [15] Feeling secure and having securebonding are desirable conditions for every individual with a maternal role.[19] It is necessary to discuss the data of the research in light of the literatureto reveal similarities with and differences from the literature. In the study, the mean scores on both the total PPSS and MIBS were similar tothose in the literature, but both scales did not have a cut-off value. Therefore, the similarities with and differences from other studies could not be handled in this aspect.[13,16,17,20] As a result of this research, the highest score was obtained from the empowering behavior sub-dimension and the lowest score from the breastfeeding sub-dimension of the PPSS, which consists of four sub-dimensions. In other studies in the literature, it was observed that the PPSS had been interpreted mostly over the mean total score.Evaluations of sub-dimensions had been performed only in studies by Persson et al. (2007) and Baykal and Karakoç (2021).[12,13,21,22] Persson et al. (2007) found that the highest sub-dimension score was on the empowering behavior and the lowest on the affinity within the family sub-dimensions.16 In the study by Baykal and Karakoç (2021), similar to our research, the highest sub-dimension score was obtained from the empowering behaviorand the lowest from the breastfeeding sub-dimension.[21] The result of the comparisons indicated that the findings of the research about the sub-dimensions were similar to those of some studies,while there were also others with different findings.

In the study, it was determined that the mean PPSS score was correlated only to the income level variable of the socio-demographic characteristics. Abrams and Curran (2011) stated in their qualitative study with a group of low-income women that some of them had postnatal depression symptoms and difficulties in developing a mother identity.[23] Jewell et al. (2015) found that economic stress experienced by women was positively correlated with postnatal depression symptoms. In addition, it can be inferred that income level and sense of security may have had an effect because women spent most of their time at home during the pandemic and they needed economic freedom more than ever.[24]

In our study, the mother-infant bonding of women with a nuclear family was higher than that of women who had an extended family. An explanation for this situation may be that family ties are stronger, there is more sharing, and that mothers can interact more easily with their babies in nuclear families. Similar to our study, Tolja et al. (2020) determined that the quality of the relationship between the couple showed a low correlation with mother-infant bonding.[25]

In our study, no significant difference was found between the mean MIBS score and socio-demographic characteristics (educational status, employment status, family type, income level), except for the family type variable. Similar to our research, no significant difference was found between mother-infant bonding and educational status in studies by Dağlar and Nur (2018) and Nath et al. (2019) and income status in the study by Başdaş et al. (2022).[26-28] Unlike our research, Kinsey et al. (2014) found a significant difference between women's educational status and bonding. The difference between the findings of our study and those of other studies can be explained by different cultural populations and sample sizes of studies.[29]

In our study, there was a statistically significant difference between the mean scores on the total PPSS and the status of getting information about antenatal, innatal, and postnatal periods and receiving spousal support, which were among the obstetric characteristics. In the study by Prescott and Mackie (2017), it was reported that getting information during pregnancy gave women confidence. This result supports the results of our study.[30] Also, it was determined that spousal support contributed to the psychological well-being of women, but inadequate spousal support increased anxiety about pregnancy.[31,32]

In our study, it was determined that there was a negative, significant, and very weak correlation between the Parents' Postnatal Sense of Security Scale and the Mother-to-Infant Bonding Scale (r=-0.181). In other words, as the mean PPSS score increased, the mean MIBS score decreased. Although there was no previous study on the examination of this relationship in the literature, in the study of Baykal and Karakoç (2021), it was similarly determined that there was a negative relationship between postnatal depression and a sense of security.[21] The mother's sense of confidence may have reduced the possibility of experiencing postnatal depression and therefore supported the formation of bonding. Motegi et al. (2022), similar to the results of our study, found that mother-infant bonding was negatively correlated with depression and anxiety in Japanese mothers. [33]

Limitations

This study is limited to 130 postnatal women registered in 10 family health centers in Amasya Province and cannot be generalized to all postnatal women. In addition, the implementation process of the study was affected due to the COVID-19 pandemic and these effects were reflected in the results, which is another limitation of the study.

CONCLUSION

It is possible to interpret the mean score on the total PPSS as an indicator of a good level of sense of security. The mean score on the total MIBS indicated that there was no mother-infant bonding problem. All healthcare professionals involved in the postnatal period should know that increasing the level of security will be an important step in strengthening bonding.

According to the results of the research, the provision of women with information was related to their sense of security, but their sources of information were the Internet and social media rather than health institutions. For this reason, all health professionals involved in antenatal services should provide women with systematic, holistic, and culturally sensitive care from the preconceptional to the postnatal period by raising awareness about their information needs.

In the study, no relationship was found between obstetric characteristics and mother-infant bonding. It may be recommended to investigate other factors affecting the mother-infant bonding levels of postnatal women and plan studies with a larger sample group.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tokat Gaziosmanpaşa University Ethics Committee (Date: 13.08.2020; Number: 83116987-243 No=20-KAEK-210)

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article / Orijinal Araştırma

Gastroprotective Effects of Jujuba (*Ziziphus jujuba*) Fruit Extract Against the Ethanol-Related Gastric Ulcer in Rats

Jujuba (*Ziziphus jujuba*) Meyve Ekstraktının Ratlarda Etanol ile Oluşturulan Mide Ülserine Karşı Gastroprotektif Etkileri

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Abstract

Aim: Gastric ulcer is a global health problem. Alcohol consumption and nonsteroidal anti-inflammatory drugs may lead to gastric ulcers. Here, we examined the possible gastroprotective effects of *Ziziphus jujuba* (Zj) fruit extract on a rat model of ethanol-induced gastric ulcer.

Material and Method: Chemical properties of Zj were specified using performance liquid chromatography coupled to mass spectrometry. The animals were administered Zj extract (4-8 ml/kg) before administering absolute ethanol. Oxidative stress and proinflammatory markers, immunoexpression of NF-κB and caspase-3 were measured to evaluate Zj's effects.

Results: Zj fruit extract significantly reduced values of cytokines such as TNF-α, IL-1β, and IL-6 and the expressions of NF-κB and caspase-3 in the immunohistologic analysis. We found out ulcerative foci in the ulcer group in the histopathological analysis, while we didn't observe ulcerative foci in the treatment groups.

Conclusion: This experimental study showed that Zj fruit ameliorated the ethanol-induced gastric ulcer model in rats.

Keywords: Ethanol, gastric ulcer, proinflammatory cytokines, caspase-3, *Ziziphus jujuba*

Öz

Amaç: Gastrik ülser global bir sağlık sorunudur. Alkol tüketimi ve nonsteroid anti-inflamatuar ilaç kullanımı mide ülserine yol açabilmektedir. Bu çalışmada, *Ziziphus jujuba* (Zj) meyve ekstraktının ratlarda oluşturduğumuz etanol kaynaklı mide ülseri modeli üzerindeki olası gastroprotektif etkilerini inceledik.

Gereç ve Yöntem: Zj'nin kimyasal özellikleri kütle spektrometresi ile birleştirilmiş performans sıvı kromatografisi kullanılarak belirlendi. Hayvanlara saf etanol verilmeden önce Zj ekstresi (4-8 ml/kg) uygulandı. Zj'nin etkilerini değerlendirmek için oksidatif stres ve proinflamatuar belirteçler, NF-κB ve kaspaz-3'ün immünoekspresyonu ölçüldü.

Bulgular: Zj meyve ektraktı, immünohistolojik analizde TNF-α, IL-1β ve IL-6 gibi sitokinlerin değerlerini ve NF-κB ve kaspaz-3 ekspresyonlarını önemli ölçüde azaltmıştır. Histopatolojik analizde ülser grubunda ülseratif odaklar tespit edilirken, tedavi gruplarında ülseratif odaklar gözlenmedi.

Sonuç: Bu deneysel çalışma, Zj meyvesinin sıçanlarda etanol ile indüklenen gastrik ülser modelini iyileştirdiğini göstermiştir.

Anahtar Kelimeler: Etanol, gastrik ülser, proinflamatuar sitokinler, kaspaz-3, *Ziziphus jujuba*

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INTRODUCTION

Gastric ulcers are among the most frequent gastrointestinal disorders worldwide,[1] and they don't have a definitive treatment.[2] Gastric ulcer is the erosion of gastric mucosa caused by nonsteroidal anti-inflammatory drugs, Helicobacter pylori, alcohol consumption, and stressful conditions.[3,4] Alcohol consumption causes necrosis and vascular damage, resulting in ulceration in the gastric cells;[4,5] thus, it increases the gastrointestinal bleeding risk.[6] Besides, the administration of alcohol is linked to the regulation of the nitric oxide pathway and disequilibrium of proinflammatory cytokines.[5] The signaling pathway of nuclear factor kappa B (NF-κB) is among the most well-known intracellular signaling pathways of the inflammatory response.[7] NF-κB acts in the arrangement of several genes that play a key role in immune responses and inflammatory processes,[8] causing activation of various proinflammatory cytokines, like interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6).[9] Ethanol-induced gastric ulcer raises the NF-κB expression and proinflammatory cytokine production.[10,11] Ethanol stimulates epithelial cell apoptosis in the gastric tissue,[12] whereas the apoptosis cascade is primarily initiated by caspase-3 activation.[13]

Ziziphus jujuba (Zj) is a fruiting plant-specific (jujube) that belongs to the Rhamnaceae family.[14] Different parts of Zj have various medicinal features.[15] Zj is a species of China with a history extending back over 4000 years.[16] Zj extract decreases oxidant and inflammation levels.[17-19] while increasing the antioxidant response.[18,20,21] Zj polysaccharides reduce various proinflammatory cytokine levels.[19,22] In a previous study, Zj stem bark extract prevented gastric mucosal injury created by ethanol in rats.[23] Zj lam leaves extract demonstrated anti-ulcer activity.[24]

Here, the possible effects of Zj fruit extract on oxidant/antioxidant parameters, inflammatory markers, and apoptosis in the gastric ulcer model were investigated using biochemicals and histopathological methods. This study's justification is finding a new molecule for the gastric ulcer treatment, which has fewer side effects and performs preventive properties comparing the similar drugs used for this purpose worldwide.

MATERIAL AND METHOD

Ziziphus jujuba Fruit Extract

The jujube fruits (*Ziziphus jujuba* Mill.) were obtained in the harvest season (last week of September) from a commercial orchard in Amasya province in Turkey. Jujube fruits belong to the commercial standard cultivar "Li". After the fruits were washed, the tiny seeds were taken out. The pulpy jujube juices were extracted using a homogenizer[25] and given to the rats intragastrically at 4 ml/kg and 8 ml/kg.

Animals and Ethical Approval

All animal applications, including surgical and medical procedures, were accepted by the Animal Experiments Local Ethics Committee, Atatürk University (Protocol no: 19.04.2016/70). The rats were supplied from the Animal Research and Application Center, Atatürk University. They were exposed to a 12 h light/dark cycle at 21°C temperature and %55 humidity. The animals were placed in cages measuring 470×312×260 mm and allowed to feed freely.

Induction of Gastric Ulcer by Ethanol and Treatments

In this study, 32 Wistar albino female rats, 20-24 weeks of age, 257±4 g weighing, were used. 4 random groups were formed (n=8). The control group was intragastrically administered with distilled water for ten days. Ulcer+Zj fruit extract groups were intragastrically administered 4 ml/kg and 8 ml/kg Zj extracts for ten days. The animals in the ulcer group and Zj fruit extract groups were fasted for 24 hours, but they were allowed to reach water before the ulcer model was performed. On the 11th day of the experiment, an ulcer model was created by intragastric 5 ml/kg absolute ethanol (99%) administration. After 90 mins, rats were sacrificed. The Stomachs were incised over the greater curvature and washed with saline to clean the blood clots. Later, the samples were fixed on a surface and photographed.

The High-Performance Liquid Chromatography (HPLC) Analysis of Fruit Extract Phenolic Profile

HPLC coupled to a photodiode array (HPLC-PDA) to able to determine the phenolic properties of the samples. HPLC-PDA levels were demonstrated as mg/100 ml. Standard calibration curves were prepared via gallic acid, caffeic acid, 4-hydroxy benzoic acid, vanillic acid, p-coumaric acid, catechin, chlorogenic acid, syringic acid, ferulic acid, cyanidin-3-glucosidase, and delphinidin-3-glucosidase. A membrane filter (0.45 µm) was used for samples and stock solutions. A filtered sample (1 ml) was used in vials for analyzing with Waters W600 HPLS system with PDA (Waters 996) detector. Luna C18 column (Phenomenex, Utrecht, The Netherlands), which is heated to 40°C, was preferred as the stationary stage. Solvent A content is distilled water with 0.1% (v/v) trifluoroacetic acid (TFA). Then, solvent B content is acetonitrile with 0.1% (v/v) TFA, acetonitrile with 0.1% (v/v) TFA formed the mobile phase. The flow rate was 1 ml/minute. The chromatograms were measured at 280, 312, 360, and 520 nm. Retention times and characteristic UV spectra determined the identification, and standard external curves formed quantification.[26]

Tissue Collection and Homogenization

Gastric tissues were excised and washed with saline to get rid of the stomach's content. Then, photographs were taken macroscopically. The entire stomach was cut into two pieces from minor and major curvatures. One part was kept in 3,7 % formaldehyde for further immunohistochemical and pathological analysis, and the other part was kept in -80°C for

further biochemical analysis. Gastric tissue with all layers was homogenized in the ice-cold phosphate buffer (50 mM, pH 7,4). Supernatants were acquired centrifuging homogenates at 3,000 rpm for 15 min at 4°C.

Spectrophotometric Assays (Evaluation of the content of *Ziziphus jujuba* Fruit Extract)

Free radical clearance activity was evaluated with ABTS (2,2-azino-di-(3-ethylbenzothialozine-sulphonic acid)). The ABTS activity measurement was the modified version of Re et al.[27] Antioxidant features of Zj fruit extract content were assessed with cupric reducing antioxidant capacity (CUPRAC) analysis.[28] The total phenolic content was examined with Folin–Ciocalteu reagent (FCR) and the method by Folin and Singleton.[29,30]

Cytokines Analyses

An enzyme-linked immunosorbent test (ELISA, BioTEK Powerwave XS Winooski, UK) was performed to examine ethanol's effect on cytokine levels in stomach homogenate. For TNF-α levels, Rat TNF-α ELISA Kit (Cat No:E-EL-R0019, Elabsience); for IL-1β levels, Rat IL-1β ELISA Kit (Cat No:E-EL-R0012, Elabsience); and for IL-6 levels, Rat IL-6 ELISA Kit (Cat No:E-EL-R0015, Elabsience) were used. The measurements were performed according to the manufacturer's instructions.

Hematoxylin and Eosin Analyses

All gastric tissues were fixed in 3,7% solution formaldehyde for 48 hours. After the fixation, all stomach samples were routinely examined for the histological tissue processing, as described previously.[31] According to this tissue follow-up procedure, all tissues were kept in increasing alcohol series (50%, 60%, 70%, 80%, 96%, 99% alcohol - 1 hour). It was then kept in 3 different xylene for 15 minutes. Finally, after waiting for 2 hours in melted paraffin, blocking was performed. After the tissue was processed, 5 micrometer thick sections were taken from each paraffin block and staining protocol was passed. Accordingly, all slides were kept in at 60 degrees for 20 minutes, and all slides were kept in xylene for 5 minutes and 3 times due to paraffin was removed. Subsequently, the slides were kept in decreasing alcohol series (99%, 96%, 80%, 70%, 60%, 50% alcohol - 5 minutes), washed for 5 minutes in running water after alcohol and stained in Mayer's hematoxylin for 5 minutes. It was kept in running water for 5 minutes to remove the excess dye. Dyeing was done in alcoholic eosin for 2 minutes. In order to remove the excess dye, it was gently shaken in 96% alcohol 10 times and kept in 99% alcohol for 5 minutes. Finally, it was passed through 3 xylene series (5 minutes), and the slides were covered with a coverslip with adhesive medium.

Immunohistochemical Analysis (IHC staining)

Inflammatory and apoptotic features of the groups were examined using caspase-3 (Novus Biological, USA) and NF-κB (Abcam, UK).[32] Immunohistochemical staining was performed by the Ventana BENCHMARK GX automatic immunohistochemistry staining system.[33] The sections were investigated by a light microscope (Olympus BH-40). Semi-quantitative scoring was made based on the immunohistochemical staining intensity and dyeing cells number.

Statistical Analysis

Statistical analysis was established using the one-way ANOVA and Tukey test. The results were demonstrated as mean±standard deviation (SD). A p-value of less than 0.05 was considered significant.

RESULTS

Determination of Phenolic Substance Content of Zj Extract

The HPLC chromatogram (360 nm) of the phenolic substances in the Zj extract is shown in **Figure 1**. The phenolic and antioxidant substances in the Zj samples are shown in **Tables 1** and **2**, respectively. Xie et al. found phenolic compounds in jujube and identified them as coumarin, gallic acid, catechin, caffeic acid, chlorogenic acid, quercetin, p-coumaric acid, epicatechin, ferulic acid, and rutin.[34] Gallic acid content of pulp samples taken from different growing stages was 3.19-81.27 ppm, catechin content was 3.81-56.62 ppm, p-coumaric acid content was 1.21-22.94 ppm, ferulic acid content was 6.16-44.39 ppm, and rutin content was 5.12-47.93 ppm. When these values were compared to this study, the contents of gallic acid, catechin, and p-coumaric acid were similar; ferulic acid and rutin contents were higher than current results.

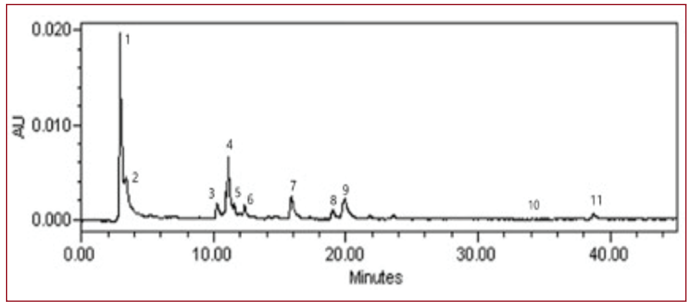

Figure 1. The HPLC chromatogram (360nm) of the phenolic substances in the Zj fruit extract. Peak identification;1 Gallic acid; 2 protocatechuic acid; 3 syringic acid; 4 catechin; 5 epigallocatechin; 6 p-coumaric acid; 7 ferulic acid; 8 ellagic acid; 9 rutin; 10 t-cinnamic acid; 11 kaempferol

Table 1. Content of antioxidant substance of jujube samples according to two different methods (CUPRAC and ABTS), Total phenolic substance content according to Folin Ciocalteu reactif (FCR) method.

Parameters	Average±St-dev (mg TEAC/100 ml)
CUPRAC	640.93±93.67
ABTS	4257.45±154.00
FCR	92.55±8.20

Table 2. Phenolic substance content of jujube samples

Parameters	Average (ppm)±St-dev
Gallic acid	3.20±1.26
Catechin	6.75±0.71
Syringic acid	1.08±0.26
EGC	2.09±0.55
Ellagic acid	1.28±0.50
t-Cinnamic acid	1.83±0.33
Protocatechuic acid	0.75±0.17
p-Coumaric acid	0.98±0.22
Ferulic acid	0.26±0.04
Kaempherol	1.09±0.46
Rutin	1.97±0.72

Oxidative Stress and Cytokine Results

Total antioxidant status (TAS), oxidative stress index (OSI), and total oxidant status (TOS) values were represented in **Table 3**. No significant difference was observed between the all-experiment groups ($p>0.05$). In the **Figure 2**, IL-1β, TNF-α, and IL-6 levels elevated in the ulcer group compared to the control group ($p<0.05$). The same parameters declined in the Ulcer+Zj 8 ml/kg group ($p<0.05$). Results are given in **Figures 2a**, **2b**, and **2c**, respectively.

Table 3. TAS, TOS and OSI levels between groups

Groups/Parameters	TAS	TOS	OSI
Control	3.5099±1.50	35.0274±9.25	2.0101±0.15
Ulcer	3.4644±2.06	55.0556±13.69	1.9880±0.36
Ulcer+Zj 4 ml/kg	3.1237±1.45	43.5756±18.78	1.6372±0.89
Ulcer+Zj 8 ml/kg	4.5172±2.77	49.1317±20.31	1.2653±0.83

Data were analyzed by one-way analysis of variance followed by Tukey test. Values are expressed as mean values±SD. N= 8 per study group. There is no statistical significance between all experimental groups.

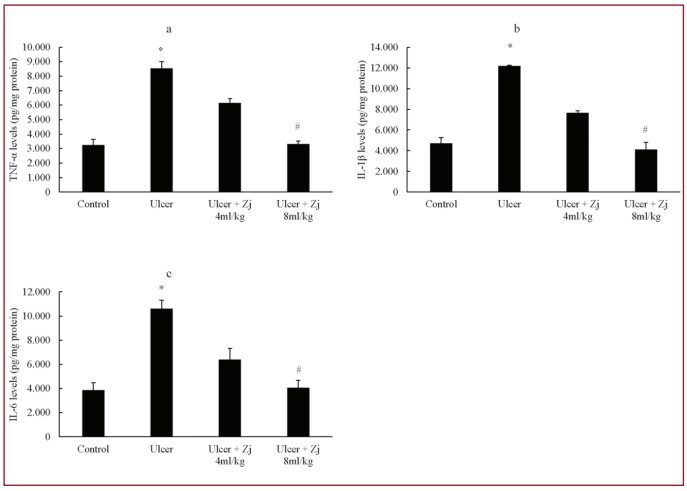

Figure 2. Effect of Zj fruit extract on gastric anti-inflammatory and proinflammatory cytokines levels decreased by ethanol. Values are mean ± SD. Data were analyzed via one-way ANOVA followed by Tukey test (n= 8 per group). Figure 2a, figure 2b, and figure 2c demonstrate TNF-α, IL-1β, and IL-6 levels, respectively. *p<0.05; compared to the control group, #p<0.05; compared to the ulcer group.

Histopathological Observations of Gastric Ulcer Tissues in Rats

Histopathological evaluation (hematoxylin and eosin staining) of groups is shown in **Figure 3**. There was no ulcerative damage in the gastric mucosa of the control group. In the ulcer group, intense neutrophil infiltration with degeneration of the surface epithelium, dilation of the gastric glands, and gastric pits were observed. In the ulcer+Zj 4 ml/kg group, partial irregularity in gastric pits and low neutrophil infiltration were observed. In the ulcer+Zj 8 ml/kg group, gastric mucosa was regular and generally resembled a healthy group. Low levels of neutrophil infiltration and necrotic cells were observed.

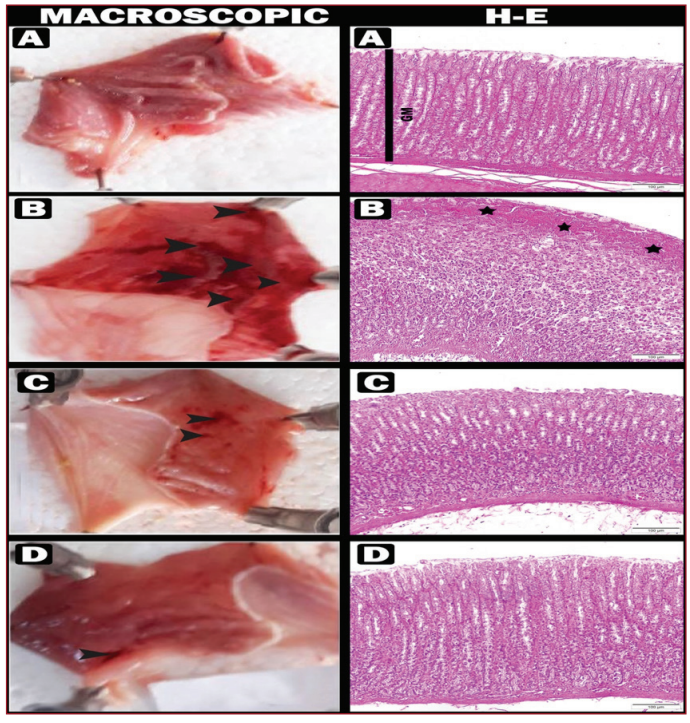

Figure 3. Histopathological evaluation of groups. A control group, B ulcer group, C and D Zj fruit extract treatment groups (4 ml/kg and 8 ml/kg, respectively). -Star: Ulcerative area, Arrow: Macroscopic Ulcer Area, GM: Gastric Mucosa, H-E: Hematoxylin and Eosin Staining

In the evaluation of NF-κB and caspase-3 immune reactivity (**Figure 4**), there was excessive immune reactivity in the ulcer group compared to the control group. Also, there was a dose-dependent low immune reactivity in the ulcer+Zj fruit extract groups compared to the ulcer group. The immunohistochemical evaluation was scored as; - (none), + (mild immune reactivity), ++ (moderate immune reactivity), and +++ (excessive immune reactivity) (**Table 4**).

Table 4. Scores of NF-κB and caspase-3 expressions of groups in ethanol-induced stomach ulcer model

Groups/Parameters	NF-κB	Caspase-3
Control	+	+
Ulcer	+++	+++
Ulcer+Zj 4 ml/kg	+	+
Ulcer+Zj 8 ml/kg	-	-

- none, + mild immune reactivity, ++ moderate immune reactivity, +++ excessive immune reactivity

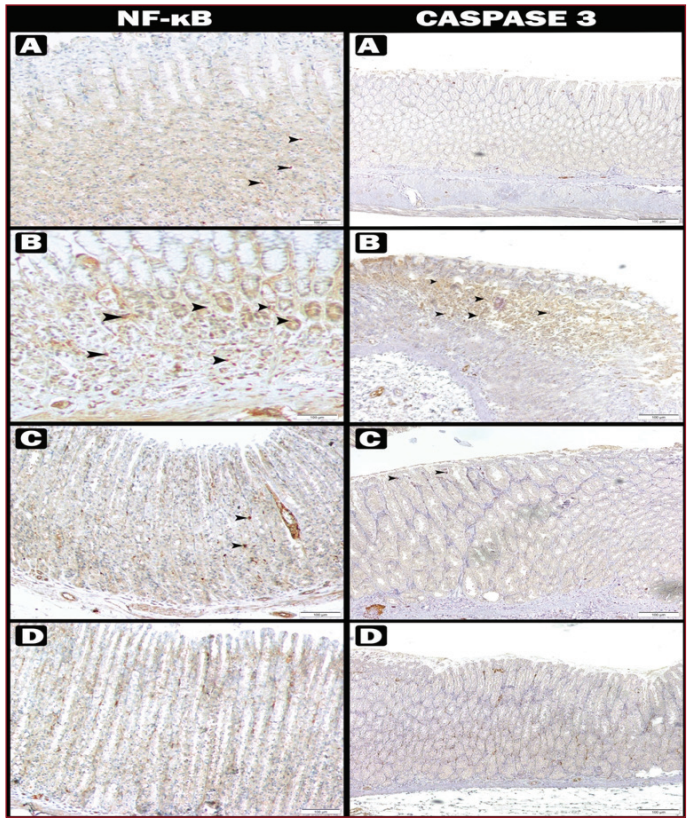

Figure 4. Immunohistochemical evaluation of groups. A control group, B ulcer group, C and D Zj fruit extract treatment groups (4 ml/kg and 8 ml/kg, respectively). -Arrowhead: Immune positive cells.

DISCUSSION

Alcohol-related gastric ulcer is the primary disorder of the gastrointestinal system.[35] Ethanol administration penetrates the gastric mucosa and causes inflammatory cell infiltration. Following, gastric blood flow diminishes, and oxidative stress occurs. Subsequently, bicarbonate decreases gastric mucus and nitric oxide secretion and induces necrotic mucosal damage, leading to cell death.[11,36-38] For the first time, this study shows that Zj extract at 4 ml/kg and 8 ml/kg attenuates ethanol-induced gastric ulcer by diminishing oxidative stress and suppressing inflammation.

Ethanol-induced animal gastric ulcer is commonly used to investigate new anti-ulcer drugs.[39] Polyphenol and phytochemical compounds have essential roles in the prevention of gastric ulcer.[40,41] Ethanol causes gastric mucosal injury through the oxidative stress stimulation pathway in the gastric tissue.[42] The leading cause of gastric ulcer is an increase in the balance between the oxidant and antioxidant system in the stomach in favor of oxidant molecules.[43] Earlier reports have shown that eliminating free radicals with antioxidant compounds alleviates ethanol-mediated gastric ulcer, and scavenging free radicals with antioxidant compounds prevents ethanol-induced gastric ulcer.[11,43] In our study, we represented many phenolic molecules obtained from the Zj extract. Possible effects of these molecules on gastrointestinal system diseases have been reported. Catechin.[44] and gallic acid[45,46] have been proven to protect the gastric mucosa by increasing antioxidant levels. Syringic, gallic, cinnamic, p-coumaric, caffeic, ferulic, and protocatechuic acids prevented gastric ulcer through free radical scavenging, lipid peroxidation inhibiting, and antioxidant effects.[47,48] Ellagic acid[49] and kaempferol[50] accelerated ulcer healing. Rutin demonstrated anti-ulcer performance via gastric proton pump inhibition.[51] Zj extract has been shown to increase antioxidant levels in various brain regions,[18] liver injury[20] and nephrotoxicity models.[21] In this study, Zj fruit extract's gastroprotective features against ethanol-induced gastric mucosal damage may be related to the phenolic compounds of Zj extract. These results indicate that Zj extract has gastroprotective effects similar to Hamedi et al.[23]

Gastric cell and tissue damage associated with acute and chronic inflammation are caused by ROS overproduction in the stomach.[42] Ethanol prompts lipid peroxidation and NF-κB expression leading to mucosal hemorrhages and edema in vascular smooth muscle cells and endothelial cells.[52] NF-κB causes transcriptional activation of various proinflammatory-cytokines, such as TNF-α, IL-1, and IL-6 translocated into the nucleus.[9] NF-κB expression and TNF-α, IL-6 production increased significantly in ethanol-induced gastric ulcer.[10,11,53] In particular, the level of cytokines, including TNF-α and IL-6, is critical in determining the severity of ethanol-induced gastric mucosal damage.[10,38] TNF-α is secreted during gastric mucosal injury and acts in several mucosal damage steps.[54] These results suggest that NF-κB inhibition is vital in gastric ulcer pathogenesis. Molecules present in Zj extract such as gallic acid,[55] catechin,[56] ellagic acid,[57] syringic acid,[58] p-Coumaric acid,[59] and kaempferol[60] suppress inflammation by inhibiting NF-κB activity. Other reports have also shown that Zj extract suppresses lipopolysaccharide-induced NF-κB activity in RAW 264.7 cells[61] and inflammation in inflammatory bowel disease and liver injury.[19,22] These results are consistent with our data.

Apoptosis is essential for development and homeostasis in most tissue types.[62] The caspases are the center of the apoptosis pathway and induce various hydrolysis reactions which cause cell death when activated.[63] It is commonly accepted that caspase-3 is a vital effector, and protease, which performs alone or in relationship with apoptosis-related proteins, participates in hydrolysis.[64,65] Caspase-3 is an executive caspase in apoptosis.[66] Ethanol induces apoptosis in the gastric tissues and causes gastric mucosal damage.[12] Zj fruit extract has decreased neurotoxicity by reducing caspase-3 levels in culture cells.[17] In this study, severe immunopositivity was observed in the ulcer group compared to the control group. The groups treated with Zj fruit extracts performed a lower immunopositivity compared to the ulcer group. Thereby, we have determined that the antiapoptotic property of Zj fruit extract may prevent gastric ulcers.

CONCLUSION

The present study showed that Zj fruit extract demonstrated immunomodulatory, anti-ulcer, and anti-inflammatory features in the gastric ulcer model induced by ethanol in rats. These effects are related to the activity of a vast number of polyphenols in Zj fruit extract. Finally, further studies are recommended to make the study results more reliable.

ETHICAL DECLARATIONS

Ethics Committee Approval: All animal applications, including surgical and medical procedures, were accepted by the Animal Experiments Local Ethics Committee, Atatürk University (Protocol no: 19.04.2016/70).

Informed Consent: Not available.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article / Orijinal Araştırma

Perceptions of COVID-19 Vaccines from the Perspectives of Healthcare Professionals and Medical Students: The Impact of Vaccine-Related Concerns on Our Decision-Making

Sağlık Çalışanları ve Tıp Fakültesi Öğrencilerinin Gözünden COVID-19 Aşılarına İlişkin Algılar: Aşı ile İlgili Endişelerin Karar Alma Sürecimize Etkisi

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Abstract

Aim: Vaccination hesitancy poses a solemn resistance to ensuring society's immunity. In our study, we aimed to investigate the level of hesitation and rejection of the Coronavirus disease of 2019 (COVID-19) vaccine and define the factors that may affect the vaccine decision-making process.

Material and Method: A survey study was conducted with the medical students, assistants and academicians of Selçuk University Faculty of Medicine. A total of 701 individuals agreed to participate in the cross-sectional study. Data were assembled from February to March 2022.

Results: 73% of the participants were students, 16% were assistants, and 11% were academics. The majority of the participants (97.7%) had the COVID-19 vaccine. 2.3% of the participants refused to be vaccinated against COVID-19, and 37.5% of the vaccinated had concerns about the vaccine. Those with hesitant about vaccines had concerns about the side effects and safety. The most significant concern was the possibility of adverse effects other than defined (n=125). The number of participants who stated there was not enough time to confirm vaccine safety was 104 (14.8%). The number of participants who thought the vaccine was not sufficiently tested enough was 96 (13.7%). The number of participants who doubted the vaccine's safety was 91 (13%) due to the vaccine production process being swift. Eighty-five (11.7%) participants thought the vaccine might fail in new viral strains.

Conclusion: Vaccine acceptance is elevated among the academics, assistants and students of the faculty of medicine. The most crucial reason for vaccine hesitation is safety and efficacy concerns. However, these concerns have not led to robust vaccine rejection.

Keywords: COVID-19, vaccine concern, healthcare professionals, medical school students

Öz

Amaç: Aşı tereddütü, toplum bağışıklığının sağlanmasında ciddi zorluklar doğurur. Çalışmamızda, COVID-19 aşı tereddüt ve red düzeyini araştırmayı ve aşı karar verme sürecini etkileyebilecek faktörleri belirlemeyi amaçladık.

Gereç ve Yöntem: Selçuk Üniversitesi Tıp Fakültesi öğrencileri,asistanları ve öğretim üyelerini kapsayan bir anket çalışması yapıldı. Toplam 701 kişi bu kesitsel çalışmaya katılmayı kabul etti. Veriler Şubat-Mart 2022 aralığında toplandı.

Bulgular: Katılımcıların %73'ü öğrenci, %16'sı asistan ve %11'İ öğretim üyesi idi. Katılımcıların çoğunluğu (%97.7) COVID-19 aşısı yaptırmıştı. Katılımcıların %2.3'ü COVID-19 aşısı olmayı reddederken, aşı yaptırmış olanların %37.5'inin aşı ile ilgi endişelere sahip olduğu tespit edildi. Aşı tereddütü yaşayanların çoğu aşıların yan etkileri ve güvenliği ile ilgili endişelere sahipti. En büyük endişe açıklanan dışında yan etki olması idi (125 kişi, %17.8). Aşının güvenliğini doğrulamak için yeterli zaman geçmediğini düşünen katılımcı sayısı 104 (%14.8) idi. Aşının yeterince fazla sayıda insan üzerinde test edilmediğini düşünen katılımcı sayısı 96 (%13.7) idi. Aşı üretim sürecinin çok acele olması nedeniyle aşının güvenilirliğinden şüphe eden katılımcı sayısı 91 (%13)di. 85 (%11.7) katılımcı aşının, yeni viral suşlara karşı etkinliğini kaybedebileceğini düşünüyordu.

Sonuç: Tıp fakültesi öğretim üyesi, asistan ve öğrencilerinde aşı kabulü oldukça yüksek düzeydedir. Aşı tereddütünün en önemli nedeni, güvenlik ve etkinlik endişeleridir. Ancak bu endişeler ciddi bir aşı reddine neden olmamıştır.

Anahtar Kelimeler: COVID-19, aşı tereddütü, sağlık çalışanları, tıp fakültesi öğrencileri

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INTRODUCTION

The primary purpose of health assistance and the main responsibility of health personnel is to sustain life healthy and to prevent getting sick. In this regard, vaccination is one of the most effective methods to protect and maintain health. During the pandemic, the mortality rates of the Coronavirus of 2019 (COVID-19) again emphasized the importance of an effective vaccine to stop the spread of COVID-19. In our country, the emergency use of the Coronavac vaccine was first approved by the Turkish Medicines and Medical Devices Agency on 13.01.2021. Currently, Pfizer-BioNTech, Coronavac and Turkovac vaccines are in use. In any way, vaccine hesitancy is likely to impair the effectiveness of the COVID-19 vaccine applicability.

Vaccine hesitancy is seen as a significant threat to global health. Reported COVID-19 vaccine acceptance rates differ around the world. However, a recent global report on the COVID-19 vaccine acceptance rate revealed that around 30% of respondents would refuse or hesitate to accept a COVID-19 vaccine once it was available. The Middle East ranks among the regions with the lowest vaccine acceptance rates globally.[1]

In a study conducted in 2015, the European Center for Disease Prevention and Control of Europe aimed to detect vaccine hesitancy between healthcare professionals and their patients. They found that the most reliable source for vaccination information was healthcare professionals. In addition, the knowledge and approaches of healthcare professionals affect their vaccination practices and recommendations.[2]

Medical students are the healthcare providers of the future who will be assigned to advise individuals who may be hesitant about vaccination. A cross-sectional study of the COVID-19 vaccine hesitancy was conducted in January 2021 among medical students at two universities in Egypt. In this study, it was seen that 35% of the students accepted the COVID-19 vaccine, whereas 46% hesitated, and 19% rejected the vaccine.[3]

In order to achieve the high vaccination rates required for society immunity, there should be a need to understand the vaccine perception, attitude and hesitation degree of the medical school team, which will scientifically guide the society. Therefore, we aimed to survey the vaccination attitude of medical faculty students, assistants, and academics. In addition, the study simultaneously aimed to investigate the acceptance, hesitation and resistance level of the COVID-19 vaccine and to determine the barriers to vaccine acceptance and the reasons that may alter the vaccine decision of individuals.

MATERIAL AND METHOD

xxxxxxxxxxxxxxxxxxxx students, faculty academics and assistants were included in this cross-sectional study. Our medical students distributed a vaccine hesitancy questionnaire to those who agreed to participate in the study. The questionnaire was accomplished by face-to-face interview method.

The questionnaire includes the following components: 1) Demographic data, 2) COVID-19 and vaccination experience, and 3) Vaccine Hesitancy Questionnaire. In this context, participants were asked whether they had a COVID-19 infection, if so, whether this was confirmed by a method, how many doses and which name of vaccines they had, and vaccine adverse effects experienced. Also, the following question was asked. "If you are against getting vaccinated, or if you decide to vaccinate or have hesitations even though you have been vaccinated, what are the reasons for your hesitations?" Possible reasons for hesitation were listed below the question, and the participants were asked to mark their suitable ones. Data were collected between February and March 2022. Prior to the study, ethics committee approval was obtained from xxxxxxxxxxxxxxx(2022/32).

Statistical analysis was performed using SPSS version 22 (IBM Corporation, USA). Normally distributed data were expressed as mean±standard deviation. Differences between groups were evaluated with the t-test or the Mann-Whitney U test. A Chi-square test was used to compare categorical data. A p-value < 0.05 was considered significant.

RESULTS

Overall, 512 students (73%), 77 academicians (11%) and 112 assistants (16%) participated in this cross-sectional study. 51.5% of the participants were male, and the age range was 18 - 64. The mean age was 25.4±8.3 years. 9.7% of the participants had no chronic disease. Concerning academic ranks, 31 of the participants (4.4%) were professors, 26 were associate professors (3.7%), and 20 were assistant professors (2.9%). Participation from students was from all classes.

301 (42.9%) participants stated that they had COVID-19 infection, 300 (42.8%) did not, and 100 (14.3%) individuals were not sure whether they had COVID-19 infection. The rates of COVID-19 infection were determined as 60.7% for assistants, 59.7% for academicians and 36.3% for students.

Table 1. Demographics of participants and their COVID-19 experiences

		n	Ratio (%)
Age	18-25	504	71.9
	26-40	137	19.5
	41-64	60	8.6
Gender	Female	340	48.5
	Male	361	51.5
Career	Student	512	73
	Assistant	112	16
	Academician	77	11
Chronic Disease	None	636	90.7
	Diabetes Mellitus	10	1.4
	Hypertension	9	1.3
	Cardiovascular Disease	7	1
	Other	39	5,6
Have you had a COVID-19 infection?	Experienced	300	42.8
	Not experienced	301	42.9
	Not sure	100	14.3
Have you ever had a COVID test?	Yes, a positive result	232	33.1
	Yes, negative result	161	23
	I had no tested	308	43.9

While 2.3% (16) of the participants refused to be vaccinated against COVID-19, 38.9% (273) had hesitations about vaccination. Four hundred twenty-eight participants (61.1%) had no hesitation about vaccination. Most of the participants were vaccinated in 2 or 3 rappel doses. The number of individuals who were vaccinated with one dose was 8 (1.1%), two doses of vaccine were 247 (35.2%), three doses of vaccine were 241 (34.4%), four doses of vaccine were 147 (21%) and five doses of vaccine were 42 (6%). The most preferred vaccine brands were Pfizer-Biontech (46.6%) and Sinovac+Pfizer-Biontech (38.8%). (**Figure 1**). After vaccination, 379 participants (55.3%) reported mild side effects, 19 participants (2.7%) reported moderate side effects, and 287 participants (41.8%) stated no experience of any side effects.

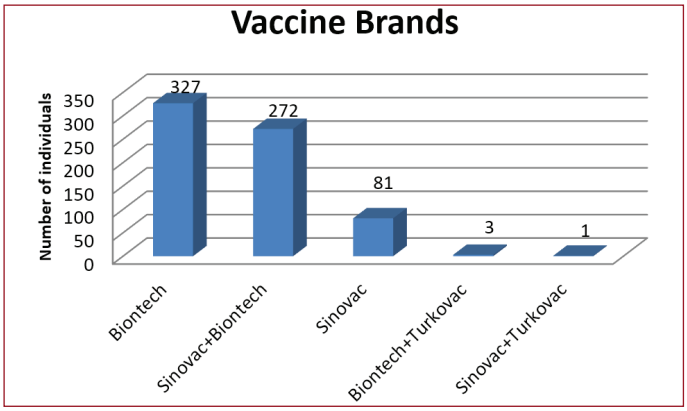

Figure 1. Preferred vaccine brands of the study. The significant factor contributing to the limited representation of the Turkovac Vaccine is primarily attributed to its unavailability during the implementation phase at the time of the research.

The side effects specific to vaccines were the following. While 65 (80%) individuals who received only the Sinovac vaccine did not develop any side effects, mild side effects were reported in 16 (19.8%). No participants vaccinated with Sinovac reported solemn side effects. While 133 (40.7%) individuals who received only the Pfizer-Biontech vaccine did not develop any side effects, mild side effects were reported in 183 (56%). Ten (3.1%) participants reported severe side effects. While 84 (30.9%) of the people who received the Sinovac+Biontech vaccine did not develop any side effects, mild side effects were reported in 179 (65.8%). Again, 9 (3.3%) participants reported severe adverse events. The prevalence of mild and severe adverse events reported was significantly higher in those who received the Biontech-Pfizer vaccine ($p < 0.001$). (**Table 2**)

Table 2. Distrubution of the Adverse effects

	No side effect	Mild side effects	Severe side effects	p value
Per vaccine type				
Sinovac, n (%)	65 (80)	16(19.8)	0	
Biontech, n (%)	133 (40.7)	183 (56)	10 (3.1)	
Sinovac + Biontech, n (%)	84 (33.9)	179 (65.8)	9 (3.3)	<0.001
Biontech + Turkovac, n (%)	2 (66.6)	1 (33.3)	0	
Sinovac + Turkovac, n (%)	1 (100)	0	0	
Per gender				
Female	135 (39.7)	194 (57.1)	11 (3.2)	0.285
Male	168 (46.5)	184 (51.2)	8 (2.2)	

Despite observing higher rates of adverse effects in female compared to male, statistical significance was not attained ($p=0.285$). While 57.1% of women reported mild and 3.2% complained of severe side effects, these rates were 51.2% and 2.2% in men, respectively (**Table 2**)

Many of the hesitant about vaccines had concerns about the side effects and safety of vaccines. The biggest concern was side effects other than those defined (125 individuals, 17.8%). The number of participants who thought sufficient time had not passed to confirm the vaccine's safety was 104 (14.8%). The number of participants who considered the vaccine was not tested on an adequate subject was 96 (13.7%). The number of participants who doubted the vaccine's safety was 91 (13%) due to the rapid vaccine production. 85 (11.7%) participants thought the vaccine might lose its effectiveness against new viral strains. Eighty-four (12%) people were hesitant about the vaccine because they heard that most vaccinated individuals had side effects such as general fatigue, muscle and joint pain, headache and fever. Having COVID-19 after vaccination also caused 82 people (11.7%) to be hesitant about vaccination. Other remained reasons for hesitation are shown in **Table 3.**

Table 3: Participants' concerns about COVID-19 vaccines

Concern	n (701)	%
Having side effects other than reported.	125	17.8
Not enough time has passed to confirm the safety of the vaccine.	104	14.8
Vaccines were not tested on large numbers of people.	96	13.7
The vaccine production process is too rushed.	91	13
The vaccine may lose efficacy against novel viral strains.	85	12.1
Most people vaccinated have side effects such as general fatigue, muscle and joint pain, headache and fever.	84	11.9
I know/heard of people infected with Covid-19 after getting vaccinated.	82	11.7
I do not want to encounter the side effects mentioned in the studies.	60	8.6
I fear that the vaccine will have irreversible and long term effects on DNA.	52	7.4
I believe immunity obtained through vaccines does not last long.	49	7
I have heard of vaccine-related deaths.	48	6.8
I am not too fond of syringes.	32	4.6
I think the vaccine itself can cause disease	29	4.1
Vaccination is not needed as the majority of infected people recover.	21	3
Because infection rates are decreasing.	19	2.7
I have an extreme allergy to certain foods or medications.	17	2.4
I have/I am still sick with coronavirus disease. Therefore, I do not need to be vaccinated.	16	2.3
I have heard that the vaccine contains aluminum or similar additives that can harm the brain.	16	2.3
The coronavirus is a conspiracy, and the vaccine is part of that.	12	1.7
I think the coronavirus epidemic is overrated. The vaccine is ineffective in preventing COVID-19 infection.	12	1.7
No vaccine is needed as most people are already infected.	11	1.6
I am pregnant / breastfeeding. I think I am not in an appropriate vaccination group.	6	0.9
I have chronic diseases and, therefore afraid of being harmed by the vaccine.	5	0.7
I don't believe in vaccines in general.	4	0.6
I do not think the virus can be transmitted.	2	0.3

Despite all these hesitations, vaccination rates were relatively high. This rate was 97.9% for academicians, 98.9% for assistants and 97.5% for students. The rates of vaccinating at least two doses were 95.9% for students, 97.9% for academicians, and 96.6% for assistants. There was no difference in age (p=0.974), gender (p=0.916), career (p=0.668), or existence of chronic disease (p=0.613) between the participants who accepted or refused the vaccine.

DISCUSSION

The concept of "vaccine hesitancy" represents delaying accepting or rejecting a vaccine even though vaccine services are available. Individuals who are hesitant about vaccination are not only considered individuals who delay or refuse vaccination. Concerns and hesitations experienced by individuals who accept vaccination are also included in the concept of vaccination hesitancy.[4]

The present study investigated the general perception of the COVID-19 vaccine and vaccine hesitancy among academicians, assistants and students at a university hospital. Many studies have shown that the attitudes and knowledge of healthcare professionals about vaccines can affect their intention to vaccinate themselves and their children and to offer vaccines to their patients.[5,6] Thus, the approach of healthcare professionals regarding vaccination is essential.

Our study's vaccination acceptance rate was relatively high at 97.7%. This rate was 97.9% for academicians and 98.9% for assistants. In studies on the COVID vaccine before the vaccination process, vaccine acceptance intentions were lower, and vaccine rejection/hesitation rates were high. In a study from our country evaluating attitudes and behaviors towards COVID-19 vaccination in December 2020, 52.3% of healthcare professionals in a university hospital desired to be vaccinated against COVID-19. However, it was observed that 31% of the health workers who stated they would not be vaccinated had the COVID-19 vaccine in the following days.[7] Similarly, in a study conducted in a university hospital at the onset of the pandemic, the rate of healthcare workers willing to have the COVID-19 vaccine was 53.6%.[8] All of these are pre-vaccination studies. We think that the vaccination initiation in the following days, the publications on the efficacy and safety of vaccines, and the low rates of severe side effects in the vaccinated healthcare staffers may have increased the vaccine acceptance rates. For a new vaccine to be accepted by healthcare professionals, monitoring vaccine-related protection and side effects may be essential.

Vaccine acceptance rates varied considerably based on country and continent, considering the healthcare staffers in different countries. This rate is 86.2%[9] in China, 64.9%[10] in Saudi Arabia, 80.9%[11] in Canada, 91.7%[12] in Germany and 59% in England.[13] The COVID-19 vaccine hesitancy was 30.7% in a study conducted in the first week of 2021 among healthcare professionals in Palestine. This study was conducted momentarily before the release of vaccine safety reports.[14] During the first wave of pandemics in France, it was reported that 76.9% of respondents accepted a vaccine against COVID-19, whereas 25.9% of respondents were hesitant about the vaccine.[15]

A retrospective analysis of COVID-19 vaccines administered to healthcare workers at a multicenter medical center between December 2020 and April 2021 was performed in the USA. Accordingly, the vaccination rate in the first four months of the vaccination campaign was 78.6% among 65,270 healthcare staffers. It was 95.8% for doctors.[16] After the vaccine became available, COVID-19 vaccine hesitancy rates were evaluated in a multinational study with 5708 participants among Arabic-speaking healthcare workers (in Arab countries and abroad).[17] The study revealed significant vaccine hesitancy among Arabic-speaking healthcare workers residing in and outside Arab countries (25.8% and 32.8%, respectively). It also detected a low vaccine acceptance rate (26.7%) among Arabic-speaking healthcare professionals.

In a meta-analysis of twenty-one studies published recently, the overall acceptance rate for the COVID-19 vaccine among healthcare professionals on the African continent was 46%. Data revealed a low vaccine acceptance among African healthcare staffers.[18] Another study investigated the COVID-19 vaccine desire and associated factors in 599 Indian healthcare staffers between February and March 2021.[19] This survey revealed that 73% of healthcare professionals were willing to accept vaccines, 10.9% refused, and 16.2% needed time to decide.

The concern was similar when the medical faculty students were evaluated. In a study conducted in India between February and March 2021, vaccine hesitancy was found to be 20.6%.[20] On the same dates, in a survey conducted on the students of six medical faculties in China, vaccine hesitancy was found to be 58.2%.[21] Among medical students in Sudan, vaccine acceptance was 55.8%, and vaccine hesitancy was 44.2%.[22] The acceptance rate of the COVID-19 vaccine in Egypt was 35%, the hesitation rate was 46%, and the rejection rate was 19%.[3] In a study conducted on Ankara University Faculty of Medicine students in April 2021, it was reported that vaccination hesitancy was 11.6%, and the rate of those who did not intend to be vaccinated was 2.7%.[23]

In our study, the vaccination rate among medical students was 97.5%. Concerning the Ministry of Health data, as of May 21, 2022, the rate of the population over 18 of age who received at least two doses of vaccination is 85.48% in Turkey and 76.1% in Konya. (covid19asi.saglik.gov.tr) In our study, the rate of getting at least two doses of vaccination was 95.9% for students, 97.9% for academicians and 96.6% for assistants. In our study group, the rate of getting at least two doses of vaccination was higher than the average in both Konya and Turkey.

In our country, the Sinovac firstly and then the Biontech vaccines were available. The most preferred vaccine by the participants was Biontech, followed by Sinovac+Biontech

addition and Sinovac. We conjectured that the Turkovac Vaccine's low presence in the data was due to its recent implementation, occurring shortly before the survey was conducted. Specifically, our survey was concluded right before the vaccine became accessible, which accounts for its limited representation in our findings.

Despite these high vaccination rates, some participants had concerns about vaccine side effects, efficacy, and safety. Similar hesitations have been reported in previous studies.[17,18] In our study, however, these concerns were not an obstacle to vaccination by most of the 37.5% population who had concerns. Because vaccine rejection is detected at 2.3%. A systematic review summarizing the results of 34 studies, evaluating 76,471 participants, suggested that vaccine hesitancy among healthcare professionals is attributed to various factors, including safety and efficacy concerns and potential side effects.[24]

There are some limitations of our study. The research was conducted in a single province. Therefore, the findings may not be representative of the whole country. Because the results of this analysis were based on healthcare professionals' responses, we could not accurately measure response bias. We could also not provide data about those who did not respond to the survey. Therefore, our cohort may not be full coverage of the target audience. Also, the study represents a specific interval in the vaccination campaign. Temporal variations may have appeared in the hesitations of healthcare professionals.

CONCLUSION

As of the study period, our data indicated higher vaccination rates among healthcare staffers and medical school students than the general population average. The most crucial reason for vaccine hesitation was safety and efficacy concerns. This was also a typical result of previous studies. Accordingly, more active dissemination of scientific evidence on COVID-19 vaccine safety will reduce vaccine hesitancy and increase vaccination rates. It appears that COVID-19 vaccine hesitancy is not a solemn problem, with a vaccination rate of over 97% in this population.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of KTO Karatay University Faculty of Medicine Non-Pharmaceutical and Medical Device Research Ethics Committee (Date: 02.03.2023, Decision No: 2023/021).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article / Orijinal Araştırma

Are Preoperative Features Effective in The Incompatibility of Intraoperative Frozen Section and Final Pathology in Operated Patients Diagnosed with Atypia Endometrial Hyperplasia?

Atipili Endometrial Hiperplazi Tanısı ile Opere Edilen Hastalarda İntraoperatif Frozen Patoloji ile Nihai Patoloji Uyumsuzluğunda Preoperatif Özellikler Etkili Midir?

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Abstract

Aim: We aim to investigate the relationship between demographic characteristics and preoperative laboratory findings with the discordance between intraoperative frozen section diagnoses and final diagnoses in patients undergoing surgery with endometrial hyperplasia with atypia.

Material and Method: The study included 154 patients who underwent surgery for endometrial hyperplasia with atypia and who received intraoperative frozen section (IFS) diagnosis between January 2015 and January 2021. Frozen section diagnoses and the final diagnoses of the patients were compared. Patient groups were split into two: patients with an IFS diagnosis concordant and patients with an IFS diagnosis discordant with the final diagnosis. These two groups were compared regarding body mass index (BMI), age, systemic diseases, laboratory parameters, and ultrasonography findings.

Results: When final diagnoses and IFS diagnoses were contrasted, the results were concordant in 126 patients and discordant in 28 patients. The agreement rate was 81.8% (Kappa=0.635; $p < 0.001$; significant agreement). When the concordant and discordant groups were compared regarding demographic characteristics and preoperative laboratory findings, it was found that the BMI was higher, and the rate of complex atypia in the preoperative pathological examination was higher in the discordant group ($p < 0.05$). Other inflammatory markers and demographic variables were not significantly different between groups ($p > 0.05$).

Conclusion: Among patients operated for endometrial hyperplasia with atypia, IFS diagnoses were mostly concordant with the final diagnoses. It should be kept in mind that the discordance rate may be higher in atypical hyperplasias with complex structures and in patients with high BMI.

Keywords: Endometrial hyperplasia, atypia, complex, malignancy, frozen section

Öz

Amaç: Atipili endometrial hiperplazi tanısı ile opere edilen hastalarda intraoperatif frozen section patoloji ile postoperatif final patoloji sonuçları arasındaki farklılıkların demografik özellikler ve preoperatif laboratuar bulguları ile ilişkisinin araştırılmasıdır.

Gereç ve Yöntem: Kliniğimizde Ocak 2015-Ocak 2021 tarihleri arasında atipili endometrial hiperplazi nedeniyle opere olan ve intraoperatif frozen section patoloji (FSP) çalışılan 154 hasta çalışmaya alındı. Hastaların FSP ve postoperatif final patoloji sonuçları karşılaştırıldı. Hastalar FSP ve final patoloji uyumlu olanlar ve uyumlu olmayanlar olmak üzere iki gruba ayrıldı. Bu iki grup; yaş, vücut kitle indeksi (VKİ), sistemik hastalıklar, laboratuar parametreleri ve ultrasonografi bulguları açısından karşılaştırıldı.

Bulgular: FSB ve final patoloji sonuçları karşılaştırıldığında 126 hastada sonuçlar uyumluyken 28 hastada sonuçlar uyumsuz olarak değerlendirildi. Uyumluluk oranı %81.8 olarak saptandı (Kappa=0.635; $p<0.001$; önemli derecede uyumlu). Uyumlu olan ve uyumlu olmayan gruplar demografik ve preoperatif laboratuar bulguları açısından karşılaştırıldığında uyumsuz grupta VKI'nin daha yüksek ve preoperatif patolojide kompleks atipi oranının daha fazla olduğu saptandı ($p<0.05$). Diğer demografik özellikler ve inflamatuar göstergeler açısından iki grup arasında fark saptanmadı ($p>0.05$).

Sonuç: Atipili endometrial hiperplazi nedeniyle opere olan hastalarda FSP sonuçları büyük oranda final patoloji sonuçları ile uyum içerisindedir. Uyumsuzluk oranının kompleks yapılı atipili hiperplazilerde ve yüksek VKI sahip hastalarda daha fazla olabileceği akılda tutulmalıdır.

Anahtar Kelimeler: Endometrial hiperplazi, atipi, kompleks, malignite, frozen section

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INTRODUCTION

Endometrial hyperplasia (EH) is a precancerous lesion associated with developing endometrial cancer (EC) risk that occurs as a result of prolonged endometrium to estrogen exposure and progesterone deficiency. In developed countries, EC is the most frequent and common gynecological malignancy, and endometrioid adenocarcinoma is the most common histological type.[1] EH is divided into four groups: complex hyperplasia with cytological atypia, complex hyperplasia without cytological atypia, simple hyperplasia with cytological atypia, and simple hyperplasia without cytological atypia. The association between stromal and glandular tissue determines the simple and complex type of hyperplasia, and atypia reflects nuclear abnormalities. The EH progressing to carcinoma risk requires cytological atypia.[2]

If a hysterectomy is performed in patients in whom EH with atypia is detected in endometrial tissue sampling, it is observed that approximately 25%–43% are accompanied by well-differentiated endometrial carcinoma.[3] For this reason, an intraoperative frozen section (IFS) examination may be required in cases with a preoperative diagnosis of EH because surgical staging is required in EC treatment. The surgical staging procedure requires bilateral salpingo-oophorectomy with dissection of the paraaortic lymph node and bilateral pelvic lymph node and total abdominal hysterectomy.[4] Since surgical staging has an association with increased perioperative mortality and morbidity, the IFS examination in this patient group prevents unnecessary staging surgery on the one hand and avoids second surgery in case postoperative pathological examination reveals cancer on the other hand.

Many studies have examined the necessity of performing an IFS examination and its comparison with final diagnoses in EH with atypia patients.[5-10] There are some reports of a high concordance rate between IFS diagnoses and final diagnoses in patients with EH with atypia, whereas some reported a low concordance rate and inadequacy in detecting EC. Although there are studies evaluating the usefulness of demographic and ultrasound findings in predicting EC detection in patients with EH with atypia, there is a paucity of studies evaluating the factors that may have an impact on the discordance between IFS diagnoses and final diagnoses.[11,12] This study investigates the relationship between demographic characteristics and preoperative laboratory findings and the discordance between IFS diagnoses and final diagnoses in patients undergoing surgery with an EH with atypia diagnosis.

MATERIAL AND METHOD

The study was carried out with the permission of İzmir Tepecik Training and Research Hospital Non-interventional Researches Ethics Committee (Date: 17.01.2022, Decision No: 2022/01-02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study included 154 patients diagnosed with EH with atypia and operated on in our clinic between January 2015 and January 2021.

The patients were examined in terms of body mass index (BMI), age, menopausal status, parity, comorbidity (diabetes, hypertension), smoking, preoperative laboratory findings (neutrophil-to-lymphocyte ratio [NLR], inflammatory markers, fibrinogen-to-albumin ratio [FAR]), endometrial thickness (ET) on preoperative ultrasonography, IFS diagnosis and final diagnosis. We considered two groups for participants: patients with an IFS diagnosis concordant and patients with an IFS diagnosis discordant with the final diagnosis. These two groups were compared regarding the demographic and medical data mentioned above. The study was performed retrospectively and medical data was retrieved from patient charts.

The patient's diagnosis was according to an endometrial biopsy. The endometrial biopsy method used in patients undergoing biopsy for gynecological reasons was fractional dilation and probe curettage (D&C). Every diagnosed patient received treatment surgically by total hysterectomy without or with bilateral salpingo-oophorectomy.

Every patient who underwent surgery received an IFS examination. In the IFS examination, the hysterectomy material was opened, and then the cavity was examined for its color and irregularity. After that, 2 to 5 thick slices were taken from the uterine wall, and the myometrial invasion's deepest area was selected for IFS. In case no obvious tumor was observed in the cavity, five or more sections were taken randomly. The freezing temperatures for all samples was −25°C, and 8 µ-thick sections were cut and stained with haematoxylin-eosin. If no tumor was observed in these sections; No additional sections were taken.

The operation was terminated in patients in whom malignancy was not detected in IFS. In patients with EC detected in IFS examination, hysterectomy materials were also evaluated regarding myometrial invasion, grade, lymph-vascular space invasion, and tumor size. As a result of these evaluations, patients having non-endometrioid histological type and high-grade tumor with deep myometrial invasion (≥1/2) and a tumor diameter >2 cm with cervical involvement underwent surgical staging.

The pathological material remaining after the IFS examination was embedded in paraffin blocks with formalin for further histopathological examination. Patients with a final diagnosis of malignancy in the postoperative pathological examination were staged based on the FIGO 2009. All materials, including preoperative endometrial biopsy pathologies, IFS pathologies and final pathologies, were examined by 5 gynecopathologists who are experts in their fields.

SPSS (SPSS Statistics version22.0, SPSS Inc.) statistical software was used for statistical analysis. The positive

predictive value (PPV), negative predictive value (NPV), specificity, sensitivity, and accuracy were calculated with a 95% confidence interval for each parameter. Using Cohen's κ coefficient, the correlation between the IFS diagnosis and the final diagnosis was determined. A t-test was used in order to compare parametric variables, and Fisher's Exact and Pearson's chi-square tests were used to compare categorical variables. Categorical variables were expressed as numbers and percentages (n; %), and numerical variables were expressed as mean±standard deviation (mean±SD) and median [quartile]. A p-value less than 0.05 was considered statistically significant.

RESULTS

The study included 154 patients with EH combined atypia in total. The patients' mean age was between 32 to 80 years, with a mean of 54.2 years. Ninety patients were postmenopausal. Although all of the D/C applications were performed in our hospital, the diagnoses of all patients were made by our pathologists. The average amount of time between D&C and surgery was 18 days (10–45 days). Table 1 shows the demographic and pathological characteristics of all participants. The IFS section revealed malignancy in 48 (31.8%) patients, whereas the final pathological examination revealed malignancy in 76 (49.4%) patients. In postoperative histopathological examination, all patients found to have malignancy had endometrioid type EC. The rates of Grade-1, 2, and 3 tumors were 29.2%, 18.8%, and 0.6%, respectively, while the rates of Stage 1a, 1b, and 2 of the disease were 39.0%, 6.5%, and 3.9%, respectively (**Table 1**).

Table 1: Demographic characteristics and pathological results of the patients

Characteristics	All patients
Age	54.2 (9.6)
BMI	32.6 (5.7)
Nulliparity	3 (1.9)
Postmenopausal	90 (58.4)
Hypertension	69 (44.8)
Diabetes	49 (31.8)
Smoking	79 (51.3)
Malignant (IFS)	48 (31.8)
Malignant (Permanent)	76 (49.4)
Grade-1	46 (29.2)
Grade-2	29 (18.8)
Grade-3	1 (0.6)
Stage 1a	60 (39.0)
Stage 1b	10 (6.5)
Stage 2	6 (3.9)

BMI; body mass index, IFS; intraoperative frozen section, Parametric variables are given as mean (standard deviation)(SD) and non-parametric variables are given as n (%)

All 48 patients reported to have malignancy in IFS examination were also found to have malignancy in postoperative histopathological examination, while 78 out of 106 patients reported to have benign lesions were also found to have benign lesions and 28 were found to have malignant lesions in postoperative histopathological examination (**Table 2**). The IFS diagnoses were concordant with the final diagnoses in 126 out of 154 patients, whereas the diagnoses were discordant in 28 patients. The agreement between the IFS diagnoses and the final diagnoses was statistically significant (Kappa=0.635; p <0.001). Cancer detection's sensitivity and specificity by IFS examination were 63.1% and 100%, and the NPV and PPV were 100% and 73.5%, respectively.

Table 2: Comparison of the IFS and the final diagnoses

	Final Diagnosis		
IFS Diagnosis	Malignant	Benign	Total
Malignant	48	0	48
Benign	28	78	106
Total	76	78	154

IFS; frozen section pathology. Sensitivity: 48/76=63.1%, Specificity: 78/78=100%, Positive predictive value (PPV): 48/48=100%, Negative predictive value (NPV): 78/106=73.5%, Concordance: 126/154=81.8% (Kappa=0.635; P< .001) with significant agreement.

When the concordant and discordant groups were compared regarding age, BMI, parity, menopausal status, systemic diseases (hypertension and diabetes mellitus), and smoking, it was found that BMI was higher in the discordant group (32.0±5.4 vs. 35.5±5.9 kg/m²; p=0.006). Regarding further demographic factors, there was no statistically significant difference between the two groups (**Table 3**). No difference was found between the two groups in the evaluation of preoperative laboratory parameters such as NLR, PLR, FAR, Ca125 and preoperative ultrasonography in terms of ET (p >0.05). The rate of EH with complex atypia was 29.4% in the concordant group in the preoperative diagnosis, whereas this rate was 50.0% in the discordant group (p=0.036).

Table 3: Comparison of demographic and laboratory variables between groups

Characteristics	Concordant (n=126)	Discordant (n=28)	P value
Age	53.9 (9.9)	55.3 (8.0)	0.437
BMI (kg/m²)	32.0 (5.4)	35.5 (5.9)	0.006
Nulliparity	2 (1.6)	1 (3.6)	0.499
Postmenopausal	71 (56.3)	19 (67.9)	0.264
Hypertension	56 (44.4)	13 (46.4)	0.849
Diabetes	40 (31.7)	9 (32.1)	0.967
Smoking	63 (50.0)	16 (57.1)	0.494
ET (before PC)	13.2 (5.3)	12.2 (4.9)	0.386
PC (complex HP)	37 (29.4)	14 (50.0)	0.036
NLR	2.4 (0.9)	2.5 (0.9)	0.467
PLR	139.5 (51.1)	130.7 (33.8)	0.270
FAR	75.0 (22.9)	83.6 (28.1)	0.296
Ca125	12 [9-17]	12 [9-17.5]	0.964

BMI; body mass index, ET; endometrial thickness, PC; probe curettage, HP; hyperplasia, NLR; neutrophil lymphocyte ratio, PLR; platelet lymphocyte ratio, FAR; fibrinogen albumin ratio, Parametric variables are given as mean (standard deviation) (SD) and median [quartiles] and non-parametric variables are given as n (%).

DISCUSSION

In our study, a comparison was made between the two groups to investigate the effect of demographic and laboratory characteristics that may have affected the discordance between the IFS and the final diagnoses in patients operated for EH with atypia. It was found that, BMI among demographic characteristics and EH with 'complex' atypia among laboratory characteristics might have affected concordance.

The use of IFS examination in gynecological practice greatly influences the care of oncology patients. IFS examination is used for differentiation between benign and malignant tumors to determine the extent of the operation. IFS examination in gynecological oncology is sufficient in sensitivity and specificity for clinical use. In general, the rate of false positives is negligible, and the rate of false negatives is low. Deferred or discordant diagnoses are usually due to technical limitations in cases such as those with mucinous ovarian tumors.[13] In a study evaluating 203 gynecological (35.6% ovarian, 22.7% cervical, 18.2% endometrial and 11.4% vulvar) operations in which IFS examination was performed, false negative, false positive, and deferred rates were 0.5%, 2.0%, and 1.0% respectively.[14] In this study, the cause of false positivity was misinterpretation, while the cause of false negativity was reported as an error in block selection. The reasons for false positivity and false negativity in the IFS examination in gynecological oncology are attributed to interpretation errors and technical reasons during the frozen section procedure.[14,15] However, since the concordance between IFS diagnoses and the final diagnoses has not been evaluated in previous studies, evaluating preoperative patients and demographic and laboratory data that increase the potential for malignancy in cases with EH with atypia were evaluated in the present study.

As known, advanced age, increased BMI (obesity), nulliparity, postmenopausal status and systemic diseases including hypertension and diabetes mellitus, are crucial demographic EC development risk factors.[16] In our study, only increased BMI among these demographic factors was associated with the discordance between the IFS and final diagnoses. Given that there is a significant relationship between rising BMI and EC and that EH with atypia may have associations with a higher cancer risk, obtaining more sections in IFS examinations may prove effective to catch cancer. A similar number of sections were taken in each case for the IFS examination in our study. In patients with increased risk factors for EC, taking more sections in the IFS examination may reduce false negativity and thus the rate of discordance.

Increased inflammation is one of the factors that are influential in cancer development and progression.[17] Inflammatory biomarkers, including NLR and PLR, are poor prognosis indicators in EC patients.[18,19] NLR or PLR has associations with overall survival and disease-free survival (DFS).[19] In our study, we found that inflammatory markers such as NLR, PLR, and FAR were not related to the discordance between the IFS and the final diagnoses in cases with EH with atypia. Detection of increased ET (≥2 cm) on preoperative ultrasonographic examination is a strong predictor for simultaneous EC in patients having a hysterectomy with a diagnosis of EH with complex atypia and endometrial intraepithelial neoplasia.[20] Our study found no difference in preoperative ET values between concordant and discordant groups. Therefore, it is considered that the ET was not associated with the discordance between the IFS and the final diagnoses.

While EC was not observed in the final pathological examination in patients operated for EH with simple atypia, EC was observed at a rate of 40%–50% in patients with EH with complex atypia.[21,22] Therefore, a structurally 'complex' feature in patients with atypical EH is a significant risk factor for malignancy. The rate of 'complex' structure in our study was 29.4% in the concordant group and 50.0% in the discordant group. The presence of EH with complex atypia is considered to be a risk factor for the discordance between the IFS and the final diagnoses.

As a secondary result of our study, IFS diagnoses significantly correlated with the final diagnoses in patients with EH with atypia. In a research comparing 66 patients with EH with atypia's ultimate diagnoses to their IFS diagnoses, Morotti et al. reported a good level of concordance (κ=0.75).[7] Moreover, the sensitivity, specificity, PPV, NPV, and accuracy rates of IFS examination to predict EC were found to be 73%, 93.1%, 73%, and 93.1%, respectively. In another study, 75% of patients operated on with a diagnosis of EH with atypia and diagnosed with EC were successfully detected with IFS examination.[8] In another study evaluating 125 patients with EH with complex atypia, 62.4% of final diagnoses were found to be concordant with the IFS diagnoses, and the sensitivity and specificity of IFS examination in detecting EC were 81.1% and 97.9%, and the negative and positive predictive values were 76.7% and 98.4%, respectively; however, the authors reported that IFS examination did not restrain the potentiality of EC in patients with a preoperative diagnosis of EH with complex atypia and adequate endometrial sampling was more important for accurate diagnosis.[9] As can be seen, the rate of EC detection with IFS examination in our study is consistent with reports in other studies in the literature.

The strengths of this study include the following: (a) it is the first study to compare the reasons for discordance between the IFS and the final diagnoses in patients undergoing hysterectomy for EH with atypia, (b) it is the most extensive series in the literature evaluating the performance of IFS examination in diagnosing EC among patients with EH with atypia, (c) the short period between preoperative diagnosis and hysterectomy (reduced risk of EC progression), (d) all

preoperative diagnoses were made by the pathologists our hospital. The limitations of this study can be listed as the following: (a) Technical problems during IFS examination are not known since the study was not a prospective study by design, (b) Preoperative D&C material, IFS and final pathological examinations were not performed by the same pathologist.

CONCLUSION

High BMI and the presence of EH with complex atypia are important factors in the discordance between the IFS and the final diagnoses. In the IFS examination of patients with EH with complex and high BMI, a higher number of sections should be taken to increase the concordance rate.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İzmir Tepecik Training and Research Hospital Non-interventional Researches Ethics Committee (Date: 17.01.2022, Decision No: 2022/01-02).

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

Referee Evaluation Process: Externally peer-reviewed.

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Original Article / Orijinal Araştırma

Paraoxonase-1 and Arylesterase Activities in Children with Acute Bronchiolitis

Akut Bronşiyolitli Çocuklarda Paraoksonaz-1 ve Arilesteraz Aktiviteleri

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Abstract

Aim: Acute bronchiolitis is a disease frequently seen in children under two years of age. Paraoxonase 1 (PON1) and arylesterase (ARES) are enzymes in the esterase group which are encoded by the same gene and whose active centers are similar. The common characteristics of PON1 and ARES are their ability to hydrolyze organophosphates, aryl and alkyl halides. PON1 enzyme functions as an antioxidant by inhibiting the oxidation of low density lipoprotein (LDL) and neutralizing free radicals such as hydrogen peroxide. ARES is accepted as an indicator of the main protein, which is not affected by changes in PON1. The aim of this study is to investigate whether PON1 and ARES activity levels can be used as an indicator of the disease in children with acute bronchiolitis.

Material and Method: Ninety one patients with acute bronchiolitis who admitted to pediatric emergency unit and 39 age- and sex-matched healthy children were included in the study. Patients were divided into 3 groups as mild, moderate and severe bronchiolitis according to Wang scoring system.

Results: The mean serum PON1 activity levels of all patients with bronchiolitis were 188.05±101.94 U/L, and the mean of the control group was 302.87±170.52 U/L. The mean serum ARES activity levels of all patients with bronchiolitis were 408.44±109.95 kU/L, and the mean of the control group was 785.45±168.45 kU/L. Mean serum PON1 and ARES activity levels were found to be statistically significantly lower in patients with acute bronchiolitis. No statistically significant difference was found among groups according to disease severity.

Conclusion: We found that PON1 and ARES activity levels were lower in patients with acute bronchiolitis than in controls. The results of our study show that low PON 1 and ARES activity levels may play a role in the pathogenesis of acute bronchiolitis and that oxidative stress may have an effect on the development of bronchiolitis.

Keywords: acute bronchiolitis, arylesterase (ARES), child, oxidative stress, paraoxonase 1 (PON1)

Öz

Amaç: Akut bronşiolit iki yaş altı çocuklarda sık görülen bir hastalıktır. Paraoksanaz-1 (PON1) ve arilesteraz (ARES) aynı gen tarafından kodlanan ve aktif merkezleri benzer olan esteraz grubunda yer alan enzimlerdir. PON1 ve ARES'in ortak özellikleri, organofosfatları, aril ve alkil halojenürleri hidrolize edebilmeleridir. PON1 enzimi, düşük yoğunluklu lipoproteinin (LDL) oksidasyonunu inhibe ederek ve hidrojen peroksit gibi serbest radikalleri nötralize ederek bir antioksidan görevi görür. ARES, PON1'deki değişikliklerden etkilenmeyen ana proteinin bir göstergesi olarak kabul edilir. Bu çalışmanın amacı, akut bronşiyolitli çocuklarda PON1 ve ARES aktivite düzeylerinin hastalık göstergesi olarak kullanılıp kullanılamayacağını araştırmaktır.

Gereç ve Yöntem: Çalışmaya çocuk acil servisine akut bronşiolit nedeniyle başvuran 91 hasta ile yaş ve cinsiyet olarak eşleştirilmiş 39 sağlıklı çocuk dahil edildi. Hastalar Wang skorlama sistemine göre hafif, orta ve şiddetli bronşiolit olarak 3 gruba ayrıldı.

Bulgular: Tüm bronşiyolitli hastaların ortalama serum PON1 aktivite düzeyleri 188,05±101,94 U/L, kontrol grubunun ortalaması 302,87±170,52 U/L idi. Tüm bronşiyolitli hastaların ortalama serum ARES aktivite düzeyleri 408,44±109,95 kU/L, kontrol grubunun ortalaması 785,45±168,45 kU/L idi. Akut bronşiyolitli hastalarda ortalama serum PON1 ve ARES aktivite düzeyleri istatistiksel olarak anlamlı derecede düşük bulundu. Hastalık şiddetine göre gruplar arasında istatistiksel olarak anlamlı fark bulunmadı.

Sonuç: Akut bronşiyolitli hastalarda PON1 ve ARES aktivite düzeylerinin kontrollere göre daha düşük olduğunu bulduk. Çalışmamızın sonuçları, düşük PON 1 ve ARES aktivite düzeylerinin, akut bronşiyolit patogenezinde rol oynayabileceğini ve oksidatif stresin bronşiolit gelişimi üzerine etkisi olabileceğini göstermektedir.

Anahtar Kelimeler: akut bronşiolit, arilesteraz(ARES), çocuk, oksidatif stress, paraoxonaz 1 (PON1)

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INTRODUCTION

Acute bronchiolitis is a disease characterized by inflammatory obstruction of small airways, characterized by tachypnea, retractions and wheezing. Viruses often play a role in the etiology of the disease. Most cases are under two years old.[1,2] Respiratory syncytial virus (RSV) is responsible for almost half of the cases. While it is accepted that bacteria do not cause disease, bacterial superinfection can be observed with bronchiolitis.[1] Frequency of bronchiolitis varies seasonally. It is more dominant in the winter months. Every year, hundreds of thousands of children under one year old in the world are hospitalized for acute bronchiolitis, and each passing year, the number of cases increases. Oxidative stress is known to contribute to the pathogenesis of acute and chronic lung inflammatory diseases.

Paraoxonase 1 (PON1) and arylesterase (ARES) are enzymes in the esterase group which are encoded by the same gene and whose active centers are similar. Despite PON1 is known to show polymorphic changes, the ARES enzyme does not show a genetic polymorphic change. Although the natural substrates of the two enzymes are different, the PON1 enzyme has the ability to hydrolyze the phenyl acetate, the natural substrate of ARES. The common characteristics of PON1 and ARES are their ability to hydrolyze organophosphates, aryl and alkyl halides. PON1 enzyme functions as an antioxidant by inhibiting the oxidation of low density lipoprotein (LDL) and neutralizing free radicals such as hydrogen peroxide. ARES is accepted as an indicator of the main protein, which is not affected by changes in PON1.[3,4]

Dundaroz et al.[5] reported that total oxidative status was higher and total antioxidant capacity was lower in patients with acute bronchiolitis compared to the control group, and this situation was effective in the pathogenesis of the disease. There are studies reporting that PON 1 and ARES activity levels contribute to the pathogenesis of diseases including asthma, pulmonary tuberculosis, allergic rhinitis, chronic obstructive pulmonary disease and beta-thalassaemia major.[6-11]

The aim of this study is to determine whether PON1 and ARES activity levels can be used as an indicator of the disease in patients with acute bronchiolitis and to investigate the association of the activities of these enzymes with the severity of the disease.

MATERIAL AND METHOD

This study was conducted with the approval of Necmettin Erbakan University Clinical Research Ethics Committee (Date: 24.02.2017, Decision No: 2017-825). All procedures were carried out in accordance with the Declaration of Helsinki.

Study Population

Patients who admitted to pediatric emergency department of Necmettin Erbakan University Meram Medical Faculty in Konya region of Turkey between the period September 2018 to May 2019, and diagnosed as acute bronchiolitis were included in the study. Informed consent was obtained from the families of the patients. Children who had a history of congenital heart disease, bronchopulmonary dysplasia, chronic lung disease, prematurity, assisted ventilation during the neonatal period, immunodeficiency, asthma and who received bronchodilator or corticosteroid treatment in the previous two weeks were not included in the study. The clinical, laboratory and demographic features of the patients were recorded in a standardized form. Serum samples that remained from the blood examination routinely taken for analysis from patients who were followed up with the diagnosis of acute bronchiolitis were used to evaluate PON1 and ARES activity levels. The blood samples were collected immediately after admitting the emergency department, before receiving any medication. No extra blood was collected from the patients for these tests. Patients were excluded from the study when the serum sample left was insufficient for evaluation.

The control group was consisted of age and gender matched healthy children who did not have any signs of septicemia, pulmonary, metabolic and rheumatological diseases, but tested for a routine check up. Remaining serum samples were used to evaluate PON1 and ARES activities.

Wang scoring system was used to evaluate the severity of acute bronchiolitis.[12] Patients were divided into 3 groups as mild, moderate and severe bronchiolitis according to this scoring. A Wang score of 1-3 points considered as mild disease, 4-8 points as moderate disease, and 9-12 points as severe disease.

Laboratory testing

Blood samples were centrifuged at 3000 rpm for 15 minutes for serum separation, and then stored at -80 ° C until analysis. When all samples were completed, frozen serums were melted at room temperature and studied on the same day.

While ARES activity was measured by using an ARES assay kit and PON1 activity by a full automatic PON activity measurement kit (Assay Rel Diagnostics, Gaziantep, Turkey).

Paraoxonase activity measurement: The method consists of two different sequential reagents. The first reagent is an appropriate Tris buffer and it also contains calcium ion, which is a cofactor of PON1 enzyme. The second reagent is a new developed stabile substrate solution. The sample is mixed with the Reagent 1 and the substrate solution is added. Linear increase of the absorbance of p-nitrophenol, produced from paraoxon, is followed at kinetic measurement mode. Nonenzymatic hydrolysis of paraoxon was substracted from the total rate of hydrolysis. The molar absorptivity of p-nitrophenol is 18,290 M^{-1} cm^{-1} and one unit of paraoxonase activity is equal to 1 mol of paraoxon hydrolyzed per liter per minute at 37°C

Arylesterase activity measurement: The assay PON1, present in the sample, hydrolyses phenyl acetate to its products which are phenol and acetic acid. The produced phenol is colorimetrically

measured via oxidative coupling with 4-aminoantipyrine and potassium ferricyanide. Nonenzymatic hydrolysis of phenyl acetate was subtracted from the total rate of hydrolysis. The molar absorptivity of colored complex is 4000 M^{-1} cm^{-1} and one unit of arylesterase activity is equal to 1 mmol of phenyl acetate hydrolyzed per liter per minute at 37°C.

Statistical Analysis

Statistical analysis of the study was done using the SPSS (Statistical Package for the Social Sciences for Windows version. 20.0) package program. Descriptive analyzes were used in the distribution and frequency analysis of the data, and chi-square tests were used in frequency data to compare two independent groups. Independent t-test was used to compare the mean of two independent groups. One-way analysis of variance was used to compare the mean of more than two independent groups. Normality analysis was performed on continuous variables. Pearson correlation analysis was used for data that distributed normal, and Spearman correlation analysis was used for data that did not match normal distribution. The significance level was accepted as <0.05 in all statistical analyzes.

RESULTS

91 patients diagnosed with bronchiolitis and 39 age- and sex-matched healthy children were included in the study. Of 91 patients diagnosed with bronchiolitis, 57 (62.6%) were boy and 34 (37.4%) were girl. The mean age of all patients was found to be 12.34±4.84 months (boys: 9.25±3.27; girls: 17.52±6.84). The control group consisted of 39 healthy children.

Twenty-two (24.2%) patients were diagnosed as mild, 44 (48.4%) moderate and 25 (27.5%) severe bronchiolitis. The analyse of hospitalization duration revealed that, 48 (52.7%) patients stayed in the hospital most frequently for less than 24 hours, followed by 33 (25.4%) hospital stays between 24-48 hours. When the number of bronchiolitis attacks were examined, it was seen that 50 (54.9%) patients had their first attack, and only 12 (13.2%) patients had more than 3 attacks. The mean attack score of all patients was 5.38±2.61, that of boys was 5.45±2.62 and girls 5.26±2.63. 84 (92.3%) patients were treated with inhaled bronchodilator, 43 (47.3%) patients with inhaled corticosteroid, 10 (11%) patients with inhaled ipratropium bromide, 13 (14.3%) patients with inhaled magnesium, and 23 patients received oseltamivir. Demographic characteristics of patients and the control group is given in **Table 1**.

Rhinovirus in 14 (15.4%) patients, Respiratory Syncytial Virus (RSV) type A in 25 (27.5%) patients, RSV type B in 24 (26.4%) patients, Human bocavirus in one (1.1%) patient, Adenovirus in five (5.5%) patients, Human metapneumovirus in six (6.6%) patients, Influenza A virus in four (4.4%) patients, Coronovirus 229E in three (3.3%) patients, Enterovirus in one (1.1%) patient, Human paraechovirus was detected in one patient (1.1%) by nasal swab test.

Table 1. Demographic and Clinical Characteristics of the Patients and the Control Group

		Bronchiolitis Group		Control Group		p
		n	%	n	%	
Gender	Male	57	62,6	23	58,9	0,594
	Female	34	37,4	16	41,1	
Disease Severity	Mild	22	24,2			
	Moderate	44	48,4			
	Severe	25	27,4			
Duration of Hospitalization (hour)	<24 hours	48	52,7			
	24-48 hours	33	36,3			
	48-72 hours	5	5,5			
	>72 hours	5	5,5			
Corticosteroid Need	Yes	39	42,9			
	No	52	57,1			
Inhaled Serum Sale Need	Yes	7	7,7			
	No	84	92,3			
Family history of atopy	No	54	59,3			
	Yes	37	40,7			
Exclusive intake of breast milk in the first 6 months of life	Yes	14	15,4			
	No	77	84,6			
Smoke Exposure	Yes	35	38,5			
	No	56	61,5			
Oxygen supplementation method	No oxygen	51	56,0			
	Simple oxygen mask	15	16,5			
	HFNC	6	6,6			
	CPAP	9	9,9			
	Hood	6	6,6			
	BIPAP	4	4,4			
		Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Age (Month)		11,96±11,34	8,64 (2,40-72,00)	12,01±6,72	9,24 (2,0-84,0)	0,788

HFNC: High Frequency Nasal Cannule Oxygen, CPAP: Continuous Positive Airway Pressure, BIPAP: Bilevel Positive Airway Pressure

It was observed that 77 (84.6%) of the patients were exclusively breastfed for the first six months of life. It was determined that 45 (49.5%) of the patients lived in a house heated by a stove, and 56 (61.5%) had contact with cigarette smoke. It was observed that 37 (40.7%) patients had a family history of asthma and/or atopy. Of 22 patients whose serum levels of IgE were measured, 18 (81.8%) were found to be above the normal range for age.

When bronchiolitis severity was compared according to gender, it was found that 12 (54.5%) of 22 patients with mild attack were boy and 10 (45.5%) were girl; 29 (65.9%) of 44 patients with medium attack were boy, 15 (34.1%) were girl; 16 (64%) of 25 patients with severe attack were boy, and 9 (36%) were girl. There was no statistically significant difference between gender and bronchiolitis severity (p> 0.05).

When the drugs used by the patients were compared according to the severity of bronchiolitis attack, 6 (60%) of 10 (11%) patients who received ipratropium bromide treatment were found to be in the severe attack group with statistical significance (p:0.019). Eight (61.5%) of 13 (14.3%) patients who received inhaled magnesium were also in the severe attack group with statistical significance (p:0.011). It was seen that 12 (52.2%) of 23 patients who received oseltamavir treatment were in moderate group, 11 (47.8%) were in severe attack group, and no patient in mild attack group was given oseltamavir treatment (p: 0.002). 5 (38.5%) of 13 patients (14.3%) who were given inhaled magnesium therapy had more than three bronchiolitis attacks, which was statistically significant (p: 0.015).

Nasal swab samples of the patients were compared with the grades of bronchiolitis. The results revealed that 8 (47.1%) of 17 (18.7%) patients with RSVA+RSVB had a statistically significant moderate bronchiolitis attack (p:0.041). 9 (52.9%) of 17 (18.7%) patients with RSVA+RSVB had experienced a mild attack. It was determined that 5 (83.3%) of 6 (6.6%) patients with metapneumovirus were found to be in severe bronchiolitis attack group with statistical significance (p: 0.023).

The mean serum PON1 activity levels of all patients with bronchiolitis were 188.05±101.94 U/L, and the mean of the control group was 302.87±170.52 U/L. The mean of those with mild, moderate and severe bronchiolitis were 199.23±133.84, 190.33±100.88, 174.20±68.80 U/L, respectively. The mean serum ARES activity levels of all patients with bronchiolitis were 408.44±109.95 kU/L, and the mean of the control group was 785.45±168.45 kU/L. The mean of the mild, moderate and severe bronchiolitis groups were 431.93±107.83, 405.65±122.03, 392.69±87.74 kU/L respectively.

The mean of serum PON1 activity levels in all bronchiolitis patients was statistically significantly lower than the mean of the control group (p: 0.001). Similar to PON1, the mean of serum ARES activity levels in all bronchiolitis patients was found statistically significantly lower than the mean of the control group (p: 0.001) (**Table 2**, **Figure 1**).

The mean of serum PON1 and ARES activity levels of the four groups; the control group, mild, moderate and severe bronchiolitis groups, were compared. No statistically significant difference was found among groups according to disease severity. PON1 and ARES activity levels according to patient characteristics are given in **Table 3**.

Table 2. Patient Characteristics According to Gender

	Boy		Girl		Total		p
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Age (months)	9,69±8,23	7,44 (2,4-49,2)	15,75±14,56	11,64 (2,4-72)	11,96±11,34	8,64 (2,4-72)	0,013
Duration of hospitalization (date)	2,20±1,49	1,00 (2-6)	1,77±0,92	2,0 (1-4)	2,07±1,35	2 (1-6)	0,499
Corticosteroid dose number	1,82±1,42	1,0 (1-6)	1,37±0,83	1,0 (1-4)	1,65±1,25	1,0 (1-6)	0,290
WANG Score	5,46±2,63	4 (1-12)	5,26±2,63	5 (1-10)	5,38±2,62	5 (1-12)	0,835
Glucose (mg/dl)	97,61±18,66	91 (71-164)	98,09±16,17	97 (52-137)	97,79±17,68	92 (52-164)	0,325
White blood cell count (/mm3)	10846,67±5033,62	10000 (0-26000)	11525,29±6016,14	10500 (0-33900)	11100,22±5398,66	10200 (0-33900)	0,631
C-reactive protein (mg/dl)	13,11±20,82	4,8 (0,1-96,7)	16,02±21,03	7,5 (0-95,1)	14,23±20,83	5,4 (0-96,7)	0,548
Sedimentation (mm/h)	16,73±13,57	13,5 (4-73)	18,85±14,18	15 (4-59)	17,54±13,75	14 (4-73)	0,533
Immunglobuline E (IU/ml))	40,32±64,54	18,5 (6-302)	54,4±54,61	32,55 (18,51-134)	42,67±62,12	18,51 (6-302)	0,103
Total eosinophil count (/ mm3)	109,35±153,09	36,5 (0,29-564)	173,21±255,77	77 (1-974)	133,4±198,91	41 (0,29-974)	0,397
ARES Activity (kU/L)	420,15±123,09	414,84 (212,32-853,16)	388,82±81,38	381,42 (207,83-552,46)	408,44±109,95	407,85 (207,83-853,16)	0,301
PON1 Activity (U/L)	181,34±97,49	177,29 (34,89-494,69)	199,30±109,55	161,00 (59,34-514,47)	188,05±101,94	166,73 (34,89-514,47)	0,431

Table 3. PON1 and ARES Activity Levels According to Patient Characteristics

		ARES			PON1		
		Mean±SD	Median (Min-max)	p	Mean±SD	Median (Min-max)	p
Study Group	Patients	408,45±109,95	407,86 (207,83 - 853,16)	<0,001	188,06±101,94	166,73 (34,89 - 514,47)	<0,001
	Controls	785,46±168,05	814,2 (394,33 - 1091,67)		302,88±170,53	281,86 (110,36 - 682,08)	
Gender	Boy	420,15±123,09	414,84 (212,32-853,16)	0,301	181,34±97,49	177,29 (34,89-494,69)	0,431
	Girl	388,82±81,38	381,42 (207,83-552,46)		199,30±109,55	161,00 (59,34-514,47)	
Disease Severity	Mild	431,93±107,83[a]	430,32 (243 - 639,07)	<0,001	199,23±133,85[a]	163,83 (34,89 - 514,47)	<0,001
	Moderate	405,66±122,04[a]	403,84 (207,83 - 853,16)		190,34±100,88[a]	167,85 (48,49 - 457,65)	
	Severe	392,7±87,74[a]	384,18 (212,32 - 575,25)		174,21±68,81[a]	182,3 (68,86 - 281,06)	
	Controls	785.45±168.05[b]	814,2 (394,33 - 1091,67)		302,88±170,53[b]	281,86 (110,36 - 682,08)	
Viral Agent	Not detected	438,83±140,61	432,03 (227,88-775,43)	0,292	216,60±132,66	186,21 (62,32-494,69)	0,445
	Detected	397,02±93,70	394,39 (207,83-639,07)		171,88±78,46	164,87 (34,89-303,42)	
Oxygen Need	No	406,06±107,33	401,33 (212,32-853,16)	0,248	189,17±98,93	171,34 (48,49-514,47)	0,347
	Yes	415,93±120,12	422,66 (207,83-636,63)		184,55±113,25	153,86 (34,89-494,69)	
Duration of Hospitalization (hour)	<24	387,71±87,82	393,61 (207,83 - 554,96)	0,503	178,4±89,3	193,35 (34,89 - 349,38)	0,450
	24-48	431,32±119,69	430,16 (243 - 853,16)		191,76±124,98	160,93 (62,32 - 514,47)	
	48-72	435,61±103,67	429,06 (307,56 - 596,86)		234,44±54,16	219,98 (171,34 - 301,63)	
	>72	429,46±212,35	387,45 (212,32 - 775,43)		209,89±87,7	200,05 (115,57 - 344,47)	
Exclusive intake of breast milk in the first 6 months of life	No	433,62±124,5	435,79 (225,17 - 639,07)	0,248	193,66±65,14	191,69 (96,83 - 297,17)	0,422
	Yes	403,87±107,36	401,34 (207,83 - 853,16)		187,04±107,58	164,35 (34,89 - 514,47)	
Ig E	Negative	394,81±107,55	426,58 (239,79 - 486,31)	0,670	188,12±100,84	186,51 (76,3 - 303,16)	0,733
	Positive	461,04±133,01	429,61 (227,88 - 775,43)		220,4±125,11	192,76 (62,32 - 494,69)	

a-b: There is no difference between values with the same letter.

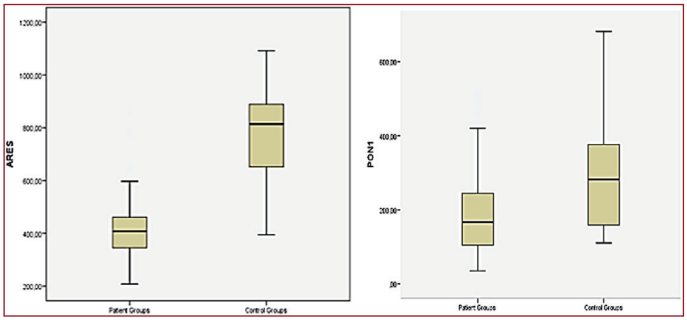

Figure 1. Comparison of serum PON-1 and ARES Activity Levels of Patients and the Control Group

Although there was a negative correlation between age and serum ARES activity levels in correlation analysis, no statistical significance was detected (r: -0.096, p> 0.05). A statistically significantly positive correlation was found between serum PON1 activity levels and age (r: 0,208, p: 0.048). The number of bronchiolitis attacks showed positive correlation with serum PON1 activity levels, but this was not statistically significant (r=0.111, p> 0.05). Despite, there was a negative correlation between the number of bronchiolitis attacks and serum ARES activity levels, no statistically significance (r: -0.157, p> 0.05) was observed.A negative correlation was found between the scores of the patients Wang score and PON1 activity levels, however, this correlation was not statistically significant (r: -0.105, p> 0.05). Similarly, there was a negative correlation between patients' Wang score and serum ARES activity levels, which was also not statistically significant (r:-0.11, p> 0.05). A moderate positive correlation was found between the activity levels of PON1 and ARES, with statistically significance (r:0.297, p<0.001) (**Table 4**).

Table 4. The correlation Analysis of PON1 and ARES Activity Levels

	ARES		PON1	
	p	r	p	r
Age	0,365	-0,096	0,211	0,132
Duration of Hospitalization	0,731	-0,054	0,845	-0,031
Number of Bronchiolitis Attacks	0,138	-0,157	0,293	0,111
Corticosteroid Need	0,408	0,117	0,957	0,008
Attack Score	0,377	0,094	0,322	-0,105
Exclusive Breastfeeding in the first 6 month of life	0,322	-0,106	0,188	0,14
White Blood Cell Count	0,163	-0,147	0,702	0,041
C-Reactive Protein Level	0,509	-0,071	0,891	0,015
Erythrocyte Sedimentation Rate	0,137	-0,178	0,444	0,092
Immunglobuline E Level	0,838	-0,044	0,948	0,014
Total Eosinophil Count	0,632	0,055	0,444	-0,089
ARES			<0,001	0,297
PON1	<0,001	0,297		

DISCUSSION

Oxidative stress contributes to the pathogenesis of various respiratory diseases such as asthma, cystic fibrosis, pulmonary tuberculosis, allergic rhinitis and chronic neonatal lung disease in children.[6-10,13-16] There is a lot of evidence that oxidative stress formation is linked to the pathogenesis of various acute and chronic inflammatory lung diseases. However, little is known about the role of oxidative stress in lung diseases caused by viruses.[17] In this study, PON1 and ARES activities, which are indicators of oxidative status, were investigated in children with acute bronchiolitis. This study showed that PON1 and ARES activities were statistically

significantly lower in patients with acute bronchiolitis than in the control group.

Free oxygen radicals usually play an important role in cellular signaling, regulation of cytokines, growth factors, transcription, immunomodulation and apoptosis. However, when there is an excessive production of free oxygen radicals, damage of DNA, lipids, and proteins can occur. This causes a loss of cellular integrity and functionality.[18] Oxidative stress is referred as an imbalance in the production of free oxygen radicals and insufficient function of detoxfying these radicals. Cells have antioxidant defense systems that they use to protect them from free oxygen radicals.[19] Antioxidants are protective against free oxygen radicals, but sometimes this is not completely sufficient. Reactive oxygen radicals (RS) often form after viral infections. Free oxygen radicals may also have the potential to facilitate viral replication in virus infections. The effect of free oxygen radicals on cellular functions depends on the amount of radicals and how long the cell is exposed to these molecules.[18,20]

Free oxygen radicals and lipid peroxidation products can affect viral replication by modulating the activation state of cells, regulating host inflammatory and immune responses, causing oxidative damage in host tissues and virus components.[21,22] PON1 and ARES have the ability to hydrolyze organophosphate compounds and aromatic carboxylic esters. In addition, it is thought to have an antioxidant effect as it protects high density lipoprotein (HDL) and low density lipoprotein (LDL) from lipid peroxidation.[4]

Studies show that oxidative stress supports lung damage and inflammation after Influenza A infection.[23] It has been shown that damage to the lung tissue is a consequence of the virus-induced cytopathic effect and also due to the cytotoxic effects of excessive inflammation.[24] In our study, it was found that both PON1 and ARES activity levels were statistically significantly lower in patients with bronchiolitis group compared to the control group. Although the results were lowest in patients with severe bronchiolitis, no stattistically significant difference was found among the severity of bronchiolitis. The lower levels of the enzyme activities in patients with acute bronchiolitis supports the view that the damage to lung tissue is caused by the cytotoxic effects of excessive inflammation.

In the study of Hennet et al.[25] endogenous concentrations of antioxidants such as glutathione, vitamin C and E in the lungs, liver and blood plasma of mice infected with Influenza A / PR8 / 34 virus were found to be lower than the control group. Lin et al.[26] reported that the antioxidant properties of superoxide dismutase 1 (SOD1) may decrease apoptosis, pro-inflammatory response and mitochondrial dysfunction, and this may play a positive role in controlling H5N1 infection. As mentioned in these aforementioned studies, infections due to Influenza virus can induce oxidative stress and contribute to viral pathogenesis. It is known that use of antioxidants can have a protective effect against viral infections. In the literature, there are no studies investigating PON1 and ARES activity levels in patients with acute bronchiolitis. Therefore, we think that our study will contribute to the literature.

Oxidative stress also plays an important role in the pathogenesis of pulmonary inflammation caused by RSV. Mochizuki et al.[27] evaluated changes in intracellular glutathione reduction status in healthy airway epithelial cells and RSV-infected bronchial epithelial cells, and showed that RSV-induced oxidative stress may cause airway inflammation. In their study, Moreno-Solis et al.[28] reported that oxidized glutathione levels showed disease severity in patients with RSV-induced bronchiolitis, and this infection increased oxidative stress. Hosakote et al.[17] reported that RSV infection causes down-regulation in the airway antioxidant system and this causes in vivo oxidative damage, in children with bronchiolitis. According to the results of our study, PON1 activity levels were found to be lower than the control group and this has been shown to contribute to oxidative stress. In our study, in the nasal swab samples, 8 (47.1%) of 17 patients with RSV type A + RSV type B were found to be moderate bronchiolitis and 9 (52.9%) were statistically significant. Although the PON1 and ARES activity levels of these patients were lower than the controls, they were not statistically significant. The reason for this may be due to the fact that none of these patients had severe bronchiolitis.

In the study of Ozkaya et al.[6] PON1 activity levels were significantly lower in patients with allergic rhinitis compared to the control group, and it was reported that it may be a predictor in showing the severity of the disease. Emin et al.[7] found that PON1 levels were lower than the control group in their study in children with asthma and reported that PON1 measurement could be used as a systemic marker in uncontrolled asthma in children. Rumora et al.[10] showed that PON1 and ARES activity levels in patients with chronic obstructive pulmonary disease had decreased independently from HDL concentrations compared to the control group. For this reason, it has been reported that PON1 and ARES activity levels can be used in the diagnosis of disease. According to the results of our study, as the severity of bronchiolitis worsened, PON1 and ARES activity levels decreased. Although larger studies are needed to for an exact suggestion, our results may suggest that PON1 and ARES activity levels may be used as predictors in determining the severity of the disease in patients with acute bronchiolitis.

Our study had some limitations. The number of patients and controls is rather small which affects the power of the study. While PON1 enzyme functions as an antioxidant by inhibiting the oxidation of LDL, absence of serum lipid levels makes another limitation of the study.

CONCLUSION

We determined that PON1 and ARES activity levels were lower in patients with acute bronchiolitis. The results of our study show that PON 1 and ARES activities may play a role

in pathogenesis of acute bronchiolitis which indicates the association of increased oxidative stress and development of bronchiolitis, in pediatric patients. However, prospective studies with larger case series are needed to better understand how the host response to viral infection occurs and the effects of oxidative stress on the cell.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was conducted with the approval of Necmettin Erbakan University Clinical Research Ethics Committee (Date: 24.02.2017, Number: 2017-825).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article / Orijinal Araştırma

Does Turkey Require Specific Legislation Regarding Occupational Health and Safety in the Field of Physiotherapy? A Survey Based on the Clinical Experiences of Physiotherapists in the Country

Türkiye'nin Fizyoterapi Alanında İş Sağlığı ve Güvenliğine İlişkin Özel Mevzuata İhtiyacı Var Mı? Ülkedeki Fizyoterapistlerin Klinik Deneyimlerine Dayanan Bir Araştırma

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Abstract

Aim: The aim of this study is to provide the condition for the contribution of physiotherapists working in Turkey to the strengthening of public interests and the development of the country. A specific law on occupational health and safety in physiotherapy is needed for the work satisfaction of physiotherapists.

Material and Method: In this study, the survey organized for the Rights Violations Research was applied to physiotherapists working in Turkey. The current problems arising from the lack of in these occupational health and safety were identified. The prepared survey was transferred to the internet via Google form and the data was sent to e-mail groups of which 128 physiotherapists are members.

Results: The most common violations are identified as follows: failure to define job descriptions (N: 117, 91.4%), absence of workplace-provided training required for the service (N: 114, 89.1%), excessive workload beyond what an employee can handle and/or that may harm the client (N: 111, 86.7%), payment of insurance premiums with lower wages than the salary (N: 108, 84.4%), and physiological/psychological harm (N: 107, 83.6%).

Conclusion: A special law on occupational health and safety in physiotherapy is required as a solution to the rights violations and psychological/physical damages experienced by physiotherapists.

Keywords: Occupational, law, health, safety, physiotherapists

Öz

Amaç: Bu çalışmanın amacı, Türkiyede çalışan fizyoterapistlerin kamu çıkarlarının güçlendirilmesine ve ülke kalkınmasına katkılarının önünü açmaya çalışmaktır. Fizyoterapistlerin çalışma memnuniyeti için fizyoterapide iş sağlığı ve güvenliğine ilişkin özel bir kanuna ihtiyaç vardır.

Gereç ve Yöntem: Bu çalışmada Hak İhlalleri Araştırması için düzenlenen anket, Türkiyede çalışan fizyoterapistlere uygulandı. İş sağlığı ve güvenliği eksikliğinden kaynaklanan mevcut sorunlar tespit edildi. Hazırlanan anket, Google formu aracılığıyla internete aktarılarak 128 fizyoterapistin üye olduğu elektronik posta gruplarına gönderildi.

Bulgular: En sık görülen ihlaller, görev tanımının belirlenmemesi (N: 117, %91.4), verilen hizmetin gerektirdiği eğitimlerin iş yeri tarafından sağlanmaması (N: 114, %89.1), iş yükünün çalışanın kaldırabileceğinden ve/veya danışanı mağdur edecek kadar fazla olması (N:111, %86.7), sigorta priminin maaştan daha düşük ücretle ödenmesi (N:108, %84.4) ve fizyolojik/psikolojik zarar (n:107, %83.6) olarak tanımlandı.

Sonuç: Fizyoterapistlerin yaşadığı hak ihlallerinin giderilmesine ve uğradıkları psikolojik/fiziksel hasarlara çözüm olarak, fizyoterapide iş sağlığı ve güvenliğine ilişkin özel bir kanun gereklidir.

Anahtar Kelimeler: Meslek, hukuk, sağlık, güvenlik, fizyoterapist

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INTRODUCTION

In case of illness, physical medicine and rehabilitation (PM&R) training of specialist physicians are related to the treatment of patients. Physicians diagnose and address medical conditions related to disabilities. PM&R physicians collaborate closely with neurologists, orthopaedic specialists, neurosurgeons, and physiotherapists to provide comprehensive care. Physiotherapist determines and applies evidence-based preventive and developer protocols by performing measurements and tests about the profession to regulate the physical activities of individuals and to increase their mobility. Physiotherapist performs the necessary applications to eliminate or improve physical dysfunction disorders. It works in cooperation with other members of the rehabilitation team in terms of the treatment of patients and gives information to the relevant physician about the course of treatment.[1,2] Hazard identification consists of identifying conditions or incidents within the workplace that have the potential to cause harm to individuals. These hazards can encompass environmental factors or be associated with specific tasks, activities, or work systems. It's worth noting that repeated muscle contractions and prolonged static loading are recognized as risk factors in the development of cumulative trauma disorders for physiotherapist. In Turkey, there has been an increasing recognition of occupational health and safety following the implementation of Law 6331.[3] This law, known as the Occupational Health and Safety Law No. 6331, was formulated in alignment with the principles outlined in EU Directive No. 89/391 and was officially put into effect on June 30, 2012.[3,4] It has been observed that groups, that do not have a occupational law such as a field of psychology, are also exposed to rights violations which include exposure to physical and psychological damage at similar rates.[5]

Occupational health and safety laws establish a structure to guarantee that both employers and employees adhere to the minimum standards necessary for preventing workplace injuries. These laws can be translated into practical documents, such as industry-specific guidelines and codes of practice. Different industries or professional groups may further elaborate on these laws and codes to develop guidelines tailored to their specific work environments. These external controls are designed to minimize injuries by impacting job design and influencing the behaviour of workers on a broader scale.[6] We observed that injuries of workers consist of not only physical harm but also psychological damage. Also, the absence of workplace-provided training essential for the required service affects negatively the job satisfaction of physiotherapist in Turkey.

Our objective is to create the conditions for physiotherapists in Turkey to meaningfully contribute to the advancement of public welfare and the progress of the country. We firmly advocate for the necessity of a specific law about occupational health and safety in physiotherapy to enhance the job satisfaction of these professionals.

MATERIAL AND METHOD

In this study, the Rights Violations Survey has been applied to physiotherapists and detects the existing problems arising from the lack of law on occupational health and safety in physiotherapy. The necessary permission was obtained from the Malatya Clinical Research Ethics Committee (Date: 27/07/2021, Decision No: 2021/2291). Since the rights violations survey was previously applied,[5] it was applied to physiotherapists who are 22-60 years of age. The Rights Violations Survey consists of demographic information about working life and 36 closed-tipped, yes/no questions.[5] Also, verbal questions asked in addition to the survey. The prepared questionnaire was transferred to the internet via Google form and the data was sent to the electronic mail groups where 128 physiotherapists are members. 83.6% of the participants (n: 107) work in special education and rehabilitation centres; 16.4% (n: 21) work in state institutions.

RESULTS

The answers given by the 128 physiotherapists participating in the study to the questions of rights violations encountered in working life have been attached (**Table 1**).

As shown in **Table 1** above, the most commonly observed violations of the task are the job description is not determined (N: 117, 91.4%), the absence of workplace-provided training essential for the required service (N: 114, 89.1%), the workload is more than the employee can handle and/or the client is a victim seen in the survey results as (N: 111, 86.7%). It has been observed that groups, that do not have a occupational law such as a field of psychology, are also exposed to rights violations at similar rates.[5] In addition, depositing the insurance premium at a fee less than salary, physical and psychological damage arising from the negligence of the workplace, failure to meet basic needs (eating, drinking, toilet, etc.) in humane and healthy conditions uninsured employment, excessive work, not payment when overtime, excess working survey results should not be underestimated.

In addition to the questionnaire responses, a significant 83.6% (n:107) of respondents expressed their uncertainty about where to turn for assistance when questioned verbally about addressing rights violations. In contrast, 16.4% (n:21) indicated that they had individually reported their issues to institutional authorities but resigned due to the lack of effective resolutions. In a separate section, participants strongly advocated for the enactment of a professional law, which they considered their most pressing demand. They believe that these rights violations are primarily a result of the absence of such professional legislation and anticipate a reduction in such violations once the law is put into effect.

Table 1: Number and rates of physiotherapists' exposure to rights violations

Rights Violations Parameters	Yes		No	
	Number (N)	Percent (%)	Number (N)	Percent (%)
1-Dismissal	81	63.3	47	36.7
2- Periodic, contracted employment	78	60.9	50	39.1
3- Unemployment by non-renewal of the contract	94	73.4	34	26.6
4- Employment in connection with the company	84	65.6	44	34.4
5- Force to resign	90	70.3	38	29.7
6- Not receiving compensation after dismissal	78	60.9	50	39.1
7- Not getting paid on time	81	63.3	47	36.7
8- Working without insurance	93	72.7	35	27.3
9- Paying the insurance premium at a lower wage than the salary	108	84.4	20	15.6
10- Physical/psychological damage	107	83.6	21	16.4
11- Working outside working hours	86	67.2	41	32.0
12- Not being able to receive overtime payment when working overtime	93	72.7	35	27.3
13- Being pressured as a result of being involved in unions and social organizations	77	60.2	51	39.8
14- Dismissal as a result of involvement in unions and social organizations	71	55.5	57	45.5
15- Being pressured as a result of participating in a rally, press release or protest	87	68.0	41	32.0
16- Dismissal as a result of participating in a rally, press statement or protest	77	60.2	51	30.8
17- Physical inadequacy of working conditions (heat, ventilation, etc.)	105	82.0	23	18.0
18- Failure to meet basic needs (eating, drinking, toilet, etc.) in humane and healthy conditions	104	81.3	24	18.8
19- The workplace does not provide the materials required for the study	77	60.2	51	39.8
20- The absence of workplace-provided training essential for the required service	114	89.1	14	10.9
21- Obtaining the necessary information for working practice (supervision, etc.) for a fee	70	54.7	58	45.3
22- Exposure to ethnic, religious or gender discrimination	86	67.2	42	32.8
23- Exposure to physical/psychological violence	79	61.7	49	38.3
24- Sexual harassment (staring, verbal, etc.)	13	10.2	115	89.8
25- The job description is not determined	117	91.4	11	8.6
26- Making a contract with another, less secure profession definition at the place of employment (being employed under contract in another position - with less rights)	78	60.9	50	39.1
27- Violation of client privacy	49	38.3	79	61.7
28- Training the expert in a way that serves a certain thought or ideology and forcing them to practice these practices	78	60.9	50	39.1
29- The workload is more than the employee can handle and/or is too much to victimize the client	111	86.7	17	13.3
30- Insufficient meeting time (insufficient time allocated to clients/service recipients due to work conditions)	87	68.0	41	32.0
31- Being exposed to threats to remain silent in the face of ethical violations committed by the institution	75	58.6	53	41.4
32- Being punished or left alone if ethical violations committed by the institution you work for are reported	77	60.2	51	39.8
33- Offering bribes (by the workplace or by service recipients with the encouragement of the employer, etc.)	66	51.6	62	48.4
34- Not allowing to continue educational activities	100	78.1	28	21.9
35- Being watched through cameras or in some other ways at work	96	75.0	32	25.0
36- The employer controls how and where the break periods will be spent.	72	56.3	56	43.8

DISCUSSION

Our study is unique in the literature for the existence of psychological and physical damage experienced by physiotherapists and proposes a specific law on occupational health and safety in physiotherapy as a solution.

Cromie et al researched that the majority of physiotherapists (91%) encounter work-related musculoskeletal disorders (WMSDs) during their careers, and one out of every six professionals changes their career due to these issues. Many of these disorders are attributed to the manual handling of patients. This article presents recommendations aimed at reducing the risk of WMSDs. These guidelines are formulated based on Australian legal requirements, insights from a survey conducted among Australian physiotherapists, and existing literature on injury prevention. The guidelines encompass various aspects of environmental and job design, as well as the physical capabilities of individual physiotherapists, all within the framework of legal regulations. The article concludes by emphasizing the need for further research to delve deeper into this area of injury prevention within the field of physiotherapy.[7] 107 (83.6%) of 128 physiotherapists who participated in the study in the results of our study were physical and psychologically damaged.

In Cromie et al.'s research, it was discovered that work-related musculoskeletal disorders (WMSDs) had the highest annual prevalence in the lower back region (63%), followed by the neck (48%), and the upper back (41%). Additionally, WMSDs were also prevalent in the thumb (34%), shoulder

(23%), as well as the wrist and hand (22%). The study revealed that therapists who engaged in manual therapy, repeated the same task frequently, had a high patient load in a single day, and did not have sufficient rest breaks faced an elevated risk of injuries in the neck and upper limbs, including the thumb. Specifically, thumb symptoms were linked to the performance of manipulation and mobilization techniques, with the prevalence of symptoms increasing with the duration of performing these techniques. Postural factors and the act of moving or transferring patients were associated with a higher risk of experiencing spinal symptoms (in the neck, upper back, and lower back). These specific body areas and their corresponding risk factors form the foundation for conducting risk assessments within the context of physiotherapy practice.[8] We found that a lot of physiotherapists in Turkey exposure physical and psychological damage because of occupational deformation and the pressure of the workplace. This study suggested that specific law on occupational health and safety in physiotherapy is needed for working satisfaction of physiotherapist.

Physical therapists employed in Kuwait face the potential of work-related musculoskeletal disorders (WMSDs). Yet, there is limited documentation regarding the prevalence rates and associated risk factors. Alrowayeh et al aimed to ascertain the prevalence, attributes, and consequences of WMSDs among physical therapists working in Kuwait. Work-related musculoskeletal disorders (WMSDs) were frequently observed among physical therapists in Kuwait, primarily impacting the lower back and neck. Lower back and neck WMSDs were associated with participant characteristics, while hand/wrist WMSDs were linked to the work environment. Further, they said that research is necessary to explore the influence of risk factors such as physical workload, psychosocial stress, and overall health status on the prevalence of musculoskeletal disorders. [9] Our study showed that physical inadequacy of working conditions (heat, ventilation, etc.) can result in physical and psychologically damaged.

Milhem et al researched that healthcare professionals, particularly those engaged in direct patient care, are among the occupational groups with the highest incidence of work-related musculoskeletal disorders (WMSDs), including physical therapists (PTs). This review aims to summarize the existing information concerning the prevalence, risk factors, and preventive measures for WMSDs among PTs. They conducted searches in Pubmed, Google Scholar, and PEDro databases, covering WMSDs in PTs from their inception to 2015. The prevalence of WMSDs among PTs was notably high, with a lifetime prevalence ranging from 55% to 91% and a 12-month prevalence varying from 40% to 91.3%. The lower back was the most frequently affected area, with estimates indicating a lifetime prevalence ranging from 26% to 79.6% and a 12-month prevalence between 22% and 73.1%. The neck, upper back, and shoulders were also commonly affected. The risk factors for work-related low back pain (LBP) included activities such as lifting, transferring patients, repetitive movements, assuming awkward and static postures, experiencing physical load, treating a high volume of patients in a single day, and working while injured. Low back pain appeared to be influenced by age and gender, with a higher prevalence observed among females, younger PTs, and those working in rehabilitation settings. They suggested that physical therapists, as a result of work-related LBP, may seek treatment, adjust their daily routines and leisure activities, utilize assistive tools and equipment, or even consider changing their specialization within the profession or leaving it altogether. It should be noted that possessing knowledge and skills related to proper body mechanics does not guarantee the prevention of work-related injuries. PTs should adopt mechanical aids for patient transfers and innovative strategies should be devised to reduce WMSDs while maintaining the quality of patient care.[10] Our findings indicated that many physiotherapists in Turkey experience physical and psychological harm due to occupational strain. This study highlights the necessity for the implementation of dedicated legislation concerning occupational health and safety in physiotherapy to enhance the job satisfaction of physiotherapists.

CONCLUSION

This study plays an important role in the fact that physiotherapists are informed about the violations of rights they may face and strive in the face of these violations. The lack of occupational laws of physiotherapists is undoubtedly a major deficiency and studies should be carried out to eliminate this deficiency and rights violations. Also, a special law on occupational health and safety in physiotherapy is required as a solution to the rights violations, defficiency of job satisfaction and psychological/physical damages experienced by physiotherapists.

ETHICAL DECLARATIONS

Ethics Committee Approval: The necessary permission was obtained from the Malatya Clinical Research Ethics Committee (Date: 27/07/2021, Decision No: 2021/2291).

Informed Consent: For this type of study informed consent is not required (Retrospective study).

Referee Evaluation Process: Externally peer-reviewed.

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Original Article / Orijinal Araştırma

Distribution of Macrophages and Plasma Cells in Odontogenic Cysts

Odontojenik Kistlerde Plazma Hücresi ve Makrofajların Dağılımı

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Abstract

Aim: Odontogenic cysts are common and important lesions of the maxillofacial region. Radicular cysts, dentigerous cysts, and odontogenic keratocysts are the most common odontogenic cysts. Macrophages and plasma cells are the main cells of inflammation and play a role in the development of many diseases. This study aimed to compare the presence and distribution of macrophages and plasma cells among the most common odontogenic cysts with clinical data.

Material and Method: Cases diagnosed with odontogenic cysts in our laboratory were included in our study. Hematoxylin-Eosin stained sections of the cases in the archive were re-evaluated. The area that best reflected the inflammation tissue was first marked on the slides and then on the blocks. Then, 2 mm diameter cylindrical-shaped paraffinized tissue samples were taken from donor blocks and transferred to multiple blocks with a manual microarray device. Anti-CD68 and anti-CD138 immunohistochemical stains were applied to multiple blocks. The stained preparations were scored between 0-2 by giving an average score. The scores were then analyzed together with clinical data between the three groups.

Results: Of the 83 odontogenic cysts included in our study, 41 were radicular cysts, 25 were dentigerous cysts, and 17 were keratocysts. The ages of the patients ranged from 17 to 77 years, with a mean of 37.55± 16.42 years. 47% of the patients were male, and 53% were female. There was no significant difference between the odontogenic cyst groups regarding age and gender ($p>0.05$). There was a significant difference between the cyst type and the proportions of CD68+ macrophages and CD138+ plasma cells ($p<0.05$). CD138+ plasma cell density was primarily observed in radicular cysts, while CD68+ macrophages were more intense in odontogenic keratocysts.

Conclusion: There was a significant difference in the distribution of CD68+ macrophages and CD138+ plasma cells in odontogenic cyst type. Therefore, it is important to have more information about the histomorphologic features of odontogenic cysts and to understand their inflammatory processes for correct diagnosis and treatment.

Keywords: Radicular cyst, odontogenic cyst, macrophage, plasma cells

Öz

Amaç: Odontojenik kistler maksillofasiyal bölgenin sık karşılaşılan önemli lezyonlarıdır. Radiküler kistler, dentijeröz kistler ve odontojenik keratokistler en sık karşılaşılan odontojenik kistlerdir. Makrofajlar ve plazma hücreleri inflamasyonun temel hücreleridir ve bir çok hastalığın oluşumunda rol oynarlar. Bu çalışmanın amacı; en sık karşılaşılan odontojenik kistlerde makrofaj ve plazma hücrelerinin varlığını ve dağılımını klinik bilgilerle birlikte karşılaştırmak amaçlanmıştır.

Gereç ve Yöntem: Çalışmamıza laboratuvarımızda Ocak 2013 ile Aralık 2022 tarihleri arasında odontojenik kist tanısı almış, eksizyonel biyopsi uygulanmış olgular dahil edildi. Olgulara ait Hematoksilen-Eozin boyalı kesitler değerlendirildi. İmmünhistokimyasal (İHK) boyama için en uygun olan alanlar işaretlendi. Daha sonra parafin bloklardan 2 mm çapta silindirik şekilli parafinize doku örnekleri manuel mikroarray cihazı ile donör bloklardan alınarak çoklu bloklara aktarıldı. Anti- CD68 ve anti- CD138 immünhistokimyasal boyası çoklu bloklara uygulandı. Boyalı preparatlar ortalama bir skor verilerek 0-2 arasında puanlandı. Daha sonra verilen skorlar 3 grup arasında klinik verilerle birlikte analiz edildi.

Bulgular: Çalışmamıza dahil edilen 83 odontojenik kistin 41 tanesi radiküler kist, 25 tanesi dentijeröz kist ve 17 tanesi keratokistti. Hastaların yaşları 17 ile 77 arasında değişiyordu ve ortalama 37,55± 16,42' idi. Hastaların %47'si erkek iken % 53 kadındı. Radiküler kist, dentijeröz kist ve keratokist grupları arasında yaş ve cinsiyet açısından anlamlı fark yoktu ($p>0.05$). Kist tipi ile CD68+ makrofajların ve CD138+ plasma hücrelerinin oranları arasında anlamlı fark saptandı. ($p<0.05$). CD138+ plazma hücre yoğunluğu özellikle radiküler kistlerde gözlemlenirken, CD68+ makrofajlar odontojenik keratokistlerde daha yüksek yoğunlukta bulunmuştur.

Sonuç: Odontojenik kist tipleri arasında CD68+ makrofajların ve CD138 + plasma hücrelerinin dağılımında anlamlı fark saptanmıştır. Bu nedenle odontojenik kistlerin histomorfolojik özellikleri hakkında daha fazla bilgi sahip olmak ve inflamatuar süreçlerini anlamak doğru tanı ve tedavi için önem arz etmektedir.

Anahtar Kelimeler: Radiküler kist, odontojenik kist, makrofaj, plazma hücresi

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INTRODUCTION

Odontogenic cysts arise from the epithelium of dental structures in the head and neck zone. Odontogenic cysts are divided into inflammatory and developmental cysts.[1]

The epithelium of odontogenic cysts originates from malassez epithelial remnants, dental lamina, enamel organ, dental papillae, and basal layer cells of the oral mucosa.[1]

The most common odontogenic cysts observed in studies are radicular cysts, dentigerous cysts, and odontogenic keratocysts.[2] Radicular cysts are in the inflammatory cyst group, while dentigerous and keratocysts are in the developmental cyst group.[2] Radicular cysts are formed in the tooth apex due to a possible inflammation stimulated by malassez residues.[3] Radicular cysts are the most common cysts in the jawbone. The cavity of radicular cysts is usually lined with stratified squamous epithelium, and there is a chronic inflammatory infiltrate in the fibrous cyst wall. Foamy macrophages, russel's bodies, cholesterol clefts, and glandular odontogenic epithelial remnants are frequently encountered in histologic findings.[4] Keratocysts are developmental cysts and usually draw attention with their aggressive clinical behavior. The recurrence rate of keratocysts is 10-30%.[5] The histologically prominent feature is parakeratosis and basal palisading of the laying epithelium.[5] The formation of odontogenic cysts is usually dominated by acute inflammation accompanied by mononuclear cells and macrophages.[6]

Macrophages and plasma cells are important cells of the inflammatory response and initiate the chronic inflammatory process with the cytokines they secrete and cause the surrounding epithelium and tissues to be affected.[4]

The formation and pathophysiology of odontogenic cysts in the maxilla have not been clearly elucidated. However, the presence of inflammatory cells detected in the cyst wall and subepithelial area in most cases reveals that inflammation is an important finding in cyst formation.[6] This study aims to demonstrate macrophage and plasma cell distributions of developmental and inflammatory odontogenic cysts using anti-CD68 and anti-CD138 autoantibodies.

MATERIAL AND METHOD

Our study included cases diagnosed as odontogenic cysts and underwent an excisional biopsy in our laboratory between January 2013 and December 2022. Accordingly, 41 of 83 odontogenic cysts were radicular cysts, 25 were dentigerous cysts, and 17 were keratocysts. Hematoxylin-Eosin (H&E) stained sections of the cases in the archive were re-evaluated. Clinical information of the patients was retrieved from the our hospital's system. Our study was approved by the ethics committee of our university (Ethics Committee Reference Number: 2022/186)

The area that best reflected the inflammation tissue and was most suitable for immunohistochemical (IHC) staining was first marked on slides and then on blocks. Biopsies that were not suitable enough for staining and sampling were excluded from the study. Then, paraffinized tissue samples of 2 mm diameter cylindrical-shaped paraffin blocks were taken from donor blocks and transferred to multiple blocks by mapping technique with a manual microarray device.

Three µm tissue sections taken from paraffin-embedded blocks were placed on 3-aminopropyltriethoxysilane-coated glass slides for immunohistochemical analysis. Anti-CD68 (MS-397-R7, Thermo Scientific) and anti-CD138 (MS- 1793-R7, Thermo Scientific) primary Mouse monoclonal antibody immunohistochemical stain was applied to multiple blocks in Leicia Bond- Max device. (**Figures 1**, **2** and **3**) Stained slides were examined under light microscopy, and the expression of each marker was classified based on the following scores: 0 (negative/focal) if there were no positive cells or less than 5% of the cells were positively stained; 1 (weak to moderate) if between 5% and 50% of the cells were positively stained; and 2 (strong) if more than 50% of the cells were positive. Three groups were formed based on the given scores, and the groups were analyzed together with clinical data.

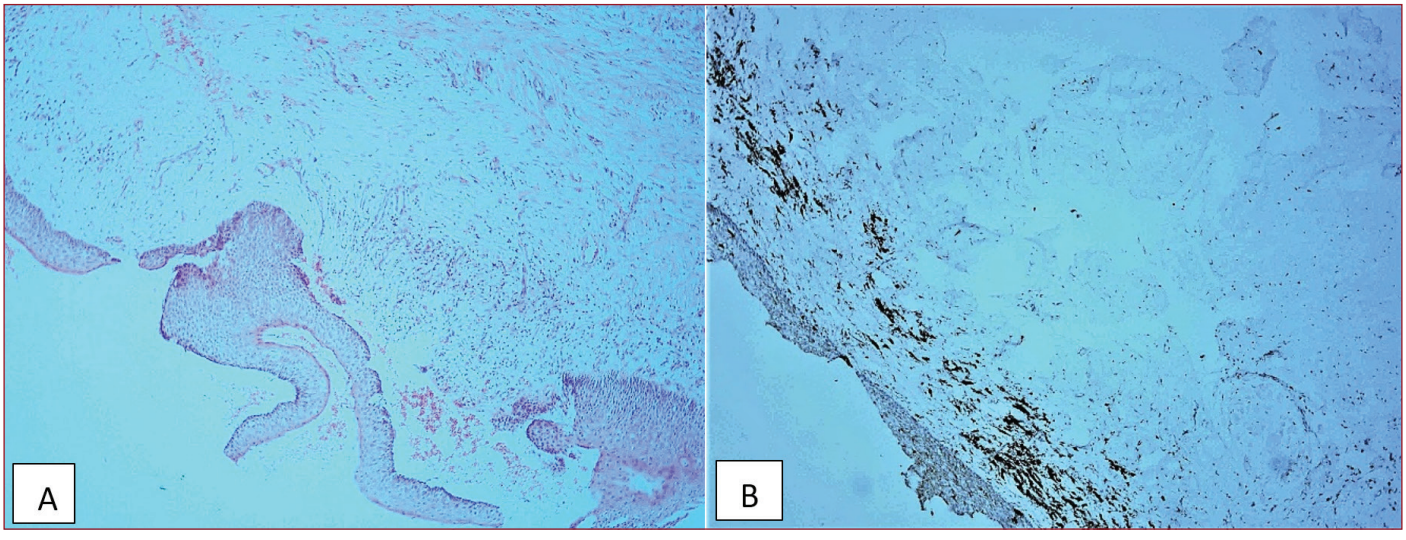

Figure 1: Dentigerous cyst, A: Hemotoxylen& Eosin section B: CD68+ macrophages (immunoperoxidase, original magnification, x200)

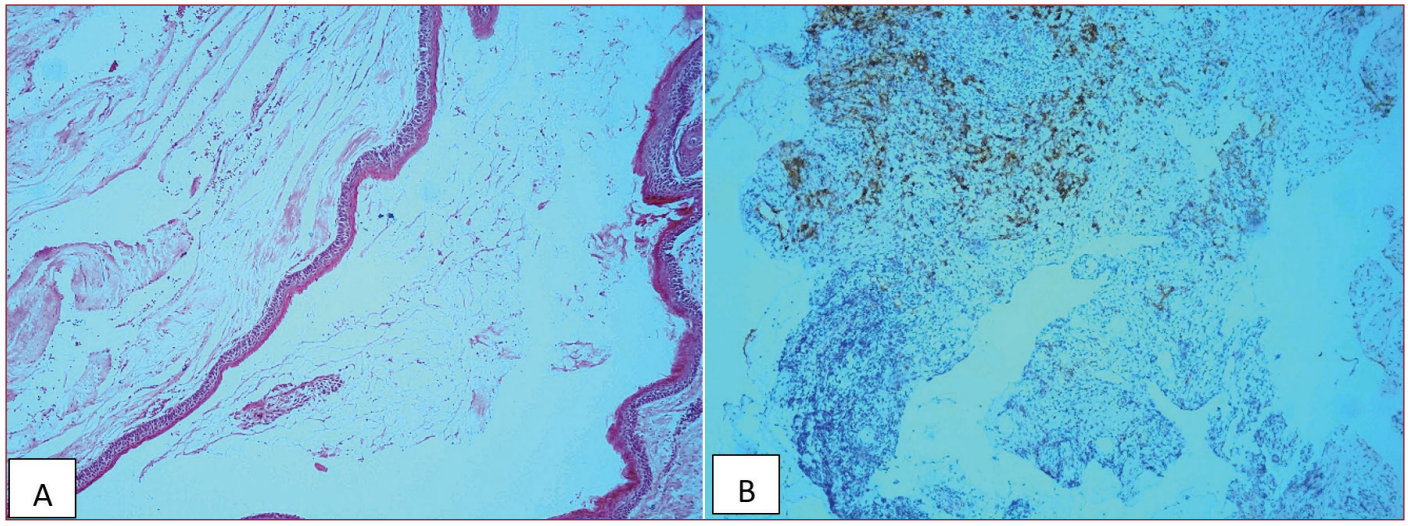

Figure 2: Odontogenic keratocyst A: Hemotoxylen & Eosin section B: CD38+ plasma cells (immunoperoxidase, original magnification, x200)

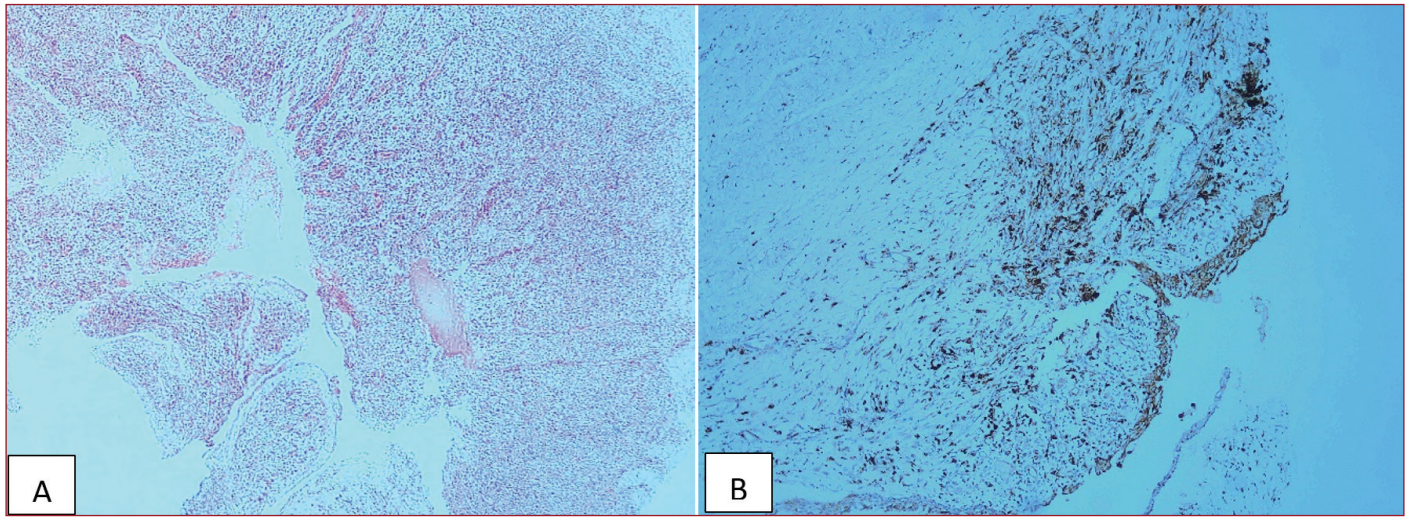

Figure 3: Radicular cyst A: Hemotoxylen & Eosin section B: CD 68+ macrophages (immunoperoxidase, original magnification, x200)

Statistical Method

The chi-square test was used to examine any relationships between categorical variables. The likelihood ratio test statistic was used instead of Pearson's test statistic when the expected counts were <5. Spearman's rank correlation coefficient was calculated to determine any relationships between the score variables. One-way anova test was used for descriptive statistical information. A $p<0.05$ value was accepted as statistically significant. All statistical analyses were performed using IBM SPSS v28 (IBM, Armonk, NY, USA).

RESULTS

Of the 83 odontogenic cysts included in our study, 41 were radicular cysts, 25 were dentigerous cysts, and 17 were keratocysts. Patients' ages ranged from 17 to 77 years, with a mean of 37.55± 16.42 years. While 47% of the patients were male, 53% were female. There was no significant difference between the radicular cyst, dentigerous cyst, and keratocyst groups regarding age and gender ($p>0.05$). (**Table 1** and **Table 2**)

Table 1: Distribution of the relationship between cyst type and gender

Crosstab

		Gender		Total
		male	female	
Cyst type				
Radicular cyst	Count	21	20	41
	% within Cyst type	51.2%	48.8%	100.0%
Keratocyst	Count	7	10	17
	% within Cyst type	41.2%	58.8%	100.0%
Dentigerous cyst	Count	11	14	25
	% within Cyst type	44.0%	56.0%	100.0%
Total	Count	39	44	83
	% within Cyst type	47.0%	53.0%	100.0%

Table 2: Distribution of the relationship between cyst type and age

Age

	N	Mean	Std. Deviation	Minimum	Maximum
Radicular cyst	41	39.39	15.349	15	77
Keratocyst	17	42.12	16.718	13	77
Dentigerous cyst	25	31.44	16.835	14	65
Total	83	37.55	16.426	13	77

There was a significant difference between the cyst type and the proportions of CD68+ macrophages and CD138+ plasma cells (p<0.05). While 51.2% of radicular cysts had more than 50% CD138+ plasma cell positivity, this rate was 12% in dentigerous cysts. (**Table 3**)

Table 3: Distribution of the immunoscore of CD138+ plasma cells in odontogenic cysts.

Crosstab

		CD138 ratio			Total
		< %5	%5-%50	≥%50	
Cyst type					
Radicular cyst	Count	9	11	21	41
	% within Cyst type	22.0%	26.8%	51.2%	100.0%
Keratocyst	Count	9	3	5	17
	% within Cyst type	52.9%	17.6%	29.4%	100.0%
Dentigerous cyst	Count	17	5	3	25
	% within Cyst type	68.0%	20.0%	12.0%	100.0%
Total	Count	35	19	29	83
	% within Cyst type	42.2%	22.9%	34.9%	100.0%

In 41.2% of keratocysts, the proportion of CD68+ macrophages was above 50%, whereas, in dentigerous and radicular cysts, it was 8% and 34.1%, respectively. (**Table 4**) There was no significant difference between the mean scores of CD68+ macrophages and CD38+ plasma cells and the age and gender of the patients (p>0.05).

Table 4: Distribution of the immunoscore of CD68+ macrophages in odontogenic cysts.

Crosstab

		cd68 ratio			Total
		<5%	5%-50%	≥50%	
Cyst type					
Radicular cyst	Count	6	21	14	41
	% within Cyst type	14.6%	51.2%	34.1%	100.0%
Keratocyst	Count	3	7	7	17
	% within Cyst type	17.6%	41.2%	41.2%	100.0%
Dentigerous cyst	Count	9	14	2	25
	% within Cyst type	36.0%	56.0%	8.0%	100.0%
Total	Count	18	42	23	83
	% within Cyst type	21.7%	50.6%	27.7%	100.0%

DISCUSSION

Due to the similar etiology and histomorphologic features of odontogenic cysts, diagnosis is sometimes challenging. Radicular cysts constitute the inflammatory cyst group, while dentigerous cysts and keratocysts belong to the developmental cyst group.[7]

The clinical manifestations of these cysts, such as aggressiveness, recurrence, and malignant transformation, vary depending on the cyst type.[2] Odontogenic keratocysts have a more aggressive course and high recurrence rates, while other cysts have a very good prognosis after treatment.[2] The different distribution of inflammatory cells involved in the histopathogenesis of these cysts and the cytokines secreted by these cells may play a role in this situation.

There are three stages in the etiopathogenesis of cyst formation. These are initiation, formation, and growth.[8] In the formation of periapical lesions and radicular cysts, pulp necrosis is usually initiated by a multibacterial infection.[9] This triggers a local humoral response, leading to the activation of B cells and plasma cells.[9] Plasma cells produce Ig G, Ig A, and Ig M in order from more to less.[10]

Macrophages are the primary cells of chronic inflammation and acquired immunity. Macrophages interact directly with the cyst epithelium and are involved in releasing cytokines such as IL-1, IL-6, and TNF-a.[8] They prepare antigen and provide it to T-helper cells.[11]

Our study showed a significant difference between cyst type and the distribution of CD68+ macrophages and CD138+ plasma cells (p<0.05). CD138+ plasma cell density was primarily observed in radicular cysts, while CD68+ macrophages were more intense in odontogenic keratocysts.

Unlike us, Azeredo et al.[12] found no significant difference between macrophage and plasma cell distributions in their study on periapical cysts and granulomas.

Gazivodo et al.[13] compared the cytokines produced in periapical lesions and found a significant difference between the amount of cytokines produced, whether the lesion was symptomatic or not, and the lesion's size. We did not include these criteria in our study, but we did not find a significant difference between demographic data such as age and gender and plasma cell-macrophage distributions.

Kouhsoltani et al.[14] found no significant difference between cyst types and the distribution of CD68+ macrophages in their study but found that macrophage density was lower in keratocyst odontogenic tumors compared to dentigerous cysts. Radicular cysts were considered the lesion with the highest macrophage density. In our study, odontogenic keratocysts had the highest macrophage distribution. This may be because we sampled from the area with the highest inflammation using the microarray method.

Many studies have investigated whether there is a relationship between the amount of macrophages in lesions and clinical course. Some studies suggest that macrophages are directly involved in the development and prognosis of the disease.[14]

In their review on macrophage distribution in periapical lesions, Song et al.[15] reported that macrophages were evaluated as M1-like and M2-like macrophages. In this article, it was suggested that M1-like macrophages are pro-inflammatory and M2-like macrophages are anti-inflammatory. For this reason, they emphasized that immunohistochemical markers and macrophage polarization should also be indicated when evaluating macrophage distribution in studies.

Weber et al.[16] conducted a study on apical granulomas, radicular cysts, and dentigerous cysts and evaluated macrophage polarization and revealed that M1-like macrophages were predominant in radicular cysts while M2-

like macrophages were predominant in apical granulomas. This may be due to the progression of apical granulomas to radicular cysts.[17]

It is very difficult to diagnose odontogenic cysts clinically, and one study reported that the initial clinical diagnosis accuracy rate was 36%.[18] Therefore, it is important to determine the distribution of inflammatory cells histologically. Marçal et al.[19] argued that mononuclear infiltration is more frequent than mixed-type infiltration in periapical cysts. Our study found more than 50% CD138+ plasma cell positivity in 51.2% of radicular cysts.

CONCLUSION

Our study showed a significant difference between cyst type and the ratios of CD68+ macrophages and CD138+ plasma cells ($p<0.05$). Although odontogenic cysts have different etiologies, it is difficult to determine the cyst type clinically and histopathologically. In addition, treatment approaches, and clinical course after treatment differ with cyst types. New information about the subtypes of inflammatory cells and their different polarizations is being revealed daily. Clinical, radiologic, and histologic evaluation of this information and new studies will allow new approaches to emerge in the diagnostic and therapeutic process.

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved by the Ordu University Clinical Researches ethics committee (Date: 05.08.2022, Decision No: 2022/186).

Informed Consent: For this type of study informed consent is not required (Retrospective study).

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article / Orijinal Araştırma

Evaluation of Surgical Nurses' Perceptions Regarding The Nursing Process

Cerrahi Hemşirelerinin Hemşirelik Sürecine İlişkin Algılarının Değerlendirilmesi

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Abstract

Aim: In this study, it is aimed to evaluate the perceptions of surgical nurses towards the nursing process.

Material and Method: In this study, power analysis was used in the G*Power computer program with medium effect size (d=0.25), 80% power and 5% type I error level. As a result, it was calculated that a sample group consisting of a minimum of 200 people was needed for the analysis to be carried out. The sample of the study consisted of a total of 200 surgical nurses reached by simple random. The data of the study were obtained with the "Nurse Data Form" and "Nursing Diagnosis Perception Scale" prepared by the researcher according to the literature containing the socio-demographic characteristics of the nurses.

Results: the distribution of surgical nurses' knowledge of the nursing process is evaluated. The level of knowledge of surgical nurses about the stages of the nursing process is as follows; evaluation (87.5%), implementation (85.3%), planning (82.8%), data collection (75.8%) and diagnosis (72.4%). On the other hand, it was determined that there was no significant difference between surgical nurses according to gender, marital status, hospital, working time in nursing and working time in the surgical unit.

Conclusion: The duty of surgical nurses in the in-service training programs, including the subject of the nursing process, is recommended. Increasing the time allocated to nursing process education in education curricula during the education and training process; organizing trainings, congresses and seminars on the missing subjects every time the process is done; it is recommended that surgical nurses be supported to participate in these scientific meetings during the education process.

Keywords: Surgical nurse, process, nurse perception

Öz

Amaç: Bu çalışmada cerrahi hemşirelerinin hemşirelik sürecine yönelik algılarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmada orta etki büyüklüğünde (d=0,25), %80 güçte ve %5 tip I hata düzeyinde G*Power bilgisayar programında güç analizi kullanılmıştır. Sonuç olarak analizin gerçekleştirilebilmesi için minimum 200 kişiden oluşan bir örneklem grubuna ihtiyaç duyulduğu hesaplanmıştır. Araştırmanın örneklemini basit tesadüfi yöntemle ulaşılan toplam 200 cerrahi hemşiresi oluşturmuştur. Araştırmanın verileri, hemşirelerin sosyo-demografik özelliklerini içeren literatüre göre araştırmacı tarafından hazırlanan "Hemşire Veri Formu" ve "Hemşirelik Tanı Algısı Ölçeği" ile elde edilmiştir.

Bulgular: Yapılan araştırmada; cerrahi hemşireleri arasında cinsiyet, hemşirelikte çalışma süresi, cerrahi ünitede çalışma süresi ve hemşirelik süreci ile ilgili eğitim alma durumu açısından anlamlı farklılık olmadığı belirlendi. Öte yandan cerrahi hemşirelerinin cinsiyet, medeni durum, hastane, hemşirelikte çalışma süresi ve cerrahi ünitede çalışma süresine göre anlamlı farklılık olmadığı belirlendi.

Sonuç: Hemşirelik süreci konusunu içeren hizmet içi eğitim programlarında cerrahi hemşirelerinin görev almaları önerilmektedir. Eğitim öğretim sürecindeyken eğitim müfredatlarında hemşirelik süreci eğitimine ayrılan sürenin arttırılması; süreç her yapıldığında eksik olan konularda eğitimler, kongreler, seminerler düzenlenmesi; cerrahi hemşirelerinin eğitim sürecinde bu bilimsel toplantılara katılmalarının desteklenmesi önerilmektedir.

Anahtar Kelimeler: Cerrahi hemşire, süreç, hemşire algısı

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INTRODUCTION

Nursing process is a process that should be given importance and emphasized in the nursing profession, and nursing diagnoses are the most important part of the nursing process. [1] The nursing process provides the nurse with a systematic perspective in the professional maintenance of care and the elimination of the problem, which is formed by determining the care needs of the healthy/diseased individual, family or society in need of care, and planning and applying.[2] Effective implementations of the nursing process leads to improved quality of care and encourages the construction of theoretical and scientific knowledge based on best clinical practice. The nursing process consists of five stages: Data collecting, diagnostic, planning, practice, evaluation.[3]

The first step in the nursing process is data collection. This stage refers to the systematic collection of information about the patient/healthy person and their relatives, which are considered data, for a specific purpose. The second phase of the nursing process, the definition phase, is at the center of nursing practice.[2] In this step, nurses analyze the data they collect using their critical thinking skills and identify one or more nursing diagnoses while providing individualized care to the patient.[4] The third stage of the nursing process, the planning stage, includes deciding what to do with the patient and solving problems. This stage begins after the analysis of the data obtained and the determination of the nursing diagnosis. The planning phase includes prioritizing problems based on the nursing diagnosis, identifying goals to be achieved, and selecting nursing interventions to achieve these goals.[5] After the planning of nursing practices, the fourth stage of the nursing process, which is the stage where nursing care takes place, is passed to the practice stage. Nurses demonstrate the artistic side of their profession with a humane approach when applying the interventions they plan to a sick person.[6] The fifth and final stage of the nursing process is the evaluation stage. This stage represents both the end of the process and a new beginning.[7,8] During the evaluation phase, it checks whether the patient's determined results are achieved by implementing the planned interventions for each target related to the patient's problems.[w] Based on the literature, it was aimed to evaluate the perceptions of surgical nurses about the nursing process.

MATERIAL AND METHOD

This quantitative study has been carried out in relational research model. All surgical nurses who can be reached from the province of Istanbul through the social communication network and accepted to participate in the research constitute the population of the research; the number of all nurses from the universe who answered at the level of significance in terms of the data of the research also formed the sample of the research. In this context, power analysis was used in the G*Power computer program with medium effect size (d=0.25), 80% power and 5% type I error level. As a result, it was calculated that a sample group consisting of a minimum of 200 people was needed for the analysis to be carried out. The sample of the study consisted of a total of 200 surgical nurses reached by simple random. In order to participate in the study, it is sufficient for the nurses to work in the surgery clinic and to be volunteers to participate in the study. The years of work in the clinic were not taken into account.

Data Collection Method

Prior to the data collection phase, permission was obtained from the Ethics Committee of The University. The research technique has been used to collect data. In this context, Google Forms application, which provides data collection over the internet, has been benefited. The link of the online questionnaire form has been sent to the participants via e-mail, Whatsapp and similar platforms. Before starting the research, voluntary consent of the participants was obtained, it was explained that their personal information is kept and only the data obtained for scientific purposes will be processed.

Data Collection Tools

The data were collected by the researchers using the "Nurse Data Form" and the "Nursing Diagnosis Perception Scale", which were prepared according to the literature on nurses' sociodemographic characteristics.

Nurse Data Form

This form, prepared in the light of literature information, consists of two parts (1, 2, 4, 5, 6, 10, 11, 12). “Identifying Sociodemographic and Occupational Characteristics” section constitutes the first part of the form. In this form age, gender, marital status, willingness to choose the profession, education level, institution, unit, job in the unit, the duration of the nurse's execution, working time in the surgical unit, satisfaction, the reason for choosing the profession are asked in this form.

In the second part of the form, the status of surgical nurses to receive training on the nursing process and to use the nursing process actively while giving care was questioned. In addition, the form includes questions evaluating the status of surgical nurses in recognizing and ordering the data collection, diagnosis, planning, application and evaluation steps of the nursing process, and this section is referred to as the "Identification of Nursing Process" form. In total, the form consists of 41 questions.

Nursing Diagnosis Perception Scale

The original name of “Nursing Diagnostic Questionnaire Perceptions” was developed by Olsen, Frost, and Orth in 1991. The scale was developed to determine nurses' perceptions of nursing diagnoses in health care areas. The scale is in a five-point Likert type, going from “strongly agree” to “strongly disagree”. The total score of the scale is calculated by dividing the total score by the number of items. The total score of the scale ranges from 1 to 5. The low total score obtained from

the scale indicates a positive perspective in the perception of nursing diagnoses. A low score on the Nursing Diagnosis Perception Scale indicates a positive perspective in the perception of nursing diagnoses. In other words, as the score obtained from the scale increases, nursing diagnoses are perceived negatively. In the validity and reliability study of the scale, the Cronbach's alpha values ranged from 0.94 and the Cronbach's alpha values of the subscales ranged from 0.79 to 0.92. The reliability and validity of the scale for our country was made by Esra Akin-Korhan, Gülendam Hakverdioğlu-Yönt, Bedriye Ak, Firdevs Erdemir in 2013. Permission for the scale was obtained from Ms. Bedriye AK via e-mail.

The scale includes 4 sub-domains and 26 items that evaluate the perceived ease of use and benefit of nursing diagnoses to the profession and treatment process.

Analysis Method

The study was conducted using SPSS version 21.0 for Windows. Data value was used as descriptive statistical methods such as percentage, arithmetic mean, frequency, standard. The suitability of the data to the normal distribution was tested with the Kolmogorov-Smirnov test on a single sample. Since the data did not show normal distribution, non-parametric statistical analysis methods (Man Whitney U Test, Kruskal Wallis Test) were used.

RESULTS

In **Table 1**, the distribution of surgical nurses' knowledge of the nursing process is evaluated. The level of knowledge of surgical nurses about the stages of the nursing process is as follows; evaluation (87.5%), implementation (85.3%), planning (82.8%), data collection (75.8%) and diagnosis (72.4%).

In **Table 2** presents the descriptive statistical analysis results for the Nursing Diagnosis Perception Scale. In this context, it was determined that surgical nurses perceived their nursing diagnoses positively ($\bar{x}$=2.60, sd=0.71). It was determined that the knowledge levels of surgical nurses about the nursing process did not show a significant difference according to their education about the nursing process (p>0.05). It was determined that surgical nurses' scale of perception of nursing diagnoses scores differed significantly according to their educational status in the nursing process. It was determined that the surgical nurses who were not trained

Table 1. Distribution of Surgical Nurses' Knowledge Regarding the Nursing Process

Stage	Question	Number of incorrect answers	Number of correct answers	Percentage success of the problem	Stage success percentage
Data Collecting	Do you think the statement "data collection in the nursing process is the systematic obtaining of information about the patient/well individual and their relatives, which are qualified as data, for a specific purpose"?	13	187	93.5	75.8
	Which of the following is not one of the actions taken by the nurse during the data collection step in the nursing process?	84	116	58.0	
	Which of the following determines the care that the individual needs but cannot afford from the stages of the nursing process?	76	124	62.0	
Diagnostics	"The nursing process is at the stage of diagnosis; It includes the analysis and interpretation of the data collected to determine the problems of the individual to be dealt with in nursing care" do you think is correct?	10	190	95.0	72.4
	What does the diagnosis phase of a patient coming to your unit include?	56	144	72.0	
	What is the purpose of nursing diagnosis?	41	159	79.5	
Planning	Which of the following is the nursing process stage that includes "data collection, validation of the collected data, analyzing and interpreting the data, and sharing the data"?	93	107	53.5	82.8
	Do you think the statement "The nurse decides on the nursing care that she/he will give in order to solve the problems that she/he identified during the planning phase of the nursing process and to meet the needs" is correct?	8	192	96.0	
	What does the planning phase of the nursing process include?	36	164	82.0	
	Which of the following is the "stage" of the nursing process, which includes deciding what to do and problem solving?	51	149	74.5	
	Which is not one of the aims of the planning phase of the nursing process?	43	157	78.5	
Application	The implementation phase of the nursing process; do you think the statement "This is the implementation phase of the written objectives and the plan created" correct?	11	189	94.5	85.3
	Which is not one of the aims of the nursing process in the implementation phase?	51	149	74.5	
	Which of the following is the stage of the nursing process where "nursing care is given and performed"?	26	174	87.0	
Evaluation	Which of the following describes the characteristics of the evaluation phase of the nursing process incorrectly?	38	162	81.0	87.5
	Which of the following is the stage of the nursing process, which is "both an end and a beginning in the nursing process"?	34	166	83.0	
	"In the evaluation phase of the nursing process; is the statement "It being checked whether the patient results determined as a result of the implementation of the planned interventions are achieved or not" is correct?	3	197	98.5	
Total		674	2726	80.2	

in the nursing process had significantly higher scale of perception of nursing diagnoses scores than the surgical nurses who received training (p<0.05).

Table 2. Surgical Nurses' Perception of Nursing Diagnoses Scale Score Distribution

Dimentions	Mean	Standart Deviation	Minimum	Maximum
Nursing diagnosis perception scale	2.60	0.71	1.04	5.00
Definition and introduction of the nursing profession	2.18	1.16	1.00	5.00
Clearly describing the patient's condition	2.69	0.74	1.00	5.00
Ease of use	2.99	0.61	1.00	5.00
Conceptual aspect	2.81	0.70	1.00	5.00

In **Table 3**, when the scale of perception of nursing diagnoses was examined in terms of dimensions, it was determined that the scores of surgical nurses from the dimensions of "definition and promotion of the nursing profession" differed significantly according to the educational status of the nursing process. In the dimension of definition and promotion of the nursing profession, the scores of the surgical nurses who did not receive training on the nursing process were found to be significantly higher than the surgical nurses who received training (p<0.05). On the other hand, it is seen that the scores of the surgical nurses in the dimensions of "clearly defining the patient's condition", "ease of use" and "conceptual aspect" do not differ significantly according to the educational status of the nursing process (p>0.05).

DISCUSSION

When the knowledge levels of surgical nurses about the nursing process are examined, it is seen that the findings are compatible with the literature. In similar studies in the literature, it is seen that the stages that surgical nurses have the most difficulty with are data collection and diagnosis.[9-14]

When Surgical Nurses' Nursing Diagnosis Perception Scale scores were examined, it was determined that surgical nurses perceived their nursing diagnoses as positive at an average level. When the Nursing Diagnostics Perception Scale was examined in terms of dimensions, it was determined that surgical nurses got the lowest score from the "definition and promotion of the nursing profession" dimension and the highest score from the "ease of use" dimension. A low score on the Nursing Diagnosis Perception Scale indicates a positive perspective in the perception of nursing diagnoses. In other words, as the score obtained from the scale increases, nursing diagnoses are perceived negatively. In this context, it can be stated that surgical nurses mostly perceive the dimension of "definition and promotion of the nursing profession" positively, while they perceive the dimension of "ease of use" negatively at least. In similar studies in the literature, it is seen that the dimension of "definition and promotion of the nursing profession" has the lowest score, but the dimension with the highest score differs between studies.[10,15,16]

It was determined that the scores of the surgical nurses from the "definition and promotion of the nursing profession" sub-dimension of the "Perception of Nursing Diagnoses" scale differed significantly in favor of the trained surgical nurses. In the literature, it is seen that there are studies that have concluded that there is no significant difference according to the educational status of the nursing process.[9,10,17]

CONCLUSION

In the research conducted; it has been determined that the level of knowledge about the nursing process is significantly higher in surgical nurses who are over 35 years old, married, undergraduate or graduate, working in a state hospital and who think that the nursing process should be used actively; it was determined that there was no significant difference between surgical nurses in terms of gender, working time in nursing, working time in the surgical unit and receiving education about the nursing process.

On the other hand, the perception of nursing diagnoses is significantly more positive among older (between 31-35 and over 35 years old) surgical nurses who received training on the nursing process and thought that the nursing process should be used actively while giving care; it was determined that there was no significant difference between surgical nurses according to gender, marital status, hospital, working time in nursing and working time in the surgical unit. It is seen that these findings are mostly compatible with the literature, but

Table 3: Distribution of Nursing Diagnoses of Surgical Nurses by the Status of Receiving Education for the Nursing Process

Variables	Education	Number	Mean	Standart Deviation	z	p
Nursing diagnosis perception scale	Educated	195	80.51	17.68	-1.559	.119
	Not Educated	5	67.06	22.24		
Definition and introduction of the nursing profession	Educated	195	2.15	1.14	2.223	.026
	Not Educated	5	3.56	1.23		
Clearly describing the patient's condition	Educated	195	2.68	.74	.929	.353
	Not Educated	5	2.94	.41		
Ease of use	Educated	195	2.98	.62	1.113	.266
	Not Educated	5	3.23	.25		
Conceptual aspect	Educated	195	2.82	.71	-.686	.492
	Not Educated	5	2.65	.34		

there are some differences between the results of the study. It is considered to be caused by contextual differences caused by factors such as studies, city, hospital, period, measurement tools and so on.

The data collection step, which is the first step in the nursing process, is very important because it forms the basis for other steps in the nursing process. A problem that arises at this stage can cause all stages to be misinterpreted. The surgical nurse, who cannot obtain correct and sufficient data, may make wrong nursing diagnoses based on these data, and this may lead to the wrong nursing intervention that she sees as correct. As a result of these errors, the needs of the patient may not be met, and the problem may not be solved due to incorrect evaluation. This structure should be suitable to give information about the whole process as it is the end of everything. In this scope, the duty of surgical nurses in the in-service training programs, including the subject of the nursing process, is recommended. Increasing the time allocated to nursing process education in education curricula during the education and training process; organizing trainings, congresses and seminars on the missing subjects every time the process is done; It is recommended that surgical nurses be supported to participate in these scientific meetings during the education process.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Committee of Istanbul Okan University (Date: 24.08.2022, Decision No:157/23)

Informed Consent: Before starting the research, voluntary consent of the participants was obtained, it was explained that their personal information is kept and only the data obtained for scientific purposes will be processed.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article / Orijinal Araştırma

Knowledge, Attitudes and Behaviors of Religious Workers in Erzincan Province on Organ and Tissue Donation

Erzincan İlinde Görev Yapan Din Görevlilerinin Organ ve Doku Bağışı Konusunda Bilgi, Tutum ve Davranışları

Sema TURAN

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Abstract

Aim: To examine the level of knowledge of religious workers about organ and tissue donation and analyze their attitudes and behaviors on the issue.

Material and Method: This descriptive and cross-sectional study was conducted in the Erzincan of Turkey with religious workers (279 people) working in the province center. The research was conducted in June 2022. The data were collected using the questionnaire prepared by the researcher.

Results: Of the religious workers included in the study, 30.8% considered their knowledge about organ donation sufficient, 64.5% thought that organ donation is religiously appropriate, and 33.3% stated that they did not advise the public about organ donation. Only 1.4% of them had donated their organs and 25.8% were considering organ donation in the future. Of the participants, 32.6% stated that they would donate the organs of a relative in the event of their brain death if they had the right to make the decision, and 60.2% stated that they would donate organs to a relative. Religious workers who were over the age of 40, who had sufficient knowledge about organ donation, and who knew about the fatwa on organ donation significantly more commonly thought that organ donation is religiously appropriate ($p<0.05$). Participants who thought that organ donation is appropriate for followers of Islam and who had relatives waiting for organ transplantation were significantly more likely to consider organ donation in the future ($p<0.05$).

Conclusion: It was determined that the religious workers had low knowledge and training on organ donation. Although the majority of the religious workers thought that organ donation is religiously appropriate, knew about the fatwa of the Presidency of Religious Affairs on the subject, and thought that organ donation is necessary for humanity, both their rates of organ donation and wanting to donate organs in the future were low.

Keywords: Organ donation, religious workers, attitude

Öz

Amaç: Bu araştırmanın amacı din görevlilerinin organ ve doku bağışı konusunda bilgi düzeylerinin değerlendirilmesi, tutum ve davranışlarının belirlenmesidir.

Gereç ve Yöntem: Erzincan il merkezinde gerçekleştirilen tanımlayıcı ve kesitsel türdeki bu araştırma il merkezinde çalışan din görevlilerinde (279 kişi) yapılmıştır. Araştırma Haziran 2022'de yapılmıştır. Araştırmacı tarafından hazırlanan anket formu kullanılarak veriler toplanmıştır.

Bulgular: Din görevlilerinin organ bağışı hakkında bilgilerini yeterli görme oranı %30,5'dir. Din görevlilerinin %64,5'i organ bağışının dini açıdan uygun olduğunu düşünmektedir. Din görevlilerinin %33,3'ü organ bağışı hakkında halka tavsiyede bulunmadığını belirtmiştir. Din görevlilerinin sadece %1,4'ü organ bağışında bulunmuş olup %25,8'i gelecekte organ bağışı yapmayı düşünmektedir. Karar verme hakkının olduğu bir yakınının beyin ölümü gerçekleşmiş olduğunda %32,6'sı organlarını bağışlayacağını belirtirken bir yakını için organ bağışlayabileceğini belirtenlerin oranı %60,2'dir. Din görevlilerinin 40 yaşın üstünde olanlarda, organ bağışı konunda bilgisini yeterli görenlerde ve organ bağışı konusunda fetvayı bilenlerde organ bağışının dinen uygun olduğunu düşünme oranı daha yüksek olup istatistiksel olarak fark anlamlıdır ($p<0,05$). Organ bağışının İslam dinine uygun olduğunu düşünen ve organ nakli bekleyen yakını olan din görevlilerinde ileride organ bağışı yapmayı düşünme oranı daha yüksektir ve fark istatistiksel anlamlıdır ($p<0,05$).

Sonuç: Yaptığımız çalışmada din görevlilerinin organ bağışı konusunda hem bilgi hem de eğitim alma oranlarının düşük olduğu tespit edilmiştir. Din görevlilerinin çoğunluğu organ bağışının dinen uygun olduğunu düşünmelerine, yüksek oranda konu hakkındaki Diyanet İşleri Başkanlığının fetvasını bilmelerine ve yüksek oranda organ bağışının insanlık için gerekli olduğunu düşünmelerine rağmen hem organ bağışı oranları hem de ileride organ bağışında bulunmayı isteme oranları düşüktür.

Anahtar Kelimeler: Organ bağışı, din görevlileri, tutum

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INTRODUCTION

Organ transplantation is the most effective treatment for irreversible organ diseases.[1,2] Despite advances in organ transplantation treatment, a lack of donor resources remains a major problem. The lack of donated organs against the number of organ donations needed negatively affects the organ transplantation process. This leads patients with organ failure to experience worse clinical symptoms and increased mortality in patients on organ waiting lists.[3]

In Turkey, organs are mostly donated by living donors and the shortage of cadaveric donors is an important problem.[4,5] In 2021, Turkey had the highest percentage of living organ donors in the world.[6] According to data from the Ministry of Health of Turkey, the number of patients waiting for organ transplantation in 2021 was 26,323. However, the number of organ transplants performed in 2021 was only 4952.[7] Organ transplantation and donation practices in Turkey are carried out according to Law No. 2238 on "Harvesting, Storage, Grafting, and Transplantation of Organs and Tissues".[8] The High Council of Religious Affairs, the highest fatwa board of the Presidency of Religious Affairs in Turkey, ruled that organ and tissue transplantation is permissible under certain conditions under a decision dated March 6th, 1980, and numbered 396/13.[9] The Holy Quran, the holy book of Muslims, also states that "whoever gives life to a human being will be rewarded as if he had given life to all human beings".[10]

Prior studies on the subject found that an individual's knowledge, education, and religious beliefs affect their decisions to donate organs.[11,12] Therefore, religious elements should be emphasized to increase organ donation.[13] In Turkey, where the majority of the population is Muslim, the clergy plays a major role in guiding people's behaviors.[14] Religious workers having adequate knowledge about organ donation and conveying this knowledge to the community can affect people's views on organ donation.[15]

Religious workers' knowledge and attitudes about organ donation and transplantation are important because of their influence on society. Thus, this study aimed to determine the views of religious workers on organ and tissue donation and examine their attitudes and behaviors on this issue.

MATERIAL AND METHOD

This descriptive and cross-sectional study was carried out in the Erzincan provincial center in June 2022. Religious workers of Turkey work under the Presidency of Religious Affairs, and the provinces have Provincial Mufti Offices under this presidency. The Erzincan provincial center has a total of 358 religious workers. Since the entirety of the defined population was included in the study, no sample selection methods were used. The Provincial Mufti's Office holds monthly training meetings with religious workers. The questionnaires were administered to the participants under supervision after the researchers provided them with information at a meeting held on June 20. Due to reasons such as being on leave or not wanting to participate in the study, only 288 people out of the total population participated in the study. Written informed consent was obtained from the volunteering participants. Moreover, 9 questionnaires were not included in the study due to missing data. The study was completed with a total of 279 participants (78% of the total population).

The questionnaire used for data collection was developed by the researcher in accordance with the literature on the subject. The questionnaire consisted of a total of 31 questions. It included questions about descriptive data such as age, occupation, gender, marital status, and educational status, and about the participants' knowledge about which organs can be donated, organ donation and transplantation, sources of information, whether organ donation and transplantation is appropriate according to Islam, and whether they inform the public about organ donation. In addition, the participants were asked whether they had donated their organs, whether they would donate their relatives' organs, whether they would donate their own organs to their relatives, whether they accepted organ donation, their reasons for wanting or not wanting to donate, and their suggestions for increasing organ donation.

Ethical Approval

This study was approved by the Erzincan Binali Yıldırım University Faculty of Medicine Human Research Health and Sport Ethics Committee (Date: 29.04.2022, Protocol No: 04/11). In addition, written permission was obtained from the Provincial Mufti's Office for the study. The study was carried out in compliance with the principles of the Declaration of Helsinki.

Statistical Analyses

The data were analyzed using IBM SPSS Statistics for Windows 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as the number, mean±standard deviation, and percentage (%). Nominal variables were statistically analyzed using the Pearson chi-square test or Fisher's exact test. Variables showing significant differences in univariate analyses were evaluated by binary logistic regression. Statistical significance was accepted as $p<0.05$.

RESULTS

Of the participants, 52% were imams and 28% were Quran instructors. The mean age of the participants was 40.51±8.94 years and 82.4% were university graduates, while 16.5% were high school graduates. It was determined that 5.4% had a relative who had received an organ transplant and 6.8% had a relative who was waiting for an organ transplant. Among the participants with chronic diseases, most had respiratory diseases (6.1%) (**Table 1**).

Table 1. Demographic Characteristics of the Religious Workers

Variables	Number	%
Age	Mean±standard deviation (SD)	
Female	37.13±6.94	
Male	41.75±9.28	
Gender		
Female	75	26.9
Male	204	73.1
Marital status		
Married	250	89.6
Single	26	9.3
Widowed/divorced	3	1.1
Educational status		
Primary school	1	0.4
Secondary school	2	0.7
High school	46	16.5
University	230	82.4
Occupation		
Imam	145	52.0
Muezzin	52	18.6
Preacher	3	1.1
Quran instructor	79	28.3
Chronic diseases		
Cardiovascular diseases	10	3.6
Diabetes	11	3.9
Respiratory system diseases	17	6.1
Kidney diseases	1	3.2
Musculoskeletal system diseases	9	0.4
Other (MS, epilepsy, FMF, Ht, migraine, hearing defect)	12	4.3
Having a relative with a history of organ transplant		
Yes	15	5.4
No	264	94.6
Having a relative waiting for an organ transplant		
Yes	19	6.8
No	260	93.2
Total	279	100.0

Of the religious workers, 30.8% considered their knowledge about organ donation sufficient. The main sources of information about organ donation were television-radio (52.7%) and the Internet (39.1%). Only 12.2% of the religious workers stated that they received training on the subject. While 48.4% of the respondents knew that there is a law on organ donation in Turkey, 90% were aware of the fatwa issued by the Presidency of Religious Affairs on the religious appropriateness of organ donation. When asked about which organs can be transplanted, the participants most commonly answered kidneys (86.7%), heart (63.1%), bone marrow (62%), and liver (61.3%). When asked if organ donation is religiously appropriate, 64.5% of the participants thought that it is. Additionally, 52% of the participants believed that religious workers should promote organ donation. The rate of participants who were asked for guidance on organ donation by the public frequently was 5.7%, while the rate of those who were never asked for guidance on the issue was 36.6%. Moreover, 33.3% of the religious workers stated that they did not advise the public about organ donation (**Table 2**). The rate of males who considered their knowledge about organ donation adequate was significantly higher than those who considered their knowledge partially adequate or inadequate (X^2=14.717, p<0.001). Those over 40 years of age and who considered their knowledge about organ donation sufficient were significantly more likely to have received training on organ donation (X^2=8.673, p=0.003 and X^2=20.845, p<0.001, respectively).

Table 2. Knowledge of Religious Workers About Organ Donation

Knowledge about organ donation	Number	%
Self-assessment of knowledge about organ donation		
Adequate	86	30.8
Partially Adequate	147	52.7
Inadequate	46	16.5
Assessment of knowledge about organ donation of other religious workers		
Adequate	74	26.5
Partially Adequate	153	54.8
Inadequate	52	18.6
Received education about organ donation		
Yes	34	12.2
No	245	87.8
Assessment of the organ donation rate in Turkey		
Adequate	21	7.5
Inadequate	172	61.6
Undecided	86	30.8
Knowing that there is a law on organ donation in Turkey		
Yes	135	48.4
No	95	34.1
Undecided	49	17.6
Knowing about the fatwa of the Presidency of Religious Affairs on organ donation		
Yes	251	90.0
No	18	6.5
Undecided	10	3.6
Believing that organ donation is appropriate according to Islam		
Yes	180	64.5
No	20	7.2
Undecided	79	28.3
Believing that religious workers should promote organ donation		
Yes	145	52.0
No	32	11.5
Undecided	102	36.6
Frequency of being asked for guidance by the public about organ donation		
Often	16	5.7
Rarely	161	57.7
Never	102	36.6
Frequency of providing guidance to the public about organ donation		
Never	93	33.3
Sometimes	78	28.0
Often	22	7.9
When asked	86	30.8
Source of information about organ donation*		
TV or radio	147	52.7
Internet	109	39.1
Social circle or friends	86	30.8
Medical staff	85	30.5
Books or magazines	57	20.4
School	29	10.4
Tissues and organs the participant thinks can be transplanted*		
Kidneys	242	86.7
Heart	176	63.1
Liver	171	61.3
Bone marrow	173	62.0
Face or scalp	107	38.4
Cornea	105	37.6
Heart valve	93	33.3
Lung	81	29.0
Skin	72	25.8
Arm or leg	62	22.2
Muscle tissue	32	11.5
Uterus	28	10.0
Pancreas	28	10.0
Bone	25	9.0
Cartilage	19	6.8
Total	279	100.0

*More than one option was selected

Only 1.4% of the participants had donated their organs and 25.8% were considering organ donation in the future. Of the participants, 32.6% stated that they would donate the organs of a relative in the event of their brain death if they had the right to make the decision, and 60.2% stated that they would donate organs to a relative. While 89.2% of the religious workers thought that organ donation is necessary for humanity, 71.3% stated that they would accept organ donation if they needed a transplant. The most prominent reasons for not wanting to donate organs were not wanting to intervene with one's body/corpse (35.4%) and not considering the issue of organ donation before (33.8%). The leading reasons for wanting to donate organs was the thought of saving lives (84.2%) and that it is a good deed (56.6%) (**Table 3**).

Table 3. Attitudes of Religious Workers About Organ Donation and their Reasons

Attitudes about organ donation and reasons	Number	%
Having donated organs before		
Yes	4	1.4
No	275	98.6
Desiring to donate organs in the future		
Yes	76	27.2
No	65	23.3
Undecided	138	49.5
Having donated blood before		
Yes	163	58.4
No	116	41.6
Would donate the organs of a relative if they are brain dead		
Yes	91	32.6
No	54	19.4
Undecided	134	48.0
Would donate own organs to a relative if needed		
Yes	168	60.2
No	31	11.1
Undecided	80	28.7
Has an organ donor in their family		
Yes	16	5.7
No	263	94.3
Believing organ donation is necessary for humanity		
Yes	249	89.2
No	27	9.7
Undecided	3	1.1
Would accept organ donations for self if needed		
Yes	199	71.3
No	22	7.9
Undecided	58	20.8
Reasons for not wanting to donate organs* (n=65)		
I don't want one's body/corpse to be interfered with	23	35.4
I did not consider the issue of organ donation before	22	33.8
I think organ donation is religiously inappropriate	17	26.2
I am afraid of getting my tissues and organs removed before death	10	15.4
I am afraid my tissues and organs could be given to people I do not want	7	10.8
I am afraid my tissues and organs could be used commercially	9	13.8
I am afraid my own life may be at risk	7	10.8
I am not eligible due to illness	8	12.8
I don't trust doctors	6	9.2
Reasons for wanting to donate organs* (n=76)		
The thought of saving lives	64	84.2
The thought that it is a good deed	43	56.6
The thought that I may need organ transplants in the future	39	51.3
Having someone in one's life waiting for an organ transplant	20	26.3
Total	279	100.0

*More than one option was selected

The effects of some characteristics of the participants on their religious approval of organ donation are presented in **Table 4**. Religious workers who were over the age of 40, who had sufficient knowledge about organ donation, and who knew about the fatwa on organ donation were significantly more likely to think that organ donation is religiously appropriate ($p<0.05$) (**Table 4**). Independent variables affecting the religious appropriateness of organ donation were analyzed by binary logistic regression As a result of the analysis, being over 40 years of age and knowing the fatwa on organ donation were determined as factors affecting the religious appropriateness of organ donation (**Table 5**)

Those who thought that organ donation is appropriate according to Islam and those who had relatives waiting for organ transplantation were significantly more likely to want to donate their organs in the future ($X^2=13.284$, $p<0.001$ and $X^2=4.168$, $p=0.041$, respectively). Independent variables affecting future organ donation were analyzed by binary logistic regression. As a result of the analysis, the effect of thinking that organ donation is religiously appropriate and having a relative waiting for organ transplantation were not found to be significant (**Table 6**)

The rate of accepting organ donation if needed was significantly higher among those who thought that organ donation is religiously appropriate (84.4%) compared to those who thought that it is not religiously appropriate or were undecided (47.5%) ($X^2=42.684$, $p< 0.001$). The rate of accepting organ donation in the case of need was also significantly higher among those who were considering organ donation in the future (93.4%) compared to those who were not considering organ donation in the future or were undecided (63.1%) ($X^2=24.933$, $p< 0.001$). Independent variables affecting the acceptance of organ donation in case of need were analyzed by binary logistic regression. As a result of the analysis, it was found that thinking that organ donation is religiously appropriate is an effective factor (**Table 7**). It was found that 41.5% of those who did not want to donate their organs and 16.7% of those who did not consider organ donation religiously appropriate stated that they would accept organ donation if they needed it.

When asked about how organ donation can be promoted, 174 participants (62.4%) answered that education should be provided in schools, while others stated that the media, health workers, and religious workers should pay more attention to the issue (147, 52.7%; 132, 47.3%; and 120, 43%, respectively).

Table 4. Effects of Some Characteristics of the Participants on their Thoughts about the Religious Appropriateness of Organ Donation

Some Characteristics and Attitudes of the Participants	Considers organ donation religiously appropriate n (%)	Does not consider organ donation religiously appropriate Undecided n (%)	Total (n)	X^2	p value
Gender					
Female	48 (64.0)	27 (36.0)	75	0.012	0.913
Male	132 (64.7)	72 (35.3)	204		
Age					
Under 40 years	69 (56.1)	54 (43.9)	123	6.810	0.009
40 years and older	111 (71.2)	45 (28.8)	156		
Marital status					
Married	163 (65.2)	87 (34.8)	250	0.491	0.483
Single/widowed	17 (58.6)	12 (41.4)	29		
Chronic diseases					
Yes	37 (62.7)	22 (37.3)	59	0.106	0.744
No	143 (65.0)	77 (35.0)	220		
Educational status					
University	31(63.3)	18(36.7)	49	0.041	0.840
High school and under	149(25.7)	81(35.2)	230		
Received education about organ donation					
Yes	22 (64.7)	12 (35.3)	34	0.001	0.980
No	158 (64.5)	87 (35.5)	245		
Self-assessment of knowledge about organ donation					
Adequate	64 (74.4)	22 (25.6)	86	5.325	0.021
Partially adequate/inadequate	116 (60.1)	77 (39.9)	193		
Knowing about the fatwa on organ donation					
Yes	169 (67.3)	82 (32.7)	251	8.654	0.003
No/undecided	11 (39.3)	17 (60.7)	28		
Knowing that there is a law about organ donation in Turkey					
Yes	94 (70.1)	40 (29.9)	134	3.574	0.059
No/undecided	86 (59.3)	59 (40.7)	145		
Having a relative with a history of organ transplant					
Yes	9 (64.3)	5 (35.7)	14		
No	171 (64.5)	94 (35.5)	265		1.000*
Having a relative waiting for an organ transplant					
Yes	15 (78.9)	4 (21.1)	19	1.855	0.173
No	165 (63.5)	95 (36.5)	260		
Having donated blood before					
Yes	111 (68.1)	52 (31.9)	163	2.197	0.138
No	69 (59.5)	47(40.5)	116		
Total	180(64.5)	99(35.5)	279		

* Fisher's exact test

Table 5. Logistic Regression Analysis of Variables Related to Thinking Organ Donation is Religiously Appropriate

Independent Variables Included in the Model	OR	95% CI	p
40 years and older	1.83	1.10-3.05	0.019
Who had sufficient knowledge about organ donation	1.69	0.95-3.02	0.074
Who knew about the fatwa on organ donation were	2.76	1.22-6.27	0.015

Nagelkerke R^2=0.084, Hosmer and Lemeshow test: $X^2(3)$= 1.311 p=0.727, OR: Odds ratio, CI: confidence interval

Table 6. Logistic Regression Analysis of Variables Related to Desiring to donate organs in the future

Independent Variables Included in the Model	OR	95% CI	p
Thinking that organ donation is religiously appropriate	1.37	0.84-2.24	0.213
Having a relative waiting for an organ transplant	1.04	0.41-2.66	0.931

Nagelkerke R^2=0.008, Hosmer and Lemeshow test: $X^2(2)$= 0.986 p=0.611, OR: Odds ratio, CI: confidence interval

Table 7. Logistic Regression Analysis of Variables Related to Acceptance of Organ Donation in case of need

Independent Variables Included in the Model	OR	95% CI	p
Thinking that organ donation is religiously appropriate	6.27	3.54-11.10	<0.001
Wanting to be an organ donor in the future	0.69	0.39-1.22	0.202

Nagelkerke R^2=0.206, Hosmer and Lemeshow test: $X^2(2)$= 3.267 p=0.195, OR: Odds ratio, CI: confidence interval

DISCUSSION

This study evaluated the knowledge, attitudes, and behaviors of religious workers in Erzincan Province about organ donation. The study included 279 people participants. Only 30.8% of the religious workers considered their level of knowledge about organ donation and transplantation sufficient, and 26.5% considered their colleagues' level of knowledge about organ donation and transplantation sufficient. In a study conducted with religious workers in İstanbul, 22.5% of the participants thought their level of knowledge on the issue was adequate, while only 10% thought their colleagues had adequate knowledge.[16] It is an important problem that religious workers, who guide society, consider their level of knowledge on organ donation insufficient.

Most of the participants stated that their primary sources of information on organ donation were television-radio (52.7%) or the Internet (39.1%). Similarly, other studies on the issue found that television-radio and the Internet were the primary sources of information on organ donation for religious workers and the general public.[17,18] Since television and the Internet are popular sources of information, it is necessary to use them more effectively to deliver accurate information to individuals.

In our study, the rate of religious workers who received training on organ donation was low (12.2%). The proportion of religious workers who stated that they gained information on the issue during their schooling was also quite low (10.4%). In a meta-analysis of studies conducted with religious workers and students of theology faculties in Turkey, it was determined that only 20% of the participants indicated that they gained information on organ donation from school and there was no separate course on organ transplantation and donation in the education programs of these faculties.[19] Institutional training for religious workers may help overcome the lack of knowledge about organ donation and transplantation. In addition, including these topics in the programs of theology faculties can ensure that future religious workers have more knowledge on the issue.

The most common answers to the question of which organs and tissues can be transplanted were kidneys (86.7%), heart (63.1%), bone marrow (62%), and liver (61.3%). In a study conducted by Khalife et al. in Saudi Arabia, most participants answered a similar question with kidneys, liver, and heart.[20] The study of Doğan et al., conducted with university students, also had similar results.[21] These results are thought to be due to the kidneys, liver, and heart being the most frequently transplanted organs and receiving more media coverage.

Most of the participants were rarely (57.7%) or never (36.6%) asked to provide guidance regarding organ donation. Moreover, 33.3% of the religious workers stated that they did not advise the public about it. In a study conducted by Tarhan et al. with religious workers, 70% of the participants stated that they were asked to provide guidance regarding organ donation and 42.5% stated that they never spoke to the public about its.[16] Of the participants in the current study, 52% thought that religious workers should promote organ donation. This rate is lower than the results of a study conducted in Kayseri with religious workers (77.6%).[22] In order to increase organ donation, it is important to sensitize both society and religious workers about organ transplantation.

Of our participants, 90% knew about the fatwa of the Presidency of Religious Affairs that organ donation and transplantation is appropriate according to Islam. This rate is much higher than the results of the study conducted by Özsaydı et al. in Kayseri with religious workers (51.5%).[22] One study conducted with mosque imams in Kahramanmaraş reached a similar result to that herein (85.4%).[23]

In our study, 64.5% of the participants thought that organ donation is religiously appropriate. Similar studies conducted in Turkey reported that 60.5% to 92.5% of religious workers think that organ donation is religiously appropriate.[16,24-27] The rate of religious officials finding organ donation appropriate according to Islam is 1.83 times higher among those over the age of 40 and 2.76 times higher among those who know that there is a fatwa on the appropriateness of organ donation. In studies conducted among religious officials in Kayseri and university students, it was observed that age was not effective in the acceptance of organ donation according to Islam.[22,28] In a study conducted with medical students in Iran, it was found that students who knew about the fatwa on organ donation were more likely to donate organs than students who were not.[29] Another study conducted with university students in Saudi Arabia determined that knowing that Islam allows organ donation increased their willingness to donate their organs.[30] These findings suggest that institutions responsible for religious affairs and training informing religious workers about the religious appropriateness of organ donation can make a significant contribution to increasing organ donation.

Although 89.2% of our participants thought that organ donation was necessary for humanity, the rate of organ donors among the participants was quite low (1.4%). Studies conducted with religious workers in Yozgat (2.9%) and Kahramanmaraş (1.4%) found similar low donation rates.[17,27] A study conducted with the general population of Burdur Province had a higher organ donation rate among its participants (14.8%).[31] The fact that the majority of religious workers think that organ donation is necessary for humanity and know of the fatwa that organ donation is appropriate according to Islam while the rate of organ donor among them

is low shows that their attitudes regarding organ donation are not reflected in their behavior. Identifying and eliminating the reasons for this discrepancy between attitudes and behavior may contribute to an increase in organ donation. A high organ donation rate among religious workers can lead to higher organ donation rates among other segments of society.

Only 25.8% of our participants stated that they would like to donate their organs in the future. This rate was higher (51.5%) in a study conducted in Isparta and lower (14.1%) in a study conducted in Kahramanmaraş.[25,27] In a study conducted by Dağcıoğlu et al. with family physicians, 36.9% of the participants considered donating their organs in the future.[32] Although not found as effective factors in the logistic regression analysis, those who think that organ donation is in accordance with their religious beliefs and those who have relatives waiting for organ transplantation have a higher rate of wanting to donate organs in the future. Similarly, in a study conducted by Akbuğa and Sürme with university students, those with relatives waiting for organ transplantation were more likely to consider donating their organs in the future.[33] Since those who think that organ donation is appropriate according to Islam are more likely to donate their organs in the future, it is necessary to eliminate the hesitations of religious workers on this issue. The results showed that having a relative in need of an organ transplant helps people notice the hardships of people needing organ transplants and contributes to raising awareness. Thus, sharing the stories of patients waiting for or receiving organ transplants through the media will contribute to raising awareness.

In the present study, 32.6% of the participants said that they would donate the organs of a relative in the event of their brain death if they had the right to make the decision, and 60.2% stated that they would donate organs to a relative. Similarly, in a nationwide study conducted in Turkey with religious workers, 52.9% of the participants stated that they would donate the organs of a relative after their death, while 81.6% stated that they would donate organs to a relative.[24] The finding that participants did not want to donate their relatives' organs while they are willing to donate their own organs to their relatives explains the high number of donations from living donors in Turkey.

Of our participants, 71.3% stated that they would accept organ donation if they needed an organ transplant. Acceptance of organ donation is 6.27 times higher among those who think that organ donation is in accordance with their religious beliefs. This shows us the importance of thinking that organ donation is religiously appropriate for acceptance. This positive effect will be enhanced by having accurate and sufficient religious knowledge on the subject. In a similar study conducted in Yozgat with religious workers, the rate of participants who would accept organ donation for themselves was slightly higher, at 85%.[17] A notable finding of the current study was that 41.5% of the participants who were reluctant to donate their organs and 16.7% of those who did not consider organ donation religiously appropriate stated that they would accept organ donation if they needed a transplant. There is a need for further studies examining the reasons underlying this result.

The foremost reasons for not wanting to donate organs among our participants were not wanting to intervene with one's body/corpse (35.4%), not considering the issue of organ donation before (33.8%), and thinking that organ donation is not religiously appropriate (26.2%). Similarly, in a study conducted in Isparta with religious workers, not considering the issue of organ donation before and not wanting to intervene with one's body/corpse were the prominent reasons for not wanting to donate organs.[25] A study conducted by Tarzi et al. with Syrian university students reported that the fear of dismemberment of their bodies was a major obstacle to organ donation among the participants.[34] This suggests that concerns about intervention with one's body/corpse lead to reluctance about being a cadaveric donor. It is also noteworthy that the second most prominent reason for not considering to be an organ donor was a lack of coverage of the issue. More work should be done to inform and sensitize both the public and clergy about organ donation.

The most common reasons for not wanting to donate one's organs were found to be the thought of saving lives (84.2%), the thought that it is a good deed (56.6%), and the thought that one may need an organ transplant in the future themselves (51.3%). Similarly, other studies conducted with religious workers and the general population found that the thought of saving lives is the foremost reason for considering organ donation.[22,35]

In our study, religious reasons were shown as the motivation for organ donation by 43 (56.6%) of the religious workers who were considering organ donation. In a similar study conducted in Kayseri, a lower rate (13%) of participants had religious reasons to want to donate their organs than in our study.[22] The finding of our study that religious beliefs have both a negative effect and a motivating effect on organ donation is noteworthy. In a qualitative study on the effect of religion on organ donation, it was suggested that although negative effects related to religion were observed in the organ donation process, these seemed to be caused not by religion, but by inexperience in organ donation and transplantation and a lack of religious knowledge on this subject.[36] These findings suggest that religious workers having sufficient and accurate religious and medical information may lead to them viewing organ donation more positively.

When asked about how organ donation can be promoted, 174 participants (62.4%) answered that education should be provided in schools, while others stated that the media, health workers, and religious workers should pay more attention to the issue (147, 52.7%; 132, 47.3%; and 120, 43%, respectively). In a study conducted by Kaymak and Aksoy with religious workers in Bolu, similar recommendations were made to increase organ donation.[37]

CONCLUSION

In this study, it was determined that religious workers had low knowledge and training on organ donation. Training on organ donation and transplantation should be provided to religious workers to alleviate their lack of both religious and medical knowledge.

Although the majority of the religious workers thought that organ donation is religiously appropriate, knew about the fatwa of the Presidency of Religious Affairs on the subject, and thought that organ donation is necessary for humanity, both their rates of organ donation and wanting to donate organs in the future were low. This study has shown that although religious workers have a positive attitude towards organ donation, they are unable to transform this attitude into action. Further research is needed to determine why religious workers do not donate organs despite their positive attitudes.

In our study, the main reasons for the negative attitudes towards organ donation were found to be the impairment of bodily integrity, the lack of coverage of the issue, and the belief that it was not religiously appropriate. Training should be planned by considering the reasons for the negative attitudes of religious workers. Religious beliefs were also found to have a motivating effect on the religious workers who were considering organ donation. Studies on the reasons for these attitudes can contribute to changing the negative attitudes of religious workers toward organ donation. Furthermore, qualitative research involving extensive interviews with religious workers can provide more detailed information about the reasons for these attitudes.

In this study, it was observed that the religious workers were rarely asked questions by the public about organ donation and they rarely informed the public on this issue. In order to increase the motivation of both religious workers and the public regarding organ and tissue donation, the Ministry of Health and the Presidency of Religious Affairs should address the issue more frequently and ensure that it is on the agenda of both the public and religious workers.

It was found that the religious workers who believed that organ donation is appropriate according to Islam and who had a relative waiting for an organ transplant were more likely to want to donate their organs in the future. The Directorate of Religious Affairs should ensure that the public is informed by religious workers that organ donation and transplantation are appropriate according to Islam. Efforts should be made to promote empathy with organ recipients, such as sharing the experiences of those who have gone through the organ transplantation process.

Limitations

Since the study included a small portion of religious workers, the results cannot be generalized to all religious workers. In the study, a structured questionnaire was used to question the level of knowledge and perspectives of the religious workers regarding organ donation. Since the data on their knowledge was self-reported, it may not reflect their actual knowledge levels.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Committee of Istanbul Okan University (Date: 24.08.2022, Decision No:157/23)

Informed Consent: Written permission was obtained from the Provincial Mufti's Office for the study.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article / Orijinal Araştırma

The Association between the Morphology of the Aortic Valve and the Dysfunction of the Aortic Valve in Pediatric Patients with a Diagnosis of Bicuspid Aortic Valve

Biküspid Aort Kapağı Tanısı Alan Pediatrik Hastalarda Aort Kapak Morfolojisi İle Aort Kapak Disfonksiyonu Arasındaki İlişki

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Abstract

Aim: The congenital heart malformation known as the bicuspid aortic valve is a prevalent condition. The objective of this study was to analyze the demographic, clinical, and echocardiographic characteristics of subjects who were children and adolescents with the bicuspid aortic valve condition. Additionally, we aimed to evaluate and compare the dimensions of the aortic root and ascending aorta as well as evaluate the level of aortic valve dysfunction in relation to the morphology of the aortic valve among the groups studied.

Material and Method: The prospective investigation was conducted among pediatric patients below the age of 18 years, who had been identified with bicuspid aortic valve through the use of echocardiography, at the Department of Pediatric Cardiology.

Results: Bicuspid aortic valve was detected in 1.42% (152 out of 10,691) of patients who underwent echocardiography. Among these patients, 72.4% (110) were male. The most frequent aortic valve morphology observed in patients with bicuspid aortic valve was the fusion of the left and right coronary cusps.

Conclusion: The results of our investigation have revealed that the diameter of the aortic annulus and sinotubular junction in the fusion of the right and non-coronary cusps cohort was markedly greater than that of the other groups. Moreover, it was observed that age, weight, and height exerted independent predictive effects on the diameters of the aortic root and ascending aorta in children diagnosed with bicuspid aortic valve.

Keywords: Adolescent, aortic root, aortic valve dysfunction, ascending aorta, bicuspid aortic valve, children

Öz

Amaç: Biküspit aort kapağı olarak bilinen konjenital kalp malformasyonu sık görülen bir durumdur. Bu çalışmanın amacı biküspid aort kapağı olan çocuk ve ergenlerin demografik, klinik ve ekokardiyografik özelliklerini analiz etmektir. Ek olarak, incelenen gruplar arasında aort kökü ve çıkan aort boyutlarını değerlendirmeyi ve karşılaştırmanın yanı sıra aort kapak fonksiyon bozukluğunun düzeyini aort kapak morfolojisi ile ilişkili olarak değerlendirmeyi amaçladık.

Gereç ve Yöntem: Prospektif çalışma, Çocuk Kardiyolojisi Bölümü'nde ekokardiyografi kullanılarak biküspit aort kapağı tanısı konulan 18 yaş altı pediatrik hastalarda gerçekleştirildi.

Bulgular: Ekokardiyografi yapılan hastaların %1,42'sinde (10.691 hastanın 152'sinde) biküspit aort kapağı tespit edildi. Bu hastaların %72,4'ü (110) erkekti. Biküspit aort kapağı olan hastalarda en sık gözlenen aort kapak morfolojisi, sol ve sağ koroner kasparın füzyonuydu.

Sonuç: Çalışmamızın sonuçları, sağ ve non-koroner kasp füzyon kohortunun aortik annulus ve sinotubüler bileşke çapının diğer gruplara göre belirgin şekilde daha büyük olduğunu ortaya koydu. Ayrıca biküspid aort kapağı tanısı alan çocuklarda yaş, kilo ve boyun aort kökü ve çıkan aort çapı üzerinde bağımsız prediktif etkiler oluşturduğu gözlendi.

Anahtar Kelimeler: Ergen, aort kökü, aort kapak disfonksiyonu, çıkan aort, biküspid aort kapağı, çocuklar

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INTRODUCTION

Bicuspid aortic valve (BAV) is the most commonly found congenital cardiac disease. It is characterized by aortic valve regurgitation and aortic dilatation in approximately 50% of individuals.[1] BAV can occur either independently or in conjunction with other heart problems, and it can also manifest as part of a syndrome. In adults, valve dysfunction requiring intervention is frequently observed, and the severity of valve dysfunction is thought to be associated with the morphologic phenotype of BAV.[2] Researches exploring the link between BAV morphology, aortic root and ascending aorta measures, and aortic valve dysfunction in juveniles has yielded varying results in the literature.[3-5] Therefore, the purpose of this prospective study is to investigate the demographic, clinical, and echocardiographic aspects of children and adolescents diagnosed with BAV and to compare the measurements of the aortic root and ascending aorta, as well as the occurrence of aortic valve dysfunction, based on their aortic valve morphology within these groups.

MATERIAL AND METHOD

During the period spanning from January 1, 2017 to December 31, 2019, children below the age of 18 who had been diagnosed with BAV via echocardiography conducted by the Department of Pediatric Cardiology within the Faculty of Medicine, were incorporated into this prospective study. Furthermore, an examination of these syndromes was also conducted, with the aim of revealing the frequency of any genetic syndromes that may be associated with BAV. Patients whose echocardiographic image was deemed suboptimal were excluded from the study. The ethical committee at our hospital provided the necessary authorization for the study protocols (as evidenced by approval number 2017/294), while signed informed consent papers were collected from the parents of the adolescent subjects. During the study, all patients underwent thorough interrogation of their medical and family histories, spanning over two generations. The registration and follow-up form documented the physical examinations conducted as per routine. The physical examination encompassed the patients' grievances during their first admission and follow-up, personal and family history, and any murmur/abnormal heart sound. Additionally, measurements of height, weight, and blood pressure values were taken. Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared.

One experted pediatric cardiologist conducted examination via the Philips EPIQ 7C device from Philips Healthcare in Minnesota, United States to the transthoracic echocardiographic. The left lateral decubitus position was used to examine apical four- and five-chamber, parasternal long-axis and short-axis, and subcostal echocardiographic images of the patients. The aortic valve morphology during systole and diastole was examined in the parasternal short axis view. Patients were diagnosed with BAV if they exhibited aortic valves with distinct bipartite ends, the characteristic systolic fish-mouth appearance of the aortic valve leaflets, or two of the three supporting features of BAV, namely systolic dome, diastolic prolapse of aortic leaflets, and eccentric leaflet closure. True BAV (BAV without raphe) was segregated based on its orientation, i.e., horizontal or vertical. Furthermore, BAV was classified into three additional types depending on the location of the raphe, which were as follows: type fusion of the left and right coronary cusps, type fusion of the right and non-coronary cusps, and type fusion of the left and non-coronary cusps. The patients underwent regular echocardiographic examinations at six-month intervals for follow-up purposes.

The measurements of the diameter for the aortic annulus, sinus of valsalva, sinotubular junction (aortic root), and proximal ascending aorta 1 cm above the sinotubular junction were conducted in the parasternal long-axis view, which was perpendicular to the long axis of the vessel, and at the end of systole. The aortic Z scores were then calculated according to the method previously described by Cantinotti et al.[6] If the resulting Z-score value was greater than +2, it was accepted as an indication of enlargement in the aortic root or ascending aorta. The classification of aortic valve stenosis was based on the peak Doppler gradient measurement, which was determined to be mild (peak Doppler gradient <40 mmHg), moderate (peak Doppler gradient between 40-70 mmHg), or severe (peak Doppler gradient >70 mmHg).[7] In addition, the grading of aortic regurgitation (AR) ranged from first degree to fourth degree, with hemodynamically significant AR considered to be of the second degree or more severe, as defined by the measurement.[8]

Statistical Analysis

The utilization of Statistical Package for the Social Sciences 21.0 (SPSS Inc., Chicago, IL, USA) was implemented for all statistical analyses. Categorical variables were represented by numbers and percentages. The distribution of parameters was examined using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Whether the data was normally distributed or not determined the usage of parametric or nonparametric tests in data analysis. Mean±standard deviation was employed for quantitative data presentation. In cases where parameters were not normally distributed, the median (minimum-maximum) was displayed. Depending on the distribution of the variables, differences in the means of the variables were examined using both parametric and nonparametric tests. The comparison of groups was conducted using the independent t test or the Mann-Whitney U test, while connections associations between parameters were investigated using the Pearson or Spearman correlation test. The Bonferroni-corrected Mann-Whitney U test was employed as a more stringent measure of statistical significance for multiple comparisons, in conjunction with the Kruskal-Wallis analysis of variance, to compare groups. To compare categorical variables between independent groups, the chi-square test was utilized. The mixed ANOVA test was employed to analyze

the group effect in repeated measurements. Subsequently, stepwise multivariate linear regression was used to ascertain which factors independently explained a significant ($p < 0.05$) proportion of the variation in the dependent variables. The Mc Nemar test was applied to compare categorical variables between dependent groups. The Wilcoxon signed rank test or the paired samples t-test were implemented to compare the research group's before and subsequent values. The significance of results was established when the value of p was less than 0.05, or when p was less than 0.05 divided by the number of comparisons made, denoted as k.

RESULTS

In the cohort of 10,691 patients presenting for initial assessment in the pediatric cardiology, a total of 152 (1.42%) individuals were identified as having been diagnosed with BAV. Among these, 42 (27.6%) were identified as female, while the remaining 110 (72.4%) were male. The mean age of the population was 7.8±4.6 years, ranging from 1 month to 17 years. Upon detailed inquiry regarding cardiovascular complaints, 115 (75.7%) of the patients with BAV reported no active symptoms during their initial presentation. However, the remaining cases exhibited a variety of symptoms, including sweating (26.3%), failure to gain weight (19.7%), chest pain (17.8%), exercise intolerance (15.1%), palpitations (15.1%), fatigue (14.5%), respiratory distress (13.2%), presyncope symptoms (10.5%), fainting (5.3%), hypoxic seizures (2.6%), and peripheral cyanosis (2%). Eight individuals, accounting for 5.2% of those with BAV, presented with syndromic conditions. Among the cohort, 2 (1.3%) had Down syndrome, 2 (1.3%) exhibited Klinefelter syndrome, 1 (0.6%) displayed Di George syndrome, 1 (0.6%) manifested Apert syndrome, 1 (0.6%) illustrated Gorlin-Goltz syndrome, and 1 (0.6%) was diagnosed with Sturge-Weber syndrome. In the family history of 33 (21.7%) of the patients, there was evidence of first-degree consanguinity. The vast majority, or 126 (82.9%), of the patients with BAV had no prior history of chronic disease. Co-occurrence of other diseases was noted in the remaining patients and included 12 (7.9%) who had allergic diseases, 4 (2.6%) who had rheumatological diseases, 3 (2.0%) who had nephrological diseases, 3 (2.0%) who had endocrinological diseases, 2 (1.3%) who had neurological diseases, 1 (0.7%) who had haematological disease, and 1 (0.7%) who had gastroenterological disease. Among the cohort of patients diagnosed with BAV, a majority of 126 (82.9%) were not using medication. Of the remaining patients, a small proportion of 15 (9.9%) were using antihypertensive drugs, while an even smaller proportion of 3 (2.0%) were using benzathine penicillin-G, 3 (1.3%) were using antiarrhythmic drugs, 2 (1.3%) were using asthma drugs, 2 (1.3%) were using colchicine, and 1 (0.7%) was using subcutaneous immunoglobulin. In terms of familial history, 33 (21.7%) patients with BAV had a history of consanguinity, with 119 (78.3%) of these cases being of the first degree. Furthermore, a large majority of 141 (92.7%) patients did not report a family history of sibling death, while a small minority of 11 (7.2%) reported such a history. In the sample population, a small percentage of individuals had a history of rhythm disorder (5.3%), sudden death (4.6%), congenital heart disease (2.6%), or syncope (1.3%). As far as it is learned from the family history, a number of individuals also had hypertension (6.6%), hyperlipidemia (2.6%), metabolic syndrome (15.8%), diabetes (13.2%), or both diabetes and hypertension (11.2%) in their relatives. Additionally, a small percentage of individuals had coronary artery disease (4.6%), thyroid dysfunction (0.7%), or neurological disease (1.3%) in their first and second degree relatives. In our study, we invited first-degree relatives of patients with BAV for family screening. BAV was diagnosed in 12 of the total 30 patients who visited our pediatric cardiology clinic through echocardiographic examination.

At the time of initial presentation, the average weight of the patient cohort (N:152) was 29.2±17.8 kilograms (median: 23, 3.7-83), while the mean height was 122.1±32.0 cm (median 124, 40-182). The patients' blood pressure was recorded as 100.6±12.4 mmHg (70-160 mmHg), with an average diastolic blood pressure of 64.9±10.5 mmHg (32-110 mmHg). The mean blood pressure of the patients was 76.9±10.4 mmHg.

When categorizing patients by age, we observed that 18 (11.8%) belonged to the infancy period (0-24 months), 27 (17.8%) to the pre-school period (2-5 years), 69 (45.4%) to the school age (5-12 years), and 38 (25%) were adolescents (>12 years old). The largest proportion of our cases was within the age group of 5-12 years. **Table 1** presents the demographic and anthropometric characteristics of the patients. In accordance with the Gomez malnutrition classification, 19 patients (12.5%) were deemed malnourished, 12 patients (7.8%) had mild malnutrition, and 7 patients (4.6%) had moderate malnutrition. There was an absence of severe malnutrition observed in our patient cohort. Within the sample, 21 individuals (13.8%) exhibited short stature. Among these, 17 patients (11.1%) demonstrated a range of -2 to -3 standard deviations (potentially indicative of a normal variant or pathological short stature), while 4 patients (2.6%) exhibited a -3-standard deviation (suggesting pathological short stature). Upon conducting cardiac auscultation examinations, 116 patients (76.3%) displayed no cardiac murmur or abnormal heart sounds. Among the remaining patients, 25 individuals (16.4%) exhibited systolic murmur and 11 patients (7.2%) displayed ejection click.

Of the patient cohort diagnosed with BAV, 65 individuals, representing 42.9% of the total sample, exhibited an isolated occurrence of the condition. Comorbid echocardiographic findings were present in the remaining patients. These included isolated trace mitral valve regurgitation in 26 patients (17.1%), ascending aorta dilatation in 19 patients (12.5%), aortic coarctation in 10 patients (6.6%), trace mitral valve regurgitation and dilatation of the ascending aorta in 8 patients (5.3%), trace mitral valve regurgitation and mitral valve prolapse in 7 patients (4.6%), atrial septal defect in 6 patients (3.9%), ventricular septal defect in 4 patients (2.6%),

trace mitral regurgitation and atrial septal defect in 2 patients (1.3%), dilatation of the ascending aorta and ventricular septal defect in 2 patients (1.3%), mitral valve prolapse and atrial septal defect in 1 patient (0.6%), mitral valve prolapse in 1 patient (0.6%), and other congenital heart anomalies in 1 patient (0.6%).

Clinical Characteristics and Aortic Measurements According To Aortic Valve Morphology

The BAV subtype of five patients could not be definitively determined by echocardiography. Of the remaining patients, the BAV types were categorized as follows: left-right fusion type in 100 patients (68%), right-noncoronary cusp fusion type in 32 patients (21%), and 13 patients (9%) without raphe. Left-noncoronary cusp fusion type was observed in only two patients (1%) and was not included in the statistical analysis due to the small sample size. The statistical analyses were conducted on a total of 145 patients. **Table 1** presents patients' clinical characteristics and echocardiographic measurements based on aortic valve morphology. The three groups showed no significant differences in sex (p: 0.913). Furthermore, no significant differences in aortic measurements were observed when analyzed by sex ($p>0.05$). When comparing the three groups based on age, weight, height, systolic blood pressure, aortic annulus, sinotubular junction, and ascending aorta measurements, a statistically significant difference was observed between the groups. However, no significant difference was noted in terms of the z-scores values of the aortic root and descending aorta diameters and diastolic blood pressure. Furthermore, when examining the three groups based on age, the left-right fusion type group exhibited a statistically significantly lower age than the right-noncoronary cusp fusion type group. Lastly, when comparing the groups based on systolic blood pressure, the right-noncoronary cusp fusion type group displayed a statistically significantly higher systolic blood pressure than the BAV without raphe group. When comparing the three groups in relation to the diameter of the aortic annulus, it was found that the aortic annulus diameter of the group with fusion of the right-noncoronary cusp type was significantly higher than that of the group with fusion of the left and right coronary cusps. Similarly, when examining the sinotubular junction diameter, the right-noncoronary cusp fusion type group exhibited a statistically significant increase compared to the BAV without raphe group. Furthermore, in terms of the diameter of the ascending aorta, the right-

Table 1. Comparison of patients' clinical features and echocardiographic measurements according to aortic valve morphology

	Total patients (N:145)	Type fusion of the left and right coronary cusps (N:100)	Type fusion of the right and non-coronary cusps (N:32)	Type without raphe (N:13)	Oneway ANOVA/ or Kruskal wallis test	P1 value	P2 value	P3 value
Sex (Male/Female)	105/40	72/28	24/8	9/4	NA			
Age (month)	96.4±56.3 96 (1-204)	89±55.4 (1-192)	122.8±54.9 (18-204)	87.1±49.5 (16-164)	**0.011**	**0.010**		
Weight (kg)	29.7±18 23 (3.7-83)	27.4±16.9 (3.7-76)	38.3±20.4 (10-83)	25.6±12.8 (9-51)	**0.019**	0.018		
Height (cm)	123±31 124 (40-182)	118±32.8 (40-175)	137±26 (75-182)	120±27 (73-155)	**0.024**	0.022		
Body Mass Index	17.07 (10.89-25.95)	16.86 (10.89-25.39)	17.93 (13.61-25.95)	16.53 (14.15-21.23)	0.404			
Systolic Bloood Pressure (mmHg)	101±12.7 100 (70-160)	100±12.8 (70-160)	105±12 (90-130)	96±12 (85-130)	**0.013**			**0.015**
Diastolic Bloood Pressure (mmHg)	65.2±10.7 60 (32-110)	64.5±10.6 (32-110)	68.9±11 (50-90)	62±8.5 (50-75)	0.100			
Aortic Annulus (mm)	15.15±3.69 15 (5.2-28)	14.67±3.86 14.70 (5.2-22.7)	17.05±3.86 16.65 (11-28)	14.36±1.57 14 (11.9-16.5)	**0.005**	**0.008**		0.037
Z score	-0.13±1.85 -0.09 (-4.62-9.87)				0.513			
Sinus Valsalva (mm)	20.79±5.10 20.65 (7.3-35.8)	20.55±5.54 20.65 (7.3-35.8)	22.29±4.13 22.5 (14-32.3)	19.13±3.14 18.80 (14.3-25.3)	0.075			
Z score	0.02±1.82 0.04 (-4.20-8.65)				0.457			
Sinotubular Junction (mm)	17.33±4.69 17.2 (6.4-30.7)	16.95±4.86 17.2 (6.4-29.6)	19.10±3.86 19 (11.8-30.7)	15.166±2.68 15.90 (10.6-19)	**0.007**	0.040		**0.012**
Z score	0.68±1.87 0.57 (-3.82-10.19)				0.119			
Ascending Aorta (mm)	21.46±5.97 20.75 (7.1-38.4)	20.67±6.1 19.90 (7.1-38.4)	24±4.97 23 (15-37.9)	21.19±5.95 20.20 (13.2-33.1)	**0.006**	**0.009**		
Z score	1.33±1.94 1.10 (-3.82-10.19)				0.581			

P1: Type fusion of the left and right coronary cusps versus type fusion of the right and non-coronary cusps, P2: Type fusion of the left and right coronary cusps versus type without raphe, P3: Type fusion of the right and noncoronary cusps versus type without raphe, Data were indicated mean±standart deviation, median (minimum-maximum). Normally distributed data were compared with the One-way ANOVA test. If the data do not fit the normal distribution, results were compared using the Kruskal–Wallis test followed by the Bonferroni-corrected Mann–Whitney U test. Significance was determined by $p<0.05$ for the Kruskal–Wallis test and $p<0.016$ ($p=0.05/3$) for the Bonferroni correction. Statistically significant differences are highlighted in bold.

noncoronary cusp fusion type group displayed a significantly higher diameter compared to the type fusion of the left and right coronary cusps group (**Table 1**).

After the diagnosis of BAV, patients underwent regular echocardiographic examinations at 6-month intervals. The patients who came for the examination had two, three, or four measurements recorded. Unfortunately, the number of patients with three and four measurements was insufficient to conduct further statistical analysis. However, for the 58 patients in the BAV group with fusion of the left and right coronary cusps, 14 patients in the right-noncoronary cusp fusion type group, and 6 patients in the BAV without raphe group, we evaluated the repeated measurements using mixed ANOVA. The results showed that aortic valve morphology did not have a statistically significant effect on the measurements of the aortic root and ascending aorta.

The Relationship between Aortic Valve morphology and Aortic Valve Stenosis and Regurgitation

The study found that among 100 patients with BAV left-right leaflet fusion, 34 (34%) displayed hemodynamically insignificant AR, 13 (13%) displayed both aortic stenosis (AS) and AR, 9 (9.0%) displayed mild AS, 2 (2.0%) displayed moderate AS, and 1 (1.0%) displayed hemodynamically significant AR. In the case of 32 patients with BAV type fusion of the right and non-coronary cusps, 12 (37.5%) displayed hemodynamically insignificant AR, 8 (25%) displayed both AS and AR, 2 (6.25%) displayed mild AS, and 1 (3.1%) displayed hemodynamically significant AR. Moreover, among 13 patients with BAV without raphe type, 7 (53.85%) displayed hemodynamically insignificant AR, while 4 (30.7%) displayed both AS and AR. Finally, among 2 patients with BAV with type fusion of the left and non-coronary cusps, both AS and AR were found in 1 (50%) patient. Patients with hemodynamically significant AR were treated with an angiotensin converting enzyme inhibitor.

When the three groups were compared in terms of isolated AS, isolated AR, and both AS and AR, coexistence of AR and AS were found to be statistically higher in the right-noncoronary cusp fusion type group compared to the other groups (p: 0.016).

Aortic Valve Morphology and Accompanying Congenital Heart Diseases

In a total of 100 BAV types formed by type fusion of the left and right coronary cusps, 40 (40%) were observed to have no additional cardiac anomaly. The remaining patients displayed various cardiac anomalies, including 17 (17%) with mild mitral regurgitation, 13 (13%) with enlargement of the ascending aorta, 7 (7%) with coarctation of the aorta, 6 (6%) with atrial septal defect, 6 (6%) with trace mitral valve prolapse accompanied by mild mitral regurgitation, 3 (3%) with enlargement of the ascending aorta coupled with mild mitral regurgitation, 2 (2%) with ventricular septal defect, 2 (2%) with atrial septal defect accompanied by mild mitral regurgitation, 2 (2%) with ventricular septal defect and enlargement of the ascending aorta, and 1 (1%) with mitral valve prolapse.

In 46.9% of the 32 BAV types resulting from the fusion of the right and non-coronary cusps, no additional cardiac anomaly was observed. Among the remaining patients, 21.9% had trace mitral regurgitation, 12.5% had an enlargement of the ascending aorta, 9.4% had an enlargement of the ascending aorta with trace mitral regurgitation, 3.1% had coarctation of the aorta, 3.1% had mitral valve prolapse with trace mitral regurgitation, and both mitral valve prolapse and ventricular septal defect were observed in 3.1% of the patients.

In the subset of patients with BAV lacking a raphe, cardiac anomalies were absent in a majority of cases (61.5%, n=8 out of 13). However, in the remaining patients, various concomitant congenital heart diseases were present, including ventricular septal defect (15.4%, n=2), coarctation of the aorta (7.7%, n=1), enlargement of the ascending aorta (7.7%, n=1), and a combination of trace mitral regurgitation and enlargement of the ascending aorta (7.7%, n=1). Among the two BAV types characterized by left-noncoronary leaflet fusion, one displayed trace mitral regurgitation while the other exhibited enlargement of the ascending aorta. Upon statistical analysis, no significant differences were observed between the groups in terms of concomitant congenital heart diseases (p: 0.320).

Correlation between Aortic Root and Ascending Aorta Measurements And Other Parameters

A positive correlation was discovered between the diameters of the aortic root and ascending aorta and various patient factors, including age, weight, height, as well as systolic and diastolic blood pressures in BAV patients as depicted in **Table 2**.

In order to determine the independent variables influencing aortic anulus, sinus Valsalva, sinotubuler junction, and ascending aorta in patients with BAV, a multiple regression analysis model was utilized. Furthermore, a multiple stepwise regression was conducted to reveal the distinct contributions of sex, age, systolic blood pressure, and aortic valve morphology groups. The independent variables found to impact aortic anulus were weight (β=0.205, p=0.032, adjusted R square 0.670, Confidence Interval 0.004-0.081) and height (β=0.637, p <0.0001, Confidence Interval 0.052-0.096). The age (β=0.302, p=0.025, adjusted R square 0.617, Confidence Interval 0.004-0.052) and height (β=0.501, p <0.0001, Confidence Interval 0.038-0.123) were the independent variables for sinus valsalva. Similarly, weight (β=0.298, p=0.007, adjusted R square 0.574, Confidence Interval 0.041-0.104) and height (β=0.490, p<0.0001, Confidence Interval 0.022-0.134) were the independent variables for sinotubuler junction. The independent variables for ascending aorta were age (β=0.313, p=0.032, adjusted R square 0.548, Confidence Interval 0.003-0.064) and height (β=0.446, p=0.002, Confidence Interval 0.030-0.138).

Table 2. The Pearson correlation analysis of a cohort of 145 patients with bicuspid aortic valve, showing the relationship between multiple parameters and measurements of the aortic root and ascending aorta

Variable	r	p
Aortic anulus		
Sex	0.125	0.135
Age	0.770	<0.0001
Weight	0.754	<0.0001
Height	0.815	<0.0001
Systolic Blood Pressure	0.573	<0.0001
Diastolic Blood Pressure	0.465	<0.0001
Sinus valsalva	0.866	<0.0001
Sinotubular Junction	0.853	<0.0001
Ascending aorta	0.767	<0.0001
Sinus valsalva		
Sex	0.092	0.271
Age	0.766	<0.0001
Weight	0.707	<0.0001
Height	0.781	<0.0001
Systolic Blood Pressure	0.507	<0.0001
Diastolic Blood Pressure	0.396	<0.0001
Sinotubular Junction	0.900	<0.0001
Ascending aorta	0.761	<0.0001
Sinutubular junction		
Sex	0.093	0.268
Age	0.744	<0.0001
Weight	0.732	<0.0001
Height	0.758	<0.0001
Systolic Blood Pressure	0.527	<0.0001
Diastolic Blood Pressure	0.491	<0.0001
Aurtic anulus	0.853	<0.0001
Sinus Valsalva	0.900	<0.0001
Ascending aorta	0.864	<0.0001
Ascending aorta		
Sex	0.095	0.26
Age	0.719	<0.0001
Weight	0.685	<0.0001
Height	0.734	<0.0001
Systolic Blood Pressure	0.559	<0.0001
Diastolic Blood Pressure	0.497	<0.0001
Aortic anulus	0.767	<0.0001
Sinus Valsalva	0.761	<0.0001
Sinotubular Junction	0.864	<0.0001

DISCUSSION

This prospective investigation proffers evidence demonstrating the commensurability of the frequency of BAV with that reported in the literature. Furthermore, the study ascertained that the incidence of BAV was more prominent among males. The most frequently detected aortic valve morphology type amongst patients with BAV was observed to be the fusion of the left and right coronary cusps fusion type. Our study evinced that the aortic annulus and sinotubular junction diameter of the right-noncoronary cusp fusion type cohort was significantly higher in a statistical sense than those of the other groups. Additionally, we demonstrated that aortic valve dysfunction was markedly more frequent in the right-noncoronary cusp fusion type group relative to the other aortic valve morphologic groups. Age, weight, and height were also independent prognosticators of aortic root and ascending aortic diameters in children with BAV, as was discovered.

The estimated occurrence of BAV among the general population is 1-2%, with a noticeable male predominance reflected in a sex ratio of 3:1. Nistri et al.[9] expounded upon a comprehensive register of echocardiographic investigations that were conducted during the military screening of 20,946 young men in the northeastern region of Italy. Correspondingly, they were able to detect BAV in 0.8% of the subjects. Furthermore, Basso et al.[10] documented an echocardiographic frequency of 0.5% in children.[9,10] It is estimated that the frequency of BAV in first-degree relatives of individuals diagnosed with BAV is 8-10%.[11,12] In our investigation, the frequency of BAV was determined to be within the range reported in the literature, with a prevalence of 1.4%. Our study also revealed that the frequency of BAV was 2.6 times higher in males as compared to females, which corresponds to previous research findings.

The 2014 guidelines published by the American Heart Association/American College of Cardiology and European Society of Cardiology recommended the implementation of echocardiographic screening for first-degree relatives of patients with BAV. However, limited data from relatively small studies have investigated the effectiveness of familial screening for first-degree relatives of patients with BAV and have reported conflicting outcomes. Recently, Massardier et al. conducted a study revealing that the prevalence of BAV was 6.6% among first-degree relatives of patients with BAV.[11] In our study, although not all first-degree relatives of patients with BAV underwent echocardiographic screening, the diagnosis of BAV was confirmed in 12 individuals who presented to us. Although we cannot draw definitive conclusions based on these findings, it remains crucial to perform echocardiographic examinations for first-degree relatives of patients with BAV.

Consanguinity is recognized to concentrate autosomal recessive genes in the offspring, however, the contribution of these genes to the heritability of cardiac malformations remains incompletely comprehended.[13] Konya, situated in Central Anatolia, has been reported to have a consanguineous marriage rate of about 22%.[14] In the family history of 33 (21.7%) of the parents of BAV patients, there was consanguinity of the first and second degree. Our study's findings demonstrate a notably higher proportion of parental first-cousin marriage among patients with BAV.

Some patients who have BAV are diagnosed based on the presence of a murmur, while others may experience symptoms as a result of valvular dysfunction. There are also cases where the condition may remain unnoticed until adulthood, potentially leading to sudden death or severe

cardiovascular deterioration due to aortic dissection or rupture.[15] In our research, we observed that individuals with BAV presented with varying complaints at differing frequencies. Specifically, approximately 16% of patients had a murmur, 13% had malnutrition, and 11% had short stature. In the realm of medical diagnosis, BAV may present itself as an independent lesion or in conjunction with certain genetic syndromes, such as Turner syndrome, as noted in previous research.[16] Our current study reveals that 5.2% of patients afflicted with BAV also exhibit co-occurring syndromes.

The phenomenon of right-left cusp fusion is well established as being more prevalent, occurring in approximately 70% of cases, when compared to right-noncoronary fusion. Conversely, left-noncoronary fusion is noted to be the least common.[5] Our study aligns with existing literature, as the overwhelmingly dominant BAV type found in patients with BAV is the fusion of the left and right coronary cusps, accounting for 68% of cases.

The presence of BAV has been linked to early onset of valvular dysfunction and dilation of the proximal aorta, which exhibits high heterogeneity.[17] Previous literature has suggested that the diverse subtypes of BAV cusp fusion morphology may be correlated with varying degrees and levels of aortic dilatation, consequently having a differential impact on treatment and prognosis. Patients with fusion of the left coronary cusp and right coronary cusp commonly experience dilatation of the ascending aorta, in addition to aortic root dilation. Conversely, individuals with fusion of the right coronary and noncoronary cusps rarely exhibit aortic root dilation, with the ascending aorta being the primary area of concern. However, the current data is insufficient to establish the strength of the aforementioned relationships. A recent meta-analysis has demonstrated that the morphology of right and left cusp fusion in BAV is positively associated with a larger aortic diameter at the level of the sinuses of Valsalva. However, no significant impact was observed on the differences in ascending aorta diameter between the two most common BAV subtypes.[18] In our study, we have identified that the aortic annulus diameter of the right-noncoronary cusps fusion type group is significantly higher than that of the type fusion of the left and right coronary cusps group. Additionally, the sinotubular junction diameter of the right-noncoronary cusps fusion type group is significantly higher than that of the BAV without raphe group. Furthermore, our findings have revealed that the ascending aorta diameter of the right-noncoronary cusps fusion type group is significantly higher than that of the type fusion of the left and right coronary cusps group. In a study conducted by Gurvitz et al. encompassing 80 cases, it was demonstrated that the augmentation of aortic root sizes corresponded with an increase in height and body surface area rather than age.[19] Additionally, another study showed that a significant correlation existed between height, weight, body surface area, aortic root, and clinical parameters.[20] Our investigation found a favorable correlation between the dimensions of the aortic root and ascending aorta and various factors such as age, weight, height, systolic and diastolic blood pressures in BAV patients. Our study further established that age, weight, and height were autonomous predictors of aortic root and ascending aortic diameters, emphasizing the relevance of utilizing z-score values.

Previous research has indicated that the prevalence of valve dysfunction is greater in individuals with the right-left valve phenotype, characterized by the fusion of the right and left coronary cusps, while aneurysm of the ascending aorta is more common in those with the right-non-coronary cusps phenotype, characterized by the fusion of the right and non-coronary cusps, in cases of BAV.[15] A more recent study conducted by Blais et al. found that there was no significant difference in the rate of proximal aorta dilatation between various leaflet fusion patterns. However, it was observed that the fusion of the right and non-coronary cusps and complex fusion types tended to be associated with a greater proportion of children exhibiting more than mild aortic valve dysfunction.[21] A recent meta-analysis has demonstrated that patients with BAV who have fused right and left cusps are prone to develop AR, while those with fused right and non-coronary cusps are more likely to develop AS.[22] Moreover, Ward et al. have revealed that aortic valve insufficiency and stenosis are more prevalent in patients with fused right and non-coronary cusps. In their investigation, the median aortic sinus z score was higher in patients with fused left and right coronary cusps than in those with fused right and non-coronary cusps.[23] However, there were no significant differences in the median ascending aorta z score between the groups. Furthermore, we have found that aortic valve dysfunction is significantly more common in patients with fused right-noncoronary cusp than the other morphologic groups of aortic valve.

The heterogeneity of our study group should be acknowledged, as we opted to incorporate all patients diagnosed with BAV in our analysis. However, we aim to carry out a subsequent investigation on this topic, where we will expand our patient sample size.

CONCLUSION

In our investigation, it was demonstrated that the frequency of children with BAV was preponderant in males, with a rate similar to that which has been documented in the literature. Additionally, the most prevalent aortic valve morphology was identified as type fusion of the left and right coronary cusps. Our data revealed that aortic root and ascending aorta measurements, as well as aortic valve dysfunction, were more elevated in the right-noncoronary cusps fusion type than in other aortic valve types. Furthermore, age, weight, and height were established as independent predictors of aortic root and ascending aorta measurements. We recommend that the exactitude of our findings can be disclosed through longitudinal studies involving a substantial cohort on this matter.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocols were approved by our hospital's ethics committee (approval number 2017/294)

Informed Consent: All participants included in the study signed the Informed Consent Form.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Original Article / Orijinal Araştırma

Investigation of the Relationship between Compassion Fatigue and Psychological Well-Being Levels of Midwives and Nurses Working in a Children's Clinic

Çocuk Kliniğinde Çalışan Ebe ve Hemşirelerin Merhamet Yorgunluğu ve Psikolojik İyi Oluş Düzeyleri Arasındaki İlişkinin İncelenmesi

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Abstract

Aim: This study was conducted to examine the relationship between compassion fatigue and psychological well-being levels of midwives and nurses working in pediatric clinics of a public hospital.

Material and Method: The sample of the study consisted of midwives and nurses actively working in pediatric clinics of a public hospital in Istanbul (Participation Rate: 91.66%). Data were collected with the "Introductory Information Form", "Compassion Fatigue Brief Scale (CFBS)" and "Psychological Well-Being Scale (PWBS)". Descriptive statistics, Mann Whitney U and Kruskal Wallis Test were used to evaluate the data.

Results: The mean age of the midwives and nurses who participated in the study was 26.92+3.96 years. It was determined that 62.7% of the midwives and nurses had been working in the pediatric clinic for 1-3 years, 52.7% of them were partially satisfied with the clinic where they worked, and 79.1% of them were affected by the clinical condition of the patient they cared for. The mean CFBS score of the participants was 70.41+18.00, while the mean PWBS score was 42.51+6.47. In the study, it was determined that the income status and duration of professional experience of midwives and nurses significantly affected their psychological well-being, and their willingness to choose the profession and the way they work significantly affected their levels of compassion fatigue and psychological well-being. It was determined that the number of patients cared by the employees in a shift significantly differentiated the level of compassion fatigue. There was no significant relationship between the levels of compassion fatigue and psychological well-being of midwives and nurses in the pediatric clinic.

Conclusion: In line with the findings of the study, it was determined that the levels of compassion fatigue and psychological well-being of the participants were differentiated by many variables related to working conditions. It is recommended that qualitative and quantitative studies should be conducted to periodically evaluate the compassion fatigue of midwives and nurses working in pediatric clinics and to determine the causes of compassion fatigue and coping strategies.

Keywords: Pediatric clinic, midwife, nurse, compassion fatigue, psychological well-being

Öz

Amaç: Bu çalışma bir kamu hastanesinin çocuk kliniklerinde çalışan ebe ve hemşirelerin merhamet yorgunluğu ve psikolojik iyi oluş düzeyleri arasındaki ilişkinin incelenmesi amacı ile yürütülmüştür.

Gereç ve Yöntem: Çalışmanın örneklemini İstanbul'da bir kamu hastanesi çocuk kliniklerinde aktif görev yapan ebe ve hemşireler oluşturmuştur (Katılım Oranı: %91,66). Veriler; "Tanıtıcı Bilgi Formu", "Merhamet Yorgunluğu Kısa Ölçeği (MYKÖ)" ve "Psikolojik İyi Oluş Ölçeği (PİOÖ)" ile toplanmıştır. Verilerin değerlendirilmesinde tanımlayıcı istatistikler, Mann Whitney U ve Kruskal Wallis Testi kullanılmıştır.

Bulgular: Çalışmaya katılan ebe ve hemşirelerin yaş ortalaması 26,92+3,96 olarak saptandı. Ebe ve hemşirelerin; %62,7'sinin 1-3 yıldır pediatri kliniğinde çalıştığı, %52,7'inin çalıştığı klinikten kısmen memnun olduğu ve %79,1'sinin ise bakım verdikleri hastanın klinik durumunun çalışma motivasyonlarını etkilediği belirlendi. Katılımcıların MYKÖ puan ortalaması 70,41+18,00 iken, PİOÖ puan ortalaması 42,51+6,47 olarak bulundu. Çalışmada ebe ve hemşirelerin gelir durumu ve mesleki deneyim sürelerinin psikolojik iyi oluş durumlarını, mesleği isteyerek tercih etme durumu ve çalışma şekilleri ise merhamet yorgunluğu ve psikolojik iyi oluş düzeylerini anlamlı olarak etkilediği belirlendi. Çalışanların bir vardiyada baktıkları hasta sayısının merhamet yorgunluğu düzeyini anlamlı olarak farklılaştırdığı saptandı. Çocuk kliniğinde ebe ve hemşirelerin merhamet yoğunluğu düzeyleri ile psikolojik iyi oluş durumları arasında anlamlı bir ilişki saptanmadı.

Sonuç: Çalışma bulguları doğrultusunda, katılımcıların merhamet yorgunluğu ve psikolojik iyi oluş düzeylerinin çalışma koşullarına ait pek çok değişken tarafından farklılaştığı saptanmıştır. Çocuk kliniklerinde çalışan ebe ve hemşirelerin periyodik olarak merhamet yorgunluğunun değerlendirilmesi, merhamet yorgunluğu düzeyinin nedenleri ve baş etme stratejilerinin belirlenmesi için ise nitel ve nicel desende çalışmalar yapılması önerilmektedir.

Anahtar Kelimeler: Çocuk kliniği, ebe, hemşire, merhamet yorgunluğu, psikolojik iyi oluş

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INTRODUCTION

Compassion fatigue affects the physical and psychological health and performance of healthcare providers and thus the quality of patient care. Compassion fatigue is different from "burnout". It can manifest itself with symptoms such as insensitivity, hopelessness, irritability and restlessness. This condition may occur when combined with stress factors such as intense workload, long working hours, severe patient conditions, shift work system and patient deaths.[1,2] It is defined as a healthcare worker's repeated exposure to patients' suffering and decreased care capacity as a result of knowledge of the patient's traumatic experiences and may affect the psychological state.[3]

In a study, it was reported that the occurrence of compassion fatigue in midwives and nurses who help suffering, traumatized people and provide health care is a natural end and 25% to 50% of health professionals show symptoms of compassion fatigue.[4] In a study conducted in pediatric nurses in the USA, it was found that 51% of nurses were in the medium risk and 27.2% in the high risk group in terms of compassion fatigue.[5] In other studies, it was found that nurses working with deceased or traumatically injured children had a higher risk of compassion fatigue.[6,7] In addition, midwives and nurses with compassion fatigue are more likely to make erroneous decisions, inattention and insensitivity to patients.

Psychological well-being includes positive states such as emotional satisfaction and the ability to maintain balance between positive or negative life events. Psychological well-being, which enables the person to be psychologically well, especially in overcoming situations with traumatic consequences, also functions to protect mental health.[4,5]

Assessing compassion fatigue and psychological well-being of midwives and nurses working in pediatric clinics is of great importance both for their own health, motivation and performance and for the quality of health services and patient safety. Therefore, this study was conducted to examine the compassion fatigue and psychological well-being of midwives and nurses working in the pediatric clinic of a public hospital in Istanbul. In addition, the results of the study are aimed to provide important data in terms of developing and improving the quality of patient care, creating methods and coping strategies to reduce compassion fatigue, protecting health personnel from long-term health problems and increasing professional satisfaction.

MATERIAL AND METHOD

Population and Sample of the Study

The study, which was planned in a descriptive design, was conducted between September 2023- October 2023 dates. The population consisted of midwives and nurses actively working in pediatric clinics in a public hospital in Istanbul. In determining the sample group, Berger et al.[7] The findings of the study conducted by was used and the frequency of compassion fatigue (27.6%) was taken into account. In calculating the sample size, the frequency of occurrence of the event was calculated by using the formula used to calculate the number of individuals to be sampled in cases where the population was known. In the formula, the confidence level is accepted as 95% and the deviation is d = 0.05. The minimum sample size of the research was calculated as 92, and 110 midwives and nurses who volunteered to participate in the research constituted the sample of the research (Participation rate: 91.66%). The criteria for inclusion in the sample included being a midwife and nurse actively working in pediatric clinics for at least 1 year and volunteering to participate in the study.

Data Collection Tools

The data were collected using the "Introductory Information Form", "Compassion Fatigue Short Scale" and "Psychological Well-Being Scale" created by the researchers.

Introductory information form: The form, which was developed by the researchers in line with the literature, includes questions evaluating the sociodemographic characteristics (marital status, age, educational status, etc.) and professional working conditions of midwives and nurses.

Compassion fatigue brief scale (CFBS): The scale was developed by Adams et al. in 2006 to measure the level of compassion fatigue in individuals. The scale was adapted into Turkish by Dinç and Ekinci in 2018. The Likert-type scale consists of 13 items. A minimum score of 13 and a maximum score of 130 can be obtained from the scale, and the increase in the total score obtained from the scale indicates that the level of compassion fatigue experienced by individuals increases. The Cronbach's alpha coefficient of the scale was calculated as 0.87.[8] For the sample of this study, Cronbach's alpha value was found to be 0.85.

Psychological well-being scale (PWBS): The scale developed by Diener et al. consists of 8 items. It was adapted into Turkish by Telef. A minimum score of 8 and a maximum score of 56 can be obtained from the seven-point Likert-type scale. A high total score indicates that the person has many psychological resources and strengths. Cronbach's alpha coefficient of the scale was calculated as 0.87.[9] For the sample of this study, Cronbach's alpha value was found to be 0.82.

Data Evaluation

The research data were evaluated in SPSS 16.0 (Statistical Package for Social Science) package program. Descriptive statistics, Mann Whitney U and Kruskal Wallis Test analysis were used in the evaluation of the data. Post-Hoc Bonferroni test was applied to reveal the group or groups that created the difference. Internal consistency analysis (Cronbach Alpha) was performed. The statistical significance level of the data was accepted as $p<0.05$.

Ethical Principles of the Study

Ethics committee approval was obtained from the Scientific Research Ethics Committee of a public university to conduct the research (Number: 21300, Date: 11.09.2023). In all stages of the study, the rules in the Declaration of Helsinki were followed. Midwives who volunteered to participate in the study were informed about the study and informed consent was obtained.

RESULTS

Table 1 shows the findings related to the descriptive characteristics of midwives and nurses. It was determined that the mean age of the midwives and nurses participating in the study was 26.92+3.96, 77% were single, 84.5% did not have children and 76.4% were undergraduate graduates.

Table 1. Findings regarding the descriptive characteristics of midwives and nurses (n=110)

		x̄±SS	Min.	Max.
Age		26.92+3.96	23	49
			n	%
Marital status	Married		33	30
	Single		77	70
Child Presence	Yes		17	15.5
	No		93	84.5
Income status	Income is less than expenses		21	19.1
	Income equals expenses		77	70
	Income exceeds expenses		12	10.9
Education level	Licence		84	76.4
	Postgraduate		26	23.6
Presence of Chronic Disease	Yes		9	8.2
	No		101	91.8
Smoking Status	Yes		57	51.8
	No		53	48.2
Alcohol Consumption Status	Yes		29	26.4
	No		81	73.6
Situation of Choosing the Profession Willingly	Yes		82	74.5
	No		28	25.5

Table 2 contains the findings regarding the professional experiences of midwives and nurses.

Table 2. Findings regarding the professional experiences of midwives and nurses (n=110)

		n	%
Working time in the pediatric clinic	1-3 years	69	62.7
	4-6 years	24	21.8
	7 years and above	17	15.5
Satisfaction with the clinic you work in	Yes	23	20.9
	No	29	26.4
	Partially	58	52.7
Average number of patients seen in a shift	1-3	62	56.4
	4-6	21	19.1
	6 and above	27	24.5
The clinical condition of the patients receiving care affects their motivation to work.	Yes	87	79.1
	No	6	5.5
	Partially	17	15.5
Receiving psychological support due to working conditions	Yes	17	15.5
	No	93	84.5
Empathy with the patients being cared for	Yes	70	63.6
	No	5	4.5
	Partially	35	31.8
Duration of professional experience	1-3 years	40	36.4
	4-6 years	42	38.2
	7 years and above	28	25.5
How it works	Daytime Weighted	12	10.9
	Night Predominant	37	33.6
	in shifts	61	55.5
Average working hours per month	40 hours	7	6.4
	Between 40-50 hours	19	17.3
	more than 50 hours	84	76.4

Midwives and nurses participating in the study; It was determined that 62.7% of them had been working in a pediatric clinic for 1-3 years and 52.7% were partially satisfied with the clinic they worked in. Participants; It was determined that 56.4% of them cared for an average of 1-3 patients in a shift, and 79.1% of them thought that the clinical condition of the patients they cared for affected their motivation to work. Midwives and nurses; It was determined that 76.4% of them worked more than 50 hours on average per month. Midwives and nurses; It was determined that 15.5% received psychological support due to their working conditions and 63.6% empathized with the patients they cared for.

Scale total score averages of the participants; Compassion Fatigue Brief Scale was determined as 70.41+18.00, and Psychological Well-Being Scale was determined as 42.51+6.47.

The variables of satisfaction status and number of patients cared for in a shift were found to significantly affect the mean scores of the CFBS (z:-3.870, p=0.000; z:-2.714, p=0.007; z:-6.691, p=0.035; z:21.472, p=0.000; z:8.164, p=0.017) (**Table 3**).

Table 3. Comparison of the Compassion Fatigue Brief Scale and Psychological Well-Being Scale Average Score of Midwives and Nurses According to Their Descriptive and Professional Characteristics

	CFBS	PWBS
Marital status		
Married	62.48+16.64	42.18+6.28
Single	73.81+17.58	42.66+6.59
	U:-3.870, p:.000	U:-.559, p:.576
Child presence		
Yes	61.41+20.06	44.00+6.27
No	72.06+17.21	42.24+6.51
	U:-2.714, p:.007	U:-.833, p:.405
Income status		
Income is less than expenses	71.04+17.73	37.09+6.74
Income equals expenses	70.62+17.32	43.96+5.56
Income exceeds expenses	68.00+23.64	42.75+6.92
	KW:.485, p:.785	KW:15.358, p:.000
Education level		
Licence	69.54+18.33	41.76+6.59
Postgraduate	73.23+16.94	44.96+5.52
	U:-1.278, p:.201	U:-2.090, p:.037
Situation of choosing the profession willingly		
Yes	67.63+17.87	43.53+5.90
No	78.57+16.05	39.53+7.22
	U:-2.564, p:.010	U:-2.392, p:.017
Duration Of Professional Experience		
1-3 year	71.22+20.64	43.86+6.50
4-6 year	71.63+13.70	42.29+6.09
7 year and above	70.41+18.00	40.27+6.76
	KW:2.410, p:.300	KW:6.198, p:.045
How it works		
Daytime Weighted	60.33+14.71	42.08+6.48
Night Predominant	79.37+12.15	45.97+5.78
in shifts	66.96+19.45	40.50+6.07
	KW:18.901, p:.000	KW:21.124, p:.000
Working time in the pediatric clinic		
1-3 year	71.29+16.52	43.44+6.14
4-6 year	75.47+17.20	40.39+6.93
7 year and above	58.46+21.77	41.33+6.81
	KW:6.691, p:.035	KW:5.193, p:.075
Satisfaction with the clinic you work in		
Yes	57.04+17.17	43.43+5.63
No	80.24+13.55	42.10+7.98
Partially	70.81+17.15	42.36+6.01
	KW:21.472, p:.000	KW:.280, p:.869
Average number of patients seen in a shift		
1-3	74.48+16.15	43.66+5.75
4-6	67.57+16.03	40.52+8.00
6 and above	63.29+21.22	41.44+6.44
	KW:8.164, p:.017	KW:4.499, p:.105
Empathy with the patients being cared for		
Yes	71.42+17.26	42.52+6.65
No	55.60+26.10	41.80+6.61
Partially	70.51+17.88	42.60+6.27
	KW:2.498, p:.287	KW:.124, p:.940

U:Mann Whitney U Test, KW: Kruskal Wallis Test, p:SignificanceValue

It was found that income status, educational level and duration of professional experience had a significant effect on the mean scores of the PWBS (z:15,357, p=0,000; z:-2,090, p=0,037; z:6,198, p=0,045, respectively). In addition, it was determined that the status of preferring the profession willingly and the type of work significantly differentiated the mean scores of both the CFBS and the PWBS scale (p<0.05) (**Table 3**).

No significant correlation was found between compassion fatigue levels and psychological well-being of midwives and nurses working in pediatric clinic.

DISCUSSION

In this study, which examined the relationship between compassion fatigue and psychological well-being of midwives and nurses working in the pediatric clinic of a public hospital in Istanbul, it was determined that compassion fatigue was at a moderate level (70.41±18.00) and psychological well-being (42.51±6.47) was above the moderate level. In a similar study conducted by Tanrıkulu and Ceylan with nurses in pediatric clinics, it was found that the participants had high levels of compassion and low levels of compassion fatigue (14.09±8.79).[10] In a study conducted by Mollamehmetoğlu with midwives, while the mean score of compassion fatigue was determined as 63.02±24.20, it was determined that the burnout levels of midwives were high, they did not feel psychologically well, but the rate of receiving professional support for this situation was very low.[11] In a study conducted by Şensoy et al. with health professionals, it was found that their psychological well-being levels were good.[12] In a similar study conducted by Şimşek with healthcare professionals, it was found that the psychological well-being levels of the participants were above average.[13] Similar to the studies in the literature, the results of the study showed that the compassion fatigue of health professionals, especially midwives and nurses, was at a moderate level, and their psychological well-being was evaluated as better than average. It can be said that working conditions, social life and personality traits affect these results and that people can cope with these situations even if they feel professional fatigue.

When the variables affecting compassion fatigue and psychological well-being of midwives and nurses were examined, it was found that the compassion fatigue levels of individuals who were single or did not have children were significantly higher. Similarly, Sacco et al. (2015),[14] in their study with intensive care nurses, found that the level of compassion fatigue was higher in single nurses. However, in a similar study conducted by Mansur et al. it was found that married individuals had higher levels of compassion fatigue.[15] According to our research findings, single individuals who do not have children may tend to spend more hours at work and work overtime because they do not have family responsibilities, may have less support network arising from family life or may tend to establish a stronger emotional bond with their patients, which may cause them to feel the pain of their patients more deeply and experience compassion fatigue at a higher level. It is important that colleagues and managers are sensitive to understand and support the needs of their employees.

When the effect of the variable of choosing the profession was examined, it was found that those who chose the profession willingly had low levels of compassion fatigue and high levels of psychological well-being. This is an expected result. In a similar study conducted by Kelly and colleagues, the compassion fatigue level of health professionals who willingly chose their profession and stated that they loved their profession was found to be low.[16] In a study conducted by Denk, burnout levels and compassion fatigue levels of those who chose their profession willingly were determined to be low.[17] It is known that individuals who choose their profession willingly are more patient with their work, can manage conflicts, remain calm and are conciliatory when necessary. This situation increases professionalism and therefore prevents the person from burnout at a higher level and in a short time, and the level of being negatively affected may be low despite more compassion and empathy arising from the willingness to do the profession. In addition, it can be said that people who feel that they belong to the profession are better at self-actualization and can meet their psychological needs, so they feel better spiritually.[18]

While the duration of professional experience did not have any effect on the level of compassion fatigue, it was found that midwives and nurses with less experience (1-3 years) had higher psychological well-being. Unlike our study findings, it has been reported that increasing professional experience increases psychological resilience and self-confidence.[19-21] It can be said that the fact that midwives and nurses with little experience have fresh desire and interest in the profession, have few negative professional experiences, and have high motivation positively affects their psychological well-being.

When evaluated according to the working style, it was found that midwives and nurses working night shifts had a higher level of compassion fatigue. Night working hours are more than daytime working hours. Therefore, midwives and nurses spend more time with patients, empathize with them and their care time is longer. Intensive work at night may affect circadian rhythm and cause not getting enough and regular sleep and feeling physically and mentally tired. This can affect their ability to show compassion. It can also disrupt the balance between the biological clock and social life, which can lead to emotional imbalances. A combination of these factors may contribute to increased levels of compassion fatigue in nurses working at night. In addition to a decrease in work performance, it can lead to decreased attention, chronic fatigue, and thus reduced tolerance and burnout.[22,23] While working predominantly at night was expected to negatively affect psychological well-being, a positive effect was found. This may be attributed to the fact

that in some periods, patients are stable after a certain time in the clinics at night and can be calmer than during the day, and that individuals can spare time for themselves and socialize in their free time during the day because they work at night.

While it was determined that the duration of working in the pediatric clinic did not affect psychological well-being, compassion fatigue was found to be higher in midwives and nurses working between 4-6 years. In the studies examined, it was found that working time did not affect the level of compassion fatigue.[10,11,24] It is an expected result that midwives and nurses with less experience of working in a pediatric clinic have less compassion fatigue. It can be said that the higher incidence of compassion fatigue in those with more working time is due to depersonalization, workload, responsibilities, emotional commitment and tendency to empathize due to spending more time in the profession. Therefore, it is important to provide regular support, psychological help and rest opportunities to healthcare professionals working in these clinics. The level of compassion fatigue was found to be higher in midwives and nurses who were dissatisfied with the clinic where they worked. This finding suggests that the working environment and job satisfaction have a significant impact on the emotional and psychological health of nurses and midwives. Dissatisfaction can often arise due to various factors such as workload, lack of communication, low level of support, unfair management practices. These negative influences can negatively affect health workers' capacity to show compassion for their work and for patients. Moreover, a constant state of dissatisfaction can lead to emotional exhaustion, low motivation and professional dissatisfaction over time, increasing compassion fatigue. Factors such as a more supportive working environment, better communication, fair management practices and ensuring work-life balance can increase the level of professional satisfaction of health professionals and thus reduce compassion fatigue. It was expected that compassion fatigue would increase as the number of patients cared for in a shift increased in the midwives and nurses participating in the study, but the results of the study showed that compassion fatigue increased as the number of patients cared for decreased. This is thought to be due to the sensitivity of providing excellent care and feeling more responsible as the number of patients decreases.

As a result of the study, no correlation was found between compassion fatigue and psychological well-being. This result shows that there is no direct relationship between compassion fatigue and psychological well-being. Research results show that the relationship between compassion fatigue and psychological well-being is complex and may be under the influence of independent factors. Therefore, more in-depth studies involving more variables are needed to determine the relationship between compassion fatigue and psychological well-being.

CONCLUSION

According to the results of the study, the level of compassion fatigue of midwives and nurses working in pediatric clinics was found to be average, while their psychological well-being was above average. It was determined that the psychological well-being and compassion fatigue levels of midwives and nurses were especially affected by willingly choosing the profession, working predominantly night shifts, having children and working time. There are measures that can be taken at both institutional and individual levels to reduce compassion fatigue in midwives and nurses. Institutional measures include training and awareness programs, fair, transparent and supportive leadership, balancing workload, rest and break arrangements, and units offering psychological support and counseling services. These services can help workers understand and cope with their emotional needs. In addition, healthcare organizations should promote a culture of empathy and respect for workers' feelings. An environment where workers can express their feelings can alleviate their emotional burden.

As for individual measures, social support and communication, stress management and effective relaxation techniques, and making time for hobbies, interests and personal projects can increase individuals' personal fulfillment and life satisfaction. Such positive emotional experiences and effective strategies can play an important role in preventing or reducing compassion fatigue.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained from the Scientific Research Ethics Committee of a public university to conduct the research (Number: 21300, Date: 11.09.2023).

Informed Consent: Midwives who volunteered to participate in the study were informed about the study and informed consent was obtained.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article / Orijinal Araştırma

Relationship between Increased Epicardial Fat Tissue and Aortic Diameter: May be an Indicator of Hypertension Complications

Epikard Yağ Dokusu Artışı ile Aort Çapı Arasındaki İlişki: Hipertansiyon Komplikasyonlarının Göstergesi Olabilir

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Abstract

Aim: Epicardial fat tissue (EFT) refers to the adipose tissue on the myocardium's surface and beneath the visceral pericardium. It participates in the endocrine system as well as the myocardium's energy metabolism. This study aimed to investigate the potential of EFT as a noninvasive marker for hypertension (HT) complications associated with aortic dilatation.

Material and Method: The study's control (CONT) group consisted of 70 patients with normal blood pressure and the HT group consisted of 82 patients with higher blood pressure. EFT was assessed by two-dimensional echocardiography from the parasternal long axis and compared between the CONT and the HT groups.

Results: The EFT thickness in the HT group was considerably higher than in the CONT (5.7±1.9 vs 4.0±1.3, p<0.05). In multivariate regression analysis, white coat blood pressure (p<0.05, 95% CI 0.827-0.935), ejection fraction (p<0.05, 95% CI 1.033-1.495), and EFT (p<0.05, 95% CI 0.413-0.807) were found to be independent variables in the separation of HT and CONT groups. EFT thickness had a sensitivity of 73.2 and a specificity of 57.1% at a cut-off value of 4.15. EFT was significantly correlated with sinus valsalva (r2=0.08, p<0.05), sinotubular junction (r2=0.06, p<0.05), and aorta ascendence diameter (r2=0.07, p<0.05), respectively. EFT among HT subgroups, no differences were identified.

Conclusion: EFT can be a marker revealing an increased risk of HT-related complications.

Keywords: hypertension, morphometry, biomarker, epicardial fat tissue, complications

Öz

Amaç: Epikardiyal yağ dokusu (EFT), miyokardın yüzeyinde ve visseral perikardın altındaki yağ dokusunu ifade eder. Endokrin sisteme ve miyokardın enerji metabolizmasına katılır. Bu çalışma, aort dilatasyonu ile ilişkili hipertansiyon (HT) komplikasyonları için EFT'nin non invaziv bir belirteç olma potansiyelini araştırmayı amaçlamıştır.

Gereç ve Yöntem: Çalışmanın kontrol (CONT) grubunu tansiyonu normal olan 70 hasta, HT grubunu ise tansiyonu yüksek olan 82 hasta oluşturdu. EFT parasternal uzun eksenden iki boyutlu ekokardiyografi ile değerlendirilerek CONT ve HT grupları arasında karşılaştırıldı.

Bulgular: HT grubunda EFT kalınlığı CONT'ye göre oldukça yüksekti (5,7±1,9 vs 4,0±1,3, p<0,05). Çok değişkenli regresyon analizinde ofis kan basıncı (p<0,05, %95 CI 0,827-0,935), ejeksiyon fraksiyonu (p<0,05, %95 CI 1,033-1,495) ve EFT (p<0,05, %95 CI 0,413-0,807) HT ve CONT gruplarının ayrılmasında bağımsız değişkenler olduğu bulunmuştur. EFT kalınlığının duyarlılığı 73,2, özgüllüğü ise 4,15 kesme değerinde %57,1 idi. EFT sırasıyla sinüs valsalva (r2=0.08, p<0.05), sinotubüler bileşke (r2=0.06, p<0.05) ve aort çıkış çapı (r2=0.07, p<0.05) ile anlamlı düzeyde koreleydi. HT alt grupları arasında EFT'de herhangi bir farklılık tespit edilmedi.

Sonuç: EFT, HT ile ilişkili komplikasyon riskinin arttığını ortaya koyan bir belirteç olabilir.

Anahtar Kelimeler: hipertansiyon, morfometri, biyobelirteç, epikardiyal yağ dokusu, komplikasyonlar

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INTRODUCTION

Hypertension (HT) is characterized by a rise in blood pressure. This major public health issue significantly contributes to preventable morbidity and mortality.[1] Salt sensitivity affects 50% to 60% of individuals, who are more likely to develop hypertension (HT).[2] More than half of the population over the age of 60 has HT, and the prevalence rises with age.[3] This means that in 2025 there may be up to 1.5 billion HT patients, an increase of almost 20% from the current number of patients.[4] Additionally, HT alters the tissue's structural and functional properties. For instance, it has an impact on certain vascular structure characteristics. HT causes changes at all levels of circulation, from the large arteries to the microcirculation. Finding these variations can help determine cardiovascular risk. Recent clinical trials have demonstrated that these alterations are reversible, at least when treated with antihypertensive medication.[5] Vascular remodeling brought on by chronically high systemic arterial blood pressure is facilitated by HT-related vascular dysfunction. This mechanism is described as causing changes in all arterial layers, from the endothelium to the perivascular adipose tissue.[6] The structural alteration in HT following the remodeling of the large and small arteries has been studied from a pathophysiological perspective.[7]

Aorta is a vital component of the circulatory system, responsible for distributing oxygenated blood throughout the body. Its unique anatomical structure and elastic properties enable it to regulate blood pressure and ensure a continuous flow of blood to meet the metabolic demands of various tissues and organs.[8] Long-term HT is associated with remodeling of the aortic wall. It can result in structural changes, including increased collagen deposition and alterations in the extracellular matrix, making the aorta less elastic and more susceptible to aortic dilation, as an HT-associated complication.[9]

Moreover, the pathophysiology of critical HT provides insight into circulating biomarkers because they are recognized to help figure out causation, diagnosis, progression, and therapy efficacy.[10] This method can lessen problems and slow the spread of the disease. As a result, all of this data offers a biomarker prediction for the diagnosis of HT-associated complications. As early identification of high-risk patients is advantageous, blood pressure control and other findings may postpone or prevent the start of cardiovascular disease. The involvement of cardiac biomarkers in the prognostic assessment of patients with HT is valuable since they may become aberrant long before the onset of cardiovascular disease.[11] Since current biomarkers have a poor ability to predict future HT risk, it has been suggested that a multi-biomarker technique may be helpful for HT prediction.[12] The development of new, additional biomarkers is crucial in this regard.

EFT is regarded as one of the new anatomical indicators in terms of tissue, even though anatomical magnetic resonance techniques had previously been proposed as a biomarker in neurological investigations.[13] EFT is referred to as the visceral fat depot of the heart and has distinctive anatomical characteristics.[14] Its thickness can be seen and evaluated using echocardiography, which also has minimal costs, easy accessibility, and good reproducibility. The thickness of the EFT on an echocardiogram represents the deposition of myocardial fat and visceral fat inside the trunk. It was found that there may be a connection between HT and EFT accumulation.[15] Therefore, EFT might aid in identifying patients with HT. EFT has been found to be a predictor of adult cardiovascular disease.[16] This study investigated the morphometric, biochemical, blood pressure, and demographic data of HT patients and explored the biomarker of EFT.

MATERIAL AND METHOD

Study Groups

We used file and image records from retrospective archive scanning for our study. Subjects were divided into HT (n=82) and CONT (n=70) groups. The University of Health Sciences ethical committee granted permission to conduct the study (ethics committee number: 22/465).

Demographic and Blood Analysis

Demographic data includes age, weight, pulse, 24-hour monitoring-blood pressure (the result of 24-hour monitoring with blood pressure Holter, day-and-night), instant white coat blood pressure, measurement of EFT thickness, measurement of the perpendicular distance of the echo-free area adjacent to the right ventricular free wall to the right ventricular wall, measurement of the end-diastolic image, measurement of the aortic annulus, measurement of the sinus valsalva, sinotubular junction, measurement of aorta ascending diameters, measurement of end-systolic and end-diastolic diameters of atria and ventricles, measurement of the interventricular septum and left ventricular posterior wall thickness, measurement of mitral E and A waves and E/A ratio, aortic and pulmonary flow rates, pulmonary artery pressure, biochemistry test parameter results, and complete blood count parameters. The left ventricular mass index was calculated according to the Devereux formula,[17] and the ejection fraction was calculated according to Simpson's method.[18] Echo measurements of the left ventricular septum, posterior wall, end-diastolic diameter, end-systolic diameters, and ejection fraction from the parasternal long axis with M-mode were shown in **Figure 1**.

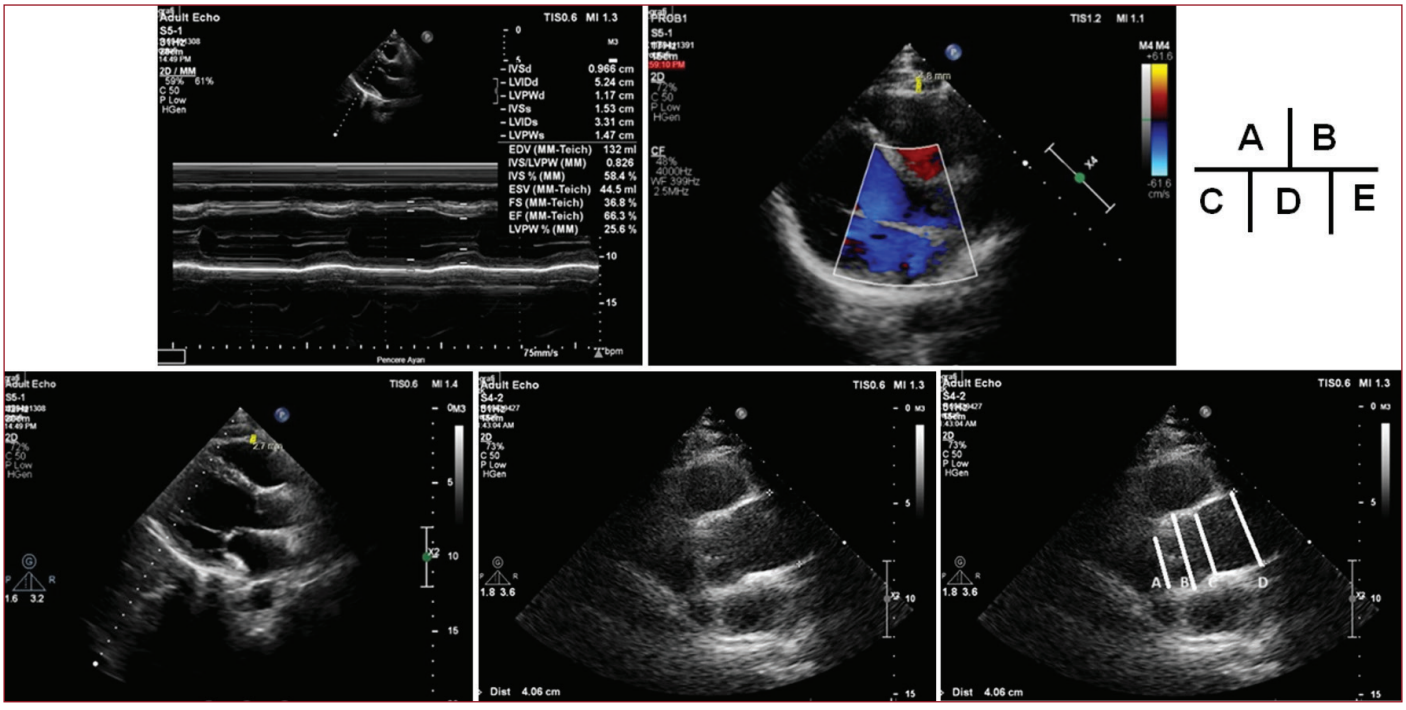

Figure 1. A) Echo measurements of the left ventricular septum, posterior wall, end-diastolic diameter, end-systolic diameters, and ejection fraction from the parasternal long axis with M-mode. B) Measurement of epicardial fat tissue from the parasternal long axis at the level of the aortic valve projection from the RV free wall at the end of diastole. Measured 4.8 mm in the sample. C) Measurement of epicardial fat tissue from the parasternal long axis at the level of the aortic valve projection from the RV free wall at the end of diastole. Measured 2.7 mm in the sample. D) Measurement of the ascending aorta. E) The way of the measurement is shown as below. A: Aortic root; B: Sinus valsalva; C: Sinotubular junction; D: Ascending aorta.

Statistical Analysis

Kolmogorov-Smirnov test was used to determine how the variables were distributed. To analyze the quantitative independent data, independent sample t-test, and Mann-Whitney u-test were utilized. The dependent data were analyzed using the Wilcoxon test and the paired-sample t-test. When analyzing qualitative independent data, the chi-square test was utilized, and the Fischer test was used when the chi-square test requirements were not met. The ROC curve was used to investigate the level and cut-off value. With the use of univariate and multivariate logistic regression, the effect level was examined. Program BMI SPSS 21.1 was used for the analysis.

RESULTS

All study participants who applied to the hospital are listed in **Table 1**. The study's candidates' age range between 18 and 89 years. 65 men (42.8%) and 87 women (57.2%) were the participants in our study. Triglyceride, creatine, uric acid, (C-reactive protein) CRP, (aspartate aminotransferase) AST, and (alanine aminotransferase) ALT were statistically significantly higher in the HT group compared to the CONT group ($p<0.05$). Complete blood count test results showed that the HT group had greater levels of RBC, HGB, HCT, monocytes, and monocytes/HDL than the CONT group ($p<0.05$). HDL value, TSH, and neutrophil count were lower in the HT group than in the CONT group ($p<0.05$) (**Table 1**).

Table 1: Comparison of metabolic variables between hypertension and healthy control groups

Variable	Hypertension (n=82) Mean±SD	Control (n=70) Mean±SD	P-value
Fasting glucose (mg/dL)	118.2±41.8	106.4±18.3	0.306
Creatinine (µmol/L)	0.8±0.2	0.7±0.2	0.000***
eGFR (mL/min/1.73m²)	93.9±16.9	95.6±20.4	0.623
Urea (mmol/L)	30.8±9.9	28.8±9.6	0.150
Uric acid (mg/dL)	6.0±1.6	4.7±1.5	0.000***
CRP (mg/L)	4.7±5.7	3.2±4.4	0.001**
Total cholesterol (mg/dL)	209.0±39.3	212.6±43.9	0.596
HDL cholesterol (mg/dL)	43.1±11.2	53.0±13.4	0.000***
LDL cholesterol (mg/dL)	128.0±32.7	131.6±37.0	0.531
Triglyceride (mg/dL)	189.4±108.2	140.4±60.6	0.002**
HGB (g/dl)	14.3±1.7	13.2±1.7	0.000***
TSH (mIU/L)	1.7±1.2	2.1±1.2	0.038*
Free T4 (pmol/L)	15.9±2.3	16.4±2.3	0.166
AST (U/L)	22.1±9.4	17.2±8.1	0.000***
ALT (U/L)	28.3±19.5	17.1±10.0	0.000***
WBC	7.8±2.0	7.9±2.8	0.897
RBC	5.0±0.6	4.6±0.6	0.000***
Platelets	259.8±64.6	265.1±66.8	0.573
Monocyte	0.618±0.188	0.536±0.183	0.002**
Monocyte / HDL	0.015±0.006	0.011±0.005	0.000***
NLR	2.0±1.1	2.6±2.3	0.306

Abbreviation: SD, Standard deviation; BMI, Body mass index; eGFR, Estimated Glomerular Filtration Rate; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HGB, Hemoglobin; TSH, thyroid stimulating hormone; AST, aspartate aminotransferase; ALT, alanine transaminase; NLR, neutrophil lymphocyte ratio. *p<0.05, **p < 0.01, ***p < 0.001.

Between the HT and CONT groups, the ages of the patients did not significantly differ. In the HT group, there were significantly more male patients than in the CONT group ($p<0.05$). In comparison to the CONT group, the HT group's weight and height were considerably higher ($p<0.05$). The BMI values were not substantially different between groups. In terms of heart rate, there was no discernible difference between the HT and CONT groups. The 24-hour mean systolic pressure in the HT group during white coat, 24-hour day, and 24-hour night was substantially greater than in the CONT group ($p<0.05$). White coat, 24-hour day, 24-hour night, and diastolic pressure in the HT group were substantially higher ($p<0.05$) than in the CONT group. The HT group's HDL, TSH, and MCV levels were considerably lower than those of the CONT group ($p<0.05$). The HT group had significantly higher values for triglycerides, creatinine, uric acid, CRP, AST, ALT, RBC, HGB, HCT, monocyte, eosinophil, and monocyte/HDL ($p<0.05$). Between the HT and CONT groups, there were no appreciable differences in LDL, total cholesterol, fasting glucose, eGFR, urea, sodium, potassium, free T4, WBC, platelet, neutrophil, lymphocyte, basophil, or NLR levels (**Table 2**).

Table 2. Comparison of various data between hypertension and healthy control groups.

Variable	Hypertension Mean±SD	Control Mean±SD	P-value
Age (years)	54.4±14.8	55.0±16.9	0.820
Gender (Male/Female)	53 / 29	12 / 58	0.000***
BMI (kg/m²)	29.7±5.3	28.2±4.7	0.186
Height (m)	1.7±0.1	1.6±0.1	0.000***
Pulse	75.6±12.6	74.1±13.4	0.146
Systolic pressure			
white coat	149.6±19.4	128.4±18.1	0.000***
24 hours of day	147.4±9.3	121.8±6.7	0.000***
24 hours night	139.6±13.3	113.0±13.9	0.000***
24 hours average	145.5±9.4	120.1±6.1	0.000***
Diastolic pressure			
white coat	89.6±10.1	78.5±8.4	0.000***
24 hours of day	90.4±8.9	73.5±6.8	0.000***
24 hours night	81.5±9.9	66.5±7.4	0.000***
24 hours average	88.4±8.6	71.8±6.5	0.000***

Abbreviation: SD, Standard deviation. *p<0.05, ***p < 0.001

The HT group's EFT thickness was substantially greater than the CONT group's ($p<0.05$) (**Figure 2**). Aortic root diameter, sinus valsalva diameter, sinotubular junction diameter, aorta ascendence diameter, left atrium diameter, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, left ventricular posterior wall thickness, interventricular septum thickness, right ventricular end-diastolic diameter, body surface area, left ventricular mass, ejection fraction, pulmonary valve flow rates were significantly higher in the HT group ($p<0.05$). Right atrium end-diastolic diameter, mitral E wave, mitral A wave, mitral E/A, left ventricular mass index, aortic valve flow velocity, and pulmonary arterial pressure did not significantly change. The rates of aortic stenosis, aortic insufficiency, mitral stenosis, mitral insufficiency, tricuspid stenosis, and pulmonary stenosis remained stable (**Table 3**).

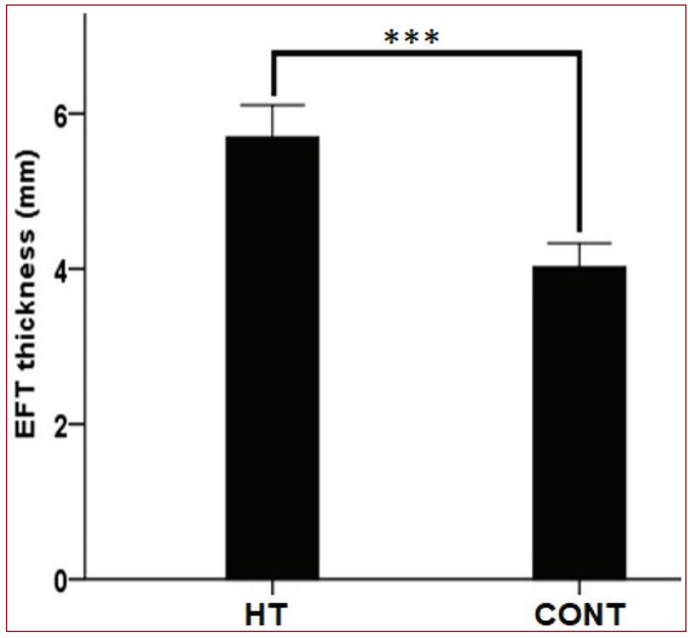

Figure 2. Comparison of epicardial fat tissue thickness between hypertension and control groups. EFT, epicardial fat tissue; HT, hypertension; CONT, control. ***p<0.000.

Table 3: Comparison of hypertension and healthy control in cardiac variables

Variable	Hypertension (n=82) Mean±SD	Control (n=70) Mean±SD	P-value
Left ventricular-end-systolic diameter (mm)	26.5±4.6	24.4±3.9	0.004**
Left ventricular-end-diastolic diameter (mm)	48.4±4.6	45.7±4.2	0.000***
Left ventricular posterior wall thickness (mm)	11.7±1.4	10.3±1.4	0.000***
Interventricular septum thickness (mm)	11.4±1.8	10.2±1.6	0.000***
Left atrium diameter (mm)	36.8±5.0	33.7±4.7	0.000***
Right atrium-end-diastolic diameter (mm)	33.7±4.4	32.2±5.0	0.050
Right ventricular-end-diastolic diameter (mm)	30.2±4.4	28.9±4.7	0.040*
Aortic ascending diameter (mm)	34.1±4.1	32.4±4.4	0.013*
Aortic root diameter (mm)	20.6±2.5	19.8±2.1	0.032*
Sinus valsalva diameter (mm)	36.9±4.2	34.9±4.5	0.002**
Sinotubular junction diameter (mm)	32.5±3.9	31.2±4.3	0.047*
Body surface area	1.99±0.39	1.65±0.28	0.000***
Ejection fraction (%)	61.2±3.6	62.8±2.5	0.006**
Aortic valve flow rate	1.37±0.13	1.40±0.17	0.473
Pulmonary valve flow rate	1.02±0.17	0.98±0.17	0.014*
Pulmonary arterial pressure (mm Hg)	19.1±5.5	19.7±5.7	0569
Epicardial fat tissue thickness (mm)	5.7±1.9	4.0±1.3	0.000***
Aortic stenosis	0 (0.0%)	0 (0.0%)	1.000
Aortic insufficiency	10 (12.2%)	12 (17.1%)	0.387
Mitral A-wave (m/s)	0.80±0.24	0.74±0.21	0.155
Mitral E-wave (m/s)	0.78±0.25	0.78±0.21	0.710
Mitral E/A-wave ratio	1.04±0.40	1.13±0.42	0.114

Abbreviation: SD, Standard deviation. *p<0.05, **p < 0.01, ***p < 0.001.

Gender, size, and white coat, diastolic 24-hour day, diastolic 24-hour night, and diastolic 24-hour mean are all terms used to describe the systolic white coat. To distinguish between the groups with and without HT, the univariate model's mean values were investigated. Measurements were made for HDL, triglycerides, creatinine, uric acid, AST, ALT, RBC, HGB, HCT, monocyte, monocyte/HDL, and EFT thickness. Additionally, the aortic root diameter, sinus valsalva diameter, sinotubular junction diameter, aorta ascendence diameter, left atrium diameter, left ventricular end-diastolic diameter, left ventricular posterior wall thickness, and interventricular septum thickness was measured. The efficiency of body surface area left ventricular mass, and ejection fraction were also significantly high (p<0.05). In the multivariate model, a significant independent efficacy of sex, diastolic white coat, HDL, EFT thickness, and ejection fraction was observed in the groups with and without HT (p<0.05) (**Table 4**). Gender, weight, white coat, systolic 24-hour day, systolic 24-hour night, systolic 24-hour mean, diastolic 24-hour day, diastolic 24-hour night, diastolic 24-hour mean, HDL, triglyceride, creatinine, uric acid, AST, ALT, RBC, HGB, HCT, eosinophil, MCV, CRP, TSH, monocyte, monocyte/HDL, EFT thickness, aortic root diameter, sinus valsalva diameter, sinotubular junction diameter, aorta ascendence diameter, left atrium diameter, left ventricular end-diastolic diameter, left ventricular posterior wall thickness, interventricular septum thickness, body surface area, left ventricular mass, and ejection fraction significant effectiveness was observed (p<0.05) (**Table 5**).

Table 4. Analysis of data with univariate and multivariate model

	Univariate Model			Multivariate Model		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Gender	0.113	0.052-0.244	0.000***	0.194	0.069-0.548	0.002**
Weight	0.920	0.888-0.953	0.000***			
white coat (Systolic)	0.944	0.925-0.964	0.000***			
24 hours day (Systolic)	0.000	0.000-	0.975			
24 hours night (Systolic)	0.741	0.669-0.821	0.000***			
24 hours average (Systolic)	0.001	0.000->100	0.985			
white coat (Diastolic)	0.881	0.843-0.921	0.000***	0.879	0.827-0.935	0.000***
24 hours day (Diastolic)	0.749	0.682-0.822	0.000***			
24 hours night (Diastolic)	0.825	0.778-0.875	0.000***			
24 hours average (Diastolic)	0.737	0.668-0.813	0.000***			
HDL	1.071	1.037-1.106	0.000***	1.056	1.014-1.100	0.009**
Triglyceride	0.992	0.988-0.997	0.002**			
Creatinine	0.035	0.005-0.264	0.001**			
Uric acid	0.626	0.504-0.777	0.000***			
Subordinate	0.925	0.880-0.972	0.002**			
Lower	0.922	0.888-0.958	0.000***			
RBC	0.300	0.161-0.558	0.000***			
HGB	0.668	0.541-0.826	0.000***			
HCT	0.861	0.795-0.933	0.000***			
Monocyte	0.081	0.012-0.552	0.010*			
Monocyte / HDL	0.000	0.000-0.000	0.000***			
EFT thickness	0.529	0.412-0.679	0.000***	0.577	0.413-0.807	0.001**
Aortic root diameter	0.853	0.736-0.988	0.034*			
Sinus valsalva diameter	0.887	0.814-0.966	0.006**			
Sinotubular junction diameter	0.919	0.846-0.999	0.048*			
Aortic ascendance diameter	0.909	0.838-0.986	0.021*			
Left atrium diameter	0.871	0.809-0.939	0.000***			
Left ventricular end-systolic diameter	0.888	0.816-0.965	0.005**			
Left ventricular end-diastolic diameter	0.867	0.800-0.941	0.001**			
Left ventricular posterior wall thickness	0.475	0.352-0.640	0.000***			
Interventricular septum thickness	0.633	0.507-0.789	0.000***			
Body surface area	0.024	0.006-0.099	0.000***			
Left ventricular mass	0.981	0.973-0.989	0.000***			
Ejection fraction	1.187	1.056-1.335	0.004**	1.924	1.033-1.495	0.021*

Logistic Regression (Forward LR), Odds Ratio (OR), Confidence Interval (CI)

Table 5. Evaluation of data by ROC analysis to differentiate patients with hypertension.

	Area under the curve	95% CI	p value
Gender	0.737	0.657-0.818	0.000
Weight	0.747	0.668-0.826	0.000
white coat (Systolic)	0.783	0.709-0.856	0.000
24 hours day (Systolic)	1.000	1.000-1.000	0.000
24 hours night (Systolic)	0.791	0.721-0.861	0.000
24 hours average (Systolic)	0.938	0.902-0.975	0.000
white coat (Diastolic)	0.883	0.828-0.938	0.000
24 hours day (Diastolic)	0.943	0.907-0.978	0.000
24 hours night (Diastolic)	0.738	0.659-0.817	0.000
24 hours average (Diastolic)	0.643	0.556-0.730	0.002
HDL	0.679	0.594-0.765	0.000
Triglyceride	0.703	0.619-0.787	0.000
Creatinine	0.650	0.562-0.738	0.001
Uric acid	0.598	0.508-0.688	0.038
CRP	0.707	0.624-0.790	0.000
TSH	0.753	0.677-0.830	0.000
AST	0.697	0.613-0.781	0.000
ALT	0.692	0.609-0.776	0.000
RBC	0.691	0.607-0.775	0.000
HGB	0.619	0.529-0.709	0.011
HCT	0.645	0.557-0.734	0.002
MCV	0.610	0.519-0.700	0.020
Monocyte	0.725	0.644-0.805	0.000
EFT thickness	0.755	0.680-0.830	0.000
Aortic root diameter	0.601	0.510-0.691	0.033
Sinus valsalva diameter	0.645	0.557-0.733	0.002
Sinotubular junction diameter	0.593	0.503-0.684	0.048
Aortic ascendance diameter	0.617	0.527-0.706	0.013
Left atrium diameter	0.673	0.588-0.759	0.000
Left ventricular end-systolic diameter	0.637	0.547-0.726	0.004
Left ventricular end-diastolic diameter	0.672	0.586-0.758	0.000
Left ventricular posterior wall thickness	0.751	0.673-0.828	0.000
Interventricular septum thickness	0.708	0.626-0.790	0.000
Right ventricular end-diastolic diameter	0.596	0.505-0.688	0.041
Body surface area	0.780	0.706-0.853	0.000
Left ventricular mass	0.769	0.696-0.843	0.000
Ejection fraction	0.614	0.524-0.703	0.016
P Vmax	0.614	0.523-0.704	0.016

ROC Curve

EFT thickness was significant [Area under the curve 0.755 (0.680-0.830)] ($p<0.05$) in the groups with and without HT. EFT thickness, at a cut-off value of 4.15; the sensitivity was 73.2; the positive estimate was 66.7%; the specificity was 57.1%, and the negative estimate was 64.5% (**Figure 3**). EFT thickness did not show a significant change according to the HT stage.

Pearson correlation analysis showed that sinus valsalva (r2=0.08, $p<0.05$), sinotubular junction (r2=0.06, $p<0.05$), and aortic ascendence diameters (r2=0.07, $p<0.05$) were significantly correlated with EFT, respectively (**Table 6**) (**Figure 3**).

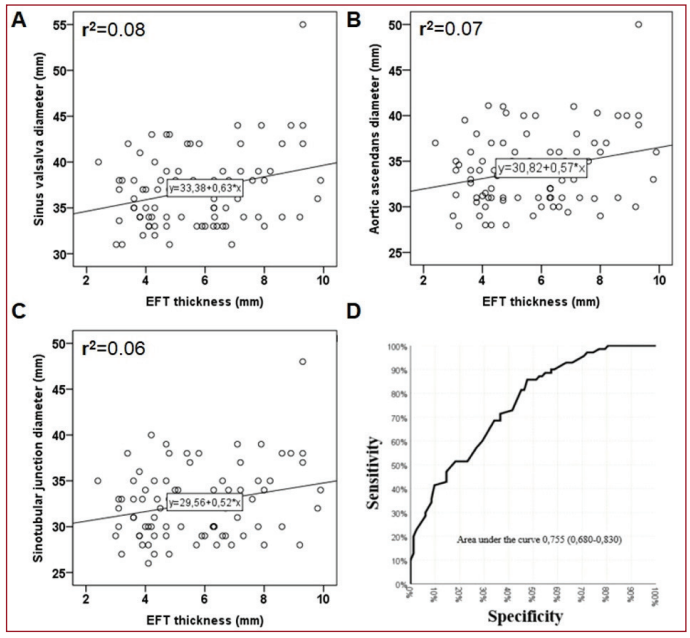

Figure 3. Correlation of EFT thickness with sinus valsalva (A), sinotubular junction (B), and aort ascendance diameters (C). Sensitivity and specificity values of epicardial fat tissue thickness for patients with hypertension (D). EFT, epicardial fat tissue thickness.

Table 6. Correlation (r2-value) of EFT thickness with sinus valsalva, sinotubular, and aort ascendance diameters.

Variable		r2	P-value
Sinus valsalva diameter	EFT thickness	0.08	0.009**
Sinotubular junction diameter	EFT thickness	0.06	0.022*
Aort ascendance diameter	EFT thickness	0.07	0.016*

Abbreviation: BMI, Body mass index. *$p<0.05$, **$p < 0.01$.

DISCUSSION

In our current investigation, our research unveiled significant findings regarding the relationship between EFT, HT, and various cardiovascular parameters. Our study indicated that EFT thickness was notably increased in HT patients, suggesting a potential link between HT and this adipose tissue depot. These findings were in line with the results of a meta-analysis that observed a tendency for HT patients to exhibit increased EFT thickness, particularly in proximity to the right ventricular wall.[19] This observation was further corroborated by a study demonstrating that EFT thickness was substantially larger in individuals with HT, reinforcing its potential role as a risk indicator for cardiovascular morbidity and HT.[20] Moreover, our research sheds light on a possible connection between the increase in EFT in hypertensive individuals and alterations in left ventricular-related parameters, such as posterior wall thickness, and end-diastolic diameter. In support of our findings, clinical studies had previously identified a correlation between EFT and left ventricular function.[21] Notably, our study also unveiled marked cardiac structural changes in hypertensive patients, including the enlargement of heart chambers and increased thickness

of the interventricular septum and posterior wall of the left ventricle. This phenomenon could be attributed to the impact of HT on the heart's structure and function, leading to cardiac remodeling, including chamber dilation. HT was recognized for its role in elevating arterial pressure, and the heart compensates for this increased pressure by adapting through structural changes. Left ventricular hypertrophy, characterized by thickening and enlargement of the left ventricle, was a common adaptation to hypertensive conditions.[22] Chronic HT could also affect the atria, potentially leading to left atrial dilation as the left ventricle becomes less compliant due to hypertrophy, resulting in increased atrial pressure. A similar process might occur in the right atrium if the right ventricle faces increased resistance in the pulmonary circulation.[23]

Furthermore, our research indicated a positive correlation between EFT thickness and the dilation of aortic structures such as the sinus of Valsalva diameter, sino-tubular junction, and aortic ascendence diameter. This relationship highlighted a potential link between EFT thickness and aortic dilation. In the long term, HT could induce structural changes in the aorta, rendering it more susceptible to dilation, a condition that could be attributed to HT itself.[24,25] Importantly, both HT and aortic dilation were independent risk factors for severe cardiovascular events, including aortic dissection, aortic rupture, and other life-threatening complications. When an individual presents with both HT and aortic dilation, their cumulative cardiovascular risk might be significantly higher than those with either condition in isolation.[26,27]

Our study also provided insights into metabolic parameters, revealing that they were notably higher in the HT group compared to the CONT group. The relationship between EFT and various metabolic parameters, such as triglycerides, creatinine, uric acid, CRP, AST, ALT, and specific blood cell counts, was an intriguing area of investigation in cardiovascular research. EFT was recognized to possess metabolic and inflammatory properties and could release bioactive molecules that might influence metabolic parameters and inflammation.[28] Notably, EFT was considered a potential source of pro-inflammatory molecules, and elevated EFT might contribute to systemic inflammation, as evidenced by higher CRP levels.[29] Furthermore, EFT's impact on the development of fatty liver could lead to increased AST and ALT levels.[30] The monocyte/HDL ratio, which serves as a marker of cardiovascular risk and inflammation, might also be influenced by EFT's pro-inflammatory properties, thus contributing to the observed association.[28]

However, it's important to acknowledge the limitations of our study. While our findings demonstrate associations between EFT, HT, cardiac parameters, and metabolic markers, it is essential to recognize that an association does not imply causation. Further research is required to establish a causal relationship and to elucidate the underlying mechanisms. Additionally, the clinical significance of these associations and their relevance to individual patient care would depend on various factors, including the strength of the association, the size of the effect, and whether these relationships hold in diverse and larger populations.

CONCLUSION

Our findings underscored the potential significance of EFT as a contributor to cardiovascular risk factors. Moreover, our study demonstrated that HT was associated with cardiac remodeling, characterized by an increase in the size of heart chambers. Furthermore, our findings suggested that EFT might play a role in metabolic dysregulation and inflammation, which were known contributors to cardiovascular disease.

In summary, our study highlights the importance of considering EFT as a potential player in the pathophysiology of HT and its associated metabolic disturbances. Future research endeavors aimed at unraveling the intricate interactions between EFT, metabolic parameters, and cardiovascular health are essential for advancing our understanding of these complex relationships and ultimately improving patient care and outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved by the Ethics Committee of the University of Health Sciences, with the decision of the ethics committee numbered 22/465

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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Original Article / Orijinal Araştırma

Evaluation of First Rescuer Interventions on Arrested Patients in In-patient and Out-patient Hospital Clinical Services: Observations of Anesthesia Technicians on Duty in the Code Blue Team

Hastanelerin Yataklı Servis ve Ayaktan Kliniklerinde Arrest Hastalara ilk Kurtarıcılar Tarafından Yapılan Müdahalelerinin Değerlendirilmesi: Mavi Kod Ekibinde Görev Yapan Anestezi Teknisyen/Teknikerlerinin Gözlemleri

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Abstract

Aim: The aim of this study was to investigate the observations and experiences of anesthesia technicians working in the Blue Code Team (BCT) regarding the interventions performed by the first rescuers in Blue Code (BC) calls and to identify their shortcomings.

Material and Method: Our study is a descriptive and cross-sectional study. The population of our study consisted of anesthesia technicians on BC calls in Turkey. The online questionnaire form included 44 questions, 9 of which were socio-demographic questions. Data were collected through social media and email between 01/02/2023 and 01/04/2023. The total number of anesthesia technicians in Turkey was found to be 382 with a margin of error of 0.05 at 95% confidence interval.

Results: The total number of anesthesia technicians in Turkey was found to be 382 with a margin of error of 0.05 at the 95% confidence interval. A total of 568 technicians were reached. The mean age of the participants was 27 ± 6.64 years. 72.9% of the participants were female, 63.0% were single, 59.7% had 0-4 years of work experience. It was found that 16.2% of the participants had no advanced life support training. Almost all responses to the questionnaire were found to have a high rate of deficiencies or errors. Particularly noteworthy parameters were that BC was given on "Monday" (74.6%), most BC was given in "internal medicine wards" (57.4%) and "no patient intervention" (10.0%), although low.

Conclusions: In this study, anesthesia technicians working in BCT were found to have a lack of training in advanced life support, there were deficiencies in the interventions performed by the first rescuers and some interventions were not performed. It is noteworthy that no procedures were initiated to intervene on patients. The frequent requests for BC from internal wards should be investigated in detail. In this way, many BC procedures can be terminated more successfully or the occurrence of BC can be prevented.

Keywords: Anesthesia technicians, blue code, cardiopulmonary arrest, first responder

Öz

Amaç: Bu çalışmanın amacı Mavi Kod Ekibinde (MKE) görev yapan anestezi teknisyen/teknikerlerinin Mavi Kod (MK) çağrılarında ilk kurtarıcıların yaptığı müdahalelere ilişkin gözlem ve deneyimlerini araştırmak ve eksikliklerini tespit etmektir.

Gereç ve Yöntem: Çalışmamız tanımlayıcı ve kesitsel bir çalışmadır. Çalışmamızın evrenini Türkiye'de MK çağrılarına katılan anestezi teknisyen/teknikerleri oluşturmuştur. Çevrimiçi anket formunda 9'u sosyo-demografik olmak üzere 44 soru yer aldı. Veriler 01/02/2023 ile 01/04/2023 tarihleri arasında sosyal medya ve e-posta yoluyla toplanmıştır. Türkiye'deki toplam anestezi teknisyeni/teknikeri sayısı %95 güven aralığında 0,05 hata payı ile 382 olarak bulundu.

Bulgular: Türkiye'deki toplam anestezi teknisyeni/teknikeri sayısı %95 güven aralığında 0,05 hata payı ile 382 olarak bulundu. Toplam 568 teknisyene ulaşıldı. Katılımcıların yaş ortalaması 27 ± 6,64 yıldı. Katılımcıların %72,9'u kadın, %63,0'ı bekar, %59,7'si 0-4 yıl arası iş tecrübesine sahipti. Katılımcıların %16,2'sinin ileri yaşam desteği eğitimi almadığı belirlendi. Ankete verilen yanıtların neredeyse tamamında yüksek oranda eksiklik veya hata olduğu görüldü. Özellikle dikkat çeken parametreler, MK çağrısının "Pazartesi" (%74,6) verilmesi, MK çağrısının çoğunun "dahiliye servislerinde" (%57,4) ve "hastaya müdahale edilmemesi" (%10,0) düşük de olsa verilmesiydi.

Sonuç: Bu çalışmada MKE'nde çalışan anestezi teknisyen/teknikerlerinin ileri yaşam desteği konusunda eğitim eksikliklerinin olduğu, ilk kurtarıcıların yaptığı müdahalelerde eksiklikler olduğu ve bazı müdahalelerin yapılmadığı belirlendi. Hastalara müdahale edecek herhangi bir işlemin başlatılmaması dikkat çekti. Dahili koğuşlardan sık sık MK talepleri ayrıntılı olarak araştırılmalıdır. Bu sayede birçok MK işlemi daha başarılı bir şekilde sonlandırılabilir veya MK ihtiyacının oluşması engellenebilir.

Anahtar Kelimeler: Anestezi teknisyeni/teknikeri, mavi kod, kardiyopulmoner arest, ilk müdahale ekibi

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INTRODUCTION

The person calling the Blue Code (BC) is responsible for providing immediate basic life support to the patient until the Blue Code Team (BCT) arrives and intervenes.[1] Although healthcare professionals working in hospitals have received basic life support training, they may have had little or no opportunity to practice this training during a BC. As a result, first responders may be reluctant to use CPR and defibrillators in the event of cardiopulmonary arrest.[2] In particular, healthcare professionals working in clinics where Blue Code (BC) calls are infrequent and who are inexperienced in this area should have basic life support skills. In addition, they should have sufficient knowledge and be able to immediately provide the patient with a normal or automatic external defibrillator, pull the crash cart, prepare emergency medications (adrenaline, dopamine, atropine, lidocaine, etc.), and prepare emergency equipment (ECG palette, airway, mask, laryngoscope, intubation tube, IV catheters, injector, aspiration probe, etc.).

BC is usually performed by a team with expertise/experience in this field. The role of this team is to be on standby and to have a technical communication system in place. Preliminary preparations and interventions should be managed by the people giving the code until the team arrives at the patient's bedside. In the process, BCT should reach the patient in time and "the first rescuers giving BC should use the available equipment appropriately, and good situation management should be done after the interventions are effectively applied to the patient".[3] BCT usually consists of a physician in charge of the team (mainly a specialist in anesthesia, cardiology, pulmonology, internal medicine, neurology, family medicine, cardiovascular surgery or thoracic surgery) and health care personnel (anesthesia technician, nurse, health officer, etc.).

The aim of this study is to find out the observations of anesthesia technicians who are part of the BCT, on the interventions of the first rescuers on the patient when they arrive at the scene after the BC call has been made, to identify the shortcomings and to discuss what solutions, if any, can be found according to the characteristics of these shortcomings. The aim is to increase the survival rate of in-hospital cardiac arrests.

MATERIAL AND METHOD

Our study is a descriptive and cross-sectional study. The ethical evaluation of the study was conducted by the Ethics Committee of Yozgat Bozok University and approved with the number 01/18 on 25/01/2023. The population of our study consists of anesthesia technicians in Turkey. The first anesthesia technicians graduated from the health vocational schools opened in 1984-1985 and the total number of graduates until today is 59763 people. Considering this number (n=59763), a sample group of 382 people is predicted with a 95% confidence interval and a margin of error of 0.05. The survey method was preferred to reach all anesthesia technicians. The survey form was prepared on Google Form and participants were reached via social media platforms and email. 657 people completed the survey form. A total of 89 people who were not anesthesia technicians or who were not on BC team were excluded from the survey. A total of 568 people were included in the study.

The questionnaire consisted of 44 questions in two parts. In the first part of the questionnaire there are nine questions about gender, age, marital status, educational status, occupation, years of employment, institution of employment, region of institution of employment, and district of institution of employment.

The second part consists of 35 questions about the observations of BC team rearding the interventions of first responders at the time they arrived the place where BC was given.

The data collected were analyzed using IBM SPSS version 20.0. Data were analyzed using percentage and frequency distributions and correlation analysis. Chi-square test was used for statistical analysis. The statistical significance level was set at $p \leq 0.05$.

RESULTS

Of the 657 participants, 568 were included in the study. The mean age was 27 ± 6.64 years. 72.9% of the participants were female, 40.7% were in the 20-24 age group, 63.0% were single, 68.0% had an associate degree, 59.7% had 0-4 years of work experience, 46.1% worked in a public hospital, 30.8% worked in the Marmara region, and 80.3% worked in the central district. The socio-demographic distribution of the participants is shown in **Table 1**.

Table 1. Socio-demographic Structure.

Socio-demographic Structure.	n=568	%
1.Gender		
Male	154	27.1
Female	414	72.9
2. Age		
20 - 24 Years	231	40.7
25 - 29 Years	191	33.6
30 - 34 Years	65	11.4
35 Years and Over	81	14.3
3. Marital Status		
Single	358	63.0
Married	210	37.0
4. Education Status		
Health Vocational High School	21	3.6
Associate Degree	386	68.0
Lisans	148	26.1
License	12	2.1
PhD	1	0.2
5. Work Experience		
0 - 4 Years	339	59.7
5 - 9 Years	96	16.9
10 - 14 Years	56	9.9
15 Years and Over	77	13.6
6. Institution of Employment		
State Hospital	262	46.1
Private Hospital	138	24.3
Training and Research Hospital	122	21.5
University Hospital	32	5.6
Foundation University Hospital	3	0.6
Other	11	1.9
7. Region of institution of employment		
Marmara Region	175	30.8
Ege Region	59	10.4
Akdeniz Region	50	8.8
İç Anadolu Region	144	25.4
Karadeniz Region	62	10.8
Doğu Anadolu Region	35	6.2
Güney Doğu Anadolu Region	43	7.6
8. District of institution of employment		
Central district	456	80.3
Provincial District	112	19.7

The ratings of the participants' responses to the assessment of the first responders are shown in **Table 2**.

When looking at the participants' answers regarding the wards where BC was given, the most BC was given in the 'internal medicine' ward, while the clinic where the least BC was given was the 'physiotherapy' ward. The wards where BC was given are shown in **Table 3**.

The rating of the first responders according to the institution of employment is shown in **Table 4**.

Table 2. The assessment of the first responders

Questions (n=568)	Yes (n)	No (n)	Sometimes (n)
1. The first intervention has been initiated by the doctors or health care staff of the clinic.	220	70	278
2. The emergency trolley, which should be available in clinics, was taken to the patient.	343	60	165
3. Patients were monitored.	250	84	234
4. Drugs that are likely to be administered to the patient (adrenaline, atropine, sodium bicarbonate, etc.) were prepared by the clinic team.	219	144	205
5. The shock position was given to the patient.	128	214	226
6. The automated external defibrillator (AED) was brought to the scene.	211	215	142
7. The defibrillator has been brought to the patient.	292	98	178
8. The patient with respiratory failure was intervened with airway materials such as bag-valve mask or airway.	241	110	217
9. The CPR backboard required for CPR was placed under the patient.	120	302	146
10. Cardiopulmonary resuscitation (CPR) was started on the patient whose breathing and circulation had stopped.	308	52	208
11. The interventions made to the patient were recorded	383	88	97
12. The patient was transferred to the nearest clinic or intensive care unit.	342	113	113
13. Security measures were taken by security personnel.	345	74	149
14. No intervention was made on the patient.	57	312	199

Table3. BC given wards

Wards	n	%
Internal Medicine	326	57.4
Thoracic diseases	245	43.1
Polyclinic	237	41.7
Cardiovascular Surgery	162	28.5
Laboratory departments (blood sampling, ultrasound, etc.)	145	25.5
General Surgery	143	25.2
Thoracic surgery	121	21.3
Dialysis Unit	119	21.0
Neurology	106	18.7
Obstetrics/Gynaecology	97	17.1
Neurosurgery	89	15.7
Infectious Diseases	75	13.2
Burn Unit	48	8.5
Urology	47	8.3
Physiotherapy	32	5.7
Other services	200	35.2

The days on which the participants were given MK are shown in **Table 5**

Table 5. Table 5 shows the days given BC according to the answers of the participants. *

Days	N	%
Monday	424	74.6
Tuesday	369	65.0
Wednesday	376	66.2
Thursday	380	66.9
Friday	402	70.8
Saturday	333	58.6
Sunday	316	55.6

* More than one option is selected.

DISCUSSION

The first person to see a patient whose general condition is deteriorating can be defined as the first rescuer. The first rescuer should assess the patient as quickly as possible and, in the case of respiratory and circulatory failure, inform the BCT quickly. The BCT should arrive at the scene within three minutes. While waiting for the BCT to arrive, the first rescuers (especially hospital staff) must intervene in the patient's care without wasting time. Baskett et al. reported that rapid initiation of basic life support and early defibrillation of the arrested patient until the arrival of BCT increased survival. [4] The aim of our study was to compile the observations of anesthesia technicians present in the BCT, to evaluate the practices of the first rescuers in their interventions and to help find solutions in the light of the information obtained here, thus increasing the survival rate.

Approximately 80% of the respondents to the questionnaire reported that incorrect BCT can be given. Eroğlu et al. reported an incorrect BC rate of 91%,[5] Baytar et al. 42.9%,[6] Kaykısız et al. 45%,[7] Canural et al. 61%,[8] and Arıkan et al. 13.3%.[9] The reason for the different results in the studies may be that most of the wrong code calls are not recorded in hospitals and the high number of patients in the hospital. In the literature, the reason for the low rate of BC practice has been attributed to the effectiveness of training given in hospitals. We thought that the reason for the high rate in our study might be the inadequacy of the training given to first responders, especially during the Covid-19 period.

The actions of first responders who intervene in patients with respiratory and circulatory arrest are critical. The earlier and more complete the intervention, the higher the survival rate of the patient. In our study, when the actions of the first responders were examined, it was found that only 60.4% pulled the emergency cart to the patient, 44% monitored the patient, 38.6% prepared emergency medications, 22.5% placed the patient in a shock position, 37.1% brought the AED to the scene, 21.1% placed the under-patient CPR board under the patient, 54.2% started CPR and, unfortunately, 10% did not intervene on the patient. A study by Incesu E. reported that 22.4% of patients did not receive any intervention before

the code team arrived at the scene.[10] When these figures were examined, it was concluded that the first responders did not intervene sufficiently, that there were deficiencies in preparation, and that these rates should be increased.

When the places where BC was given were examined, internal medicine services were the first with 57.4%, throacic diseases were the second with 43.1% and polyclinics were the third with 41.7%. In the study conducted by Baytar, Arıkan and Kayır et al, internal medicine and neurology services were reported as the services where blue code was given the most.[6,9,11] The studies in the literature were compatible with our study. Since the general condition of the patients admitted to the internal medicine and thoracic clinic was poor, the BC rates may have been high.

Table 4. Evaluation of first responders by institution of employment.

		Institution of employment								P
		State Hospital		Training and Research Hospital		Private Hospital		University Hospital		
		N	%	n	%	N	%	n	%	
1. The first intervention has been initiated by the doctors or health care staff of the clinic.	Sometimes	149	55.8%	70	54.7%	46	33.3%	13	37.1%	.000
	Yes	75	28.1%	46	35.9%	79	57.2%	20	57.1%	
	No	43	16.1%	12	9.4%	13	9.4%	2	5.7%	
2. The emergency trolley, which should be available in clinics, was taken to the patient.	Sometimes	86	32.2%	47	36.7%	23	16.7%	9	25.7%	.000
	Yes	145	54.3%	72	56.3%	105	76.1%	21	60.0%	
	No	36	13.5%	9	7.0%	10	7.2%	5	14.3%	
3. Patients were monitored.	Sometimes	119	44.6%	68	53.1%	35	25.4%	12	34.3%	.000
	Yes	96	36.0%	48	37.5%	92	66.7%	14	40.0%	
	No	52	19.5%	12	9.4%	11	8.0%	9	25.7%	
4. Drugs that are likely to be administered to the patient (adrenaline, atropine, sodium bicarbonate, etc.) were prepared by the clinic team.	Sometimes	101	37.8%	61	47.7%	27	19.6%	16	45.7%	.000
	Yes	88	33.0%	35	27.3%	86	62.3%	10	28.6%	
	No	78	29.2%	32	25.0%	25	18.1%	9	25.7%	
5. The shock position was given to the patient.	Sometimes	105	39.3%	59	46.1%	50	36.2%	12	34.3%	.000
	Yes	54	20.2%	10	7.8%	54	39.1%	10	28.6%	
	No	108	40.4%	59	46.1%	34	24.6%	13	37.1%	
6. The automated external defibrillator (AED) was brought to the scene.	Sometimes	64	24.0%	43	33.6%	27	19.6%	8	22.9%	.000
	Yes	86	32.2%	32	25.0%	79	57.2%	14	40.0%	
	No	117	43.8%	53	41.4%	32	23.2%	13	37.1%	
7. The defibrillator has been brought to the patient.	Sometimes	79	29.6%	66	51.6%	24	17.4%	9	25.7%	.000
	Yes	127	47.6%	47	36.7%	104	75.4%	14	40.0%	
	No	61	22.8%	15	11.7%	10	7.2%	12	34.3%	
8. The patient with respiratory failure was intervened with airway materials such as bag-valve mask or airway.	Sometimes	115	43.1%	62	48.4%	24	17.4%	16	45.7%	.000
	Yes	86	32.2%	44	34.4%	97	70.3%	14	40.0%	
	No	66	24.7%	22	17.2%	17	12.3%	5	14.3%	
9. The CPR backboard required for CPR was placed under the patient.	Sometimes	56	21.0%	36	28.1%	42	30.4%	12	34.3%	.000
	Yes	51	19.1%	13	10.2%	50	36.2%	6	17.1%	
	No	160	59.9%	79	61.7%	46	33.3%	17	48.6%	
10. Cardiopulmonary resuscitation (CPR) was started on the patient whose breathing and circulation had stopped.	Sometimes	108	40.4%	59	46.1%	27	19.6%	14	40.0%	.000
	Yes	126	47.2%	59	46.1%	104	75.4%	19	54.3%	
	No	33	12.4%	10	7.8%	7	5.1%	2	5.7%	
11. The interventions made to the patient were recorded	Sometimes	58	21.7%	20	15.6%	13	9.4%	6	17.1%	.005
	Yes	171	64.0%	81	63.3%	110	79.7%	21	60.0%	
	No	38	14.2%	27	21.1%	15	10.9%	8	22.9%	
12. The patient was transferred to the nearest clinic or intensive care unit.	Sometimes	54	20.2%	31	24.2%	21	15.2%	7	20.0%	.003
	Yes	150	56.2%	69	53.9%	104	75.4%	19	54.3%	
	No	63	23.6%	28	21.9%	13	9.4%	9	25.7%	
13. Security measures were taken by security personnel.	Sometimes	84	31.5%	40	31.3%	18	13.0%	7	20.0%	.000
	Yes	147	55.1%	66	51.6%	110	79.7%	22	62.9%	
	No	36	13.5%	22	17.2%	10	7.2%	6	17.1%	
14. No intervention was made on the patient.	Sometimes	108	40.4%	57	44.5%	24	17.4%	10	28.6%	.000
	Yes	29	10.9%	12	9.4%	14	10.1%	2	5.7%	
	No	130	48.7%	59	46.1%	100	72.5%	23	65.7%	

*Chi-Square Test

The interventions of the first rescuers when BC was given were compared in terms of hospitals. All questions except 'No intervention was made on the patient' were answered positively by private hospital staff in a statistically significant way. Although this may indicate a more sensitive approach to the situation in private hospitals, the possibility of bias cannot be ruled out. Looking at the situation from a different perspective, deficiencies of between 30% and 80% were found in practices other than private hospitals. This situation indicates a lack of training, experience or skills in general, which should be taken into account and efforts should be made to remedy it.

When the days on which BC was given were examined, it was found that code blue calls were mostly given on weekdays and most frequently on Monday. In the study by Çiçek F. et al, 73.4% were reported to be given on weekdays.[12]

CONCLUSION

The fact that the first rescuer is trained, experienced and has intervention skills is of great importance during the 3-minute critical period when the BCT is expected to reach the patient after the warning is given. The anesthesia technicians who took part in the survey reported what they saw when they reached the patient within this three-minute period. The available data showed that there was up to 70% agreement in practice for very few of the procedures performed. For some of the procedures that should have been performed, it was found that there was a low level of practice of 20% and, unfortunately, 10% of patients were not treated at all. These results cannot be considered acceptable. People who have the potential to be first responders should definitely be highlighted and trained.

As BC practices are frequent on Mondays and in some clinics, it should be ensured that those working in these departments improve their skills in particular and that the follow-up of patients on weekends and during the week is of similar quality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The ethical evaluation of the study was conducted by the Ethics Committee of Yozgat Bozok University and approved with the number 01/18 on 25/01/2023.

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article / Orijinal Araştırma

Effect of Abdominal Obesity on Body Composition and Obesity Markers in Healthy Adults

Sağlıklı Yetişkinlerde Abdominal Obezitenin Vücut Kompozisyonu ve Obezite Belirteçlerine Etkisi

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Abstract

Aim: To reveal possible metabolic risks that may occur in the future by evaluating the effects of abdominal obesity on body composition and peptide hormones (adropin, ghrelin, obestatin), which are obesity markers, in healthy individuals.

Material and Method: 69 healthy participants between the ages of 25-52 were divided into two groups as abdominally obese and non-obese. Anthropometric measurements and body composition of the participants were analyzed and blood sample was taken from the antecubital vein to measure adropin, obestatin and ghrelin levels after 8-10 hours of fasting.

Results: In the abdominal obese group, body mass ındex (BMI), waist circumference, body fat ratio, visceral fat rating and obesity degree were statistically higher, while skeletal muscle ratio, serum adropin and ghrelin levels were statistically lower compared to the control group. BMI and body fat ratio were negatively correlated with adropin, obestatin and ghrelin levels, while waist circumference and visceral fat rating were only negatively correlated with ghrelin levels.

Conclusion: As a result of this study BMI, body weight, body fat ratio, visceral fat rating and obesity degree increased and muscle ratio, serum adropin and ghrelin levels decreased in healthy abdominal obese individuals. It is suggested that in the light of this and similar studies, the relationship between obesity related hormones and obesity also metabolic risks will be understood better in the future.

Keywords: Abdominal obesity, anthropometric measurement, body composition, adropin, obestatin, ghrelin

Öz

Amaç: Abdominal obezitenin sağlıklı bireylerde vücut kompozisyonu ve obezite belirteçleri olan peptit hormonlar (adropin, ghrelin, obestatin) üzerindeki etkilerini değerlendirerek ileride oluşabilecek metabolik riskleri ortaya çıkarmaktır.

Gereç ve Yöntem: 25-52 yaş aralığındaki 69 katılımcı abdominal obezitesi olan ve olmayan şeklinde iki gruba ayrılmıştır. Katılımcıların antropometrik ölçümleri ve vücut kompozisyon analizi yapılmış; serum adropin, ghrelin ve obestatin düzeyleri 8-10 saat açlık sonrası antekübital venden kan alınarak ölçülmüştür.

Bulgular: Abdominal obez grupta kontrol grubuna kıyasla vücut kitle endeksi (VKİ), bel çevresi, vücut yağ oranı, iç yağlanma, obezite derecesinin istatistiksel olarak daha yüksek olduğu görülürken; iskelet kas oranı, serum adropin ve ghrelin düzeylerinin istatistiksel olarak daha düşük olduğu bulunmuştur. VKİ ve vücut yağ oranı adropin, obestatin ve ghrelin düzeyleri ile negatif korelasyon gösterirken; bel çevresi ve iç yağlanma sadece ghrelin düzeyi ile negatif korelasyon göstermiştir.

Sonuç: Sağlıklı bireylerde abdominal obeziteyle birlikte VKI, vücut ağırlığı, vücut yağ oranı, iç yağlanma derecesi ve obezite derecesinin arttığı; kas oranı, serum adropin ve ghrelin düzeyinin ise azaldığı görülmüştür. Bu ve benzer çalışmalar sayesinde, obezite ile ilgili hormonların obezite ve metabolik risklerle olan ilişkisinin gelecekte daha iyi anlaşılacağı düşünülmektedir.

Anahtar Kelimeler: Abdominal obezite, antropometrik ölçüm, vücut kompozisyonu, adropin, obestatin, ghrelin

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INTRODUCTION

Obesity is defined by the World Health Organization (WHO) as excess fat in the body.[1] Abdominal obesity is better known as the increase in fat tissue around the internal organs.[2] Abdominal obesity is more closely associated with many chronic disease components compared to gluteal obesity.[3] Therefore, recently measuring waist circumference along with body mass index (BMI) has become an important indicator in anthropometric evaluation.[4] Although BMI is a widely used method in the diagnosis of obesity, waist circumference measurement gives better results in calculating abdominal obesity.[5] According to the Turkish Society of Endocrinology and Metabolism (TEMD) guidelines, the diagnostic criteria for abdominal obesity include a waist circumference of ≥100 cm in men and ≥90 cm in women.[6]

Analysis of body composition is an essential part of nutritional status assessment, especially in weight loss programs. Body weight and composition are the result of genetics, metabolism, environment, behavior and culture. Additionally, local fat accumulation has been shown to have a significant, negative impact on morbidity, disability, emotional well-being, and quality of life.[7] Bioelectrical impedance analysis (BIA) is a simple, noninvasive, fast, portable, repeatable and convenient method of measuring body composition (fat, muscle, soft tissue, etc.) and fluid distribution with less physical requirements.[8]

Adropin was first used by Kumar et al. (2008), it is a nutritionally regulated peptide hormone that is secreted mainly by the liver and modulates metabolic homeostasis in many tissues.[9,10] It has been proven by animal and human studies that adropin is associated with adiposity and weight management by interacting with receptors that play a role in the regulation of energy metabolism and glucose lipid homeostasis.[11] Adropin has also been shown to suppress lipogenic genes, lipid accumulation, and differentiation of preadipocytes into mature adipocytes.[12]

Ghrelin is an orexigenic hormone that was first detected in the mouse stomach in 1999.[13] While ghrelin level in the body reaches its peak during fasting, its level decreases immediately after a meal and satiety develops.[14] Circulating ghrelin increases abdominal fat by a mechanism independent of its central orexigenic activity. However, the effect of ghrelin on adipocytes is controversial. Ghrelin has been reported to inhibit and/or increase adipogenesis, increase fat storage enzyme activity, and reduce fat utilization/lipolysis.[15]

Obestatin is an anorexigenic peptide hormone produced in the same endocrine cell type as ghrelin and primarily in the stomach.[16] As the opposite of obestatin and ghrelin; It has adverse effects such as reducing food intake, body weight and delaying gastric emptying, and when both peptides are administered together, obestatin antagonizes the actions of ghrelin.[17] Existing studies have shown that plasma obestatin is significantly lower in obese subjects compared to controls.[18]

The aim of this study was to evaluate the effects of abdominal obesity, which poses a great risk for many chronic diseases, especially metabolic syndrome,[19] on body composition and peptide hormones, which are markers of obesity, in healthy individuals and to obtain information about future metabolic risks.

MATERIAL AND METHOD

Study Design and Population

Approval for this study was received from Amasya University Faculty of Medicine Clinical Studies Ethics Committee (Decision date and number: 28/02/2020-E-5735). The research was carried out in accordance with the Ethics Committee Directive. All participants included in the study signed the Informed Consent Form. This study was admitted to Amasya Gümüşhacıköy State Hospital. None of the participants had any chronic disease and had never smoked or consumed alcohol. 69 participants were divided into two groups: abdominally obese (n=35) (waist circumference >90 cm for women, >100 cm for men) and non-obese (control group) (n=34)) (waist circumference <90 cm for women, <100 cm for men). Anthropometric measurements and body composition tests of the participants were analyzed at Amasya Gümüşhacıköy State Hospital. TANITA MC 580 type BIA device was used for body composition analysis. A 5 ml blood sample was taken from the antecubital vein to examine adropin, obestatin and ghrelin levels in the morning after 8-10 hours of fasting during routine admission in the study groups.The blood taken into the biochemistry tube was kept for 45 minutes and then centrifuged at 3500-4000 rpm for 5 minutes and the serum was separated. The separated serums were stored in 2 mm Eppendorf tubes in a deep freezer at -80ºC in Amasya University Faculty of Science and Letters Laboratory to measure adropin, obestatin and ghrelin levels. ELISA kits (SUNRED ELISA kit, kit no. 201-12-3107, and 201-12-0091; Shanghai Sunred Biological Technology Co., Ltd., Shanghai, China) were used. These parameters were studied in Amasya University Faculty of Science and Letters Laboratory in accordance with the working method.

Statistical Analysis of Data

For continuous data, mean (μ), standard deviation (SD) and confidence interval values were determined. Categorical data are expressed as percentages. Student's t test was used for pairwise comparisons of data conforming to normal distribution, and Mann Whitney U test was used for pairwise comparisons of data not conforming to normal distribution. Pearson and Spearman tests were chosen appropriately for significance testing of categorical variables. The obtained results were subjected to statistical evaluation at a %95 confidence interval with a significance level of $p<0.05$.

RESULTS

Comparisons and correlation statistics of study findings with study groups are shown below with tables and explanations. This research was conducted with 40 healthy women and 29

healthy men, aged between 25 and 52 years. The mean age of the participants was 36.39±6.72 years.

It was observed that BMI, waist circumference, body weight, body fat ratio, visceral fat rating and obesity degree were statistically significantly higher in the abdominal obese group compared to the control group (p=0.0001). Skeletal muscle ratio and ghrelin level were highly significant (p=0.0001); serum adropin level was significantly (p<0.05) lower in obese group compared to non-obese group (p=0.0001). Although obestatin level was lower in the obese group, there was no statistical difference between the groups (p>0.05) (**Table 1**).

The waist circumference showed a positive, moderately significant correlation with body fat ratio (r=0.643) and a positive, highly significant correlation with visceral fat rating and obesity degree (r=0.921; 0.896, respectively) in all participants. Waist circumference showed negative and moderately significant correlations with skeletal muscle ratio and ghrelin level (r =-0.644; -0.461, respectively). There was a high positive (r=0.928; 0.904, respectively) and significant correlation between body weight and visceral fat rating and obesity degree of all participants, and a moderate positive correlation (r=0.644) with body fat ratio. Statistically significant negative correlation was found between body weight and skeletal muscle ratio and ghrelin levels (r=-0.644; -0.416, respectively). There was a statistically significant positive correlation between BMI and body fat ratio, visceral fat rating and obesity degree (r=0.844; 0.900; 0.995, respectively). Similarly, significant negative correlation was found between BMI and skeletal muscle ratio (r=-0.844) and moderate negative correlation was found with adropin, obestatin and ghrelin levels (r=-0.414; -0.353; -0.379, respectively) (**Table 2**).

A statistically significant negative correlation was observed between the body fat ratio and adropin, obestatin and ghrelin levels of all participants (r=-0.494; -0.434; -0.309 respectively). A moderately significant negative correlation was found between obesity degree and adropin, obestatin and ghrelin (r=-0.401; -0.348; -0.356 respectively). Likewise, skeletal muscle ratio showed a statistically significant negative correlation with these three obesity markers (r =-0.492; -0.433; -0.309, respectively). Visceral fat rating showed only a moderate negative correlation (r=-0.342) with ghrelin level (**Table 3**).

Table 1. Comparison of groups in terms of anthropometric, body composition and biochemical markers

	Mean±SD				
	Abdominal Obese Group (n=35)	Non-obese Group (n=34)	p	95% Confidence Interval	
BMI (kg/m²)	35.96±7.32	22.35±2.04	0.0001[b]	11.01	16.21
Body Weight (kg)	98.31±16.74	16.74±8.78	0.0001[b]	29.37	42.28
Waist Circumference (cm)	109.80±10.46	75.94±8.26	0.0001[b]	29.31	38.39
Body Fat (%)	37.15±8.81	23.82±5.91	0.0001[a]	9.70	16.94
Visceral Fat Rating	12.06±4.43	3.65±1.84	0.0001[b]	6.77	10.05
Obesity Degree*	53.44±31.16	-2.60±8.47	0.0001[b]	45.00	67.09
Skeletal Muscle (%)	35.59±4.96	43.14±3.33	0.0001[a]	-9.58	-5.51
Adropin (pg/ml)	319.35±321.99	432.10±247.82	0.0180[b]	-251.10	-25.60
Obestatin (ng/ml)	8.13±6.87	10.59±5.45	0.1050[b]	-0.45	-0.52
Ghrelin (ng/ml)	1.80±0.53	2.40±0.67	0.0001[a]	-0.89	-0.30

a: Student's t test (data follow a normal distribution), b: Mann Whitney U (data follow a non-normal distribution), *Obesity Degree expresses distance from the most ideally calculated weight as %

Table 2. Correlation of anthropometric measurements with body composition and obesity markers

	Waist Circumference		Body Weight		BMI	
	Correlation Coefficient	p	Correlation Coefficient	p	Correlation Coefficient	p
Body fat ratio	0.643	<0.001	0.644	<0.001	0.844	<0.001
Visceral fat rating	0.921	<0.001	0.928	<0.001	0.900	<0.001
Obesity degree	0.896	<0.001	0.904	<0.001	0.995	<0.001
Skeletal muscle	-0.644	<0.001	-0.644	<0.001	-0.844	<0.001
Adropin	-0.215	0.077	-0.189	0.121	-0.414	<0.001
Obestatin	-0.183	0.132	-0.157	0.199	-0.353	0.003
Ghrelin	-0.461	0.012	-0.416	<0.001	-0.379	<0.001

Table 3. Correlation of body composition with obesity markers

	Body Fat Ratio		Visceral Fat Rating		Obesity Degree		Skeletal Muscle Ratio	
	Correlation Coefficient	p	Correlation Coefficient	p	Correlation Coefficient	p	Correlation Coefficient	p
Adropin	-0.494	<0.001	-0.182	0.135	-0.401	0.001	0.492	<0.001
Obestatin	-0.434	<0.001	-0.124	0.310	-0.348	0.003	0.433	<0.001
Ghrelin	-0.309	0.010	-0.342	0.004	-0.356	0.003	0.309	0.010

DISCUSSION

Acoording to results of this study, in the abdominal obese group, body mass ındex (BMI), waist circumference, body fat ratio, visceral fat rating and obesity degree were statistically higher, while skeletal muscle ratio, serum adropin and ghrelin levels were statistically lower compared to the control group. BMI and body fat ratio were negatively correlated with adropin, obestatin and ghrelin levels, while waist circumference and visceral fat rating were only negatively correlated with ghrelin levels.

In support of this research, in a study investigating the relationship between muscle mass to visceral fat (MVF) ratio and metabolic syndrome in 1464 young adult university students in Colombia; the study population was divided into four groups according to MVF ratio. Participants' muscle and visceral fat measurements were determined by BIA and cardiometabolic risk factors including anthropometry and biochemical parameters were evaluated. As a result of the study, it was stated that a low MVF ratio was associated with a high cardiometabolic risk and that clinicians could use this ratio to determine the cardiometabolic risk in adult individuals.[20] Similarly, Kim et al. (2014) investigated whether low cardiorespiratory condition (CRF) is associated with low muscle mass, visceral obesity, and low muscle mass with visceral obesity in 298 healthy adults aged 20-70 years and classified the participants into four groups according to the muscle mass/visceral fat ratio. It has been reported that individuals with low CRF have low muscle mass and an increased risk of visceral obesity with combined low muscle mass. These results emphasize that low CRF may be a potential indicator for low muscle mass and visceral obesity.[21]

In a randomized controlled study, it was aimed to determine whether serum adropin level is related to cardiorespiratory condition, carotid β stiffness, plasma nitrite/nitrate (NOx) level and abdominal visceral fat in 27 normal weight, 20 overweight and 25 obese adult individuals (age 41-70 ages) and it was reported that serum adropin level is negatively correlated with carotid β-stifness and abdominal visceral fat in all adults.[22] Likewise, Zaki et al. (2022) researched the relationship between serum adropin level, DNA damage and body composition in 40 women with NAFLD and 40 healthy obese women in a similar age it was observed that NAFLD patients had significantly lower serum adropin and higher visceral fat and waist-hip ratio compared to controls. Additionally, serum adropin level was negatively correlated with obesity-related parameters in all subjects similar to this study.[23] Similarly, in Shanghai Hospital in China 16 abdominally obese and 14 normal weight adults were included in a study that hypothesized that obesity might present with imbalance in circulating ghrelin and obestatin levels. It was found that preprandial plasma ghrelin and obestatin levels and obestatin levels were lower in the obese individuals compared with normal-weight controls and also reported that the ghrelin/obestatin ratio may affect the etiology and pathophysiology of obesity.[24] In a case-control study involving nine healthy controls, nine morbidly obese subjects, and eight post-gastrectomy individuals investigated the obestatin response in the body after a fixed meal it has been shown that plasma obestatin does not change substantially following a fixed-energy meal, but is significantly lower in obese subjects than in controls. This suggests that obestatin may have an important role in long-term body weight regulation.[18]

CONCLUSION

Anthropometric measurements, body composition and obesity markers levels of healthy adult individuals with abdominal obesity showed significant differences (higher BMI, body weight, waist circumference, body fat ratio, visceral fat rating, obesity degree; lower skeletal muscle ratio, adropin and ghrelin levels) compared to the control group. As the body fat ratio increases with obesity, obesity-related hormones have been found to decrease. There are very few studies on obesity related hormones in healty individuals. Since this research was conducted in healthy adults, it is believed that it will contribute to the literature to reveal the relationship of these newly identified hormones with obesity and metabolic risks.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for this study was received from Amasya University Faculty of Medicine Clinical Studies Ethics Committee (Decision date and number: 28/02/2020-E-5735).

Informed Consent: All participants included in the study signed the Informed Consent Form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article / Orijinal Araştırma

Comparison of the Early-Middle Period Results of the All-Inside Method and the Transtibial Method in Anterior Cruciate Ligament Reconstruction

Ön Çapraz Bağ Rekonstrüksiyonunda All-Inside Yöntem ile Transtibial Yöntemin Erken-Orta Dönem Sonuçlarının Karşılaştırılması

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Abstract

Aim: This study compares transtibial and All-inside techniques frequently used in ACL reconstruction.

Material and Method: Patients with acute or chronic ACL rupture, reconstruction with one of the transtibial and All-inside techniques, using hamstring autograft, having adequate pre- and postoperative documentation and completing the 24th postoperative month were included in the study and compared retrospectively.

Results: Forty-five patients, 22 of whom were operated on with the transtibial technique and 23 with the All-inside technique, were included in the study. Age, sex-sex distribution and BMI values were similar. While better clinical results were obtained in the early postoperative period in the all-inside group, the results were identical in both groups at 2-year follow-ups.

Conclusion: Transtibial and All-inside techniques are reliable and promise good clinical results in ACL reconstructions.

Keywords: ACL, All-inside, transtibial, reconstruction

Öz

Amaç: Bu çalışma, ÖÇB rekonstrüksiyonunda transtibial ve All-inside tekniklerini karşılaştırmaktadır.

Gereç ve Yöntem: Akut veya kronik ÖÇB rüptürü olan, transtibial veya All-inside tekniklerinden biriyle rekonstrüksiyon yapılan ve hamstring otogrefti kullanılan hastalar retrospektif olarak çalışmaya dahil edildi.

Bulgular: Çalışmaya 22'si transtibial teknikle, 23'ü All-inside tekniğiyle opere edilen 45 hasta dahil edildi. Yaş, cinsiyet dağılımı ve VKİ değerleri benzerdi. All-inside grubunda postoperatif erken dönemde daha iyi klinik sonuçlar elde edilirken, 2 yıllık takipte sonuçlar her iki grupta da benzerdi.

Sonuç: Transtibial ve All-inside teknikleri her ikisi de güvenilirdir ve ÖÇB rekonstrüksiyonlarında iyi klinik sonuçlar vaat etmektedir.

Anahtar Kelimeler: ACL, All-inside, transtibial, rekonstrüksiyon

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INTRODUCTION

Anterior cruciate ligament (ACL) injuries are common and essential injuries to the knee region. The increased sports activities and accessibility in diagnosis-treatment processes cause us to see ACL injuries more frequently. The ACL plays a crucial role in the anteroposterior and rotational stability of the knee joint. Therefore, after ACL injury, instability may develop.[1,2] ACL treatment principles vary due to increasing surgical techniques and changing rehabilitation programs in recent years. Both the selection of the graft to be used and the method of fixation of the graft are among the main topics discussed. Opening tunnels with the transtibial (TT) method is a method that has been used for many years and has proven its success.[3] In recent years, the all-inside technique, which has come to the forefront with its features such as opening sockets instead of tunnels and dual suspensory fixation, has started to be used widely.[4] This study compares patients' clinical outcomes who underwent ACL reconstruction with TT and All-inside techniques.

MATERIAL AND METHOD

This research has been approved by the IRB of the authors. **The inclusion criteria are as follows:** Patients with acute or chronic ACL rupture who underwent reconstruction with either the transtibial or All-inside techniques using hamstring autograft, and who had adequate pre- and postoperative documentation, with a completed 24-month follow-up.

The exclusion criteria are as follows: Patients with meniscal repair, advanced chondral lesions, collateral ligament repair, incomplete documentation, and those who did not complete their 24-month follow-up. In terms of clinical evaluation, parameters such as preoperative age, gender, surgical site, Body Mass Index (BMI), visual analogue scale (VAS), Tegner-Lysholm activity scale, Knee Society Score (KSS), International Knee Documentation Committee (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS) were taken into account for the evaluation. In the TT method, an endobutton was used for the femoral fixation of the graft, and a U stable and a bioabsorbable screw were used for the fixation of the tibia in all patients. All patients used an endobutton for both femoral and tibial graft fixation in the all-inside method.

Statistical Analysis

Conformity of continuous variables to normal distribution was tested with the Shapiro-Wilk test. Descriptive statistics were used to describe continuous variables. (mean, standard deviation, minimum, median, maximum).

The comparison of two independent and non-normally distributed variables was made using the Mann-Whitney U test. A comparison of two independent and normally distributed variables was made with Student's t-test.

Chi-Square (or Fisher Exact test, Continuity Correction, Likelihood Ratio where appropriate) was used to examine the relationship between categorical variables.

The comparison of dependent and non-normally distributed variables was made using the Wilcoxon test. Comparing two variables with dependent and normal distribution was made with Paired Samples t-test.

A comparison of more than two variables that did not fit the dependent and normal distribution was made with the Friedman test.

The statistical significance level was determined as 0.05. Analyses were performed using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

Ethical Approval

The study was carried out with the permission of Maltepe University Faculty of Medicine Hospital Ethics Committee (Date: 18.12.2019, Decision No: 2019/900/74). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

RESULTS

The general information about the patients is summarised in **Table 1**.

Table 1. Generel informations of Transtibial (TT) and All-inside Group

	TT	All-inside
Number (n)	22	23
Age	35.5(min:18-max:56)	32(min:16-max:47
Gender		
Male	19	15
Female	3	8
Side		
Right	12	11
Left	10	12
Follow-up time (months)	48,5 (min:35-max:71)	28,5 min:24-max:38)
Body mass index (BMI)	24,91±3,27 std (min:19,3-max:33,7)	26,17±2,77 std (min:22-max:33,3)

Semitendinosus and gracilis tendon (ST-G) grafts were taken from the ipsilateral extremity in 6 patients in the all-inside group. From 17 patients, only semitendinosus graft (ST) was taken, and it was four folded. In the TT group, ST and G autografts from all patients were taken from the same side extremity, and each was folded in itself. While the mean graft diameter was 8±0.7 mm in the TT group, it was 8.2±0.4 mm in the All-inside group. There was no statistically significant difference between the two groups regarding graft thicknesses.

When the clinical results of the patients who were operated on with the all-inside and TT method were compared, there was a superiority in favour of the All-inside technique in the 2nd week postoperatively. Still, no significant difference was found in the 2nd year (**Figure 1**).

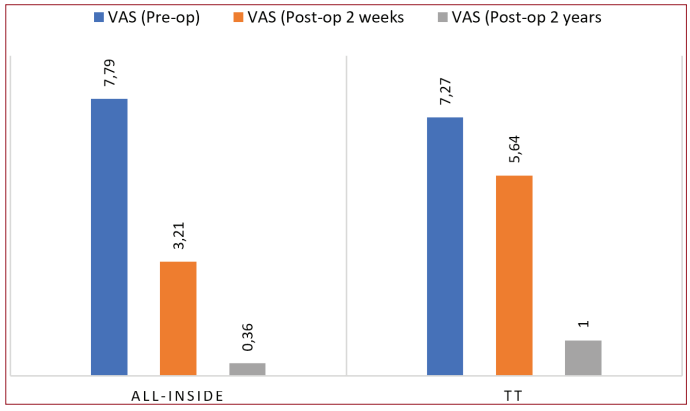

Figure 1. Comparison of pre-op and post-op Visual Analog Scale (VAS) changes in All-inside and TT groups

TI and TT groups found a statistically significant difference regarding the Lachman test in ACL reconstructions at postoperative two years ($p<0.05$). While the Lachman 1+ rate is high in TT, the Lachman negative rate is high in All-inside.

A KSS, KOOS, Tegner-Lysholm, and IKDC subjective knee evaluations have statistically significant positive results compared to preoperatively in the All-inside and TT groups in ACL reconstructions. However, no statistically significant difference was detected between the groups. Complications are summarised in **Table 2**.

Table 2. Complications

Complications	TT (n)	All-inside (n)
Hypoestesia	1	0
Greft failure	0	1
Infection	0	1
Tunel malposition	4	0
Tunel widening	2	0

DISCUSSION

The TT method has been used for many years in anterior cruciate ligament reconstructions. The all-inside technique is also a technique whose popularity has been increasing among orthopaedic surgeons in recent years. As with many different techniques, it is wondered whether All-inside and TT methods are advantageous or disadvantageous against each other. In this study, we retrospectively compared the results of 45 patients who were operated on with All-inside and TT methods.

In the study by Blackman et al. in 2014, ACL reconstruction was performed with the All-inside method in 95 patients. In the 6th month follow-up of 82 patients, Lachman was negative in 71 patients, and Lachman 1+ was found in 11 patients. Pivot shift was positive in only one patient, while pivot shift was negative in all other patients.[5] In another retrospective study involving 136 patients, the TT and All-inside methods were compared, and the pivot shift test was negative in all patients in the All-inside group. In contrast, the pivot shift test was 1+ in 6 (13.6%) patients in the TT group. Lachman test was found to be 1+ in only one patient (1.4%) in the all-inside group, 1+ in 5 patients (11.4%) and 2+ in 1 patient (2.3%) in the TT group.[6] In our study, 12 patients (52.2%) with negative Lachman in the All-inside group, ten patients with 1+ (43.5%), and one patient with 2+ (4.3%) in the physical examinations performed in the 2nd year postoperatively. In the TT group, there were 3 (13.6%) Lachman-negative patients, 13 patients (59.1%) with 1+, and 6 patients (27.3%) with 2+. In addition, while the pivot shift test was 1+ in 8 patients in the TT group, the pivot shift test was negative in all patients in the TI group, similar to the literature. A statistically significant difference was found in postoperative Lachman findings between the all-inside and TT groups ($p:0.0142$). Postop better anteroposterior stability was observed in the all-inside group. In addition, tunnel malposition was observed in 4 (18.1%) patients in the TT group, while tunnel malposition was not observed in the TI group. We attributed this to the fact that the TI method allows more anatomical femoral and tibial sockets to be opened and that the bone-tendon healing of the graft is better due to the half-tunnel opening. For these reasons, we think that rotational and anterior-posterior laxity is seen less in the TI method, and the method provides a more stable knee restoration.

In our study, the VAS values of the patients at the 2nd week after surgery were 5±3 in the TT group and 4±2 in the All-inside group. A statistically significant difference was found between the postoperative 2nd week VAS values ($p:0.0281$). Postoperative 2nd-year VAS values of the patients were 2±1 in the TT group and 1±2 in the TI group. No statistically significant difference was found in the 2nd year VAS values ($p:0.1472$). In the literature, it has been shown that VAS values are lower in the early period in ACL reconstructions performed with the all-inside technique.[7,8]

In our study, Tegner-Lysholm activity scale, Knee Society Score (KSS), International Knee Documentation Committee (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaires were taken preoperatively, and in the 2nd year postoperatively from all our patients. Similar to the literature, no statistically significant difference was found between the two groups in the IKDC, KOOS and Tegner-Lysholm scores at the second-year follow-up.[8-11]

CONCLUSION

Both the transtibial (TT) and all-inside techniques show promising results in anterior cruciate ligament (ACL) reconstructions, providing good clinical outcomes and knee stabilization. The all-inside technique appears to offer certain advantages, such as reduced donor site morbidity, less pain in the early postoperative period, and the preservation of bone reserve for potential revision surgeries. Additionally, the all-inside method allows for more anatomical femoral and tibial sockets, leading to improved functional results.

However, both techniques yielded similar clinical outcomes at the two-year follow-up, with no significant difference observed in patient-based subjective tests. Further research with larger and standardized patient groups is needed to establish a clear superiority between the two methods.

In conclusion, both the transtibial and all-inside techniques are reliable and effective options for ACL reconstruction, and the choice between them may depend on specific patient characteristics and surgeon preferences.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Maltepe University Faculty of Medicine Hospital Ethics Committee (Date: 18.12.2019, Decision No: 2019/900/74).

Informed Consent: Written informed consent was obtained from the patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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Case Report / Olgu sunumu

Adamantinoma-Like Ewing Sarcoma of the Parotid With ESWR1-FLI1 Rearrangement: A Case Report and Review of the Literature

Parotisin ESWR1-FLI1 Yeniden Düzenlenmesi Gösteren Adamantinoma Benzeri Ewing Sarkomu: Olgu Sunumu Ve Literatürün Gözden Geçirilmesi

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Abstract

Adamantinoma-like Ewing sarcoma (ALES) is a rare tumor that shows epithelial differentiation in addition to EWSR1-FLI1 rearrangement. We describe a case of ALES detected as a parotid mass in a 20-year-old woman. This is the ninth case of ALES arising in parotid gland. Histopathologically, the tumor consisted of diffuse pattern and solid sheets of basaloid cells with oval, round nuclei, coarse chromatin and scant cytoplasm. Immunohistochemically, tumor cells were positive with CD99, NKX2.2, p40, pancytokeratin and synaptophysin. Additionally, ESWR1-FLI1 rearrangement was demonstrated with FISH. The diagnosis of ALES may be very challenging due to the potential mimics. The precise diagnosis of ALES depends on both morphologic and immunohistochemical findings and has to be supported by molecular analysis determining EWSR1-FLI1 rearrangement.

Keywords: Adamantinoma-like, Ewing sarcoma, ESWR1-FLI1 rearrangement, parotid

Öz

Adamantinoma benzeri Ewing sarkomu (ALES), EWSR1-FLI1 yeniden düzenlenmesine ek olarak epitelyal farklılaşma gösteren nadir bir tümördür. Burada, 20 yaşında bir kadın hastada parotis kitlesi olarak saptanan bir ALES olgusunu sunuyoruz. Bu, parotis bezinde ortaya çıkan dokuzuncu ALES vakasıdır. Histopatolojik olarak tümör, oval, yuvarlak çekirdekli, kaba kromatinli ve dar sitoplazmalı diffüz paternli ve solid kitleler oluşturan bazaloid hücre tabakalarından oluşmaktaydı. İmmünohistokimyasal olarak, tümör hücreleri CD99, NKX2.2, p40, pansitokeratin ve sinaptofizin ile pozitifti. Ek olarak, FISH ile ESWR1-FLI1 yeniden düzenlemesi gösterildi. Olası taklitçiler nedeniyle ALES tanısı oldukça zorlayıcı olabilir. ALES'in kesin tanısı hem morfolojik hem de immünohistokimyasal bulgulara bağlıdır ve EWSR1-FLI1 yeniden düzenlemesini belirleyen moleküler analiz ile desteklenmelidir.

Anahtar Kelimeler: Adamantinoma benzeri, Ewing sarkomu, ESWR1-FLI1 rearanjmanı, parotis

INTRODUCTION

Ewing sarcoma (ES) is a mesenchymal malignancy with small round cell morphology that has a predilection for bone and soft tissue and mainly affecting children.[1,2] Adamantinoma-like Ewing sarcoma (ALES) is a rare variant of ES that demonstrates the EWSR1-FLI1 rearrangement as well as epithelial differentiation morphologically and immunophenotypically.[3] Although firstly described in long bones, many cases of ALES were reported at head and neck site.[3-5] In the current literature, ten of those cases were originated from salivary glands including parotid and submandibular gland. Of these, eigth tumors were described in parotid.[3]

Herein, in the light of literature, we aimed to present a case of ALES diagnosed in a 20-year-old woman with a parotid mass. To the best of our knowledge, our case is the ninth case of ALES arising in parotid gland. We confirmed the diagnosis by demonstrating EWSR1-FLI1 rearrangement with fluorescence in situ hybridization (FISH).

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CASE REPORT

A 20-year-old woman admitted to hospital with a localized painless swelling standing for 3 months at right preauricular region. On physical examination, a 4×3 cm solid and mobile mass was detected at right parotid gland. There was no palpable lymph node. On ultrasonography, a 3,5×2 cm hipoechoic heterogeneous solid mass was seen at anterior region of right parotid gland. Total parotidectomy was performed.

On macroscopic examination of the excised material, a solid, gray-white colored, encapsulated lesion adjacent to the parotid gland was observed. Microscopic examination of the lesion revealed a tumor infiltrating parotid gland composed of diffuse pattern and solid sheets of basaloid cells with oval, round nuclei, coarse chromatin and scant cytoplasm (**Figure 1A**, **1B**). Tumor cells were positive with CD99 (**Figure 1C**), NKX2.2 (**Figure 1E**), p40 (**Figure 1F**), pancytokeratin (**Figure 1G**) and synaptophysin (**Figure 1H**), but negative with CD3, CD20, TdT, chromogranin, myogenin, WT-1, CD56, calretinin, INSM-1 and high molecular weight keratin. Ki-67 proliferation index was high (**Figure 1D**). Depending on these findings, Adamantinoma-like Ewing sarcoma was the first differential diagnosis. To support the diagnosis, ESWR1-FLI1 reaarangement was demonstrated with FISH. Eighty percent of tumor cells counted on FISH slide revealed ESWR1-FLI1 break-apart signals (**Figure 1I**). So the final diagnosis was 'Adamantinoma-like Ewing sarcoma of parotid gland'.

One month after the initial diagnosis, a positron emission tomography (PET) scan was performed. No residual tumor or distant metastasis were detected on PET. The patient then admitted to oncology department and chemotherapy was began. She is going on uneventfully.

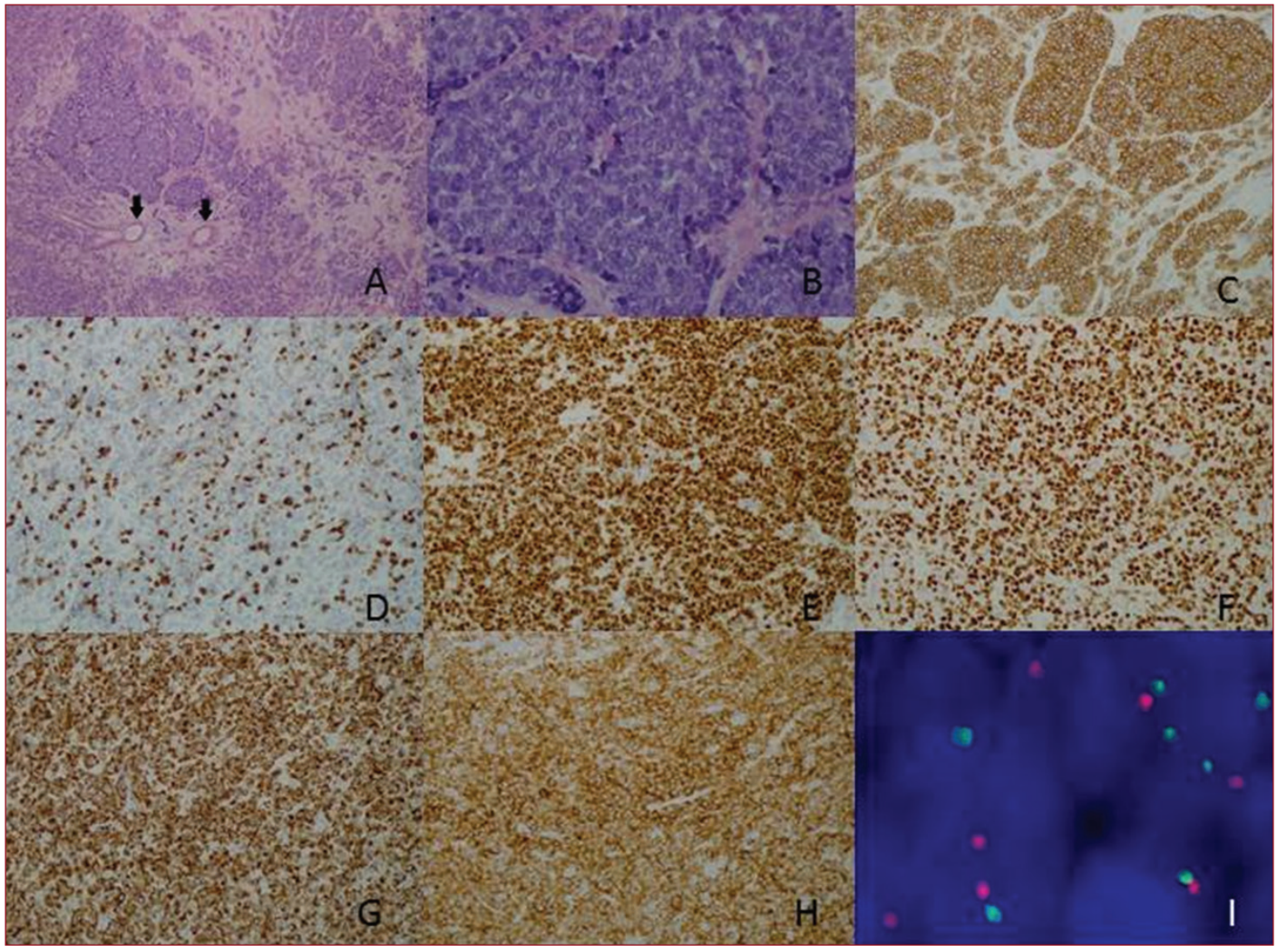

Figure 1:
A: Two salivary gland ductus (arrows) (Hematoxylin-eosin, original magnification, X 100)
B: (Hematoxylin-eosin, original magnification, X 400)
C: (CD99, original magnification, X 200)
D: (Ki67, original magnification, X 200)
E: (NKX2.2, original magnification, X 200)
F: (p40, original magnification, X 200)
G: (Pancytokeratin, original magnification, X 200)
H: (Synaptophysin, original magnification, X 200)
I: Fluorescence in situ hybridization photomicrograph demonstrating EWSR1-FLI1 breakapart signals.

DISCUSSION

ALES, initially described by Bridge et al.[6] in 1999, is an unusual tumor increasingly encountered at head and neck site in recent years.[5] In the current literature, ten cases of ALES were described at salivary glands.[3,5,7] In that region, ALES can mimic many tumors with small round cell morphology as well as basaloid or myoepithelial features. Diagnosis depends on both morphologic and immunohistocehimal features and has to be confirmed by molecular analysis.

In addition to classic small round cell morphology, ALES can show focal or overt keratinization including squamous pearls, palisating of basaloid cells,[3] and exhibit p40 and pancytokeratin expression suggestive of epithelial neoplasms.[7-9] Strong membranous CD99 immuno-positivity may aid to establish differential diagnosis including ALES. Molecular testing indicating the presence of EWSR1-FLI1 rearrangement has to be performed to establish the diagnosis of ALES.[7]

In the literature, the first ALES case in parotid was reported by Lezcano et al.[8] in 2015. In this case, the tumor demonstrated basal cell adenocarcinoma-like morphologic features. In differential diagnosis, they mainly considered basal cell adenocarcinoma and solid patterned adenoid cystic carcinoma of the parotid, and secondly take into account metastatic squamous cell carcinoma (SCC), neuroendocrine tumors, desmoplastic small round cell tumor and hyalinizing clear cell carcinoma. The ALES diagnosis was confirmed by immunohistochemical and molecular tests in addition to morphologic features.

Rooper and Bishop[5] analyzed 23 cases of ALES at head and neck region including eight parotid located ALESs and revealed the morphologic, immunohistochemical and molecular featues of this rare entity. In their case series, only one case was correctly diagnosed as ALES previously.[9] Other tumors was diagnosed as basal cell adenoma, basal cell adenocarcinoma, poorly differentiated carcinoma with basaloid features, high grade neuroendocrine carcinoma and even Merkel cell carcinoma. In this case series,[5] the youngest patient with ALES of the parotid was 32-year-old and the mean age was 47. Our 20-year-old patient is the youngest one reported in the current literature with ALES arising in parotid.

Lilo et al.[9] presented the cytopathologic findings of ALES detected in a 72-year-old male with left parotid mass. In their report, the tumor displayed primitive small round blue cell morphology admixed with groups of epithelioid cells with amphophilic cytoplasm and focal squamous differentiation. They emphasized that cytopathologists need to be aware of and consider this entity in the differential diagnosis of a lesion with this appearance and include CD99 and/or FLI1 in the immunohistochemistry panel.

Kikuchi et al.[10] reported ALES of soft tissue arising in the neck and associated with the vagus nerve in an 11-year-old girl. The tumor demonstrated a biphasic growth pattern consisting of epithelioid nests and spindle cell components. They suggested consideration of the subtype of ES with epithelial differentiation can occur in the neck of young people and can mimic other types of carcinoma such as SCC with unknown primary or malignant salivary gland tumors.

CONCLUSION

We described the ninth and the youngest case of ALES arising in parotid and briefly discussed some of the previously reported cases. We consider pathologists must be aware of this rare entity and take into account in differential diagnosis of tumors with small round cell morphology accompanied by epithelial features. It must be kept in mind that precise diagnosis of ALES depends on both morphologic and immunohistochemical findings and has to be supported by molecular analysis determining EWSR1-FLI1 rearrangement.

ETHICAL DECLARATIONS

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

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