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## ARTICLES

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- Relationship of atherogenic index of plasma with exercise, obesity and biochemical parameters ..... 33-38  
*Olgun E, Topçu E, Çetin Ş.*
- Evaluation of the effect of the COVID-19 pandemic on the depression, anxiety and stress levels of anesthesiology and reanimation doctors, and their work and social lives..... 39-44  
*Soylu NB, Başağan Moğol E, Eker SS, Akesen S, Sezer Soylu H.*
- Perceptions of intensive care nurses on the concepts of brain death and coma: a metaphor analysis..... 45-51  
*Kaş C, Durmuş İskender M, Akın Eroğlu S.*
- Comparison of detailed brain volume measurements in schizophrenia with healthy individuals..... 52-61  
*Deniz G, Karakurt, N, Özcan H, Acer N.*
- Evaluation of patients presenting with headache to the emergency outpatient clinic..... 62-67  
*Ay M, Erden V.*
- Assessment of first-time attendees at a pain clinic using a pain inventory tool..... 68-72  
*Gülen D, Erden V.*
- A rare case of lipoid pneumonia due to diesel aspiration ..... 73-75  
*Işık Ş.*
- Hairy tongue secondary to antibiotic usage ..... 76-77  
*Durak Anşin DM, Kurt İ.*
- Optimizing patient care: rethinking referrals for iron deficiency anemia in internal medicine..... 78-79  
*Ünal S.*

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# Relationship of atherogenic index of plasma with exercise, obesity and biochemical parameters

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## ABSTRACT

**Aims:** It is well-known that regular moderate-intensity aerobic exercise has positive effects on various health indicators, including obesity and cardiovascular diseases (CVD) and atherogenic index of plasma (AIP) is defined as a highly sensitive predictor of plasma atherogenicity and cardiovascular risk. Furthermore, it is known that physical activity has a reducing effect on AIP with its ability to decrease visceral fat and its positive impact on blood lipids. Additionally, large-scale AIP screenings are recommended for the early detection of obese individuals and effective intervention. This study aims to determine the relationship between regular exercise and cardiometabolic parameters and obesity based on current data.

**Methods:** The study involved a total of 126 participants aged 18-65 and it was conducted in the form of file screening, where the medical history reports of all patients were examined, and systemic physical findings were assessed. Fasting blood samples were used to determine the lipid profile. Anthropometric measurements and biochemical parameters of the participants were determined and AIP was calculated using the formula  $AIP = \log_{10}(TG/HDL-C)$ . Participants were categorized into groups based on their exercise status, BMI, and AIP risks, and the data of the study groups were evaluated statistically.

**Results:** Participants were divided into two groups based on exercise status, and in the exercise group, body mass index (BMI), body weight, waist circumference, AIP, and triglyceride levels were found to be lower, while high-density lipoprotein (HDL) levels were higher compared to the non-exercise group. In all participants, moderate-intensity exercise was negatively correlated with AIP, body weight, BMI, waist circumference, triglyceride, and low-density lipoprotein (LDL) levels; and positively correlated with HDL levels.

**Conclusion:** The relationships uncovered in this study among exercise, cardiometabolic parameters, and obesity status are expected to contribute to future research, especially in studies focusing on the impact of exercise on CVD and obesity.

**Keywords:** Exercise, physical activity, atherogenic index of plasma, obesity

## INTRODUCTION

Cardiovascular diseases (CVD) constitute a significant portion of global diseases. Despite advances in medical science and quality healthcare, the prognosis, diagnosis, and treatment of CVD have improved, yet coronary heart disease and stroke continue to be the leading two causes of the global disease burden. According to World Health Organization (WHO) data, in the year 2019, 17.9 million individuals lost their lives due to CVD.<sup>1,2</sup> All these data indicate the necessity of setting new goals for the prevention of CVD.<sup>3</sup>

Atherogenic Index of Plasma (AIP) is defined as a highly sensitive predictor of plasma atherogenicity and cardiovascular risk. It is known that AIP exhibits a strong and positive correlation with the fractional esterification ratio of high-density lipoprotein (HDL) and an inverse correlation with

low-density lipoprotein (LDL) particle size.<sup>4</sup> AIP is calculated by the base 10 logarithm of the ratio of triglyceride (TG) concentration to HDL cholesterol (HDL-C) [ $AIP = \log_{10}(TG/HDL-C)$ ].<sup>5</sup> Additionally, it has been demonstrated that AIP has a stronger correlation with cardiovascular diseases (CVD) compared to other lipid risk scores.<sup>6</sup>

The World Health Organization (WHO) defines obesity as “the abnormal or excessive accumulation of fat that presents a risk to health”.<sup>7</sup> In contrast to the perspective that obesity is solely a risk factor for the development of pathology in individuals, the World Obesity Federation characterizes obesity as a chronic, recurrent, and progressive disease.<sup>8</sup> Over the past quarter-century, obesity has raised serious concerns due to its association with the development, progression, impaired

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quality of life, and reduced life expectancy of chronic diseases such as cardiovascular diseases (CVD), diabetes mellitus (DM), cancer, and osteoarthritis. However, the individual risk for the development of obesity-related comorbidities is a complex issue that cannot be explained solely by the degree of adiposity.<sup>9,10</sup>

WHO has reported that physical activity has numerous benefits, including reducing weight, lowering blood pressure, and improving blood lipid and glucose levels.<sup>11</sup> There is a wealth of research suggesting that regular exercise can reduce the risk of developing cardiovascular diseases CVD, including coronary heart disease, stroke, type 2 diabetes mellitus DM, and hypertension. Exercise is recognized as a natural anti-atherogenic agent, and several studies support its role in atheroprotection. Additionally, exercise is known to play a significant mechanical endothelial stimulatory role, serving as a precursor to a series of events that support atheroprotection.<sup>11-13</sup>

While physical activity, especially moderate to vigorous physical activity, has many benefits such as weight loss, lowering blood pressure, and improving blood lipid and glucose levels, studies also indicate its reducing effect on AIP with its ability to decrease visceral fat and its positive impact on blood lipids.<sup>14-17</sup> The detailed mechanism is explained by the effect of exercise on increasing lecithin-cholesterol acyltransferase (LCAT) levels, a key enzyme for the esterification of free cholesterol and its transfer to high-density lipoprotein (HDL) that carries reverse cholesterol. Additionally, exercise may increase lipoprotein lipase (LPL) levels, the primary enzyme responsible for removing circulating triglycerides associated with lipoproteins.<sup>18,19</sup>

Another consideration is that while AIP predicts abnormal weight, there is a limited body of research on the relationship between obesity, excess weight, and AIP. Based on the few studies conducted, it is suggested that AIP is a robust lipid indicator for understanding the risk of obesity. Due to its cost-effectiveness and the simplicity of the testing procedure, large-scale AIP screenings are also recommended for early detection of obese individuals and effective intervention.<sup>20,21</sup> In this study, considering all this information, the aim is to determine the relationship between physical activity status and AIP, biochemical markers, and obesity.

## METHODS

### Study Design and Population

This study received approval from the Ethics Committee of Clinical Studies at Amasya University Faculty of Medicine (Date: 07.12.2023, Decision No: 2023/135). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The research was conducted with a total of 126 participants, including 95 females and 31 males, aged between 18 and 65, who applied to Ruhi Tingiz Physical Therapy Rehabilitation Center-Physical Therapy clinic of Amasya University Sabuncuğlu Şerefeddin Training and Research Hospital, Amasya University, from July 15, 2020 to September 15, 2023.

The study was conducted in the form of file screening, where the medical history reports of all patients were examined, and systemic physical findings were assessed. The body-mass index (BMI) values of all patients were calculated using the formula  $BMI = \text{Weight (kg)} / \text{Height (m)}^2$ . AIP values of the patients were calculated using the formula  $AIP = \log_{10} (TG/HDL-C)$ .

Individuals with diabetes, heart failure, acute and chronic kidney failure, chronic liver disease, and acute infectious diseases were excluded from the study.

The laboratory results of individuals who had blood samples taken from the antecubital vein after an overnight fast during routine visits to Amasya University Sabuncuğlu Şerefeddin Training and Research Hospital between July 15, 2020 and September 15, 2023 were utilized in the study. The laboratory results of the patients were obtained retrospectively from the patient files.

### Statistical Analysis

Continuous data were summarized using mean ( $\mu$ ), standard deviation (Sd), and lower subgroups. Categorical data were expressed as percentages. Student's t-test was employed for binary comparisons of normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. For normally distributed data with more than two groups, the ANOVA test was utilized, and for non-normally distributed data with more than two groups, the Kruskal-Wallis ANOVA test was applied. Chi-square test was used for the analysis of categorical variables. Statistical analyses were conducted using the SPSS software package, and a significance level of  $p < 0.05$  was considered.

## RESULTS

The comparisons and correlation statistics of the study groups with the study findings are presented in the tables and explanations below.

This study was conducted with a total of 126 participants, comprising 95 females and 31 males. The mean age of the participants was  $38.02 \pm 9.78$ , with an age range between 18 and 65. When questioned about engaging in at least 45 minutes of light-to-moderate intensity aerobic exercise (such as brisk walking, swimming, cycling, etc.) at least 3 days a week for the past three months, 45.2% of the participants (57 individuals) reported exercising, while 54.8% (69 individuals) indicated a lack of exercise routine, suggesting a sedentary lifestyle.

AIP, the minimum value was -0.41, the maximum value was 0.89, and the mean value was  $0.31 \pm 0.27$  across all participants. Concerning AIP risk categories, 23% of participants (29 individuals) were classified as low risk, 17.5% (22 individuals) as moderate risk, and 59.5% (75 individuals) as high risk.

When clinical and biochemical findings were evaluated in two groups based on exercise status, it was observed that BMI, body weight, and waist circumference were statistically significantly higher in those who did not exercise compared to those who did exercise ( $p < 0.001$ ). In the non-exercise group, triglyceride levels were found to be significantly higher ( $p < 0.001$ ), while HDL levels were statistically significantly higher ( $p < 0.001$ ) in the exercise group. AIP, a marker for CVD, was significantly higher ( $p < 0.001$ ) in the non-exercise group, and the AIP average was classified as high risk ( $AIP > 0.21$ ). There was no statistically significant difference between the groups in terms of total cholesterol and LDL levels ( $p > 0.05$ ) (Table 1).

There was a statistically significant difference ( $p < 0.001$ ) among obesity risk groups based on exercise status and BMI in the groups. The non-exercise group had a higher risk of obesity, while the exercising group showed a lower risk (Table 2).



**Table 1. Comparison of clinical and biochemical findings according to exercise groups**

	Mean±SD		P	95% CI	
	Non-exercise (n=69)	Exercise (n=57)		Minimum	Maximum
Age (year)	40.96±9.83	34.47±8.55	0.0001	3.33	10.21
BMI (kg/m <sup>2</sup> )	32.23±8.28	25.31±4.62	0.0001	4.48	9.36
Body weight (kg)	84.38±19.65	68.74±12.92	0.0001	9.63	21.64
Waist circumference (cm)	101.42±15.23	82.58±14.91	0.0001	13.49	24.18
AIP	0.47±0.20	0.11±0.21	0.0001	0.28	0.43
Total cholesterol (mg/dl)	187.90±49.08	172.28±40.86	0.0580	-0.51	31.76
Triglyceride (mg/dl)	151.35±71.76	77.35±32.18	0.0001	53.67	94.32
HDL (mg/dl)	46.79±10.28	55.72±11.49	0.0001	-12.77	-5.08
LDL (mg/dl)	113.75±28.74	100.04±31.49	0.0812	3.08	24.35

Mann Whitney U (data follow a non-normal distribution), Student's t-test (data follow a normal distribution), CI: Confidence interval, SD: Standart deviation, BMI: Body mass index, AIP: Atherogenic index of plasma, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

**Table 2. Distribution of groups according to exercise status and obesity risk groups**

	Normal weight (BMI=18.5-25 kg/m <sup>2</sup> ) (n=43)	Overweight (BMI=25-30 kg/m <sup>2</sup> ) (n=36)	Obese (BMI>30 kg/m <sup>2</sup> ) (n=47)
Non-exercise (n=69) n (%)	11 (15.9%)	22 (31.9%)	36 (52.2%)
Exercise (n=57) n (%)	32 (56.1%)	14 (24.6%)	11 (19.3%)

Chi-Square test (p<0.001), BMI: Body mass index

A statistically significant difference (p<0.001) was observed among AIP risk groups based on exercise status in the groups. In the non-exercise group, the proportion of individuals in the high-risk category for AIP was higher, while in the exercise group, the proportion of individuals in the high-risk category for AIP was lower (Table 3).

**Table 3. Distribution of groups according to exercise status and AIP risk groups**

	Low risk (AIP<0.11) (n=29)	Intermediate risk (AIP=0.11-0.21) (n=22)	High Risk (AIP>0.21) (n=75)
Non-exercise (n=69) n (%)	0 (0.0%)	10 (14.5%)	59 (85.5%)
Exercise (n=57) n (%)	29 (50.9%)	12 (21.1%)	16 (28.1%)

Chi-Square test (p<0.001), AIP: Atherogenic index of plasma

In all participants, there is a statistically significant negative moderate-level correlation (p<0.001; correlation coefficients are respectively r=-0.654; -0.330; -0.420; -0.451; -0.531; -0.543; -0.405) between engaging in moderate-intensity exercise and AIP, age, body weight, BMI, waist circumference, triglyceride level, and obesity status. There is also a statistically significant negative moderate-level correlation (p=0.012; r=-0.220) between exercise and LDL level. This indicates that as exercise increases, there is a decrease in these biochemical, anthropometric, and demographic parameters. A statistically significant positive moderate-level correlation (p<0.001; r=0.382) is found between exercise and HDL level. However, there is no statistically significant relationship between exercise status and total cholesterol level or the occurrence of metabolic syndrome (p>0.05) (Table 4).

**Table 4. Correlation between exercise status and anthropometric and biochemical parameters in all participants**

	Correlation Coefficient	p
AIP	-0.654	<0.001
Age (year)	-0.330	<0.001
Body weight (kg)	-0.420	<0.001
BMI (kg/m <sup>2</sup> )	-0.451	<0.001
Waist circumference (cm)	-0.531	<0.001
Total cholesterol (mg/dl)	-0.170	0.580
LDL (mg/dl)	-0.220	0.012
HDL (mg/dl)	0.382	<0.001
Triglyceride (mg/dl)	-0.543	<0.001
Obesity	-0.405	<0.001

AIP: Atherogenic index of plasma, BMI: Body mass index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

When clinical and biochemical findings were grouped and evaluated according to AIP risk categories, it was found that body weight, BMI, and waist circumference were statistically significantly different (p<0.01) and increased across all groups as the risk level increased. The LDL level was significantly different (p<0.01) in all risk groups, and as the risk increased, this value increased in all groups. Additionally, the total cholesterol level was statistically significantly higher (p<0.05) in the high risk group compared to the intermediate risk group (Table 5).

## DISCUSSION

In individuals with excessive weight and obesity, there is a risk of CVD and many metabolic diseases. However, it is known that especially abdominal obesity and visceral adiposity are stronger indicators in terms of mortality and morbidity risk compared to obesity. There is evidence indicating that moderate-intensity exercise intervention is clinically associated with a significant decrease in waist circumference and abdominal obesity.<sup>22,23</sup>

In this study, when comparing groups, it was found that body weight, BMI, and waist circumference were significantly lower in individuals who engaged in regular, moderate-intensity exercise compared to those who did not exercise.

**Table 5. Comparison of clinical and biochemical findings according to AIP risk groups**

Mean±SD				p	Difference
	1 (n=29)	2 (n=22)	3 (n=75)		
Age (year)	33.48±8.45	38.73±13.92	39.57±8.31	0.0180	3>1, 2>1
Body weight (kg)	64.26±11.97	71.54±11.58	84.03±19.23	0.0001	3>2, 3>1
BMI (kg/m <sup>2</sup> )	24.43±4.76	27.55±5.59	31.36±8.22	0.0001	3>2, 3>1
Waist circumference (cm)	78.14±15.73	87.45±17.37	100.20±14.26	0.0001	3>1, 3>2, 2>1
Total cholesterol (mg/dl)	168.17±41.53	168.04±40.65	189.48±47.66	0.0370	3>2, 3>1
LDL (mg/dl)	96.31±31.66	97.50±31.23	114.84±28.27	0.0050	3>2, 3>1

AIP: Atherogenic index of plasma, SD: Standart deviation, BMI: Body-mass index, 1=Low risk (AIP<0.11), 2=Intermediate risk (AIP=0.11-0.21), 3=High risk (AIP>0.21)

These findings are consistent with a systematic review and meta-analysis report that included 25 randomized controlled trials (1686 participants) investigating the impact of aerobic exercise on waist circumference in overweight or obese individuals. According to this report, regular aerobic exercise significantly reduces waist circumference, and this change is associated with changes in visceral fat tissue. The study aimed to determine the relationship between waist circumference, visceral fat accumulation, and body weight changes as a result of aerobic exercise intervention. It also aimed to ascertain whether the reduction in waist circumference due to exercise is managed by components of the aerobic exercise prescription.<sup>24</sup>

Another finding of the study was that engaging in moderate-intensity exercise positively influenced the lipid profile, especially triglyceride, HDL, and LDL levels. This finding is supported by a systematic review and meta-analysis study that examined research conducted between 2007 and 2016 to assess the relationship between exercise, obesity, and lipid profile. The study reported a beneficial effect of exercise intervention on BMI, waist circumference, total cholesterol, triglycerides, LDL, and HDL. It was also noted that the continuity and intensity of exercise correlated with greater and more consistent improvements in adult obesity and lipid profile compared to exercise duration.<sup>25</sup> Consistent with the findings of the present study, a systematic review conducted on animals aimed to provide a general overview of the effects of regular low to moderate-intensity exercise, performed for at least two weeks, on apolipoproteins (Apo A-I, Apo-E), Paraoxonase-1 (PON1), ATP-binding cassette transporters (ABCA1, ABCG1, ABCG4, ABCG5, ABCG8), scavenger receptor class B type I (SR-BI), cholesteryl ester transfer protein (CETP), low-density lipoprotein receptor (LDLr), cholesterol 7 alpha-hydroxylase (CYP7A1), and Niemann-Pick C1-like 1 (NPC1L1). The review revealed that in studies predominantly focused on moderate-intensity aerobic exercise, exercise had a positive effect on atherosclerosis and reduced the risk of CVD, which is a primary concern of contemporary health systems. It emphasized that various mechanisms, including the modification of reverse cholesterol transport (RCTr) process elements, mediate the positive effects of exercise on CVD. The review highlighted that several mechanisms, involving PPAR, LXR, FXR, and PXR, along with various hormones and cytokines, influence RCTr elements, but the mechanism of RCTr changes associated with exercise remains unclear.<sup>26</sup>

There is ample evidence from various studies supporting the idea that aerobic exercise partially lowers serum TG and LDL levels while increasing HDL levels, thereby reducing the risk of coronary heart disease (CHD) associated with high or abnormal lipid and/or lipoprotein levels. Additionally, exercise has an impact on HDL maturation and composition, influencing reverse cholesterol transport from peripheral cells to the liver. This process contributes to the prevention of atherosclerosis, improvement of cardiac lipid metabolism, and thus demonstrates a protective effect against CVD.<sup>27</sup> It is well-established that regular physical activity and exercise have both direct and indirect physiological adaptations, as well as numerous pleiotropic benefits on cardiovascular health. Higher levels of physical activity, exercise, and cardiorespiratory fitness (CRF) are associated with a reduced risk of CVD, including myocardial infarction and mortality related to CVD and all causes.<sup>28</sup> In a meta-analysis study

involving thirty-eight articles encompassing a total of 2089 CVD patients, it was indicated that aerobic exercise significantly reduces aortic systolic pressure (ASP), improves carotid-femoral pulse wave velocity, cardiac output, and left ventricular ejection fraction. Aerobic exercise intervention in CVD patients has substantially enhanced central arterial stiffness and cardiac function. These findings suggest that a well-designed regimen intervention could optimize the beneficial effects of exercise and provide guidance for those involved in cardiovascular rehabilitation of CVD patients.<sup>29</sup> A review aimed at summarizing recent findings on the multiple benefits of exercise on CVD highlighted that physical activity could enhance insulin sensitivity, alleviate plasma dyslipidemia, normalize high blood pressure, reduce blood viscosity, stimulate endothelial nitric oxide production, and enhance leptin sensitivity to protect the heart and vessels. The same review emphasized the general exercise intensity recommended by the American Heart Association for preventing CVD, highlighting 30 minutes of moderate-intensity exercise five times a week. However, it was noted that even the easiest activity is better than a completely sedentary lifestyle. Furthermore, considering individual differences in physical fitness, it was emphasized that a standardized exercise regimen might not provide a complete treatment for everyone, and thus, exercise should be personalized.<sup>30</sup>

In the current study, the average AIP of the exercise group was significantly lower than that of the non-exercise group. Non-exercisers were found to have moderate and high-risk AIP classifications, and there was a statistically significant negative correlation between exercise status and AIP at a moderate level. These findings align with a cross-sectional study involving 27,827 middle-aged Chinese men, where a correlation between moderate-intensity aerobic exercise duration and AIP was determined. In the PA1 (non-exercise), PA2 (occasional exercise), and PA3 (frequent exercise) groups, AIP levels were significantly higher in PA1 and PA2 groups compared to the PA3 group. Additionally, the percentage of the population at high risk for atherosclerosis (AIP  $\geq 0.21$ ) was significantly lower in the PA3 group compared to the PA1 and PA2 groups. It was suggested that engaging in at least 90 minutes of moderate-intensity aerobic exercise per week was associated with a reduction in AIP among middle-aged Chinese men.<sup>31</sup> In a study involving 2,701 adults investigating the relationship between moderate to vigorous physical activity, dietary behavior, and AIP, engaging in regular physical activity despite unhealthy dietary behavior was associated with a reduced likelihood of having a high AIP. The same study highlighted that visceral fat mediated the relationship between physical activity and AIP.<sup>32</sup> Similarly, in another study aimed at investigating the effects of 8 weeks of aerobic exercise on anthropometric indices, AIP, and some cardiovascular risk factors in inactive men, participants who underwent aerobic exercise at 70% of their maximum heart rate were evaluated with blood samples taken before and after exercise. The results indicated a significant decrease in body fat percentage, cholesterol, LDL/HDL ratio, TG/HDL ratio, and apo- $\beta$  after 8 weeks of aerobic exercise. Additionally, VO<sub>2</sub>max and HDL showed a significant increase after 8 weeks of aerobic activity, suggesting that an increase in physical activity could reduce the risk of cardiovascular disease.<sup>33</sup> When examining a study that investigated the relationship between AIP and acute aerobic exercise in healthy young men aged 18-25, blood samples were taken before, immediately

after, and 15 minutes after exercise to assess biochemical parameters. The results revealed a statistically significant increase in average HDL values at different stages of aerobic exercise, along with a significant decrease in triglycerides, AIP, and weight averages at different stages of exercise. The study suggested that exercise has the potential to reduce CVD risk in sedentary, non-obese young men who aim to maintain a physically active lifestyle. Moreover, the correlation observed between different stages of aerobic exercise and AIP indicated the significant role of short-term aerobic exercise in mitigating CVD risk.<sup>34</sup>

## CONCLUSION

CVD constitutes a significant portion of the global disease burden, and AIP is commonly used as a sensitive and practical criterion for assessing CVD risk. Obesity, like many chronic diseases, is a substantial risk factor for CVD. However, regular exercise plays a crucial role in both preventing obesity and supporting atheroprotection. This study further demonstrated that regular moderate-intensity exercise is directly associated with body weight, BMI, waist circumference, and obesity status. Additionally, it revealed correlations between regular exercise and key cardiometabolic parameters such as LDL, triglyceride levels, and AIP. The findings of this study, which align with current literature, are expected to shed light on future research exploring the relationships between exercise, obesity, and AIP.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Amasya University Non-invasive Clinical Researches Ethics Committee (Date: 07.12.2023, Decision No: 2023/135).

### 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 declared no conflicts of interest with respect to the authorship and/or publication of this article.

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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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# Evaluation of the effect of the COVID-19 pandemic on the depression, anxiety and stress levels of anesthesiology and reanimation doctors, and their work and social lives

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## ABSTRACT

**Aims:** To measure the effects of the coronavirus disease-19 (COVID-19) pandemic on the social and economic status and their depression, anxiety and stress scores of anesthesiology and reanimation specialists, using the depression, anxiety and stress scale-21 (DASS-21).

**Methods:** The study was conducted with an online questionnaire directed to the participants online, following the approval of Uludağ University Ethics Committee labeled 2020-16/1. The questionnaire was prepared on SurveyMonkey and distributed via a specially acquired link. Participants were prevented from submitting the questionnaire more than once. 38 questions were asked to the participants. At the end of the questionnaire, the participants were asked to fill the DASS-21. Questionnaire has been distributed through social media and mobile communication applications.

**Results:** 198 volunteers participated in the study. 122 of the participants were female (61.62%) and 76 (38.38%) were males. 75 of the participants (37.88%) were trainees, 113 (57.07%) were anesthesiology and reanimation specialists, 2 (1.01%) were specialist physicians undergoing intensive care training, 4 (2.02%) were intensive care specialists, 1 was a specialist physician receiving algology training, and 3 (1.52%) were algologists. 42 participants were (21.21%) in a training-research hospital, 87 participants (43.94%) in a university hospital, 35 participants (17.68%) in a state hospital, 13 participants (6.57%) in city hospitals, and 21 participants (10.61%) were working in private hospitals. 81.6% of all physicians participating in the survey show depression symptoms, 62% of participants were showing symptoms of anxiety and 71.1% of participants described stress symptoms. All scores were higher in female physicians ( $p < 0.05$ ). Depression scores of residents were higher than specialists ( $p < 0.05$ ). All scores of physicians working in training-research hospitals are higher than physicians working in other institutions ( $p < 0.05$ ).

**Conclusion:** Almost all physicians have experienced changes in workload, income and workplaces during the pandemic. High DASS-21 scores in all physicians were thought-provoking and highlighted the psychological pressure that anesthesiology and reanimation physicians had been under.

**Keywords:** COVID-19, anesthesiology and reanimation, DASS-21 scale

## INTRODUCTION

Despite its geographical location and its place in international transportation, Türkiye has not disclosed any COVID-19 cases for a long time. The first case of COVID-19 was reported by the Minister of Health at a press conference on March 10, 2020.

In the days following the first case reported during the pandemic, a rapid increase in number was recorded. In April and May of 2020, as in many countries of the world, dramatic increases were seen in the number of cases. Healthcare system has been reorganized by the Ministry in response to the pandemic in

line with the suggestions and recommendations from the scientific committee. Healthcare workers were organized in this sense, financial incentives were offered to encourage them, and hospitals were tried to be brought to the fore in the fight against the pandemic. Regulations were enforced on transportation and curfews, restrictions on international transportation came first, and intercity travel restrictions and additional quarantine measures were taken due to the increase in number of cases. There was some slowdown in the pace of the epidemic in May 2020.

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Number of new cases were relatively low during summer, and restrictions were lifted in part, but as of September, an increase in the number of patients began; and especially in December 2020, Türkiye has been one of the countries with the highest number of new cases in the world.

The fight against the pandemic has affected health workers in almost all fields. Employees have served in pandemic clinics, other clinics, intensive care units, pandemic intensive care units and operating rooms with and without a pandemic unit. Services were also provided in the fields like emergency departments, primary care clinics, emergency transportation services and filiation services. In the early period of the pandemic, as of April 29, 2020, the number of infected healthcare workers in Türkiye was 7428. This corresponded to 6.5% of all COVID-19 cases.

The high rate of infection and related deaths among health care workers adversely affected the mental health of healthcare staff and caused the situation of those who already have a psychological disorder to progress. Negative reports from various countries, increasing death toll, loss of loved ones, fear of infecting family members, death of colleagues, and having to work for a long time with protective equipment were the potential triggers for psychological problems.

Anesthesiology and reanimation specialists and residents have played a key role in the fight against the pandemic, especially in the treatment of patients with severe disease and therefore faced with high mortality rates and the psychological burden of deceasing patients despite intensive treatment. Additionally, the increased need for airway interventions such as high-flow O<sub>2</sub> treatments, non-invasive and invasive mechanical ventilation, and intubation of patients with COVID-19 infection indisputably increased the coronavirus exposure of physicians in this specialty.

Some studies have been carried out on the healthcare personnel who are at the forefront of the fight against the pandemic in Türkiye, and with these studies, lifestyle changes, how they are affected socially and economically, as well as their psychological state are examined. However, this study is the first to be conducted on anesthesiology and reanimation physicians. The aim of our study is to evaluate how anesthesiology and reanimation physicians are affected socially, economically and psychologically during the pandemic.

## METHODS

Preliminary research was carried out on the most appropriate method in which psychological measurements could be made. To this purpose, consultancy was received from Uludağ University, Department of Psychiatry, similar local and international publications were scanned, and in the end, we decided to use the depression, anxiety and stress scale-21 (DASS-21), which is the most appropriate scale for the purpose of the study ([See Appendix](#)).

The survey was created on the website [www.surveymonkey.com](http://www.surveymonkey.com) (Copyright © 1999-2021 SurveyMonkey, Dublin, Ireland) following the approval of Uludağ University Faculty of Medicine Clinical Researches Ethics Committee (Date: 16.09.2020, Decision No: 2020-16/1). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The questionnaire created on this site was distributed via a special link (<https://tr.surveymonkey.com/r/PandemiAnesReak>). Participants received this weblink via e-mail and internet-based mobile communication applications.

Participants were prevented from filling out the questionnaire more than once, thus ensuring the authenticity and reliability of the data. 38 questions were asked in the survey. Demographic data were collected in the first 16 questions. In the following 21 questions, the volunteers were asked about their social habits and the way they were affected economically during the pandemic period. In addition, they were asked to indicate their sources of information in this process. In the 38<sup>th</sup> question, the participants were asked to fill in the DASS-21 scale and to mark the option that best suited them without thinking too long on each item.

The grouping, comparison and collection of the data was done with the response analysis engine provided by the survey site ([www.surveymonkey.com](http://www.surveymonkey.com)). Kruskal-Wallis and Mann-Whitney U tests were used in the analysis of statistical data, and Pearson's chi-square test was used for data in which multiple categories were evaluated. SPSS 23.0 (IBM, Armonk, New York, United States) was used for statistical analysis. Confidence level for statistical significance was determined as 95% ( $p < 0.05$ ).

## RESULTS

The demographics of the participants are as shown in [Table 1](#). A total of 198 participants joined the survey. Average completion time was 6 minutes and 57 seconds. Survey completion rate of participants was 77%.

### Data on the Effects of the Pandemic on Social and Economic Life

23 (11.61%) of all participants stated that they were infected with coronavirus at least once during the pandemic. There is no proportional difference between physicians who have had COVID-19 infection, according to the branches of specialist physicians, or between assistants and specialist physicians. In addition, no significant difference was observed when the rates of COVID-19 infections were compared according to the institution where the physicians work.

176 (89.34%) of the physicians stated that they were worried about transmitting diseases to those living at home during the pandemic. Among the physicians who expressed this concern, married people (130 married people, 97.01%) had a higher level of concern than those who were single (46 single people, 73.02%) ( $p < 0.05$ ). 64 of all participants (32.49%) stated that they accommodated in a place different from their families.

Fifty-three people (27.04%) stated that they had at least one of their relatives infected with COVID-19, and 14 participants (7.07%) reported that at least one of their relatives died. All physicians whose relatives passed away are physicians working in university and state hospitals.

### Effects on Worklife

179 (90.4%) of all physicians stated that their work routine changed in March, April, and May 2020, when the first virus spread in Türkiye was seen ([Table 2](#)). 176 people answered in the survey how the nature of the change in the way they work and how their income was affected. Participants were able to choose more than one option. Of those who stated that their working style has changed, 95 (54%) stated that their workload has increased, 48 (27.3%) stated that their workload has decreased, and 33 (18.7%) stated that their workload has not

changed. 61 people (34.7%) stated that their income increased in this period, 34 people stated that their income decreased (19.3%), and 81 people (46%) stated that their income did not change.

**Table 1. Demographics of the participants**

	n	%
Average Age (year)	36.50±9.71	
Gender		
Male	76	38.38
Female	122	61.62
Marital status		
Married	135	68.18
Single	63	31.82
Children		
1 or more	112	56.56
None	86	43.44
Accommodating with		
Single	48	24.4
Nuclear family	129	65.15
Extended family	21	10.61
Chronic disease		
Yes	34	17.17
No	164	82.83
Cigarette-alcohol consumption		
Cigarettes only	48	25.4
Alcohol only	62	32.8
Both	18	9.09
None	106	56.08
Title		
Resident-trainee	75	37.88
Anesthesiology and reanimation specialist	113	57.07
Algology resident	1	0.5
Algology specialist	3	1.52
Intensive care specialist	4	2.02
Intensive care resident	2	1.01
Institution		
University hospital	87	21.21
Research and education hospital	42	43.94
State hospital	35	17.68
City hospital	13	6.57
Private healthcare institution	21	10.61

**Table 2. Changes in the work routine**

Changes	Amount (%), n
I worked in a different clinic than i normally work in	8.6% 15
I worked at the pandemic clinic	18.3% 32
I worked in a different intensive care unit where i don't normally work	14.3% 25
I worked in the pandemic intensive care unit	57.1% 100
I was assigned to another institution	11.4% 20
Other	19.4% 34

Percentage of residents (16 physicians, 22.53%) who were sent to another institution were significantly higher than those of specialists (4 physicians, 3.80%) ( $p<0.05$ ). The proportion of specialists who stated that their workload increased (68

physicians, 64.70%) was significantly higher than that of residents (27 physicians, 38%) ( $p<0.05$ ). The rate of specialists who stated that they lost more income in this period (26 physicians, 24.77%) was higher than that of research assistant physicians (8 physicians, 11.52%) ( $p<0.05$ ). In addition, it is seen that most of the physicians working in university hospitals are assigned to different institutions. 20 physicians stated that they were sent to different institutions, and 17 of them (85%) were physicians working in university hospitals. Physicians working in public hospitals (20 physicians, 64.52%) reported the highest increase in workload compared to physicians in other institutions ( $p<0.05$ ).

In this period, the group with the highest income increase was the physicians working in training-research hospitals (21 physicians, 52.5%) ( $p<0.05$ ). Among the physicians who stated that their working style did not change, there was not enough response to examine the statistical significance in terms of income or workload. It is obvious that the working routine of most of the participants was affected.

When questioned how their income was affected, 47 participants (25.7%) stated that their income increased relatively, 46 participants (24.9%) stated that their incomes decreased, and 92 participants (49.7%) stated that their income did not change. There is no statistical difference between institutions. However, income of the anesthesiology and reanimation specialists decreased more than the other groups ( $p<0.05$ ).

Participants were also asked whether they would receive a vaccine if it was ever developed. There was no vaccine developed at the time the question was asked. 94 of the participants answered yes (50.5%) to this question. 171 (92%) of the physicians do not think that the pandemic would end soon, and life would return to normal. Among residents, percentage of those who do not want to receive a vaccine to be released is higher than other physician groups ( $p<0.05$ ).

### DASS-21 Scoring Data

In the DASS-21 scoring, the presence and severity of stress, anxiety or depression are evaluated with the scores in Table 3, according to the responses of the individuals.

**Table 3. Evaluation of the severity of depression, anxiety and stress according to the total scores in the DASS-21 scale**

Severity	Depression	Anxiety	Stress
Normal	0-4	0-3	0-7
Mild	5-6	4-5	8-9
Moderate	7-10	6-7	10-12
Severe	11-13	8-9	13-16
Very severe	14+	10+	17+

At the end of the survey, participants were asked to fill DASS-21 scale and 152 participants (84 specialists, 68 residents) completed the DASS-21 questionnaire. Accordingly, the scores according to the answers given by the participants on the DASS-21 scale are summarized in Table 4. The scoring values given in the depression, anxiety and stress columns are average values. Participants were analyzed by dividing into groups, and the depression, anxiety and stress scores of each group were calculated separately.

Table 5 presents the distribution of depression, anxiety and stress symptoms. According to this table, 81.6% of all physicians participating in the survey had some level of depression, 62% had some level of anxiety and 71.1% had some level of stress.

**Table 4. Distribution of severity of symptoms among all physicians**

Severity	Depression (n, %)	Anxiety (n, %)	Stress (n, %)
Normal	28 (18,4%)	58 (38,0%)	44 (28,9%)
Mild	16 (10,5%)	29 (19,1%)	16 (10,5%)
Moderate	31 (20,4%)	16 (10,6%)	26 (17,1%)
Severe	28 (18,4%)	18 (11,8%)	40 (26,4%)
Very severe	49 (32,3%)	31 (21,5%)	26 (17,1%)
<b>Residents</b>			
Normal	13 (%19,1)	24 (%35,2)	18 (%26,5)
Mild	5 (%7,4)	12 (%17,6)	7 (%10,3)
Moderate	13 (%19,1)	9 (%13,2)	10 (%14,7)
Severe	9 (%13,2)	9 (%13,2)	18 (%26,5)
Very severe	28 (%41,2)	14 (%20,6)	15 (%22,0)
<b>Specialists</b>			
Normal	15 (%17,9)	34 (%40,5)	26 (%31,0)
Mild	11 (%13,1)	17 (%20,2)	9 (%10,7)
Moderate	18 (%21,4)	7 (%8,3)	16 (%19,0)
Severe	19 (%22,6)	9 (%10,7)	22 (%26,2)
Very severe	21 (%25,0)	17 (%20,2)	11 (%13,1)

**Table 5. Evaluation of the severity of depression, anxiety and stress according to the total scores according to the DASS-21 scale**

By groups	Depression score	Anxiety score	Stress score
All groups (n=152)	10.35	5.63	10.85
Female (n=97)	11.47	6.66	11.47
Male (n=55)	8.76	3.86	8.35
Residents (n=68)	11.31	5.83	10.75
Specialists (n=84)	10.46	5.49	10.01
<b>By institution</b>			
University hospital (n=75)	10.24	5.06	9.97
Research and training hospital (n=31)	12.16	6.81	11.53
City hospital (n=9)	14.32	5.94	11.39
State hospital (n=24)	10.84	6.5	11.01
Private healthcare institution (n=13)	8.98	4.38	7.68

## DISCUSSION

The pandemic has undoubtedly brought about changes in the existing orders in many areas all over the world. Chaos caused by the virus, turmoil in the economies, shutdown measures, heavy burden faced by the healthcare systems, problems experienced by the political administrations and social explosions have made 2020 an extraordinary year. Undoubtedly, the most prominent ones have been healthcare professionals as they have completely shouldered the burden brought by the virus, adapted quickly and battled with the pandemic. Healthcare professionals were confronted with an unprecedented situation, forcing them to make tough decisions or work under severe pressure. Factors such as moral and ethical dilemmas, being a decision maker in the optimum distribution and use of limited resources, trying to protect the physical and mental wellbeing of patients, and balancing work and social life can be counted among the pressure elements.

Trying to overcome so many factors have of course caused "moral trauma" or mental health problems.<sup>5</sup> Moral trauma can roughly be defined as moral hardening or loss of ethical sensitivity because of actions taken or being under psychological stress.<sup>5,6</sup> This is not a psychological disorder or

mental illness, but a response to the stress. In general, it may result in post-traumatic empowerment such as increase in self-confidence, acquiring different perspectives, and increase in psychological resistance; but can sometimes cause depressive mood and even suicidal ideation.<sup>5</sup>

In the COVID-19 pandemic, many healthcare workers faced increased workload, economic and moral difficulties, limited social interaction, witnessed severe disease and therefore increased mortality and morbidity. It would be reasonable to say that the ground for moral trauma was formed for the healthcare workers who had to say to the relative of a deceased patient "we could only do so much in line with the information and possibilities at our disposal" instead of "we did everything we could".<sup>5</sup> Due to the difficulties experienced during the pandemic, it can be interpreted that almost all healthcare workers were under similar stress and have been prone to moral trauma.

The DASS-21 scale (depression, anxiety and stress scale-21) is a 21-item short version of the DASS scale, also known as the Self-Analysis Questionnaire. It aims to quickly measure short-term depression, anxiety and stress scores. Seven of the twenty-one questions score depression, seven questions score anxiety, and seven questions score stress. It is an easy scale to apply and answer. Although this scale is a self-consistent and reliable scoring system, there are also publications suggesting that it gives contradictory results in some races or individual groups.<sup>7,8</sup> However, in general, we can state that DASS-21 is a scale that provides fast and reliable results.

In our study, we preferred the DASS-21 scoring system because it would give us an idea about depression, anxiety and stress levels, and it would be easy to place into the questionnaire. We think that we made the right choice because of the high completion rate of the DASS-21 scales in our survey, as we also observed the expected results in different groups at first glance.

In their study, Mak et al.,<sup>9</sup> reported stress response like depression, anxiety, somatization and aggression in 10% of healthcare personnel in the period following the epidemic of severe acute respiratory syndrome (SARS) in 2008. In another study conducted by Liu et al.,<sup>10</sup> depressive symptoms were noticed in 23% of all healthcare personnel in 3 -year follow-up after the SARS epidemic. Lai et al.<sup>11</sup> also reported that during the COVID-19 epidemic, the proportion of symptoms associated with depression, anxiety and stress in Chinese healthcare personnel was 50.7%, 44.7% and 73.4%, respectively. A study conducted by Elbay et al.<sup>12</sup> reported that 64.7% of the healthcare professionals working on the front lines in the fight against the pandemic had high depression scores, 51.6% had high anxiety scores and 41.2% had high stress scores. In our study, 81.6% of anesthesiology and reanimation physicians had high depression scores, 62% had high anxiety scores and 71.1% had high stress scores. In another study conducted on all teams (anesthesiologists, anesthesia technicians, and operating room nurses) working in the operating room, Li et al.<sup>13</sup> showed that depression and anxiety scores were high, although they used different scales and evaluated groups other than physicians. In our study, when the average of all scores of the anesthesiology and reanimation physicians participating in the study was taken, depression, anxiety and stress scores were higher than the normal levels. Due to the fact that anesthesiology and reanimation physicians offer treatment to patients with advanced disease, especially in intensive care



units, they have to work long hours with personal protection equipments (overalls, visors, gloves...) and the high mortality and morbidity of the disease in the intensive care stage, the excess amount of treatment processes that fail, and situations such as high risk of contact with the virus may have caused this high scoring.<sup>14</sup> And it should be noted that all scores were higher in women. Women's more intense response to stressful stimuli may have contributed to the emergence of these results.<sup>15</sup> Another remarkable result is that depression scores of residents are higher than those of specialist physicians. Reasons such as increased workload of resident doctors, being assigned to different places from where they normally work during the pandemic, more exposure to organizational changes, or the psychological pressures created by the hierarchical position can be counted as factors that create these results.<sup>16-18</sup>

During the pandemic, the Ministry of Health took action in all hospitals affiliated to it and introduced the concept of "Pandemic Hospital". Accordingly, hospitals with at least two branches of these three, infectious diseases, respiratory diseases and internal diseases specialists, and a third level adult intensive care bed were declared as pandemic hospitals. Although the number of hospitals that do not meet these criteria is high, most training-research hospitals and city hospitals meet these criteria. Rapidly increasing number of patients has increased the workload of these three groups of hospitals. Although not enough volunteers participated to make it statistically significant, working in a pandemic work order from the beginning of the pandemic may have been effective in the high depression scores of the physicians working in the city hospital. However, a more comprehensive study with a larger sample is needed to prove this inference. In addition, this may have caused the high DASS-21 scores of residents working in training-research hospitals.

The environment of uncertainty of the pandemic, delays in taking action by institutions, disruptions in the supply of PPE and medical equipment, and doubts about the safety of the working environment may have adversely affected the mental health of the employees. Many physicians stated that they were afraid of transmitting the illness to those living in their home, and in consequence, they accommodated in another place, parting with their families, for a while. Almost all physicians worked in a different place than the unit they normally work in. Factors such as getting used to the new environment, adaptation to new teammates, and organizational differences may have been factors that created stress, especially in physicians who were sent to different institutions.

Considering all these data, one can infer how important it is to ensure and maintain the mental well-being of the healthcare providers. Inadequate mental well-being and lack of an environmental sustainability may lead to feelings such as demotivation, despair, moral trauma, and a sense of guilt in healthcare professionals. In their study, Elbay et al.<sup>12</sup> stated that providing a suitable working environment for the staff and them receiving support from both team members and their superiors would contribute to their psychological well-being.

In addition, the subjective thoughts of physicians about the pandemic were evaluated in our study. At the time of this publication, there were vaccines produced by 5 different companies on the market. CoronaVac (Sinopharm, China) was the first vaccine applied in Türkiye. At the time of the study, there was no vaccine released yet. The fact that physicians were

almost split in half on whether to be or not to be vaccinated may be evidence that doubts about the vaccine have not been cleared. In addition, it is noteworthy that, among the resident physicians, those who do not want to be vaccinated are higher. Another important result is that 92% of the participants think that the pandemic process would not end soon. Some factors such as severe deviation of some data-based studies that have been done before, repetitive lock down measures and social isolation they bring along and uncertainties brought about by new variants may have caused physicians to move away from the thought that the pandemic will end soon.<sup>19-24</sup> The results of the vaccines in the near future, the course of the closures, the decisions to be taken by the administrations and the period of returning to normal may perhaps change the answer of physicians to this question.

Although there are similar studies conducted on frontline physicians in the fight against the pandemic in our country, as far as we know, this is the first study conducted directly on anesthesiology and reanimation residents and specialists. However, the relatively small number of samples, low participation rate of sub-specialists and low participation rate in the survey from the physicians working in private hospitals caused some data not to be analyzed statistically. In addition, the absence of face-to-face meetings due to the pandemic and the distribution of the survey with a link, although increased the freedom of the participants and eliminated possible health risks, unfortunately reduced the rates of completing the survey. A larger study in which face-to-face interviews can be conducted can increase both the participation and completion rate of the survey. A study with a large sample may also provide more up-to-date and more accurate results. Especially when the pandemic is over, the variables related to this process will also disappear (elimination of the uncertainty of the effectiveness of the vaccine, reduction of possible changes in the way of working, decrease in the risk of material loss, elimination of the risk of infection, etc.), so a healthier assessment can be made for the past.

## CONCLUSION

Almost all physicians have experienced changes in workload, income and workplaces during the pandemic. High DASS-21 scores in all physicians were thought-provoking and highlighted the psychological pressure that anesthesiology and reanimation physicians had been under.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Uludağ University Faculty of Medicine Clinical Researches Ethics Committee (Date: 16.09.2020, Decision No: 2020-16/1).

### Informed Consent

All patients signed and 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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# Perceptions of intensive care nurses on the concepts of brain death and coma: a metaphor analysis

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## ABSTRACT

**Aims:** It is important for intensive care nurses to have knowledge about the concepts of brain death and coma and to take precautions against ethical problems. This study aimed to determine the perceptions of intensive care nurses regarding the concepts of brain death and coma through metaphors.

**Methods:** Metaphor analysis, one of the qualitative research designs, was used. The metaphors produced by the intensive care nurses were defined as concepts and a list was created. Using content analysis, 20 intensive care nurses produced 20 different metaphors for the question, "Coma is similar to ..., because ...". Nurses mostly likened the concept of a "coma" to a "plant", "stay together", and "deep sleep". They also produced 20 different metaphors for the question, "brain death is similar to ..., because...".

**Results:** Nurses mostly likened the concept of brain death to a "plant", "absolute death", and a "coma". Brain death and a coma were common to three of the metaphors produced by nurses ("uncertainty/unresponsiveness", "death/eternity", and "permanent breakdown" metaphors). The answers given to the questions about the concepts of brain death and a coma were "uncertainty/unresponsiveness", "death/eternity", and "permanent breakdown" metaphors.

**Conclusion:** The nurses confused the concepts of a coma and brain death with each other and had similar perceptions of the two concepts.

**Keywords:** Brain death, coma, intensive care, metaphor, nurse

## INTRODUCTION

In consciousness disorders, consciousness is partially or completely lost, starting from a sleep state and progressing to a state of unresponsiveness to any stimulus (coma), as a result of impairment in the normal functions of the brain for any reason. Being in a coma is a result of serious brain dysfunction caused by structural, chemical, electrical, or toxic disorders of the brain.<sup>1</sup> The comatose patient is unstimulated and unresponsive. The absence of eye-opening movement even in the presence of strong stimuli is a characteristic clinical finding for a coma.<sup>2</sup> Comatose patients are unconscious but have circulation and respiration. The patient in a coma may clinically recover, progress to brain death, or fall into a vegetative state.<sup>3,4</sup>

The concept of brain death is defined as the irreversible loss of brain, brain stem, and cerebellum activities. In adults, brain death often results from traumatic brain injury or subarachnoid hemorrhage. In children, the most common cause of brain death is non-accidental trauma. The most common extracranial causes of brain death include cardiopulmonary arrest and inadequate cardiopulmonary resuscitation.<sup>5,6</sup> According to the American Academy of Neurology (AAN), three findings

(being in a coma, the absence of brainstem reflexes, and the presence of apnea) are necessary to confirm the diagnosis of brain death.<sup>7,8</sup> Patients suspected of having brain death are primarily evaluated for exclusion criteria and a detailed history is reviewed. Comprehensive laboratory tests are performed to exclude endocrine problems and acid-base and electrolyte disturbances that may cause changes in consciousness. Patients suspected of having brain death are evaluated in terms of drug-related poisoning.<sup>5,7</sup> Brainstem reflexes are carefully examined for the evaluation of brain death.<sup>7</sup> Patients who develop brain death give no response to painful stimuli, except for spinal reflexes and purposeless involuntary movements.<sup>5</sup>

Intensive care nurses take active roles in the treatment and care practices of patients who are in critical condition and who develop neurological problems such as coma and brain death. They have critical roles in the process of diagnosing patients with altered consciousness, providing hemodynamic and emergency medical support, and meeting their care needs. Recognition of changes in consciousness in the early period affects the treatment results and the clinical picture of

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the patient. Intensive care nurses closely evaluate the state of consciousness of patients. It assumes important responsibilities in pharmacological and non-pharmacological interventions to support cardiopulmonary functions.

It is stated that intensive care nurses who participate in the decisions regarding the condition of end-stage patients or take the role of practitioners frequently experience ethical problems related to the patient's condition. To cope with the ethical problems that nurses face, they need to have knowledge about the subject and take precautions against ethical problems.<sup>9,10</sup> At the same time, the level of knowledge and perceptions of nurses about brain death and coma increase the performance of intensive care nurses, their adaptation to the profession, and work efficiency, and affect their professional development.

A metaphor is an indicator of an individual's perceptions of a concept. Metaphors are a way of expressing positive or negative feelings with their thoughts.<sup>11</sup> Metaphors have unique meanings, contribute to creating perspectives,<sup>12,13</sup> enable the experiences and previous lives of the individual to be directed from a certain way of understanding to another one through the mind, and lead to the formation of different structures related to concepts.<sup>14</sup>

It is important to determine the metaphorical interpretation to understand the perceptions of intensive care nurses on these concepts and to provide a different understanding of nursing care. The analysis of nurses' perceptions of a concept is a new approach used to improve nursing care. The metaphorical perceptions of intensive care nurses will bring a new dimension to nursing care. The results of this research will provide data on the development of the awareness of nurses who provide care to comatose patients regarding brain death and changes in consciousness.

The present study aimed to determine the perceptions of intensive care nurses on the concepts of brain death and coma through metaphors. In this study, we sought to identify the metaphors for coma and brain death used by intensive care nurses.

## METHODS

### Ethics

Written approval (Date: 06.08.2022, Decision No: 2022-KAEK-62) was received from the Kastamonu University Clinical Researches Ethics Committee to implement the study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Research Setting

The research was carried out in the intensive care units of a training and research hospital located in the western Black Sea region of Türkiye. The hospital has five intensive care units: the pediatric intensive care unit, the adult intensive care unit, the coronary intensive care unit, the cardiovascular surgery intensive care unit, and the neonatal intensive care unit.

### Research Design

Phenomenology, a qualitative research design, was used in the research. The phenomenology design focuses on phenomena of which we are aware but do not have an in-depth or detailed understanding. Phenomenology evaluates lived experiences. Phenomenology is first experienced by individuals to discover the common meanings underlying the phenomenon who then try to describe the world and explain the essence of lived experiences. There is a link between the phenomenon and the

individuals who experience the phenomenon; the starting point of phenomenology is the facts themselves.<sup>15</sup>

This research method borrows experiences from individuals to describe and interpret their experiences. All the phenomena experienced by individuals can be researched and explained. Through phenomenology, individuals' experiences, perceptions, and meanings related to a phenomenon are uncovered.<sup>15,16</sup> During the determination of the target area in metaphor analysis, the subject and the questions to be asked are selected at first and a template is created for the research and evaluation process.<sup>17</sup> After these preparations are completed, the metaphors collected in the research are grouped and the subject headings are identified. Researchers need to understand and correctly analyze the metaphors used to conduct their research properly. The analysis to be made within the concept of prepared subjects requires a detailed evaluation.<sup>18,19</sup>

### Research Population and Sample

In this study, the population consisted of 112 nurses working in the intensive care units of the Kastamonu Training and Research Hospital in Türkiye. The data were collected between 1 July and 31 August 2022. The semi-structured interview survey was presented to three experts. After approval, the research was initiated.

Twenty nurses were not included in the study since they were on sick or paid leave between these dates. Thus, a total of 92 nurses were invited to the study. Of the 92 invited nurses, 25 agreed to participate in the study. Five nurses were not included in the study since they did not fully complete the data collection form in their justifications for the metaphors. Therefore, 20 nurses constituted the sample of the study, reaching 18% of the research population. Nurses participating in the study were given surveys and asked to fill them out. There is no relationship between nurses and researchers.

The metaphors produced by the intensive care nurses were defined as concepts and a list was created. Accordingly, whether the metaphors were expressed clearly was reviewed throughout the study.

### Data Collection Tools

The data were collected after working hours using a nurse information survey and the metaphoric perceptions data collection survey.

**Nurse information survey:** The survey consisted of six questions regarding the nurses' age, gender, education level, professional experience, and previous experiences of providing care to brain-dead and comatose patients.

**Metaphoric perceptions data collection survey:** The researchers prepared the survey. The survey included the following sentences: "Coma is like/similar to ..... Because it is ....." and "Brain death is like/similar to ..... Because it is .....". The relationship between the subject and the source of the metaphor was examined using the word "like". The meaning and reason attributed to this metaphor were revealed using the word "because".

### Data Collection

The nurses were first asked to complete the nurse information survey after working hours. The completion of the surveys lasted approximately 10 minutes. To reveal the metaphors identified by the nurses regarding the concepts of "Coma"

and “Brain death”, they were asked to fill in the gaps in the statements “Coma is like/similar to ..... Because .....” and “Brain death is like/similar to ..... Because .....”.

The nurses were asked to liken “coma” and “brain death” phenomena to something else (an entity, living thing, object, etc.) and briefly state the reason for this likening. These compositions, written by the nurses in their handwriting, were used as the main data source in the study. The data were collected using surveys in Turkish. After the manuscript was written, the manuscript was translated from Turkish to English.

### Statistical Analysis

Content analysis was performed to determine the themes in a way that readers could easily understand the raw verbal or written data.<sup>20</sup> In the study, the data were primarily analyzed using content analysis.

Secondly, the metaphors determined as a result of the content analysis were grouped into conceptual categories and correlated with the thoughts in the related metaphor. To reveal the perceptions of the nurses regarding a “coma” and “brain death”, metaphors were specified as “because .....”. Considering the explanations in the interview surveys, categories were determined based on the nurses’ sentences according to content integrity. Frequency was also examined in the data analysis.

The analysis and interpretation of the data were performed in five stages.<sup>21</sup> In this study, the analysis of the data was carried out in the following five stages using “content analysis”:

**Coding and extraction stage:** The data were primarily subjected to an extraction process. Complete data were numbered and given a code (such as CMC or BDMC). The code “CMC” formed the code for the metaphor produced for a coma. The code “BDMC” formed the code for the metaphor produced for brain death. Four “interview forms”, in which a metaphor was included but not justified, were eliminated and not evaluated since they included meaningless statements. A visual metaphor chart was created according to the participants’ answers. In line with this chart, it was also evaluated whether the nurses clearly defined a certain metaphor in the collected data.

**Sample metaphor analysis:** The metaphors produced by the participants were analyzed by creating codes. The relationship between similarly identified metaphors was examined.

**Categorization:** The metaphor images created by the participants were grouped according to similar characteristics related to the concept of a coma and brain death. Three valid metaphors of coma and five valid metaphors of brain death identified by the 20 nurses were collected under the conceptual category. Each metaphor was correlated with the meaning and perception that the nurses attributed to the concepts of a coma and brain death.

**Validity and reliability:** The approximate ratio representing the number of nurses participating in the research, the categories as the main themes from the obtained concepts, and the metaphors in the sub-headings were determined. To ensure reliability, after the categories were created, a paper on which the metaphors, justifications, and names of the conceptual categories were written was given to three faculty members working in the nursing department and they were asked to fill in. All metaphors were matched with a category. Thereafter, the matching made by the faculty members between the metaphors and the created categories was compared with the matching

made by the researchers. Following this comparison, the formula “reliability=consensus/consensus+disagreement” was used. In metaphors, the reliability of the metaphor categories was calculated using this formula. As a result, the reliability was calculated as “19/19+1=0.95”. The result meant that the study was reliable.

**Transfer of data to computer environment:** The metaphors were divided into categories according to their justifications and the frequency (f) of participants in the category they represented was calculated. The metaphors, which were categorized according to the justifications, were coded and reported on according to the participants. The letter M was used for male participants and the letter F was used for female participants to identify to whom the citations belonged. The metaphors that emerged as a result of the research were categorized according to their common features and analogy aspects. In the analysis of the nurses’ descriptive characteristics, frequency and percentages were calculated using the Statistical Program for the Social Sciences (SPSS) 21.0 software program.

## RESULTS

This section includes information on the descriptive characteristics of the participants and the metaphors they identified regarding the concepts of a coma and brain death. The mean age of the participants was 30.75±1.59 years (min: 22 years, max: 45 years) and 65% of them were female. Of these participants, 60% had been working in the intensive care unit for less than five years and 90% reported that they had previously provided care to a patient in a vegetative state and/or in a coma (Table 1).

**Table 1. Descriptive characteristics of the intensive care nurses (n=20)**

Variables	Frequency (n)	Percentage (%)
<b>Age mean (SD): 0.75 (1.59) (min: 22, max: 45)</b>		
<b>Gender</b>		
Female	13	65
Male	7	35
<b>Education status</b>		
High school	2	10
Undergraduate degree	14	70
Master’s degree	4	20
<b>Duration of employment in the nursing profession</b>		
Less than 5 years	50	50
5-10 years	25	25
15-20 years	15	15
20 years and over	10	10
<b>Duration of employment in the intensive care unit</b>		
Less than 5 years	12	60
5-10 years	4	20
15-20 years	3	15
20 years and over	1	5
<b>Experience providing care to a brain-dead patient</b>		
Yes	18	90
No	2	10
<b>Experience in providing care to a comatose patient</b>		
Yes	18	90
No	2	10

SD: Standart deviation, min: Minimum, max: Maximum

Table 2 shows the metaphors that the intensive care nurses identified for the concept of a “coma”. The intensive care nurses identified 10 different metaphors for the question, “Coma is similar to ..., because ...”. Nurses mostly likened the concept of a “coma” to a “plant” (n=4, 20%), “stay together” (n=4, 20%), and “deep sleep” (n=4, 20%).

**Table 2. Metaphors identified by the intensive care nurses for coma (n=20)**

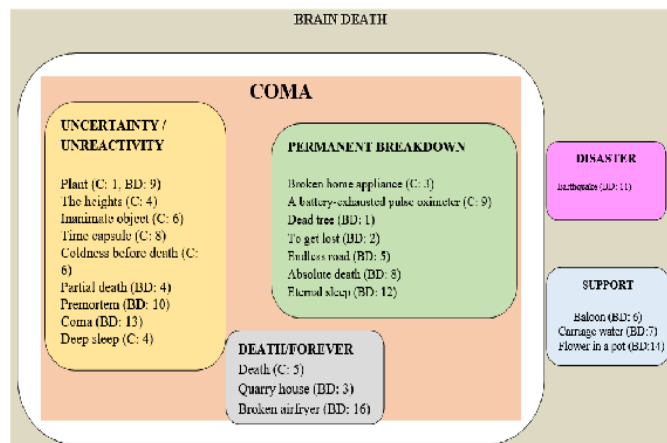
Metaphor Code	Metaphors	Frequency	%	Expressions of the nurses about the reasons for the metaphors they identified
1	Plant	4	20	“A coma is like a plant. Because it is there but cannot tell us his condition.” (F, A27) “A coma is like a dehydrated plant because it is in a bad condition” (F, A22) “A coma is like a plant because it performs vital functions but there is no reaction.” (M, A28) “A coma is like a tree because it can hear us but has motion and response.” (F, A26)
2	Unresponsiveness	2	10	“A coma is like deep sleep because there is no response.” (M, A29) “A coma is like an inability to perform vital functions because the patient is unconscious and unresponsive to any stimulus.” (M, A29)
3	Stay together	4	20	“A coma is like being half-dead because there is no consciousness and breathing but the heart works.” (M, A40) “A coma is like being in limbo because you are either here or you are not.” (F, A27) “A coma is like being unconscious for a long time because the patient in a coma has no reaction and is unconscious.” (M, A27) “A coma is similar to a partial and temporary loss of vital functions because the patient is unconscious and does not move.” (F, A42)
4	Broken electrical home appliance	1	5	“A coma is like a broken electrical home appliance because it only transmits electricity without any function.” (F, A43)
5	Deep sleep	4	20	“A coma is like deep sleep because the brain functions are working but the perception is limited.” (M, A26) “A coma is like deep sleep because the patient cannot react to anything.” (F, A23) “A coma is like deep sleep because the patient is unresponsive for a long time.” (F, A26) “A coma is similar to a patient in deep sleep because there is no response to painful stimuli.” (F, A45)
6	Death	1	5	“A coma is like the end of life because there is no function.” (F, A27)
7	Non-living object	1	5	“A coma is like a non-living object because it cannot perceive anything.” (F, A39)
8	Pre-death coldness	1	5	“A coma is similar to pre-death coldness because the person has lost all functions literally but is breathing and the heart is working.” (M, A30)
9	Time capsule	1	5	“A coma is like a time capsule because the patient wakes up and continues life when the right time comes.” (F, A28)
10	Pulse oximeter out of battery	1	5	“Coma is similar to a pulse oximeter out of battery because it appears to be present but not functionally here.” (F, A29)

Table 3 shows the metaphors that the intensive care nurses identified regarding the concept of “brain death”. The intensive care nurses identified 16 different metaphors for the question, “Brain death is like/similar to ....., because ..……”. Nurses mostly likened the concept of brain death to a “plant” (n=3, 15%), “absolute death” (n=2, 10%), and a “coma” (n=2, 10%).

The categories of the metaphors obtained as a result of the content analysis are; in this study, the answers given by the nurses to the questions about the concepts of brain death and coma produced three common metaphors (“uncertainty/unresponsiveness”, “death/eternity”, and “permanent breakdown”). According to this result, the nurses were confused due to the concepts of coma and brain death and they had similar perceptions regarding the two concepts (Figure).

**Table 3. Metaphors identified by the intensive care nurses for brain death (n=20)**

Metaphor Code	Metaphors	Frequency	%	Expressions of the nurses about the reasons for the metaphors they identified
1	Dead tree	1	5	“Brain death is like a dead tree because the patient is there as an entity but has no system to manage and develop.”
2	Being lost	1	5	“Brain death is like being lost because it is irreversible.”
3	Perished house	1	5	“Brain death is like a perished house because it is a difficult situation.”
4	Partially dead	1	5	“Brain death is like partial death because the brain does not work, but all body organs work without respiratory arrest.”
5	Endless road	1	5	“Brain death is an endless road because the patient has entered a road with no end.”
6	Balloon	1	5	“Brain death is like a balloon because if you inflate it, it flies, if you cut off the support it deflates (dies).”
7	Carriage water	1	5	“Brain death is like carriage water because when you cut off the life support (carriage water), death occurs.”
8	Absolute death	2	10	“Brain death is like the loss of all functions because the patient’s brain stem is completely dysfunctional. It is a condition that results in absolute death.” “Brain death is like the irreversible loss of brain functions because the patient is inadequate for all kinds of treatment and the life can be terminated.”
9	Plant	3	15	“Brain death is like a vegetative state because brain functions stop and other functions are active.” “Brain death is like a plant because there is no movement.” “Brain death is a vegetative state because the brain has lost its function, except for vital organs such as the heart and lungs.”
10	Pre-death	1	5	“Brain death is similar to pre-death because the patient cannot perform respiratory and vital activities without support.”
11	Earthquake	1	5	“Brain death is like an earthquake because it causes destruction and unexpected pain to the family.”
12	Eternal sleep	1	5	“Brain death is like eternal sleep because the patient cannot survive without mechanical support.”
13	Coma	2	10	“Brain death is similar to the condition of a comatose patient because there is no response.” “Brain death is like coma because there is no reaction at all.”
14	Flower in a pot	1	5	“Brain death is like a flower in a pot because functions remain when the appropriate environment is provided.”
15	Sculpture	1	5	“Brain death is like a sculpture because there is no reaction.”
16	Broken air fryer	1	5	“Brain death is like a broken air fryer because it exists physically but does not function.”



**Figure.** Categories of the metaphors obtained as a result of the content analysis (C: Coma, BD: Brain death).

## DISCUSSION

Metaphors are powerful mental tools used to understand and explain an abstract, complex, or theoretical phenomenon. This study aimed to reveal the metaphor perceptions of intensive care nurses on the concepts of brain death and coma. It was seen that three of the metaphors produced by nurses were common (uncertainty/unresponsiveness, death/eternity, and permanent breakdown). Metaphors produced by the nurses regarding the concept of brain death were categorized as disaster and support.

### Uncertainty/Unresponsiveness

According to Pearson, the uncertainties and contradictions regarding the concept of brain death and its uncertainty are directly correlated with the concept of death by nurses working in intensive care units,<sup>22</sup> because brain death is defined as real death without the hope of recovery. However, the feeling that the brain-dead patient is still alive due to his/her physical appearance increases the feeling of uncertainty. In studies examining the level of knowledge of nurses working in various clinics on brain death, it was stated that the level of knowledge of nurses was not sufficient.<sup>23-25</sup> Metaphors created by some of the intensive care nurses regarding the concept of brain death were partially dead, a plant, pre-death, a coma, and a sculpture. This finding suggests that some of the nurses perceived that the condition of brain-dead patients is reversible. Therefore, reducing the uncertainty about brain death will contribute to the nurses' ability to explain brain death to patient relatives and reduce the stress they experience.

Most comatose patients recover over time. Waking up from a coma can be quick or slow. Comatose patients are unconscious but have circulation and respiration. The patient may recover clinically, develop brain death, or progress to a vegetative or minimally conscious state.<sup>3,4</sup> In this study, the metaphors created by the intensive care nurses on the concept of a coma stay together, deep sleep, a non-living object, and a time capsule. This finding suggests that some of the nurses had perceptions of uncertainty between life and death regarding the concept of a coma. In another study conducted with nurses, the answer, "As long as the individual receives care, they can live for years without knowing their environment", was given at a rate of 87%.<sup>23</sup> This finding of the study supports the literature.

### Death/Eternity

Before the modern era, the concept of death was defined as the fact that the soul leaves the body after respiratory and cardiac

arrest. In the modern age, the concept of death has changed. Death has become institutionalized as it is transferred from home to hospital. Eighty percent of deaths occur in health institutions, which makes death a cold, medical death.<sup>26,27</sup> Brain death is considered the death of a person. The irreversibility in the definition of death expresses the impossibility of recovery. In the study by Sapulu,<sup>28</sup> it was determined that 92.67% of intensive care nurses gave the correct answer to the statement, "If the brain functions stopped even if the heartbeat is provided with mechanical support, brain death has occurred". In this study, the intensive care nurses expressed their metaphors, using comparisons such as a dead tree, being lost, an endless road, absolute death, and endless sleep, by reflecting that brain death is similar to death and eternity.

### Permanent Breakdown

Death is always considered a permanent breakdown as well as deviating from the norm in today's societies. New technologies are creating a new patient population and a new type of hospital space. The life of this patient population whose death is inevitable under normal conditions can be sustained artificially and/or delayed by these new technologies in intensive care units where these technological treatments and care applications are performed.<sup>29</sup> It would be appropriate to say that the new place of death in the 21<sup>st</sup> century is intensive care units. Moreover, considering all these discussions, intensive care units where this "technical death", defined as a life permanent breakdown and deviation from the norm, is closed are spaces for otherness.<sup>30</sup> The intensive care nurses also expressed their metaphors as a "perished house", a "broken air fryer", a "pulse oximeter out of battery" and a "broken electrical home appliance", stating that brain death and comas are crises.

### Disaster

An earthquake is a disaster that cannot be predicted or controlled. After an earthquake, buildings of people may be damaged and a relative may die. The devastating and unavoidable effects of earthquakes often lead to reactions such as fear, helplessness, and terror in victims. This result is one of the most prominent features of disasters such as earthquakes that exceed the limits of humans and show that they are inadequate.<sup>31,32</sup> In this study, the intensive care nurses developed an earthquake metaphor regarding the concept of brain death. It is thought that the sudden and uncontrollable occurrence of brain death and the psychological reactions in families after the loss were effective in the creation of this metaphor.

### Support

Among the criteria for diagnosing brain death, the lack of movement or spontaneous breathing after four minutes of separation from the mechanical ventilator and the presence of apnea indicate that brain death will occur without a support system.<sup>23,32</sup> Karaman<sup>31</sup> found that 85.8% of the intensive nurses answered that "respiration and circulation can be maintained for a short time in a brain-dead individual by connecting to mechanical support". In this study, the metaphors of a balloon, carriage water, and a flower in a pot reflected comparisons such as deflating like a balloon, being dehydrated when the water is cut off, and continuing life when necessary conditions are provided for a flower in a pot. This result shows that brain death is perceived similarly to the findings in the literature. However, when the brain death tests are positive, the patient will be

considered dead even if support continues and the patient's relatives will be informed about organ donation. Considering this information, the produced metaphors conflict with the literature since the patient cannot continue living even if support is provided.

### Limitations

The study was conducted in a single center, namely a training and research hospital in Türkiye. The findings of the research represented the opinions of 20 intensive care nurses working in the hospital where the research was conducted. Therefore, the findings cannot be generalized to all intensive care nurses.

Since the nurses included in the research used their expressions, they were not affected by each other, which increases the accuracy of the data.

### CONCLUSION

In this research, the answers given by nurses to the questions about the concepts of brain death and comas produced three common metaphors ("uncertainty/unresponsiveness", "death/eternity", and "permanent breakdown"). According to this result, it was seen that the nurses confused the concepts of a coma and brain death and had similar perceptions of the two concepts. The results of this research showed that the awareness of nurses, who provide care to brain-dead and comatose patients, on the changes in consciousness should be increased. It is recommended to improve the knowledge of the concepts of brain death and coma with regular in-service training sessions.

### ETHICAL DECLARATIONS

#### Ethical approval

Written approval (Date: 06.08.2022, Decision No: 2022-KAEK-62) was received from the Kastamonu University Clinical Researches Ethics Committee to implement the study. Institutional permission was obtained for data collection.

#### Informed Consent

All participants were informed about the research and their informed consent was received.

#### Referee Evaluation Process

Externally peer-reviewed.

#### Conflict of Interest Statement

The authors declared no conflicts of interest concerning the authorship and/or publication of this article.

#### Financial Disclosure

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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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# Comparison of detailed brain volume measurements in schizophrenia with healthy individuals

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## ABSTRACT

**Aims:** This study aims to provide insights into the preliminary and definitive diagnosis, treatment modalities, and elucidation of the underlying pathophysiological mechanisms of schizophrenia, alongside ongoing research efforts.

**Methods:** This retrospective study examined a cohort of 31 patients (17 male, 14 female) diagnosed with schizophrenia according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders (DSM V) at the psychiatry clinic of the university hospital. The healthy control group, comprising 31 individuals (17 male, 14 female), was selected from archived records at the same hospital, with sociodemographic characteristics matching those of the patient group. High-resolution T1-weighted MRI images of the individuals were analyzed using the VolBrain AssemblyNet program.

**Results:** It has been observed that the volumes of various brain structures, including white matter (WM), gray matter (GM), subcortical GM, cortical GM, WM+GM, IC, total cerebrum, right cerebrum, left cerebrum, cerebrum WM, cerebrum GM, are significantly reduced ( $p < 0.05$ ) in patients diagnosed with schizophrenia compared to healthy controls. Additionally, volumes of cerebellar WM, GM, vermis, brainstem, accumbens, hippocampus, thalamus, ventral diencephalon, amygdala, and basal forebrain were found to be decreased in schizophrenia patients compared to healthy controls. Conversely, volumes of the pallidum, caudate, putamen, inferior lateral ventricle, lateral ventricle, third ventricle, fourth ventricle, and CSF were observed to be increased.

**Conclusion:** These findings underscore the widespread nature of neuroanatomical alterations in schizophrenia and highlight the importance of understanding these changes for elucidating the disorder's pathophysiology and developing targeted therapeutic interventions. Further research is warranted to explore the interplay of genetic, developmental, and environmental factors in schizophrenia.

**Keywords:** Schizophrenia, brain volume, VolBrain, volumetric measurements

## INTRODUCTION

Schizophrenia, characterized as a severe psychiatric disorder, impacts around 0.4% of the global populace.<sup>1</sup> Its onset often commences during early adulthood but can manifest in adolescence. Notably, its prevalence spans across all strata of society, irrespective of socioeconomic status. This disorder follows a chronic and recurrent trajectory, persisting throughout an individual's lifespan. Schizophrenia stands as a paramount mental health concern in contemporary society due to its profound ramifications.<sup>2</sup> These include diminished productivity, shortened life expectancy, substantial utilization of hospital resources, exorbitant healthcare expenditures, and elevated suicide rates. The multifaceted impact of schizophrenia underscores the imperative for comprehensive

strategies encompassing research, clinical interventions, and public health initiatives to address its complexities effectively.<sup>1,2</sup>

Consequential behavioral findings have significantly propelled the investigation into the neurobiology of schizophrenia. Advanced brain imaging techniques allow the scrutinizing of brain structures within naturalistic settings through noninvasive means, a rapidly evolving field owing to technological advancements. The utility of brain imaging in elucidating schizophrenia and fostering novel therapeutic approaches lies in its capacity to reveal global aberrations throughout the brain while integrating regional, morphological, and physiological anomalies with findings

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from clinical and neurobehavioral studies.<sup>3</sup> This multifaceted approach facilitates a comprehensive understanding of the disorder, thereby offering avenues for innovative interventions and treatment strategies.

Due to its advantages, magnetic resonance imaging (MRI) has supplanted numerous conventional imaging modalities in contemporary medical practice across various diseases.<sup>4</sup> Foremost among these is its noninvasive nature, obviating the need for invasive procedures, and its inherent safety by being free from ionizing radiation exposure. Moreover, MRI offers superior soft tissue resolution, enabling precise visualization of anatomical structures.<sup>5</sup> Beyond morphological insights, MRI also furnishes functional information, thus affording a comprehensive understanding of tissue physiology. This amalgamation of benefits positions MRI as a pivotal diagnostic tool, facilitating anatomical delineation and functional assessment in clinical contexts.<sup>6</sup>

Extensive scholarly attention has been devoted to investigating central nervous system (CNS) manifestations in schizophrenia. However, uncertainties persist regarding discrepancies in brain volume measurements within the CNS. Leveraging MRI's enhanced soft tissue imaging capabilities, we aimed to scrutinize brain volumes with greater precision. Specifically, employing the volbrain method, we calculated the volumes of 238 different brain structures, focusing on white and gray matter volumes, in individuals diagnosed with schizophrenia. This study aims to provide insights into the preliminary and definitive diagnosis treatment modalities, elucidating the underlying pathophysiological mechanisms of schizophrenia and ongoing research efforts.

## METHODS

### Ethics

The study was carried out with the permission of the Atatürk University Faculty of Medicine Clinical Researches Ethics Committee (Date: 206.01.2023, Decision No: 18). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Participants

This retrospective study analyzed a cohort comprising 31 patients diagnosed with schizophrenia based on the diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM V). These patients were under the care and follow-up of the Psychiatry Clinic at the University Hospital. The control group consisted of 31 participants retrieved from archival records at the University Hospital, matched with the patient group regarding sociodemographic characteristics. These controls were deemed healthy, with no reported health issues. The cohort distribution consists of 17 male and 14 female due to the higher number of male individuals with schizophrenia in the experimental group. The control group consisted of 17 male and 14 female individuals, consistent with the experimental group.

### MRI Protocol

MRI imaging protocol utilized in this study comprised high-resolution T1-weighted 3D magnetization prepared rapid gradient echo (MPRAGE) sequences for anatomical visualization. T1-weighted 3D MPRAGE sequences comprised retrospective data acquired during the routine acquisition

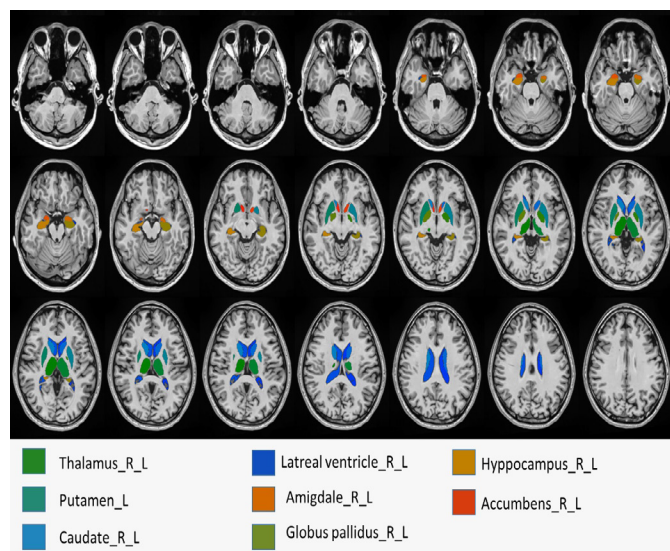
process. The imaging parameters were as follows: sagittal orientation, repetition time (TR) of 1900 ms/2.84s, flip angle of 15 degrees, echo time (TE) of 2.67 ms, field of view (FOV) of 256 mm<sup>2</sup>, matrix size of 256x256, acquisition of 160 slices, each with a thickness of 1 mm, and a spatial resolution of 1x1x1 mm<sup>3</sup> isotropic.<sup>4</sup>

### VolBrain Method

The study employed VolBrain (<https://volbrain.net/>), an open-access platform designed for automated segmentation of diverse brain structures. Utilizing default VolBrain T1-weighted volumetric images, total cerebrum volumetric analysis was conducted across the study groups. Additionally, the study utilized the mricloud method, a web-based software developed by Johns Hopkins University, for volume calculation incorporating brain parcellation in MR images. To facilitate volume calculation using VolBrain, MR images underwent conversion to either 'gz' or 'rar' format. The process involved a series of prescribed steps to enable accurate volumetric analyses. The process commences with the opening of a file denoted by the extension 'DICOMDIR' via a DICOM viewer software application. Subsequently, to visualize the anatomical structure, high-resolution T1-weighted 3D magnetization prepared rapid gradient echo (MPRAGE) images are accessed using the software 'mricron', culminating in the creation of a compressed file with a 'gz' extension in the FSL format. Following this initial step, the images, now converted to 'gz' format, are uploaded onto the VolBrain web interface. Registration procedures are executed, whereby the 'gz' extension files are submitted to the system for processing. Upon completion of the upload, the system initiates volumetric analyses for all brain regions, typically within a time frame ranging from 5 to 10 minutes. The resultant volumetric data are then compiled and saved in portable document format (PDF).

In this study, the AssemblyNet partition was selected from VolBrain measurements. AssemblyNet is a large CNN ensemble for 3D whole-brain MRI segmentation. Volumetric values of all parts of the brain were measured in cm<sup>3</sup> and percentages, and total-right-left ratios were measured. A total of 462 different data were obtained from each participant. White matter (WM), grey matter (GM), subcortical GM, cortical GM, cerebellar GM, cerebro spinal fluid (CSF), brain (WM+GM), intracranial cavity (IC), cerebrum, cerebrum WM, cerebrum GM, cerebellum, cerebellum WM, cerebellum GM, vermis, brainstem were measured. Subcortical structures Accumbens, amygdala, basal forebrain, caudate, hippocampus, pallidum, putamen, thalamus, and ventral diencephalon (DC) were measured (Figure). Among the cortical structures, frontal lobe and frontal lobe parts, the frontal pole, gyrus rectus, opercular inferior frontal gyrus, orbital inferior frontal gyrus, triangular inferior frontal gyrus, medial frontal cortex, middle frontal gyrus, anterior orbital gyrus, lateral orbital gyrus, medial orbital gyrus, posterior orbital gyrus, precentral gyrus, precentral gyrus medial segment, subcallosal area, superior frontal gyrus, superior frontal gyrus medial segment, supplementary motor cortex were measured. Temporal lobe and fusiform gyrus, planum polare, planum temporale, inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, transverse temporal gyrus, and temporal pole were measured. The parietal lobe and angular gyrus, postcentral gyrus, postcentral gyrus medial segment, precuneus, superior parietal lobule, and supramarginal gyrus were measured. The occipital lobe and calcarine cortex, cuneus, lingual gyrus,

occipital fusiform gyrus, inferior occipital gyrus, middle occipital gyrus, superior occipital gyrus, and occipital pole were measured. The limbic cortex and entorhinal area, anterior cingulate gyrus, middle cingulate gyrus, posterior cingulate gyrus, and parahippocampal gyrus were measured. The insular and insular cortex parts, anterior insula, posterior insula, central operculum, frontal operculum, and parietal operculum were measured. CSF, inferior lateral ventricle, lateral ventricle, third ventricle, fourth ventricle, and external CSF were measured.<sup>4</sup>



**Figure.** Volbrain images of subcortical structures measured in schizophrenia patients

### Statistical Analysis

All statistical analyses were conducted using IBM Corporation's Statistical Package for the Social Sciences (SPSS) version 22.0. Before data analysis, an a priori power analysis was performed using the G-Power 3.1.9.7 software to ensure adequate sample size. The analysis determined that with an effect size of 0.96, a power of 0.95 could be achieved at a 95% confidence interval, with a significance level set at 0.05. These parameters were selected to ensure robust statistical power and confidence in the findings.<sup>7</sup> Data were presented as means and standard deviations. Kurtosis and Skewness values revealed that our data showed normal distribution (between -2 and +2).<sup>8</sup> Since parametric test assumptions were met, the Student-t test determined The significant difference between independent groups. The significance level for all comparisons was set at  $p < 0.05$ .

### RESULTS

In this study, 17 male (54.84%) and 14 female (45.16%) patients diagnosed with schizophrenia were evaluated, alongside 17 male (54.84%) and 14 female (45.16%) healthy controls. The mean age of male schizophrenia patients in our study was calculated as  $37.47 \pm 6.54$  years, while for females, it was  $38.43 \pm 7.89$  years. For the control group, the mean age was  $35.94 \pm 7.69$  years for males and  $34.14 \pm 7.26$  years for females ( $p > 0.05$ ). The average body-mass index (BMI) among male schizophrenia patients was  $29.53 \pm 2.43$ , and among female patients, it was  $29.16 \pm 1.85$ . In the control group, the average BMI was  $28.11 \pm 1.85$  for males and  $27.67 \pm 2.04$  for females ( $p > 0.05$ ).

It has been observed that the volumes of various brain structures, including WM, GM, subcortical GM, cortical GM, WM+GM, IC, total cerebrum, right cerebrum, left cerebrum, cerebrum WM, cerebrum GM, are significantly reduced ( $p < 0.05$ ) in patients diagnosed with schizophrenia compared to healthy controls. CSF was observed to increase statistically significantly in both male and female patients with schizophrenia compared to the control group (Table 1). In both genders of schizophrenia patients, it was observed that volume measurements of the total, right, and left segments of the cerebellum, cerebellum WM, cerebellum GM, vermis, brainstem, accumbens, hippocampus, thalamus, and ventral DC regions, were lower compared to those in healthy individuals (Table 2, Figure). Specifically, statistically significant decreases in volume were determined for cerebellar WM, cerebellar GM, vermis, brainstem, accumbens, thalamus, and ventral DC in female schizophrenia patients ( $p < 0.05$ ). It has been observed that the volume measurements of the total, right, and left parts of the amygdala and basal forebrain, in schizophrenia patients are lower compared to healthy individuals. However, no statistically significant difference has been found (Table 2). It was determined that the volumes of the pallidum, caudate, putamen, inferior lateral ventricle, lateral ventricle, third ventricle, fourth ventricle, and external CSF in schizophrenia patients were higher than those in healthy individuals. This difference was found to be statistically significant, except for ventricular and pallidum volumes (Table 3). It has been noted that volume measurements of the frontal lobe, temporal lobe, occipital lobe, limbic cortex, and insular cortex are reduced in patients diagnosed with schizophrenia compared to healthy individuals. Specifically, in male patients with schizophrenia, significant reductions in volume measurements were observed in the triangular inferior frontal gyrus, anterior orbital gyrus, precentral gyrus medial segment, middle temporal gyrus, postcentral gyrus, precuneus, occipital lobe, occipital fusiform gyrus, and middle occipital gyrus ( $p < 0.05$ ). It was observed that the volume measurements of the frontal lobe, temporal lobe, occipital lobe, limbic cortex and insular cortex decreased statistically significantly in female patients with schizophrenia ( $p < 0.05$ ), (Table 4).

### DISCUSSION

There exists a substantial body of volumetric studies investigating morphological alterations in the brain, which hold significance in elucidating the etiopathogenesis of schizophrenia-an affliction characterized by both neurodevelopmental and neurodegenerative components.<sup>3,5,7</sup> However, to the best of our knowledge, there is a dearth of literature on studies employing the VolBrain AssemblyNet program, a novel automated measurement method, for comprehensive volume analysis across all brain regions. In studies conducted on individuals with schizophrenia, certain brain regions have been assessed, with specific affected areas identified; however, a comprehensive examination of all brain structures as a whole has been lacking. In this study, a total of 238 distinct brain areas were evaluated in both schizophrenia patients and healthy controls using the VolBrain method, marking one of the essential attempts to undertake such a comprehensive analysis. The objective of our investigation was to elucidate potential alterations in brain structure among individuals diagnosed with schizophrenia.

Table 1. Comparison of overall brain volume measurements in schizophrenia and healthy individuals

	Schizophrenia male (X±SD)	Control male (X±SD)	P	Schizophrenia female (X±SD)	Control female (X±SD)	P
White matter cm <sup>3</sup>	438.172±45.56	495.68±27.71	0.001**	369.17±77.64	420.11±19.51	0.025*
White matter %	31.61±3.08	34.21±2.39	0.010*	31.51±3.85	32.59±2.73	0.398
Grey matter cm <sup>3</sup>	738.24±99.51	807.33±75.49	0.029*	590.83±159.27	699.51±39.18	0.020*
Grey matter %	53.12±5.64	55.53±3.36	0.140	49.53±6.71	54.17±3.27	0.028*
Subcortical cm <sup>3</sup>	38.03±13.29	43.66±9.85	0.170	27.77±16.08	40.17±4.71	0.010*
Subcortical %	2.76±0.92	3.03±0.69	0.373	2.24±1.24	3.12±0.48	0.019*
Cortical GM cm <sup>3</sup>	589.35±81.14	649.41±65.71	0.024*	470.07±125.34	554.91±36.92	0.022*
Cortical GM %	42.37±4.38	44.67±3.18	0.090	39.46±5.31	42.95±2.65	0.037*
Cerebellar GM cm <sup>3</sup>	110.84±14.62	114.25±17.81	0.546	92.98±22.94	104.42±9.93	0.099
Cerebellar GM %	7.97±0.78	7.83±0.74	0.585	7.83±0.72	8.09±0.81	0.380
CSF cm <sup>3</sup>	198.67±100.44	133.46±60.41	0.029*	210.14±88.61	158.64±84.93	0.129
CSF %	14.06±6.29	9.02±3.49	0.007**	17.83±6.06	11.91±5.43	0.011*
Brain (WM+GM) cm <sup>3</sup>	1176.35±123.22	1303.01±84.13	0.001**	959.94±218.74	1119.61±47.52	0.013*
Brain (WM+GM) %	84.72±6.21	89.74±3.55	0.007**	81.05±5.89	86.77±5.42	0.013*
Intracranial cavity cm <sup>3</sup>	1391.75±147.62	1454.38±113.58	0.175	1182.96±253.49	1295.31±101.35	0.136
Cerebrum total cm <sup>3</sup>	1042.76±109.05	1165.55±74.38	0.001**	848.98±191.95	991.77±47.18	0.012*
Cerebrum total %	75.11±5.44	80.29±3.59	0.02*	71.75±5.51	76.86±4.99	0.016*
Cerebrum right cm <sup>3</sup>	544.42±49.16	576.99±37.32	0.037*	447.25±118.77	512.32±48.92	0.069
Cerebrum right %	39.27±2.81	39.79±2.61	0.578	37.56±4.36	39.56±2.24	0.138
Cerebrum left cm <sup>3</sup>	498.34±94.34	588.55±43.44	0.001**	401.72±106.49	479.44±59.95	0.025*
Cerebrum left %	35.82±5.94	40.49±1.25	0.003**	34.19±6.05	37.29±5.55	0.170
Cerebrum total WM cm <sup>3</sup>	390.53±101.13	472.48±30.62	0.003**	320.97±105.36	396.68±20.09	0.014*
Cerebrum total WM %	46.61±70.45	32.59±2.31	0.418	50.27±77.67	30.77±2.61	0.357
Cerebrum right WM cm <sup>3</sup>	206.03±59.89	236.01±17.92	0.057	176.36±67.36	202.07±13.82	0.174
Cerebrum right WM %	22.73±30.01	16.27±1.31	0.382*	24.96±33.01	15.64±1.11	0.301
Cerebrum left WM cm <sup>3</sup>	184.51±53.22	236.47±14.21	0.001**	144.61±61.96	194.61±17.64	0.007**
Cerebrum left WM %	36.69±93.31	16.31±1.08	0.375	40.87±103.04629	15.13±1.91	0.358
Cerebrum total GM cm <sup>3</sup>	617.21±120.03	693.07±67.63	0.030*	485.48±154.81	595.08±35.66	0.016*
Cerebrum total GM %	44.32±7.76	47.71±3.52	0.112	40.71±8.63	46.08±2.87	0.036*
Cerebrum right GM cm <sup>3</sup>	317.99±55.59	340.98±38.33	0.170	246.13±81.88	310.25±38.01	0.013*
Cerebrum right GM %	22.96±3.81	23.51±2.51	0.620	20.40±4.53	23.92±1.67	0.011*
Cerebrum left GM cm <sup>3</sup>	301.61±83.27	352.08±36.47	0.029*	242.25±74.93	284.83±44.23	0.079
Cerebrum left GM %	21.55±5.19	24.18±1.31	0.052	20.53±4.52	22.16±3.81	0.315

X: Mean, SD: Standard deviation, CSF: Cerebro spinal fluid, WM: White matter, GM: Grey matter. \*\*: p <0.01, \*: p <0.05

Early investigations into brain volume measurements among individuals diagnosed with schizophrenia revealed heterogeneous findings, characterized by divergent alterations in specific brain regions. Some studies suggested an augmentation in WM volume in certain regions, juxtaposed with reductions in other areas.<sup>9,10</sup> However, a substantial body of contemporary research has provided converging evidence indicating a consistent diminution in WM volume among schizophrenia patients relative to healthy control counterparts. This prevailing trend towards reduced WM volume in schizophrenia has been substantiated by numerous recent studies, underscoring a growing consensus within the scientific community.<sup>11-13</sup> In this study, statistically significant reductions were observed in both the WM volumes in the right hemisphere, left hemisphere, and total WM in schizophrenia patients compared to those in the control group (Table 1). The observed reduction in WM volume represents a significant neuropathological hallmark of schizophrenia, implicating

disrupted neural connectivity and communication across brain regions<sup>12</sup>. Understanding these neuroanatomical alterations is critical for elucidating the underlying pathophysiological mechanisms of schizophrenia and may hold implications for the development of novel therapeutic interventions aimed at ameliorating the associated cognitive and functional deficits in affected individuals.

In schizophrenia patients' studies, reductions in gray matter volume measurements, one of the most extensively studied metrics, have been consistently reported.<sup>14,15</sup> It has been suggested that this phenomenon may indicate structural alterations in the brain, particularly within regions associated with decision-making, emotion regulation, and cognitive control. In line with existing literature,<sup>16</sup> this study identified decreases in both right-left and total gray matter volume within cortical structures among individuals with schizophrenia compared to control groups.

Table 2. Cerebellum, accumbens, hippocampus, Thalamus, ventral diencephalon volume, amygdala, and basal forebrain measurements comparison in schizophrenia and healthy individuals

	Schizophrenia Male (X±SD)	Control Male (X±SD)	p	Schizophrenia Female (X±SD)	Control Female (X±SD)	p
Cerebellum total cm <sup>3</sup>	117.52±32.11	125.63±13.23	0.343	96.99±38.25	116.42±9.53	0.077
Cerebellum total %	10.24±5.49	8.63±0.61	0.241	10.33±6.11	9.03±0.91	0.435
Cerebellum right cm <sup>3</sup>	59.81±16.26	63.11±5.79	0.435	49.41±20.11	60.95±6.59	0.052
Cerebellum right %	4.99±1.88	4.34±0.31	0.169	4.97±2.11	4.71±0.39	0.653
Cerebellum left cm <sup>3</sup>	57.63±18.37	62.51±7.61	0.319	47.47±18.76	55.47±6.63	0.145
Cerebellum left %	4.77±1.77	4.29±0.32	0.284	4.79±1.89	4.32±0.67	0.390
Cerebellum WM total cm <sup>3</sup>	22.08±7.49	23.21±5.37	0.621	17.17±8.71	23.42±2.96	0.017*
Cerebellum WM total %	1.59±0.54	1.61±0.39	0.909	1.39±0.65	1.82±0.28	0.035*
Cerebellum WM right cm <sup>3</sup>	16.32±16.81	11.69±2.75	0.271	15.79±19.24	12.09±1.71	0.479
Cerebellum WM right %	1.21±1.36	0.81±0.21	0.243	1.27±1.52	0.93±0.14	0.425
Cerebellum WM left cm <sup>3</sup>	13.44±10.07	11.51±2.65	0.447	10.71±12.51	11.33±1.44	0.855
Cerebellum WM left %	0.99±0.81	0.79±0.19	0.338	0.87±0.99	0.88±0.15	0.972
Cerebellum GM total cm <sup>3</sup>	95.34±27.18	102.42±15.13	0.355	79.69±31.22	93.01±9.44	0.139
Cerebellum GM total %	7.01±1.11	7.02±0.62	0.985	6.96±1.18	7.21±0.77	0.525
Cerebellum GM right cm <sup>3</sup>	48.11±13.35	51.41±6.62	0.368	39.24±15.72	48.86±6.17	0.043*
Cerebellum GM right %	4.22±2.32	3.52±0.26	0.228	4.24±2.59	3.77±0.34	0.508
Cerebellum GM left cm <sup>3</sup>	47.16±16.59	51.01±8.58	0.402	40.37±16.05	44.13±6.52	0.424
Cerebellum GM left %	3.38±0.93	3.49±0.36	0.669	3.45±0.88	3.43±0.59	0.962
Vermis cm <sup>3</sup>	10.68±3.08	11.83±2.83	0.269	7.44±4.13	11.41±1.26	0.002**
Vermis %	0.77±0.23	0.81±0.13	0.596	0.64±0.31	0.88±0.07	0.010*
Brainstem cm <sup>3</sup>	15.97±4.26	17.91±2.58	0.120	11.96±5.74	17.03±1.71	0.004**
Brainstem %	1.15±0.32	1.23±0.12	0.359	1.03±0.44	1.31±0.11	0.031*
Accumbens total cm <sup>3</sup>	0.78±0.36	0.93±0.28	0.206	0.48±0.36	0.77±0.23	0.018*
Accumbens total %	0.05±0.02	0.06±0.02	0.338	0.03±0.02	0.06±0.02	0.031*
Accumbens right cm <sup>3</sup>	0.38±0.16	0.43±0.15	0.327	0.22±0.16	0.38±0.11	0.006**
Accumbens right %	0.02±0.01	0.03±0.01	0.509	0.01±0.01	0.02±0.01	0.015*
Accumbens left cm <sup>3</sup>	0.41±0.21	0.49±0.14	0.147	0.25±0.21	0.39±0.14	0.050
Accumbens left %	0.02±0.01	0.03±0.01	0.244	0.02±0.01	0.03±0.01	0.063
Hippocampus total cm <sup>3</sup>	5.52±2.65	6.71±2.15	0.159	4.55±3.31	6.11±1.35	0.114
Hippocampus total %	0.39±0.18	0.46±0.14	0.246	0.37±0.26	0.47±0.11	0.178
Hippocampus right cm <sup>3</sup>	3.08±1.03	3.41±1.11	0.367	2.53±1.47	3.24±0.64	0.109
Hippocampus right %	0.22±0.07	0.23±0.07	0.599	0.21±0.11	0.25±0.05	0.177
Hippocampus left cm <sup>3</sup>	2.81±1.27	3.29±1.04	0.222	2.45±1.61	2.87±0.84	0.406
Hippocampus left %	0.21±0.08	0.22±0.06	0.354	0.21±0.12	0.22±0.07	0.532
Thalamus total cm <sup>3</sup>	14.15±3.92	16.02±3.06	0.132	10.43±5.21	14.96±1.31	0.004**
Thalamus total %	5.59±18.72	1.11±0.22	0.332	6.36±20.68	1.15±0.11	0.355
Thalamus right cm <sup>3</sup>	7.26±1.95	7.87±1.72	0.340	5.66±2.63	7.35±0.98	0.033*
Thalamus right %	3.51±12.24	0.54±0.12	0.327	4.05±13.51	0.57±0.07	0.343
Thalamus left cm <sup>3</sup>	6.89±2.14	8.14±1.39	0.051	4.76±3.24	7.61±0.47	0.003**
Thalamus left %	0.79±1.15	0.56±0.11	0.422	0.73±1.31	0.58±0.04	0.673
Ventral DC total cm <sup>3</sup>	8.78±2.61	9.32±1.83	0.492	6.47±3.11	9.19±1.13	0.005**
Ventral DC total %	0.63±0.18	0.64±0.13	0.874	0.52±0.23	0.71±0.07	0.009**
Ventral DC right cm <sup>3</sup>	4.38±1.33	4.54±1.06	0.710	3.48±1.47	4.51±0.59	0.022*
Ventral DC right %	0.31±0.09	0.31±0.07	0.942	0.28±0.11	0.34±0.04	0.034*
Ventral DC left cm <sup>3</sup>	4.29±1.53	4.78±0.79	0.256	2.86±2.09	4.67±0.56	0.004**
Ventral DC left %	0.31±0.11	0.33±0.05	0.531	0.23±0.16	0.36±0.03	0.013*
Amygdala total cm <sup>3</sup>	1.63±0.83	1.92±0.56	0.249	1.22±0.98	1.58±0.47	0.224
Amygdala total %	0.12±0.04	0.13±0.03	0.657	0.11±0.07	0.12±0.04	0.532
Amygdala right cm <sup>3</sup>	0.85±0.41	0.98±0.31	0.290	0.61±0.49	0.83±0.27	0.164
Amygdala right %	0.06±0.02	0.068±0.02	0.422	0.05±0.03	0.06±0.02	0.228
Amygdala left cm <sup>3</sup>	0.78±0.44	0.93±0.26	0.225	0.61±0.48	0.75±0.29	0.346
Amygdala left %	0.11±0.17	0.06±0.01	0.396	0.11±0.19	0.05±0.02	0.398
Basal forebrain total cm <sup>3</sup>	0.50±0.28	0.63±0.14	0.089	0.42±0.27	0.52±0.17	0.167
Basal forebrain total %	0.03±0.01	0.04±0.01	0.217	0.03±0.02	0.03±0.01	0.353
Basal forebrain right cm <sup>3</sup>	0.20±0.14	0.27±0.08	0.109	0.17±0.12	0.23±0.10	0.106
Basal forebrain right %	0.01±0.01	0.01±0.01	0.149	0.01±0.01	0.01±0.01	0.346
Basal forebrain left cm <sup>3</sup>	0.32±0.30	0.39±0.26	0.505	0.28±0.34	0.29±0.08	0.529
Basal forebrain left %	0.02±0.02	0.02±0.02	0.720	0.02±0.02	0.02±0.01	0.593

X: Mean, SD: Standard deviation, CSF: Cerebro spinal fluid, WM: White matter, GM: Grey matter. \*\*: p <0.01, \*: p <0.05

Table 3. Comparison of volume measurements of caudate, pallidum, and putamen and ventricles in schizophrenia and healthy individuals

	Schizophrenia Male (X±SD)	Control Male (X±SD)	p	Schizophrenia Female (X±SD)	Control Female (X±SD)	p
Caudate total cm <sup>3</sup>	6.30±1.21	5.04±2.13	0.042*	5.48±1.02	3.23±2.54	0.005**
Caudate total %	0.44±0.06	0.35±0.15	0.031*	0.41±0.03	0.25±0.21	0.008**
Caudate right cm <sup>3</sup>	3.17±0.55	2.52±1.02	0.028*	2.73±0.55	1.62±1.36	0.009**
Caudate right %	0.22±0.02	0.17±0.07	0.020*	0.21±0.02	0.12±0.11	0.012*
Caudate left cm <sup>3</sup>	3.13±0.66	2.52±1.22	0.080	2.74±0.48	1.61±1.33	0.006**
Caudate left %	0.22±0.03	0.17±0.08	0.061	0.21±0.01	0.12±0.11	0.009**
Pallidum total cm <sup>3</sup>	2.99±0.49	2.51±1.20	0.137	2.63±0.76	2.08±1.22	0.167
Pallidum total %	0.21±0.02	0.67±2.01	0.356	0.20±0.05	0.76±2.20	0.353
Pallidum right cm <sup>3</sup>	1.55±0.25	1.26±0.56	0.058	1.39±0.36	1.07±0.61	0.106
Pallidum right %	0.11±0.01	0.55±1.91	0.348	0.10±0.02	0.65±2.11	0.346
Pallidum left cm <sup>3</sup>	1.44±0.43	1.33±0.50	0.492	1.23±0.59	1.10±0.53	0.529
Pallidum left %	0.10±0.02	0.11±0.09	0.630	0.09±0.04	0.11±0.10	0.593
Putamen total cm <sup>3</sup>	8.73±1.53	7.99±2.88	0.357	8.01±1.71	6.05±2.93	0.042*
Putamen total %	0.63±0.08	0.55±0.21	0.181	0.59±0.11	0.47±0.23	0.102
Putamen right cm <sup>3</sup>	4.53±0.62	4.11±1.33	0.249	4.22±0.84	3.36±1.61	0.091
Putamen right %	0.32±0.03	0.28±0.09	0.117	0.31±0.05	0.26±0.12	0.182
Putamen left cm <sup>3</sup>	4.21±1.06	3.88±1.74	0.524	3.77±1.34	2.68±1.96	0.099
Putamen left %	0.31±0.06	0.27±0.12	0.349	0.27±0.09	0.21±0.15	0.175
Inf. lateral ventricle total cm <sup>3</sup>	1.03±0.71	0.96±0.57	0.737	0.83±0.74	1.04±0.94	0.523
Inf. lateral ventricle total %	0.07±0.04	0.06±0.03	0.633	0.06±0.05	0.07±0.06	0.564
Inf. lateral ventricle right cm <sup>3</sup>	0.56±0.41	0.54±0.36	0.872	0.48±0.47	0.56±0.31	0.611
Inf. lateral ventricle right %	0.03±0.02	0.03±0.02	0.767	0.03±0.03	0.04±0.02	0.652
Inf. lateral ventricle left cm <sup>3</sup>	0.47±0.31	0.41±0.26	0.601	0.34±0.31	0.47±0.71	0.540
Inf. lateral ventricle left %	0.03±0.02	0.02±0.01	0.517	0.02±0.02	0.03±0.05	0.580
Lateral ventricle total cm <sup>3</sup>	20.21±11.61	16.16±14.45	0.375	23.09±15.47	20.21±21.01	0.681
Lateral ventricle total %	1.39±0.74	1.08±0.88	0.266	2.02±1.28	1.51±1.46	0.330
Lateral ventricle right cm <sup>3</sup>	9.63±6.13	7.95±8.26	0.507	12.17±10.17	9.27±10.12	0.457
Lateral ventricle right %	0.65±0.36	0.52±0.51	0.398	1.03±0.76	0.69±0.71	0.231
Lateral ventricle left cm <sup>3</sup>	10.57±8.77	8.21±6.28	0.371	10.92±6.12	10.92±11.13	0.952
Lateral ventricle left %	0.73±0.57	0.55±0.38	0.272	0.98±0.64	0.81±0.77	0.518
Third ventricle total cm <sup>3</sup>	1.08±0.87	0.89±0.65	0.472	0.93±0.91	1.09±0.99	0.668
Third ventricle total %	0.07±0.05	0.06±0.04	0.369	0.07±0.06	0.08±0.06	0.704
Fourth ventricle total cm <sup>3</sup>	1.51±0.77	1.36±0.45	0.517	1.21±0.92	1.62±0.98	0.260
Fourth ventricle total %	0.11±0.05	0.09±0.03	0.392	0.09±0.07	0.12±0.06	0.339
External CSF total cm <sup>3</sup>	170.74±93.81	114.07±50.17	0.035*	173.27±83.39630	134.69±78.26	0.048*
External CSF total %	11.87±5.71	7.72±2.89	0.038*	14.68±5.76	10.11±5.07	0.035*

X: Mean, SD: Standard deviation, CSF: Cerebro spinal fluid, \*\*: p <0.01, \*: p <0.05

CSF is vital for maintaining the structural integrity, metabolic balance, and physiological function of the brain and spinal cord. Any disruption in the dynamics or composition of CSF within the brain and spinal cord can significantly contribute to the development of various neurological disorders. Hence, CSF is one of the primary parameters measured in studies pertaining to schizophrenia in the existing literature. Some studies have reported that CSF volume remains unchanged in schizophrenia patients compared to healthy controls,<sup>17</sup> while a majority of recent studies indicate an increase in CSF volume.<sup>18,19</sup> In this study, a statistically significant increase in CSF volume was observed in both genders among schizophrenia patients.

The cerebellum, recognized as a densely organized structure, encompasses many functions spanning movement

coordination, emotional processing, planning, and perception. Existing literature has consistently reported reductions in both white matter and gray matter volumes within the cerebellum in studies investigating individuals diagnosed with schizophrenia.<sup>20,21</sup> In the context of this study, analyses revealed decreases in cerebellar white matter, gray matter, and total volume among schizophrenia patients compared to a control group. Notably, the reduction in cerebellar volume observed in female schizophrenia patients reached statistical significance. The cerebellum's multifaceted role underscores its significance in understanding the neurobiology of schizophrenia. The identified volumetric reductions in white and gray matter within this structure suggest potential disruptions across a spectrum of cognitive and affective processes implicated in schizophrenia.

**Table 4. Comparison of volume measurements of frontal lobe, temporal lobe, occipital lobe, limbic cortex, and insular cortex in schizophrenia and healthy individuals**

Cortical	Schizophrenia male (X±SD)	Control male (X±SD)	P	Schizophrenia female (X±SD)	Control female (X±SD)	P
Frontal lobe	185.56±51.48	208.81±18.52	0.089	143.07±56.54	183.43±13.64	0.015*
Frontal pole	7.31±2.36	8.01±1.48	0.304	5.46±1.78	7.07±1.21	0.009**
Gyrus rectus	4.15±1.42	4.61±1.41	0.361	2.78±1.71	4.41±0.51	0.002**
Opercular inf. frontal gyrus	6.22±2.27	7.28±1.23	0.100	5.36±2.68	6.43±1.01	0.173
Orbital inf. frontal gyrus	2.87±0.85	3.55±1.13	0.058	2.41±1.11	2.81±0.62	0.482
Triangular inf. frontal gyrus	6.96±2.15	8.45±1.52	0.026*	6.28±2.06	6.81±1.77	0.481
Medial frontal cortex	3.51±1.34	3.89±1.41	0.430	2.27±1.67	3.61±0.96	0.016*
Middle frontal gyrus	41.69±17.96	45.66±4.95	0.387	35.17±15.71	38.03±4.66	0.519
Anterior orbital gyrus	4.37±1.61	5.41±1.07	0.036*	3.36±1.44	4.23±0.75	0.055
Lateral orbital gyrus	5.03±1.54	5.61±1.01	0.210	3.66±1.77	4.77±1.04	0.056
Medial orbital gyrus	8.66±2.83	9.67±1.65	0.211	6.22±3.28	9.21±1.01	0.003**
Posterior orbital gyrus	7.31±2.65	7.12±1.11	0.799	5.38±3.53	6.58±1.11	0.237
Precentral gyrus	25.92±7.92	29.53±3.45	0.095	19.01±8.51	26.02±1.91	0.006**
Precentral gyrus medial seg.	5.39±1.13	6.08±0.77	0.047*	4.13±1.85	5.37±0.75	0.028*
Subcallosal area	2.26±0.75	2.41±0.86	0.586	1.82±0.96	2.23±0.94	0.272
Sup. frontal gyrus	31.29±8.28	35.07±4.88	0.116	23.94±8.55	31.37±4.35	0.008**
Sup. frontal gyrus medial seg.	13.04±4.11	14.81±2.58	0.145	9.59±4.18	13.49±2.27	0.005**
Supplementary motor cortex	12.12±1.74	11.61±2.16	0.454	9.32±2.71	10.92±1.61	0.069
Temporal lobe	114.84±33.89	132.51±17.43	0.065	88.33±34.73	109.07±12.81	0.046*
Fusiform gyrus	16.08±5.31	18.67±2.52	0.079	12.94±4.12	14.86±3.15	0.178
Planum polare	3.53±1.31	4.31±1.03	0.067	2.54±1.47	3.87±0.84	0.007**
Planum temporale	8.57±19.84	4.31±1.89	0.384	8.58±22.15	3.21±0.51	0.373
Inf. temporal gyrus	26.13±9.64	29.17±3.97	0.238	21.35±7.77	24.23±3.79	0.225
Middle temporal gyrus	30.56±6.84	34.84±4.84	0.043*	22.76±7.58	28.58±3.66	0.016*
Sup. temporal gyrus	14.57±4.31	16.54±3.01	0.133	11.11±5.03	13.87±2.67	0.080
Transverse temporal gyrus	3.08±1.04	3.17±0.96	0.790	2.27±1.08	2.61±0.66	0.334
Temporal pole	18.42±5.05	21.47±3.69	0.054	14.21±5.81	17.82±1.18	0.031*
Parietal lobe	118.73±22.15	133.74±21.98	0.056	95.31±29.61	112.91±10.25	0.045*
Angular gyrus	25.69±11.97	29.33±10.86	0.360	21.81±12.32	22.36±3.71	0.874
Postcentral gyrus	22.11±6.62	25.76±3.11	0.048*	16.41±7.45	21.96±2.52	0.014*
Postcentral gyrus medial seg.	2.08±0.78	2.35±0.41	0.218	1.73±1.21	2.16±0.38	0.217
Precuneus	23.63±5.56	28.45±7.04	0.034*	17.14±6.57	23.29±2.73	0.003**
Sup. parietal lobule	24.23±7.85	27.41±4.71	0.162	20.71±8.29	24.75±4.24	0.116
Supramarginal gyrus	18.67±4.17	20.42±3.73	0.207	14.71±4.89	18.36±2.71	0.021*
Occipital lobe	87.07±23.78	100.34±12.07	0.049*	70.12±29.47	86.06±10.17	0.067
Calcarine cortex	8.33±2.25	9.05±1.69	0.300	6.56±2.65	7.05±1.42	0.551
Cuneus	10.11±3.11	10.83±2.91	0.485	7.04±4.24	10.52±2.17	0.011*
Lingual gyrus	18.19±5.36	20.29±2.81	0.164	13.46±6.35	17.75±3.02	0.031*
Occipital fusiform gyrus	8.96±2.63	11.43±2.51	0.009**	8.06±3.58	8.67±1.07	0.548
Inf. occipital gyrus	16.42±6.53	17.84±5.11	0.487	15.41±9.03	15.32±2.49	0.975
Middle occipital gyrus	11.81±3.39	14.81±2.83	0.009**	9.05±4.14	11.91±2.06	0.029*
Sup. occipital gyrus	8.86±2.25	9.98±1.67	0.110	7.34±2.53	8.95±1.79	0.064
Occipital pole	5.24±1.58	6.11±1.41	0.104	4.21±2.32	5.86±1.48	0.034*
Limbic cortex	38.04±11.74	43.86±6.99	0.089	30.96±13.05	37.26±3.66	0.094
Entorhinal area	3.79±1.31	3.77±0.63	0.966	2.96±1.63	3.81±0.71	0.085
Anterior cingulate gyrus	9.73±3.18	11.11±2.36	0.160	7.50±3.53	9.37±1.92	0.094
Middle cingulate gyrus	9.22±2.42	10.78±2.25	0.061	7.25±3.35	8.84±1.69	0.126
Posterior cingulate gyrus	9.17±2.95	10.91±3.59	0.133	8.21±3.16	8.52±0.79	0.717
Parahippocampal gyrus	6.29±2.02	7.27±1.31	0.103	5.24±2.03	6.71±0.75	0.018*
Insular cortex	28.08±9.11	30.13±7.93	0.490	21.11±9.63	26.15±4.45	0.087
Anterior insula	7.76±2.65	8.33±1.82	0.475	5.93±2.98	7.55±1.59	0.085
Posterior insula	4.25±1.33	4.46±1.26	0.640	3.01±1.51	4.07±0.76	0.026*
Central operculum	7.66±2.19	8.31±2.26	0.402	5.97±2.36	6.72±1.06	0.591
Frontal operculum	3.66±1.38	3.99±1.37	0.491	3.01±1.46	3.57±1.12	0.263
Parietal operculum	4.72±1.86	5.02±1.87	0.653	3.18±1.67	4.23±0.75	0.043*

X: Mean, SD: Standard deviation, Sup: Superior, Inf: Inferior, Seg: Segment, \*\*: p <0.01, \*: p <0.05



Research investigating brainstem volume measurements in schizophrenia patients has consistently demonstrated a reduction compared to control groups, a phenomenon also observed in association with various other psychiatric conditions.<sup>22</sup> In alignment with existing literature, this study similarly identified decreased brainstem volumes among schizophrenia patients compared to the control group.

The nucleus accumbens, interconnected with various brain regions, particularly the limbic system, is pivotal in modulating the reward system, motivation, pleasure, addiction, and emotional functions. Existing literature indicates a consistent finding of reduced volume in the accumbens among schizophrenia patients compared to healthy controls.<sup>23</sup> This study observed a similar reduction in accumbens volume in schizophrenia patients relative to healthy controls. Additionally, statistically significant decreases in accumbens volume were noted among female schizophrenia patients.

The thalamus plays a pivotal role in processing and transmitting sensory information. Moreover, it influences cognitive processes encompassing memory, attention, language, and emotional functions. Given the presence of cognitive and emotional aberrations in individuals with schizophrenia, the association between the thalamus and schizophrenia has garnered attention. Numerous studies have demonstrated a reduction in thalamic volume among schizophrenia patients.<sup>24,25</sup> In this study, it is reported that thalamic volume is diminished in both male and female schizophrenia patients and statistically significant differences were found in women.

The term 'ventral DC' does not refer to a singular anatomical structure but rather encompasses a group of structures that are not readily distinguishable with standard MRI imaging. This composite region includes the hypothalamus, mammillary body, subthalamic nuclei, substantia nigra, red nucleus, lateral geniculate nucleus, and medial geniculate nucleus. Additionally, white matter areas such as the zona incerta, cerebral peduncle (*crus cerebri*), lenticular fasciculus, and medial lemniscus are encompassed within this area. The optic tract is also considered part of the ventral diencephalon in its most anterior extent. Each structure exhibits temporal variability within the ventral diencephalon, leading to considerable variation in its composition across different MRI slices. The ventral diencephalon houses structures integral to functions, including sensory relay, motor control, autonomic regulation, hormone secretion, and various aspects of cognition and emotion. In the literature, studies investigating ventral diencephalon volume measurements in patients with schizophrenia report divergent findings, encompassing observations of both volume increases<sup>26</sup> and decreases,<sup>27</sup> as well as instances where no significant change is noted.<sup>28</sup> This study observed smaller ventral diencephalon volume measurements in schizophrenia patients compared to healthy controls. Several factors may contribute to the observed smaller volume of the ventral diencephalon in individuals with schizophrenia compared to healthy controls. However, the precise mechanisms underlying this difference remain incompletely understood and likely involve a multifaceted interplay of genetic predispositions, developmental abnormalities, environmental influences, and neurobiological alterations.

In addition to regulating motor movements, the basal ganglia significantly contribute to various cognitive processes such as decision-making and behavioral planning. These

nuclei facilitate these pivotal functions through intricate communication among themselves and with the cortex. While the basal ganglia predominantly control motor functions via the dorsal corticostriatal circuit, they also play a crucial role in cognitive and sensory functions through the ventral corticostriatal circuit. Notably, while the caudate nucleus, one of the two components of the striatum, is particularly implicated in the ventral circuit, the putamen, the other component, predominantly governs motor functions within the dorsal circuit. Recent studies have underscored disruptions in these circuits across various psychiatric disorders, notably schizophrenia. Numerous investigations focusing on basal ganglia volume measurements in schizophrenia patients consistently report increases in both caudate and putamen volumes compared to healthy controls.<sup>29,30</sup> Consistent with the prevailing literature, this study reveals increases in pallidum, caudate, and putamen volumes among schizophrenia patients when compared to the control group. However, these increases are statistically significant in both sexes only in the caudate nucleus.

In the literature, alterations in the ventricular system have been extensively investigated in patients with schizophrenia since the inception of such studies.<sup>31</sup> Primarily, volume measurements of the lateral and third ventricles have been the focus of examination.<sup>32</sup> Previous studies have consistently reported enlarged ventricular volumes in schizophrenia patients compared to healthy individuals. This study assessed volumes of the inferior lateral ventricle, lateral ventricle, third ventricle, and fourth ventricle. It was observed that all ventricular volumes were greater in schizophrenia patients when compared to healthy controls, albeit without achieving statistical significance.

In the literature, schizophrenia is characterized by widespread alterations in brain morphology, with volumetric reductions noted across various brain regions in both male and female patients when compared to healthy controls.<sup>3,17-19,28</sup> In this study, in male patients with schizophrenia compared to healthy controls, volume reductions are noted across various brain regions, including the frontal lobe, temporal lobe, parietal lobe, occipital lobe, limbic cortex, and insular cortex. Furthermore, statistically significant decreases in the volumes of specific regions such as the triangular inferior frontal gyrus, anterior orbital gyrus, medial segment of the precentral gyrus, middle temporal gyrus, postcentral gyrus, precuneus, occipital fusiform gyrus, and middle occipital gyrus are observed when compared to healthy controls. In female patients with schizophrenia compared to healthy controls, there are notable volumetric reductions observed across a range of brain regions. These reductions encompass the frontal lobe, including the frontal pole, gyrus rectus, medial frontal cortex, medial orbital gyrus, precentral gyrus, and its medial segment, as well as the superior frontal gyrus and its medial segment. Similarly, reductions are evident in the temporal lobe, covering the planum polare, middle temporal gyrus, and temporal pole. Additionally, decreases in volume are observed in the parietal lobe, postcentral gyrus, precuneus, supramarginal gyrus, cuneus, lingual gyrus, middle occipital gyrus, occipital pole, parahippocampal gyrus, posterior insula, and parietal operculum. These findings underscore the widespread alterations in brain morphology associated with schizophrenia, highlighting the complex neuropathological underpinnings of the disorder.

## CONCLUSION

The findings of this study provide a comprehensive insight into the complex neuroanatomical alterations associated with schizophrenia. Utilizing the novel automated measurement method of the VolBrain AssemblyNet program, this research encompassed a thorough examination of 238 distinct brain areas, revealing significant volumetric changes across various structures. Consistent with existing literature, reductions in cerebellar WM, cerebellar GM, vermis, brainstem, accumbens, hippocampus, thalamus, and ventral DC, as well as changes in the amygdala and basal forebrain, were detected in schizophrenia. Increases in pallidum, caudate, putamen, inferior lateral ventricle, lateral ventricle, third ventricle, fourth ventricle, and CSF values were observed in individuals diagnosed with schizophrenia compared to healthy controls. Additionally, specific regional volumetric reductions were identified in key brain regions implicated in cognitive processing, emotional regulation, and motor control. Notably, the study highlights the widespread nature of these alterations, underscoring the multifaceted neuropathological underpinnings of schizophrenia. Understanding these neuroanatomical changes is vital for elucidating the underlying pathophysiological mechanisms of the disorder. It may pave the way for developing targeted therapeutic interventions to alleviate cognitive and functional deficits. Further research exploring the interplay of genetic, developmental, environmental, and neurobiological factors is warranted to deepen our understanding and improve treatment outcomes for individuals affected by schizophrenia.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of the Atatürk University Faculty of Medicine Clinical Researches Ethics Committee (Date: 26.10.2023, Decision No: 18).

### 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 declared no conflicts of interest concerning the authorship and/or publication of this article.

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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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# Evaluation of patients presenting with headache to the emergency outpatient clinic

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## ABSTRACT

**Aims:** This study aimed to explore the factors contributing to headache presentation in patients by recognizing headache as a symptom of various potential ailments. It is crucial to understand these factors for appropriate assessment and treatment planning in patients with headaches. Additionally, this study investigated patients preferences for headache management, which is an understudied aspect in the field.

**Methods:** In 2012, a two-month study was conducted at an emergency department outpatient clinic to assess the general characteristics, severity, frequency, duration, and location of headache episodes among patients presenting with headache complaints. The study analyzed various parameters, including the different types of pain, such as throbbing, stabbing, and burning, as well as the impact of headaches on daily performance, medication use, specific medications taken, and alternative treatment methods via a headache questionnaire.

**Results:** The survey results revealed that 21.7% of the patients described their pain as extremely severe, 52.2% as severe, and 26.1% as distressing. Pain descriptions were predominantly throbbing (79.4%) and pain (62.2%), with sensations of pressure (20%), stabbing (18.3%), pulsating (13.3%), burning (10.6%), and constriction-like a band (2.8%). The localization of pain was bilateral in 15.0% of patients, unilateral in 18.3%, around or behind the eyes in 28.3%, and in the neck or back of the head in 38.3%. Headaches were found to affect the work life of 40.6% of patients, 20% reported no impact, and 39.4% experienced occasional interference. No significant statistical difference was observed regarding the intensity, frequency, and duration of pain, and its impact on work life with respect to sex. The usage of non-prescription medication was high (92.8%), whereas prescription medication usage was 57.8%. Regarding alternative treatment methods, massage therapy was used by 53.6% of the patients and herbal treatments by 17.8%.

**Conclusion:** This study examined the frequency and handling of headaches among patients visiting an emergency department. The results indicate that headaches affect both sexes equally, with a marginal prevalence in females. To provide better care, addressing patients' preferences and experiences is important. As patients rely on non-prescription medications and alternative therapies, concerns regarding healthcare accessibility arise. A combination of medication management, patient education, and non-pharmacological therapies is necessary to achieve better outcomes and decrease the burden on healthcare systems.

**Keywords:** Emergency patient, epidemiology, headache, prevalence, headache evaluation

## INTRODUCTION

The prominence of headache disorders has escalated significantly in public health discussions, with over a decade and a half of consistent evidence revealing the profound impact of these conditions on individuals, societies, and healthcare systems globally.<sup>1</sup> The Global Burden of Disease (GBD) studies, notably GBD 2010 and GBD 2015, have positioned headaches, particularly tension-type headaches (TTH) and migraines, as leading contributors to global disability-adjusted life years (DALYs), surpassing all other neurological disorders.<sup>2</sup>

Headaches are one of the most common complaints in emergency departments (EDs), accounting for a notable 1-4%

of all visits. This clinical manifestation ranges from benign to life-threatening, presenting a considerable diagnostic and management challenge for healthcare providers. The urgency and complexity of headache disorders in emergency settings necessitate a comprehensive understanding of their prevalence, diagnostic evaluations, and treatment strategies.<sup>1,3</sup>

Differentiating primary headache disorders from secondary, potentially life-threatening conditions is crucial and complex in emergency care. Data suggest that secondary headaches, which constitute approximately 5% of severe headache cases in the ED, can be both life threatening and severely disabling.

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Despite this, most headaches diagnosed in EDs are benign. A broad range of headache types, coupled with varying presentations and individual patient factors, can complicate the clinical decision-making process. Emergency clinicians must balance the need for immediate diagnostic procedures such as neuroimaging and lumbar puncture against the need for efficient and targeted treatment.<sup>1,4</sup>

Headache questionnaires are useful tools for epidemiological studies to comprehend the prevalence and impact of headaches on populations. They serve as clinical instruments to obtain detailed information about a patient's headache experiences and differentiate between various types of headaches. The questionnaire followed a systematic approach to collect relevant information for the diagnosis and management of headache disorders. For research purposes, standardized questionnaires are used to quantify the impact of headaches on a patient's quality of life and to measure outcomes in clinical studies.<sup>5-8</sup>

This study aimed to systematically evaluate the clinical characteristics and treatment methods applied to adult patients presenting with headache complaints to the emergency department via a structured questionnaire. Additionally, we intended to collect the necessary clinical and epidemiological data to overcome the challenges encountered in the diagnosis and management of patients presenting with headaches to the ED.

## METHODS

### Study Design and Data Collection

A cross-sectional study was conducted by administering a "Headache Questionnaire" to 180 participants who presented to the Emergency Outpatient Clinic of Istanbul Education and Research Hospital between September and October 2012. Individuals with mental retardation, cancer pain, or diagnosed rheumatic diseases were excluded from the study. Demographic characteristics, such as age, sex, and occupation, of the included participants were assessed.

The Headache Questionnaire used for data collection was a brief, easily applicable assessment tool designed to evaluate the severity, frequency, duration, and location of headache episodes. Types of pain (throbbing, pain, weight, stabbing, pulsating, burning, and belt-like), the impact of headaches on daily performance, use of prescription or non-prescription medications, specific medications taken, and the use of alternative treatment methods were among the queried parameters. This questionnaire was administered to patients only once **Table 1**.

### Ethical Considerations

Institutional approval was obtained in this thesis study. Ethics committee approval is not required for this study since it is produced from a thesis before 2020. The purpose of the study was clearly explained to the participants by the researcher and written informed consent was obtained. This article has been written in accordance with the principles of the Helsinki Declaration for medical research.

### Statistical Analysis

Statistical analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). In the evaluation of the data, descriptive statistical methods (mean, standard deviation, frequency distributions, and percentage distributions) were utilized in conjunction with chi-square and Fisher's exact tests for comparisons of

qualitative data. The results were considered statistically significant at  $p$  of less than 0.05.

**Table 1. Headache questionnaire**

Patient's name:	Age:	Gender:	Education status:	Job:
1) Describe your typical headache attack.				
2) Number the severity of your pain. No pain (0)      Very mild (2-4)      Discomforting (5-6) Severe (7-8)      Extremely severe(9-10)				
3) How often do your headaches occur? Every day Every week (if every week, how many times a week) Less than once a month				
4) Do your headaches affect your performance at work?      Does it prevent you from doing your Daily activities? Yes      No      Sometimes				
5) How long did your last headache last? Minutes      Hours      Days				
6) Which of the following best describes your headache? (You can tick more than one option) 1 Weight      2 Throbbing      3 Painful      4 Belt style 5 Burning      6 Palpitating      7 Freezing sensation      8 Stabbing				
7) Where does your pain occur? On both sides of the head      On one side of the head Behind or around the eyes.      On the neck or back of the head				
8) Is your headache accompanied by any of the following findings? (You can tick more than one option) 1 Nausea      2 Nasal congestion      3 Sensitivity to loud noise 4 Sensitivity to light      5 Dizziness      6 Drooping eyelids 7 Loss of strength      8 Clouding of consciousness      9 Flashes of light 10 Loss of vision      11 Tears      12 Heart palpitations 13 Shortness of breath      14 Numbness, tingling      15 Blurred vision 16 Fatigue      17 Dazed feeling      18 Crying				
9) Which of the following triggers your headache? (You can tick more than one option) 1 Menstrual period      2 Odors      3 Medications.      4 Alcohol 5 Exercise      6 Foods      7 Smoking 8 Changes in weather (Low pressure systems or storms)      9 Stress      10 Other.....				
10) Did you have warning symptoms such as low or high energy, restlessness before your headache? Yes      No				
11) Have you had or are you experiencing any of the following? Uncontrolled blood pressure      Heart attack or cardiovascular disease Stroke      Reynaud's disease      Stroke or transient ischemic attack Abnormal heartbeat ( arrhythmia)      Pregnancy				
12) Which of the following over-the-counter medications did you use for your headache? 1 Acetaminophen      2 Aspirin      3 Ibuprofen      4 Excedrin 5 Naprosyn      6 Paracetamol      7 Other.....				
13) Have you ever used prescribed medication to stop your headache? Which ones did you use? What are the consequences?				
14) Have you ever used prescribed medication to prevent your headache? Which ones did you use? What are the consequences?				
15) Have you tried alternative treatment methods to relieve your headache? 1 Massage therapy      Yes, (if yes, did it work?)      -No 2 Behavioral therapy      Yes, (if yes, did it work?)      -No 3 Acupuncture      Yes, (if yes, did it work?)      -No 4 Herbal treatments      Yes, (if yes, did it work?)      -No 5 Treatment with spine massage      Yes, (if yes, did it work?)      -No				

## RESULTS

This study included 180 patients presenting with headaches to an emergency outpatient clinic. The cohort comprised of 49 male (27.2%) and 131 female (72.8%). The mean age of the male patients was  $42.47 \pm 12.72$  years, ranging from 20 to 68 years, while the mean age for female patients was  $42.06 \pm 13.2$  years, ranging from 18 to 81 years. Overall, the mean age of all patients was calculated to be  $42.17 \pm 13.04$  years, with an age range of 18 to 81 years.

The distribution of educational status among our patients was as follows: 18 (10.0%) were not literate, 80 (44.4%) had a primary education, 32 (17.8%) had a middle school education, 34 (18.9%) had a high school education, and 16 (8.9%) had university degrees. The occupational distribution was diverse, including 10 (5.6%) retirees, 92 (51.1%) housewives, 31 (17.2%) laborers, 17 (9.6%) civil servants, 6 (3.3%) students, and 24 (13.3%) from the private sector.

In terms of pain severity, 39 patients (21.7%) reported extremely severe pain, 94 patients (52.2%) reported severe pain, and 47 patients (26.1%) described their pain as uncomfortable. When asked about the frequency of headaches, 37 patients (20.6%) reported daily occurrences, 66 (36.7%) weekly, and 77 (42.8%) less than once a month. Regarding the impact of headaches on work performance, 36 (20%) answered 'No, 73 (40.6%) answered Yes, and 71 (39.4%) answered Sometimes'. Duration of the last headache was reported as 'minutes' by 6 patients (3.3%), 'hours' by 120 patients (66.7%), and 'days' by 54 patients (30%).

The types of headaches described were throbbing (79.4%), painful (62.2%), pressure (20%), stabbing (18.3%), pulsating (13.3%), burning (10.6%), and band-like (2.8%). The location of the headaches varied, with 27 patients (15.0%) experiencing bilateral headaches, 33 (18.3%) unilateral, 51 (28.3%) behind or around the eyes, and 69 (38.3%) in the neck or back of the head.

The distribution of comorbid diseases and the events triggering the headache were investigated and are presented in Table 2 and Table 3.

**Table 2. Distribution of diseases and conditions accompanying headache**

Condition/disease	n	%
Hypertension	40	22.2
Cardiovascular disease	8	4.4
Stroke	0	0.0
Raynaud's disease	1	0.6
Stroke or transient ischemic attack	2	1.1
Arrhythmia	8	4.4
Pregnancy	92	70.2

In the study, 104 patients (57.8%) used prescribed medications to alleviate their headaches. Moreover, most patients used non-prescription drugs for headache relief. The distribution of non-prescription drug use was as follows: paracetamol was the most commonly used, with 97 patients (53.9%) reporting its use. This was followed by 'Other' non-prescribed medications, reported by 89 patients (49.4%). Aspirin was administered to 26 patients (14.4%). Naprosyn was used in 4 patients (2.2%). Ibuprofen was reported in 3 patients (1.7%).

No usage of Acetaminophen or Excedrin was reported. In total, 167 patients (92.8 %) used some form of nonprescription medication for their headaches.

Apart from medical therapy, patients have reported alternative therapy for headache relief (Table 4).

Gender-based comparisons showed no significant difference in the general features of headaches. Only the presence of a burning-type headache was significantly higher in males, with 9 cases (18.3%), than in females, who reported 10 cases (7.63%), resulting in a statistically significant difference (p=0.037) (Table 5).

**Table 3. Comorbidities and triggers associated with headache**

Symptom/Trigger	n	%
<b>Comorbidities</b>		
Fatigue	138	76.7
Sensitivity to loud noises	102	56.7
Light sensitivity	82	45.6
Nausea	80	44.4
Dizziness	67	37.2
Tearing of eyes	41	22.8
Blurred vision	38	21.1
Dazed feeling	30	16.7
Nasal congestion	29	16.1
Numbness and tingling	16	8.9
Photopsia (flashing lights)	13	7.2
Palpitations	13	7.2
Crying	12	6.7
Loss of strength	8	4.4
Vision loss	8	4.4
Ptosis (drooping eyelid)	7	3.9
Shortness of breath	2	1.1
Clouding of consciousness	0	0.0
<b>Triggers</b>		
Stress	152	84.4
Exercise	51	28.3
Weather changes	40	22.2
Menstruation	36	27.5
Smoking	13	7.2
Odors	12	6.7
Foods	8	4.4
Alcohol	4	2.2
Medications	0	0.0

**Table 4. Distribution of alternative methods used for headache relief**

Alternative method	Effective (n)	Effective (%)	Not effective (n)	Not effective (%)
Massage therapy	58	32.2	38	21.1
Herbal treatments	13	7.2	19	10.6
Behavioral therapy	0	0.0	0	0.0
Acupuncture	0	0.0	0	0.0

There were no significant differences in the use of alternative therapies for headaches between the male and female participants. A total of 48.98% of male participants and 45.80% of female participants did not use massage therapy to alleviate headaches, with 32.65% of male and 32.06% of female participants finding it effective. 18.37% of males and 22.14% of females tried massage therapy but did not find it effective. Most participants did not use herbal remedies, with 87.76% males and 80.15% females reporting no use. Among those who found herbal treatments effective, 6.12% of males and 7.63% of females used them.

**Table 5. Gender-based comparison of headache intensity, frequency, duration, and description**

Description	Male (%)	Female (%)	*p
<b>Headache intensity</b>			
Discomforting	30.61	24.43	0.313
Severe	55.10	51.15	
Extremely severe	14.29	24.43	
<b>Headache frequency</b>			
Daily	22.45	19.85	0.588
Weekly	30.61	38.93	
Less than once a month	46.94	41.22	
<b>Impact on work performance</b>			
No impact	26.53	17.56	0.115
Yes impact	28.57	45.04	
Sometimes impact	44.90	37.40	
<b>Duration of last headache</b>			
Minutes	6.84	2.29	0.214
Hours	71.43	64.89	
Days	22.45	32.82	
<b>Headache description</b>			
Weighty feeling	20.41	19.85	0.933
Throbbing	71.43	82.44	0.104
Painful	55.10	64.89	0.228
Belt-Like	2.85	3.05	0.713
Burning	18.37	7.63	0.037*
Pulsating	14.29	12.98	0.818
Freezing sensation	0.00	0.00	
Stabbing	21.43	21.37	0.085

\*Chi-square test

Statistically significant differences were observed in the intensity of pain and distribution of medication use ( $p=0.003$ ). Triptans were notably higher in the extremely severe pain group, and non-medication use was higher in the discomforting pain group. Differences were also observed in the duration of last headache and medication use ( $p=0.040$ ). NSAIDs were more frequently used by those with headaches lasting days, whereas those with pain lasting minutes had a higher tendency to avoid medication. Table 6 shows the detailed relationship between the intensity and duration of headaches and corresponding medication use among the participants.

## DISCUSSION

The current study enrolled 180 patients who sought treatment for headaches at an emergency outpatient clinic. Of these, 72.8% were female, which aligns with previous studies that reported a higher prevalence of headaches in females. The average age of the participants did not vary significantly between sexes, and the prevalence of headaches appeared to be consistent across different age groups. This study found that headache prevalence was not influenced by socioeconomic status, which further emphasizes the universal nature of headache disorders. Pain severity was described as severe or extremely severe by more than half of the patients, highlighting the significant impact of headache on individuals. The study also noted that headache disorders can be chronic, with many patients experiencing frequent and long-lasting headaches, thus emphasizing the need for ongoing management strategies.

Our study found that most headaches reported by our participants were throbbing and located on one side of the head, which is consistent with previous findings on migraine headaches.<sup>9,10</sup> However, we also observed a significant number of bilateral and posterior headaches, indicating that tension-type headaches were common. This highlights the need for a nuanced approach to characterize headache in clinical practice. Additionally, hypertension was the most common comorbidity, whereas pregnancy showed a strong correlation with headache occurrence, warranting further investigation of the potential links between these factors and headache pathology.

Stress has emerged as the primary instigator of headaches, which aligns with the well-documented association between stress and headache episodes. Factors such as weather changes and menstruation, identified as other triggers, underscore the complex nature of headache precipitants, as supported by existing research.<sup>8,9,11</sup> The extensive utilization of non-prescription medications (92.8%) among participants suggests that many patients may be self-medicating, potentially due to barriers to healthcare access or a preference for self-management strategies. This trend may also reflect dissatisfaction with conventional treatments or a desire for holistic care approaches, as patients resort to alternative therapies. Paracetamol, widely used for self-medication (53.9%), aligns with its global reputation as a first-line pain

**Table 6. Comparison of headache characteristics with prescribed medication use**

Headache characteristic	No medication	Metamizole	NSAIDs	Paracetamol	SSRIs	Triptans	p
<b>Intensity of pain</b>							
Discomforting	51.10%	0.00%	34.00%	12.80%	0.00%	2.10%	0.003*
Severe	40.40%	1.10%	31.90%	17.00%	4.30%	5.30%	
Extremely severe	35.90%	0.00%	25.60%	10.30%	0.00%	28.20%	
<b>Frequency of headaches</b>							
Daily	45.90%	0.00%	35.10%	13.50%	0.00%	5.40%	0.319
Weekly	43.90%	1.50%	19.70%	18.20%	4.50%	12.10%	
Less than once a month	39.00%	0.00%	39.00%	11.70%	1.30%	9.10%	
<b>Impact on work performance</b>							
No	47.20%	0.00%	27.80%	16.70%	0.00%	8.30%	0.345
Yes	38.40%	0.00%	30.10%	12.30%	5.50%	13.70%	
Sometimes	43.70%	1.40%	33.80%	15.50%	0.00%	5.60%	
<b>Duration of last headache</b>							
Minutes	66.70%	0.00%	16.70%	0.00%	0.00%	16.70%	0.040*
Hours	45.80%	0.00%	29.20%	18.30%	0.80%	5.80%	
Days	31.50%	1.90%	37.00%	7.40%	5.60%	16.70%	

\*Chi-square test, NSAID: Nonsteroidal anti-inflammatory drug

reliever due to its accessibility, efficacy, and safety profile when used appropriately. However, concerns over potential overuse or misuse have been raised given that headache disorders are a significant cause of emergency outpatient visits.<sup>12,13</sup>

The findings indicated that a significant number of patients (49.4%) used 'other' non-prescribed medications to treat their headaches, suggesting that many individuals may be exploring various over-the-counter options or relying on traditional remedies not classified as conventional medications. This suggests that patients may seek alternative treatment because of unmet needs in professional healthcare or personal preferences for self-directed care. While a smaller percentage of patients (14.4%) used aspirin, along with Naprosyn (2.2%) and ibuprofen (1.7%), the absence of Acetaminophen or Excedrin use may indicate regional or cultural preferences in medication choices or awareness of their side effects or ineffectiveness. Regarding alternative therapies, massage therapy was found to be effective in 32.2% of those who tried it, indicating that non-pharmacological interventions could play a role in headache management strategies, particularly for patients who may not respond well to medical therapies or those seeking complementary approaches, that aligns with the previous studies.<sup>14,15</sup>

The relatively low efficacy reported for herbal treatments (7.2%) and the lack of use of behavioral therapy and acupuncture may be indicative of a lack of awareness, accessibility, skepticism, or insufficient evidence supporting these methods. This also reflects the necessity for increased education and research on the effectiveness of various alternative therapies for headache.

In clinical practice, these findings underscore the need for healthcare providers to inquire about all forms of medication and alternative treatments patients utilize. This is crucial for preventing potential drug interactions, recognizing patterns of medication overuse headaches, and ensuring that patients are advised about the range of available effective treatments, both medical and alternative.

Reevaluating current headache management protocols and patient education practices may be necessary because of the high reliance on non-prescription medications. Medical professionals should provide more comprehensive guidance on the appropriate use of OTC drugs and investigate the reasons for low uptake or reported ineffectiveness of prescribed medications and alternative therapies. This approach could lead to more personalized and effective headache management plans, better patient outcomes, and fewer emergency department visits for headaches.

The study findings on sex differences in headache characteristics and treatment approaches showed no significant disparities between males and females in most headache features. However, a notable exception was the occurrence of burning-type headaches, which was significantly more prevalent in males (18.3%) than in females (7.63%,  $p=0.037$ ). This result is interesting, as it suggests possible sex differences in the experience of pain or the phenomenology of headaches, an area that warrants further exploration. Although migraine headaches, which are more common in women, are typically described as pulsating or throbbing, the finding of more burning-type headaches in men suggests a potential difference in the underlying pathophysiology or reporting bias, which requires further investigation.<sup>16-18</sup>

The effectiveness of alternative therapies varied among the study participants. Although approximately 32% of both men and women found massage therapy helpful, almost half of the participants did not use this nonpharmacological treatment option. This suggests a lack of awareness regarding the benefits of these therapies or a preference for pharmacological interventions. The reported low efficacy of herbal treatments among those who use them indicates that although some patients are exploring these options, they may not be widely perceived as effective. These findings are consistent with the literature, which often highlights the variability in patient responses to both pharmacological and non-pharmacological treatments, emphasizing the need for personalized treatment plans that consider patient preferences and experiences with different therapies.<sup>19,20</sup>

This study highlights the need for better education on headache management for patients, as suggested by their preference for self-medication with OTC drugs. Clinicians should advise patients on the correct use of OTC medications and the risks of overuse, as well as guide them towards alternative therapies that can alleviate symptoms and improve overall well-being and work performance. The findings of this study can inform the development of educational materials and interventions aimed at promoting more effective self-management of headaches, potentially reducing the burden of headaches on individuals and the healthcare system.

The frequency of headaches also influences the use of medication, with nonsteroidal anti-inflammatory drugs (NSAIDs) being more commonly used by those whose headaches persist for several days. This may indicate a pattern of chronic tension-type headaches or poorly controlled migraines. Those with shorter headache episodes tended to avoid medication more often, possibly because of the natural resolution of their pain or belief that medication would not be effective. These data suggest that healthcare providers should personalize treatment recommendations based on the unique features of each headache presentation. For instance, patients with milder or shorter headaches may benefit from discussing the pros and cons of 'watchful waiting' or using non-pharmacological methods, such as relaxation techniques or biofeedback. Additionally, the higher reliance on NSAIDs among patients with longer-lasting headaches highlights the need to address the risk of medication overuse in patient education and headache management strategies.

Therefore, clinicians must engage with patients to ensure that the chosen treatments align with the severity, frequency, and impact of headaches while also considering patient preferences and the potential risks of medication overuse. The findings of this study emphasize the complexity of headache management and the necessity of personalized treatment approaches that account for the multifaceted nature of headache disorders.

### Limitations

This study has some limitations.

**1. Cross-sectional design:** The study's cross-sectional nature allows for the observation of a snapshot in time, which can identify associations, but not causal relationships. This design limits the ability to determine progression or changes in headache characteristics or medication use over time.

**2. Selection bias:** Participants were drawn from an emergency outpatient clinic, which may not be representative of the general



population with headaches. This could lead to a selection bias, as the severity of headaches might be higher in an emergency care setting than in a primary care setting.

**3. Exclusion criteria:** The exclusion of individuals with mental retardation, cancer pain, or diagnosed rheumatic diseases could limit the generalizability of the findings to all patients with headache, as these conditions could also influence headache characteristics and treatment responses.

**4. Self-reported data:** The reliance on self-reported data in the “Headache Questionnaire” can introduce recall bias, as participants may not accurately remember or report the severity, frequency, or duration of their headaches.

**5. Geographic and cultural factors:** Conducted in a specific location, the study’s findings might not be applicable to different geographic or cultural settings where headache prevalence and treatment approaches could differ.

These limitations highlight areas for future research, such as longitudinal studies, broader participant selection, and in-depth analyses of treatment patterns and efficacy. Addressing these limitations in subsequent research can deepen our understanding of headache disorders and improve the care for those affected.

## CONCLUSION

This study sheds light on the prevalence and management of headache disorders in patients attending an emergency outpatient clinic. The findings reveal that headaches affect both sexes equally, with a higher prevalence among females. The study also highlights the need for patient education on headache management, given the frequent use of prescribed and nonprescription medications. The distinctive finding that males are more prone to burning-type headaches warrants further research. Personalized care that considers patient preferences and experiences is crucial for effective headache management. Stress is a significant trigger emphasizing the need for comprehensive management strategies. The reliance on non-prescription medications and alternative therapies, such as massage, raises questions about accessibility to healthcare services. A holistic approach that combines medication management with patient education and non-pharmacological therapies is essential for improving patient outcomes and reducing the burden on the healthcare system.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

Institutional approval was obtained. Ethics committee approval is not required for this study since it is produced from a thesis before 2020.

### Informed Consent

All patients signed and 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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# Assessment of first-time attendees at a pain clinic using a pain inventory tool

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## ABSTRACT

**Aims:** Pain presents a complex challenge affecting the quality of life of over a million adults annually. Understanding the variety and distribution of pain types is vital for effective management and intervention strategies. This study aimed to assess the characteristics and distribution of pain among first-time attendees at a pain clinic using the Brief pain inventory (BPI).

**Methods:** A cross-sectional survey was conducted with 100 adult outpatients at the pain clinic of the İstanbul Training and Research Hospital from July to November 2012. The BPI was administered face-to-face and demographic data were collected. Individuals under 18 years of age, mentally retarded, previous pain clinic attendance, cancer pain, or diagnosed rheumatic diseases was excluded. Written informed consent was obtained from all participants. Descriptive statistics were used to describe the means, standard deviations, and frequency distributions.

**Results:** The study included 100 adult patients with a mean age of 46.4, predominantly female (65%), who sought treatment for various pain complaints at a pain clinic. The majority reported throbbing (41% knee, 31% lumbar, and 65% shoulder) and exhausting pain (74% knee, 73% lumbar, and 65% shoulder), with significant proportions experiencing constant pain, especially in the knee (82%) and lumbar region (81%). Regular analgesic use was noted in 54% of the patients, with 65% requiring daily medication, indicating high demand for pain management. Despite treatment, 90% expressed the need for stronger pain relief and 50% reported side effects from analgesics. Various nonpharmacological methods have been used, such as hot compression (38%) and relaxation techniques (30%).

**Conclusion:** The study reveals the significant pain burden among first-time pain clinic patients, with throbbing and exhausting sensations prevalent in knee and lumbar regions. The extensive use of analgesics and need for stronger pain relief indicate ongoing pain management challenges. The adoption of nonpharmacological methods highlights the need for a multifaceted approach. These findings emphasize the necessity of tailored, multidimensional pain management strategies for enhanced patient care and quality of life.

**Keywords:** Brief pain inventory (BPI), pain assessment, pain clinic, outpatient pain characteristics

## INTRODUCTION

The pervasive nature of pain, especially chronic pain, presents a significant global challenge to the healthcare system. The burden of chronic pain extends beyond an individual's physical and emotional suffering to substantial socioeconomic costs, with annual expenditures in the United States ranging between \$550 and \$625 billion. These costs encompass direct healthcare expenses as well as indirect implications such as diminished work productivity, reduced tax revenue, legal costs, and disability benefits.<sup>1</sup> On average, current treatment modalities offer a 30-40% reduction in pain intensity and benefit less than half of those treated, leaving a majority to endure ongoing pain that substantially hampers their quality of life and induces considerable physical and psychological strain.<sup>2</sup>

Healthcare providers and the public usually assume that pain originates from a pathological condition. Consequently, the standard procedure involves exhaustive physical examinations and diagnostic tests to identify a "pain generator".<sup>3</sup> However, when organic issues are not detected, the healthcare system often attributes symptoms to psychological factors, perpetuating a binary view of pain as either somatic or psychogenic.<sup>4</sup> This outdated perspective, rooted in historical medical practice since Descartes's time, does not align with contemporary research or the current understanding of chronic pain.<sup>5</sup>

To adequately manage chronic pain, a comprehensive evaluation approach that incorporates the biological causes of pain and

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a thorough assessment of the individual's psychosocial and behavioral contexts is required. This includes understanding the patients' emotional state, their perception and cognitive evaluation of symptoms, and the social dynamics surrounding their condition. A multifactorial perspective of chronic pain acknowledges its complexity and various influences on an individual's experience and functional capacity within the context of chronic pain.<sup>4</sup>

The Brief Pain Inventory (BPI) is a scientifically validated questionnaire that is widely used to measure both the intensity of pain and the degree to which pain hampers patients' daily functions. Originally developed by Cleeland and Ryan<sup>6</sup> in 1991, the BPI has become an essential tool for clinical pain assessment and is utilised globally in a variety of healthcare settings.

The BPI is renowned for its balanced focus on both quantitative and qualitative aspects of a patient's pain experience. It requires patients to score their pain on a scale of 0 to 10, where 0 signifies "no pain" and 10 indicates "pain as severe as imaginable." This rating was accompanied by enquiries about pain location, quality, and relief. Furthermore, the BPI evaluates the consequences of pain on various aspects of life, including mood, mobility, work, social relationships, sleep, and the overall quality of life. Patients can report their pain severity at four different points: "at its worst," "at its least," "on average," and "" right now over the past 24 hours.

This study aimed to evaluate the pain characteristics of patients who attended a pain clinic for their initial consultation. BPI measures how much pain has interfered with seven daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. This evaluation was performed using the BPI, with a focus on assessing the severity of pain and its impact on patients' daily activities. This study sought to elucidate the distribution of pain experiences within this cohort, thereby facilitating the refinement of pain management strategies.

## METHODS

### Study Design

This study was a cross-sectional assessment conducted at the Department of Anesthesiology and Reanimation, İstanbul Training and Research Hospital, between July and November 2012. This study aimed to administer the BPI through face-to-face interviews with participants attending a pain clinic for the first time.

### Study Population

This study included 100 outpatients aged  $\geq 18$  years. The exclusion criteria were individuals below 18 years of age, those with mental retardation, prior attendance at any pain clinic, current cancer pain, or a diagnosis of rheumatic diseases. Demographic data, including age, sex, and occupation, were systematically collected from all eligible participants.

### Ethical Considerations

Institutional approval was obtained in this thesis study. Since this study is produced from a thesis before 2020, ethics committee approval is not required. This article has been written in accordance with the principles of Helsinki Declaration. The purpose of the study was explained to the participants and informed consent was obtained in writing.

## Statistical Analysis

Statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). Descriptive statistical methods, including means, standard deviations, frequency distributions, and percentages were used to evaluate the data.

## RESULTS

In this study, 100 individuals presenting with pain complaints during their initial visit to the Pain Clinic were included. The composition of the patient population was 35% male ( $n=35$ ) and 65% female ( $n=65$ ). The mean age of the patients was found to be 46.4 years, range: 21-76 years). The average age of female patients was 46.78 years (range, 21-76 years), while for male patients, the mean age was 46.68 years (range, 21-69 years). Regarding marital status, 18% of the patients ( $n=18$ ) were never married, 75% ( $n=75$ ) were married, 4% ( $n=4$ ) were widowed, and 3% ( $n=3$ ) were divorced.

Regarding educational background, 10% of the patients ( $n=10$ ) were not literate, 3% ( $n=3$ ) were literate without formal education, 40% ( $n=40$ ) had primary school education, 8% ( $n=8$ ) had middle school education, 23% ( $n=23$ ) had completed high school, 4% ( $n=4$ ) had some college education, 10% ( $n=10$ ) were university graduates, and 2% ( $n=2$ ) held doctoral degrees.

Employment status was reported as follows: working full-time outside the home by 29.3% ( $n=29$ ), part-time by 3% ( $n=3$ ), working at home by 27.3% ( $n=27$ ), retired by 18.2% ( $n=18$ ), unemployed by 12.1% ( $n=12$ ), and other situations accounting for 10.1% ( $n=10$ ).

Pain complaints were as follows: knee pain was reported by 39% of patients ( $n=39$ ), back pain by 26% ( $n=26$ ), shoulder pain by 17% ( $n=17$ ), head pain by 15% ( $n=15$ ), hip pain by 13% ( $n=13$ ), ankle pain by 9% ( $n=9$ ), back pain by 8% ( $n=8$ ), wrist pain by 8% ( $n=8$ ), neck pain by 7% ( $n=7$ ), elbow pain by 5% ( $n=5$ ), abdominal pain by 5% ( $n=5$ ), and chest pain by 1% ( $n=1$ ).

The distribution of pain among the participants was evaluated (Table 1).

**Table 1. Patient reported pain experiences**

Question	n	%
Have you experienced any pain due to your current condition?	96	96
Was pain one of your complaints when you first received your diagnosis?	91	91
Have you undergone any surgery in recent months?	28	28
Have you experienced any pain in the past week, other than these?	87	87
Have you taken any medication for pain in the past week?	87	87
Do you feel as though you have a type of pain that is present every day and requires treatment?	83	83
n:number		

The patterns of analgesic use among the study participants were examined. It was reported that 54 individuals (54%) regularly took medication for pain, whereas 46 participants (46%) took medication only when necessary. Within a 24-hour period, the frequency of analgesic intake was as follows: 65 individuals (65%) took medication daily, 21 (21%) took it once or twice a day, 12 (12%) three to four times a day, and 2 (2%) five to six times a day. Ninety participants (90%) indicated a need for stronger pain medication and 47 (47%) reported a need for more

analgesics than prescribed by their doctors. Twenty individuals (20%) believed that taking a large quantity of pain relievers protected them from pain, whereas 50 (50%) experienced side effects from pain relief. Moreover, 68 participants (68%) felt the need for more information regarding analgesics. In efforts to alleviate pain, non-pharmacological methods were also utilized: 38 individuals (38%) used hot compresses, 14 (14%) used cold compresses, 30 (30%) practiced relaxation techniques, 5 (5%) engaged in distraction activities, and 13 (13%) used other methods.

Assessment of the characteristics of pain and its implications are documented and presented in Tables 2-5.

**Table 2. Average pain intensity among patients**

Description (n=100)	Mean (±SD)	Min.	Max.
Time elapsed since initial diagnosis	24.8 (±47.32)	1	276
Worst pain experienced in the past week	7.5 (±2.24)	0	10
Least severe pain experienced in the past week	5.18 (±3.03)	0	10
Average pain experienced over the past week	6.33 (±2.41)	0	10
Current pain intensity	5.94 (±2.97)	0	10
Reduction in pain due to medication/ treatment in the past week	4.39 (±2.82)	0	10

n: Number, SD: Standard deviation, Min: Minimum, Max: maximum

The distribution of pain intensity among participants was evaluated (Table 2).

The distribution of the impact of pain on daily activities of the participants was evaluated (Table 3).

**Table 3. Impact of pain on daily activities in the past week**

Daily activity affected by pain (n=100)	Mean (±SD)	Min.	Max.
General activity	6.79 (±2.95)	0	10
Mood (emotional state)	6.9 (±2.81)	0	10
Walking ability	5.77 (±3.37)	0	10
Normal work (including home and outside work)	6.92 (±2.87)	0	10
Relationships with other people	5.48 (±3.09)	0	10
Sleep	6.41 (±3.07)	0	10
Enjoyment of life	6.66 (±3.20)	0	10

n: Number, SD: Standard deviation, Min: Minimum, Max: maximum

The duration of pain relief delivered through analgesic use was also assessed (Table 4).

The analysis of the patients' pain characterisation across different body regions provided a comprehensive breakdown of the data (Table 5).

**Table 4. Duration of pain relief and type distribution**

Duration until pain recurrence after medication	n	%
Medication did not help	20	20
1 hour	2	2
2 hours	15	15
3 hours	8	8
4 hours	18	18
5-12 hours	19	19
>12 hours	14	14
Did not take pain reliever	4	4
<b>Effectiveness of treatment (e.g., medication, surgery, radiation, prosthetic device)</b>	<b>n</b>	<b>%</b>
Yes	20	20
No	80	80
<b>Relation to primary treated condition</b>	<b>n</b>	<b>%</b>
Yes	88	88
No	12	12
<b>From another medical problem unrelated to primary disease (e.g., arthritis)</b>	<b>n</b>	<b>%</b>
Yes	6	6
No	94	94

n: Number

## DISCUSSION

This study is one of the minorities to examine the diverse nature and severity of pain among individuals attending pain clinics. The patient population in this study exhibited a predominance of female patients, which is consistent with the broader consensus in pain literature that women are more likely to seek help for pain. The average age of male and female patients is nearly equal, indicating that pain affects adults in mid-life similarly across genders. However, the slightly higher age range for women may suggest a greater exposure or delayed reporting of pain symptoms. Most patients are

**Table 5. Distribution of pain descriptors across different body regions**

Pain character	Knee	Lumbar	Shoulder	Headache	Hip	Ankle	Back	Wrist
Tolerable	6 (15%)	7 (27%)	4 (24%)	1 (7%)	4 (31%)	1 (11%)	2 (25%)	1 (13%)
Throbbing	16 (41%)	8 (31%)	11 (65%)	12 (80%)	5 (39%)	6 (67%)	3 (38%)	5 (63%)
Burning	5 (13%)	3 (12%)	4 (24%)	2 (13%)	3 (23%)	2 (22%)	1 (13%)	1 (13%)
Stabbing	16 (41%)	12 (46%)	9 (53%)	3 (20%)	6 (46%)	3 (33%)	3 (38%)	3 (38%)
Soft	2 (5%)	4 (15%)	1 (6%)	1 (7%)	3 (23%)	0 (0%)	0 (0%)	1 (13%)
Exhausting, draining	29 (74%)	19 (73%)	11 (65%)	12 (80%)	13 (100%)	7 (78%)	4 (50%)	5 (63%)
Piercing	12 (31%)	5 (19%)	7 (41%)	3 (20%)	4 (31%)	1 (11%)	3 (38%)	2 (25%)
Constantly bothersome	32 (82%)	21 (81%)	14 (82%)	9 (60%)	9 (69%)	6 (67%)	5 (63%)	6 (75%)
Numbness	23 (59%)	13 (50%)	10 (59%)	6 (40%)	10 (77%)	5 (56%)	1 (13%)	4 (50%)
Terrible	20 (51%)	13 (50%)	10 (59%)	10 (67%)	8 (62%)	7 (78%)	7 (88%)	4 (50%)

married, which could be due to an age-related increase in pain conditions or the support structure of marriage encouraging patients to seek medical advice. The educational background of patients is diverse, with a notable proportion lacking formal education. This emphasizes the importance of patient education in managing pain, as those with higher education levels may have better access to information and resources for pain management. The findings align with the global burden of chronic pain, with a higher prevalence of pain in women (65%). This aligns with existing research, which indicates that women are more likely to report and experience pain more intensely. The most common descriptors of pain were 'throbbing' and 'exhausting', particularly in the knee (41%) and lumbar regions (73%), highlighting the significant discomfort associated with these areas.

A global study conducted by the World Health Organization across Asia, Europe, Africa, and the Americas found that 21.5% of primary healthcare services reported chronic pain (64). In Italy, 91.2% of inpatients experienced pain.<sup>7</sup> Hasse et al.<sup>8</sup> identified headaches as the third most common reason for visiting family physicians. Despite no clear consensus on the prevalence of pain, it is universally recognised that pain affects all individuals. Sociocultural and cognitive factors influence the location, expression, intensity, and coping methods for pain, and manifest differently across cultures and in various forms. Sertel Berk et al.<sup>9</sup> emphasised in a literature review the significance of subjective beliefs about pain control, beliefs about pain, and the behaviours exhibited in coping with pain, as well as the effectiveness of these behaviours.

Our analysis revealed that 54% of the patients consistently relied on analgesics, with 65% requiring daily pain management, emphasising the need for more effective pain management. The finding that 90% of patients desired stronger pain medication highlights the limitations of current pain control measures. Moreover, 50% of the patients experienced adverse effects from analgesics, suggesting a gap in the effectiveness and tolerability of pain treatment options.

In our study, we found that 54% of the participants regularly took medication for pain, whereas 46% did so when needed. Regarding dosage, 65% of the participants took medication every 24 h, 21% once or twice a day, 12% three or four times a day, and 2% five or six times a day. Additionally, 90% of the participants felt the need for stronger medication, 47% required more analgesics than prescribed, and 20% believed that excessive use of painkillers was protective against pain. Furthermore, 50% of the participants experienced side effects, and 68% sought more information on analgesics. To manage pain, 38% of participants used hot compresses, 14% used cold compresses, 30% used relaxation techniques, 5% engaged in distraction activities, and 13% used other methods. Our study also found varying rates of nonpharmacological interventions, such as hot compresses (38%) and relaxation techniques (30%), indicating the potential benefits of a multimodal approach for pain management. However, the impact of these methods on pain relief was not the focus of this study and warrants further investigation.

This study found that most patients experienced persistent pain in various body regions, with the knee and lumbar regions being the most affected. This persistent nature of pain could have a significant impact on the quality of life and healthcare utilisation. The prevalence of 'piercing' pain in the knee and

elbow suggests potential joint or musculoskeletal issues, while the 'numbness' reported in the hip region may indicate neuropathic pain requiring a different treatment approach. This study also highlights the global prevalence of pain, which is influenced by sociocultural and cognitive factors, as evidenced by the diverse descriptors used by patients to describe their pain.

Pain is a common occurrence, with studies revealing that over 50% of the population experiences it.<sup>10</sup> Factors such as social, cultural, and economic changes as well as longer life expectancy may contribute to this high prevalence.<sup>11</sup> An epidemiological study in Sweden showed that 54% of the population suffers from chronic pain. In Turkey, headaches, back pain, and lumbar pain are among the most common reasons for patient visits to clinics.<sup>12</sup> Japanese research on musculoskeletal pain indicated that neck and shoulder pain was more common than other types of pain, followed by lumbar pain.<sup>13,14</sup> In Iran, 22.7% of musculoskeletal complaints in rural areas are related to shoulder pain.<sup>15</sup>

In the US, approximately one-fourth of adults experience daily lumbar pain within a three-month period, while 7.6% report severe lumbar pain at least once annually.<sup>16</sup> Eliot et al. discovered that back and joint pain were the most frequent complaints, with back pain more common among younger age groups and males, and joint pain was common in older age groups and females. Another study found that headache was the most common complaint among adolescents. In our study, the areas most affected by pain were the knee, lumbar, and shoulder regions. Our results indicate that pain in the shoulder and lumbar regions was more intense than that in other areas and significantly impacted work capabilities. Although the literature on pain often focuses on prevalence, studies examining pain intensity are rare; therefore, we cannot compare our results in this regard. A study on pain prevalence found that 91 patients (96.7%) used medication to relieve their pain and 67.8% used daily analgesics. In older individuals, only analgesic use as a pain-relief method has been reported, with a prevalence ranging from 27% to 44%.<sup>17</sup>

### Limitations

The limitations of our study include its cross-sectional design and reliance on self-reported measures, which may have introduced a bias. Additionally, the lack of distinction between acute and chronic pain in our assessment may have masked the differences in pain patterns. Future studies could benefit from longitudinal designs and objective pain measures to enrich the understanding of pain experiences.

### CONCLUSION

The key findings of this study underscore the importance of understanding pain and its various expressions in different demographic groups. By focusing on pain in crucial areas, such as the knee, lower back, and shoulder, as well as emphasising the reliance on medication and non-pharmacological methods for pain relief, this research provides valuable information for improving pain management. In conclusion, the significant variations in how people experience, and report pain highlight the need for a personalised, patient-centred approach to pain management. By considering both medication and nonmedication pain relief options, healthcare providers can develop a comprehensive treatment plan that considers the

unique experiences of individuals with pain. Such an approach not only improves patient outcomes but also informs the development of more effective pain management strategies and the allocation of healthcare resources to enhance patient well-being.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

Institutional approval was obtained in this thesis study. Since this study is produced from a thesis before 2020, ethics committee approval is not required.

### Informed Consent

All patients signed and 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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# A rare case of lipoid pneumonia due to diesel aspiration

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## ABSTRACT

Acute exogenous lipoid pneumonia is a rare chemical pneumonia following aspiration of volatile hydrocarbon compounds. In this case report, we present a 63-year-old male patient who developed acute exogenous lipoid pneumonia following accidental aspiration of diesel oil from the fuel tank of his vehicle with a hose. The patient presented with sore throat, cough, dyspnoea and tachypnoea. Posteroanterior chest radiography showed paracardiac infiltrations in the right lower and left lower lung fields. The patient presented again on the 21<sup>st</sup> day after aspiration with cough and sputum production. Chest X-ray showed a cavitory lesion with air-fluid level in the lower right probe. One month after the treatment, radiological regression of the consolidations was observed in the chest radiograph. In conclusion, this rare disease occurs after inhalation of hydrocarbon products. Symptoms and radiological findings develop rapidly and may lead to serious pulmonary complications and sequelae.

**Keywords:** Lipoid pneumonia, aspiration, diesel

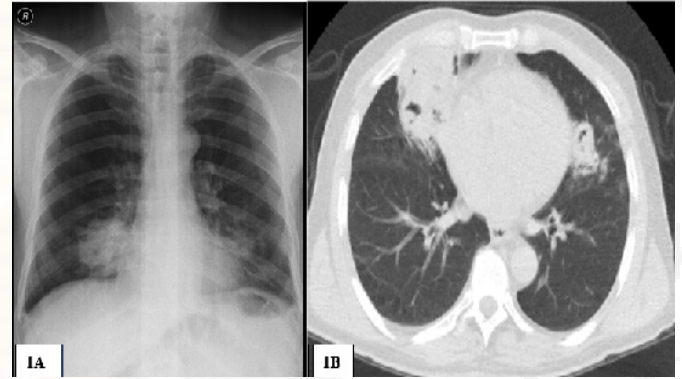
## INTRODUCTION

Lipoid pneumonia (LP) is a type of pneumonia where lipids (fats) are found in the lung tissue. It can result from the inhalation or aspiration of oily or fatty substances. Lipoid pneumonias are classified as endogenous and exogenous.<sup>1</sup> Exogenous lipoid pneumonia occurs when external substances, such as diesel, paraffin oil, mineral oil or vegetable oils are inhaled or aspirated into the lungs.<sup>2</sup> Inhalation or consumption of diesel may lead to hydrocarbon pneumonitis, which is a type of exogenous LP.<sup>3</sup> This report presents a case of a patient who accidentally consumed diesel while siphoning.

## CASE

A 63 year old man, with no previous medical illness reported experiencing a seven day sore throat, cough and dyspnea. Seven days before, he had aspirated accidentally a water glass of diesel fuel, while attempting to siphon it from the fuel tank of his vehicle. His respiratory rate was 30 breaths/min. His pulse rate was 110 beats/min, the temperature was 38°C, blood pressure was 110/60 mmHg, oxygen saturation 94% under room air and the patient did not need oxygen therapy. Patient was dyspnoeic but there was no cyanosis. Physical exam was notable for normal oral mucosa without lesions. In the auscultation, mild rales were heard bilaterally. His total leucocyte count was  $7 \times 10^3$  cells/ $\mu$ L with a differential of 81% polymorphonuclear leucocytes and 11% lymphocytes. Arterial blood gas analysis was within the reference range. C-reactive protein (CRP) level was 102 mg/L. The posteroanterior chest radiograph showed opacifications and infiltrations paracardiac

right lower and left lower lung fields (Figure 1A). Computed tomography of the thorax revealed bilateral consolidation in the lower lobes (Figure 1B).



**Figure 1.** A. Posteroanterior chest radiograph demonstrating opacifications and infiltrations paracardiac right lower and left lower zone B. Computed tomography scan of the thorax demonstrating right lower and left lower lobe consolidation

The patient's bacterial sputum culture was negative. Since Türkiye is an endemic region in terms of tuberculosis, sputum acid-fast organism test was performed and it was negative. He was diagnosed with hydrocarbon pneumonitis and treated with piperacillin/tazobactam (3x4500 mg/day, IV), clindamycin (3x600 mg/day, IV) and oxygen supplementation. He was discharged from hospital after nine days of treatment. After two weeks patient presented with recurrence of cough associated with expectoration. His chest radiograph showed

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features of worsening consolidation and a cavitory lesion with an air-fluid level over the lower zones of right lung (Figure 2).



**Figure 2.** Posterioranterior chest radiograph demonstrating features of worsening consolidation and a cavitory lesion with an air-fluid level over the lower zones of right lung

His leukocyte counts was  $14 \times 10^3$  cells/ $\mu$ L, CRP level was 123 mg/L. Bacterial sputum culture and acid-fast organism test were negative. During follow-up the patient's sputum culture was negative for *Mycobacterium tuberculosis*. There was no history of drug use that would cause immunosuppression and serology tests were regular.

Meropenem  $3 \times 1000$  mg/day IV was implemented for 14 days. A follow-up computed tomography of the thorax (Figure 3) a month after discharge showed radiological regression of consolidations.



**Figure 3.** Computed tomography scan of the thorax demonstrating resolution of the pulmonary infiltrates

## DISCUSSION

LP is a chronic inflammation of the lung parenchyma caused by the accumulation of fat-containing substances within the distal airways. This accumulation leads to an inflammatory response that inhibits exchange of gases.<sup>4</sup> LP are classified as endogenous and exogenous. Endogenous LP, also known as cholesterol pneumonitis occurs due to the distal obstruction of the airways by tumors and suppurative processes.<sup>5</sup> Exogenous LP is occurred by the aspiration or inhalation of

animal, mineral or vegetable oils. Petrol, diesel and gasoline are the most used hydrocarbons in daily life. Inhaling these hydrocarbons, either intentionally or accidentally, can result in hydrocarbon pneumonitis.<sup>6</sup> In our case, the patient accidentally aspirated diesel when siphoning it from the fuel tank of his vehicle. The airways do not readily absorb hydrocarbons after being inhaled can easily reach the alveoli and this causes structural damage in the alveoli. These pathologic changes are caused by the inflammatory response that develops due to increased cytokine release from macrophages and leads to chemical pneumonia.<sup>7</sup> Acute LP is typically characterized by common clinical symptoms such as cough, dyspnea, fever, and chest pain.<sup>8</sup> Radiological abnormalities are bronchovascular markings, consolidations with an air bronchogram which may become cavitated and/or develop pneumatoceles, ground-glass opacifications, pneumothorax, and pleural effusion or pneumo mediastinum. It usually takes between two weeks and eight months for radiological opacities to resolve after clinical recovery.<sup>9</sup> The blood or lungs have no specific tests to detect the level of diesel exposure. The diagnosis is typically based on the patient's anamnes.<sup>10</sup> The identification of lipid-laden macrophages in bronchoalveolar lavage fluid and the presence of alveoli in bronchoscopic lung biopsy results in a definitive diagnosis.<sup>11</sup> In our cases, we could not do bronchoscopy because there is no bronchoscopy unit in our hospital and applied non-invasive diagnostic technique like sputum. Treatment options for LP are not well-defined, and reports of cases only provide an overview of their progress. The primary focus of treatment is on avoiding continuous exposure and providing support. Hydrocarbon pneumonitis cannot be treated with antibiotics, but the majority of patients receive antibiotic treatment due to the inability to differentiate between hydrocarbon and superimposed pulmonary infections. Systemic corticosteroids limits the inflammation and ongoing fibrosis but are supported only by case reports. The other treatment options include bronchoalveolar lavage, immunoglobulins and surgery.<sup>12</sup> Our patient was treated with antibiotic and oxygen supplementation. He had complete clinical and nearly complete radiological improvement two weeks after discharge from hospital.

## CONCLUSION

Hydrocarbon pneumonia, resulting from the accidental inhalation of diesel fuel, can lead to extensive and severe lung damage. It's important for healthcare professionals to be aware of the potential respiratory hazards associated with hydrocarbon exposure and to consider this diagnosis in individuals with relevant symptoms and exposure history.

## ETHICAL DECLARATIONS

### Informed Consent

The patient signed and 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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# Hairy tongue secondary to antibiotic usage

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## ABSTRACT

Hairy tongue, also known as black hairy tongue, is a non-malignant disorder characterized by the enlargement of the filiform papillae, resulting in a velvety appearance on the surface of the tongue. The elongated papillae exhibit a range of coloration, spanning from a yellowish white hue to shades of brown to black. The precise cause of this illness remains uncertain; nevertheless, it has been linked to many predisposing factors, including extensive tobacco use, inadequate oral hygiene practices, the administration of topical or systemic antibiotics, and other related disorders. In this case report, we describe the clinical presentation of a 27-year-old patient who was diagnosed with hairy tongue as a result of antibiotic use. In addition to that, we provide a concise summary of the ailment.

**Keywords:** Antibiotics, brown discoloration of the tongue, hairy tongue

## CASE

A 27-year-old female patient presented to our polyclinic with symptoms including halitosis, a metallic taste, and tongue discoloration. During the course of her medical history, she had a persistent infection of the hepatitis B virus without necessitating any kind of therapeutic intervention. Two weeks ago, the patient was prescribed antibiotic therapy for dyspepsia and a *Helicobacter pylori* infection. A sequential regimen was given to the patient, consisting of the following medications: during the first week, pantoprazole 40 mg was twice daily, amoxicillin 1000 mg twice daily; in the second week, pantoprazole 40 mg and clarithromycin 500 mg twice daily, metronidazole 500 mg three times daily. On the last day of the therapy, the patient began experiencing symptoms. A brown discoloration with a hairy look was seen on the dorsal surface of the tongue (Figure). The patient had a comprehensive evaluation, which revealed no abnormalities during systemic assessment. The laboratory results indicated no abnormalities. The swab culture yielded no results for the presence of any specific pathogen. The diagnosis of hairy tongue was attributed to the recent use of antibiotics, based on the available evidence. The administration of medications was ceased, and a gentle brushing of the tongue was advised. The lesion had disappeared after a two-week period.

## DISCUSSION

The complete understanding of the pathophysiology of hairy tongue remains elusive. The condition is believed to originate from impaired desquamation of the lingual dorsal surface.



Figure. (a) Brown discoloration on the dorsal surface of the tongue. (b) Hair-like coating on the dorsum of the tongue (red arrows)

Consequently, it impedes the process of regular debridement, resulting in the buildup of keratinized layers. Typically measuring less than 1 mm in length, the elongated papillae have the potential to extend up to a length of 12-18 mm and a width of 2 mm. The appearance of abnormally hypertrophied and elongated filiform papillae characterizes the acquired, benign condition known as “hairy tongue.” The misconception behind the term stems from the fact that traditionally, this growth has been depicted as a black, hairy carpet-like outgrowth on the tongue. Hairy tongue may manifest with various pigmentation patterns, including brown, yellow,

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green, blue, or even unpigmented. Inadequate dental hygiene, a variety of diseases, drugs, and medicines are believed to be potential etiological contributors of hairy tongue.<sup>1,2</sup> Hairy tongue has been documented as a potential adverse effect of several medications, including antipsychotics, methyl dopa, lansoprazole, interferon, antidepressants, antineoplastics, and antibiotics such as cephalosporins, penicillins, tetracyclines, clarithromycin, and linezolid.<sup>3</sup> Hairy tongue often does not exhibit symptoms; however, some individuals may experience nausea, loss of taste, halitosis, or a burning or tingling sensation in the tongue. Nevertheless, the primary concern for patients is the negative impact on their aesthetic appearance. In the realm of management, the first course of action is the elimination of inciting factors and the prioritization of dental cleanliness. Additional therapy options for second-line management include antifungal agents, retinoids, antibiotics, topical urea solution, trichloroacetic acid, salicylic acid, and thymol.<sup>4</sup> The use of antibiotics for the treatment of *Helicobacter pylori* was shown to be the causative factor in our case. After using conservative treatment strategies, the condition completely resolved over a span of two weeks.

## CONCLUSION

A hairy tongue is a benign condition that may be a sign of underlying diseases, inadequate dental hygiene, or a side effect of different drugs. Often asymptomatic, it may cause halitosis, nausea, loss of taste, burning, or tingling sensations in the tongue. It will be quickly resolved after eliminating the contributing factor.

## ETHICAL DECLARATIONS

### Informed Consent

The patient signed and 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

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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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# Optimizing patient care: rethinking referrals for iron deficiency anemia in internal medicine

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Dear Editor,

I am writing to express my concern about the prevailing trend of inappropriate referrals of patients with iron deficiency anemia to hematologists by internal medicine specialists. Iron deficiency anemia, while involving the blood, is not solely a hematological disorder. It is essential for internal medicine specialists and primary care clinicians to be cognizant of the distinct nature of this condition and consider a broader range of differential diagnoses before making referrals.

Iron deficiency anemia (IDA) is a condition characterized by a deficiency of iron, an essential component for the proper functioning of red blood cells<sup>1</sup>. While hematologists play a crucial role in the management of blood disorders, it is important to recognize that iron deficiency can arise from various causes, including gastrointestinal bleeding, malabsorption, and nutritional deficiencies.<sup>1</sup> Consequently, not all cases of iron deficiency anemia necessarily require the expertise of a hematologist.

It is crucial to acknowledge the specific implications of iron deficiency in women, often stemming from gynecological factors such as menstrual blood loss, pregnancy, and reproductive health issues. In light of this, collaboration with gynecologists becomes paramount in ensuring a thorough evaluation and a more accurate diagnosis.<sup>2</sup> Thus, collaboration with gynecologists assumes significance to ensure comprehensive evaluation and accurate diagnosis. Menstrual blood loss alone can result in significant iron depletion, leading to anemia in premenopausal women.<sup>3</sup>

The inappropriate referrals of such cases to hematologists can result in unnecessary burden on specialized services, leading to increased healthcare costs and potential delays in the diagnosis and treatment of other, potentially more severe, conditions. Moreover, it places an additional strain on the already stretched resources of hematologists, who could be better utilized for cases that truly necessitate their expertise.

I urge internal medicine specialists and primary care clinicians to enhance their understanding of the differential diagnosis of iron deficiency anemia and consider collaborating with other relevant specialties, such as gastroenterology

and nutrition, when appropriate. For instance, chronic gastrointestinal bleeding due to conditions like peptic ulcer disease or colorectal cancer can lead to iron deficiency anemia. Similarly, malabsorption syndromes such as celiac disease or inflammatory bowel disease can impair iron absorption, contributing to anemia.<sup>4</sup> This interdisciplinary approach will ensure a more comprehensive evaluation of patients, leading to improved patient outcomes and more efficient use of healthcare resources.

A comprehensive national study on anemia and its underlying causes revealed significant insights into the prevalence and impact of IDA across different demographics in Turkiye. The study highlighted the substantial burden of anemia, particularly among women of reproductive age and children. Several clinical trials have been conducted to evaluate different treatments for IDA in Turkiye. For instance, a study published in the Journal of Hematology & Oncology explored the effectiveness of oral iron supplements versus intravenous iron treatments in pregnant women with IDA. This study aimed to find the most effective and safe treatment protocols for this vulnerable population. These studies and trials underscore the ongoing efforts in Turkiye to better understand and mitigate the impact of iron deficiency anemia through research, dietary recommendations, and clinical interventions.

In conclusion, the prevalence of inappropriate referrals of iron deficiency anemia patients to hematologists by internal medicine specialists is a matter that warrants attention. By fostering a better understanding of the diverse etiologies of iron deficiency anemia among primary care clinicians, we can promote a more efficient and effective healthcare system.

**Keywords:** Iron, internal medicine, anemia

## ETHICAL DECLARATIONS

### Referee Evaluation Process

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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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