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Research Article

Evaluation of Cardiorenal Metabolic Syndrome in Patients with Heart Failure with Preserved Ejection Fraction. How Aware Are We?

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Aim: Despite the prevalence of cardiorenal metabolic diseases (CRMD) in heart failure with preserved ejection fraction (HFpEF) patients and their significant complications, they are thought to be under-recognized and under-screened. In our study, we aimed to evaluate patients with HFpEF who were followed up in our internal medicine clinic.

Methods: Our retrospective and cross-sectional study included 348 patients with HFpEF. Patients were evaluated according to laboratory, demographic, clinical, electrocardiographic and ultrasonographic findings.

Results: Of the patients, 37.95% had diabetes mellitus, 23.3% had chronic kidney disease, 70.1% had hypertension and 59.2% had metabolic dysfunction-associated steatotic liver disease. The mean NT-proBNP level was 360.7 ± 13.7.

Conclusion: We recommend that HFpEF, which is associated with increased cardiovascular mortality and morbidity in patients with CRMD, should be screened clinically and with NT-proBNP and evaluated with transthoracic echocardiography if necessary.

Keywords: CRMD, Diabetes mellitus, HFpEF, Hypertension, MASLD

1. INTRODUCTION

Heart failure (HF) is a major public health problem, affecting millions of adults worldwide. According to the definition of heart failure with preserved ejection fraction (HFpEF) by the European Society of Cardiology (ESC), HFpEF is present in individuals with symptoms and signs of heart failure, structural and/or functional cardiac abnormalities, and/or elevated natriuretic peptides (NPs), and a left ventricular ejection fraction (LVEF) of at least 50%.[1]

HFpEF accounts for more than half of all HF cases and is the most common form of HF in patients over 65 years of age. Its incidence and

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prevalence increase as the population ages and the prevalence of metabolic disorders such as obesity, diabetes mellitus (DM) and hypertension (HT) increases.[2,3] HFpEF is associated with high morbidity and mortality. Although cardiovascular mortality is lower in HFpEF compared to low ejection fraction HF (HFrEF), recurrent hospitalizations are frequent and quality of life is poor. Patients with HFpEF have similarly high rates of recurrent hospitalizations as patients with HFrEF. The risk of death in patients with HFpEF increases with increasing comorbidity burden.[4,5]

HFpEF is frequently associated with metabolic comorbidities. More than 80% of patients are overweight or obese, approximately 20-40% have diabetes and more than 40% have hyperlipidemia.[6] Cardiorenal metabolic diseases (CRMD) such as coronary artery disease (CAD), chronic kidney disease (CKD) and DM are the leading and pathophysiologically interrelated causes of death and disability worldwide. CRMD frequently coexist in individuals with HFpEF.[7]

The approach to HF has changed significantly in recent years. Despite the high prevalence of HFpEF and its increasing frequency in the elderly population, it has now become an important healthcare problem due to a marked lack of evidence-based prognostic treatments.[8] There are currently very few effective treatments for HFpEF. Most of the treatments approved for HFrEF have been shown to be ineffective for HFpEF. This suggests that there are important differences in the basic pathophysiology and therapeutic targets in HFpEF compared to HFrEF. Our understanding and awareness of this highly prevalent disease needs to be improved.[9]

Despite the prevalence and significant complications of CRMD in patients with HFpEF, it is thought that it is often overlooked, under-recognized and under-screened in clinical practice. By increasing the awareness of clinicians about the risk and clinical importance of patients with HFpEF, early diagnosis and timely intervention, the disease can be reversed. In our study, we aimed to evaluate patients with HFpEF who were followed up in our internal medicine clinic.

2. MATERIAL AND METHOD

2.1. Study population and laboratory measurements

Our retrospective and cross-sectional study included 348 patients with HFpEF whose medical history and previous examinations did not constitute an obstacle to their inclusion in the study. HFpEF was defined according to the 2021 ESC HF guidelines. Our study included symptomatic adults with HFpEF, clinical evidence of HF and confirmed LVEF≥50% on transthoracic echocardiography (TTE).[1] In patients with HFrEF, acute coronary syndrome, malignancies, pregnant women were excluded from the study. Patients between 01.01.2024 and 31.12.2024 were included in the study. Patients followed up in the inpatient and outpatient departments of the internal medicine clinic were included in the study. Diabetes diagnosis was made according to ADA guidelines, hypertension diagnosis according to ESC guidelines, and chronic kidney disease diagnosis according to KDIGO guidelines.[10] The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee. Adana City Training and Research Hospital Ethics Committee approved the study with decision number 318 dated 02.01.2025. After 5 minutes of rest, in a dim and quiet environment, blood pressure measurements were taken from both arms using a suitable cuff and pulses were monitored. Anthropometric body weight measurements were performed. Height was measured with the feet bare and together, leaning perpendicular to the height measurement ruler. BMI was calculated as body weight (kg) divided by the square of height in meters (BMI=kg/m2). Laboratory procedures of the study were performed in the Biochemistry Laboratory of Health Sciences University Adana Training and Research Hospital. Venous blood was drawn from the antecubital vein after at least 8 hours of overnight fasting from the patients and the control group during routine controls. Laboratory measurements of participants were measured using automated laboratory methods (Abbott Aeroset, Minneapolis, MN) and appropriate commercial kits (Abbott). The FIB-4

score is calculated using the formula: (Age × AST) / [Platelet count × (ALT)^(1/2)]. Electrocardiographic findings of the patients, QRS and QTC were evaluated.

All patients underwent liver US screening using a high resolution USG device (Philips EPIQ 7), using a 1- to 5-MHz high-resolution convex probe (Philips Health Care, Bothell, WA). The liver US was performed after a minimum fasting of 8 hours initially with B-mode US in the gray scale, which was used to assess the liver dimensions and parenchymal echogenicity. Subjects were evaluated independently by two experienced radiologists. The diagnosis of MASLD was made based on the presence of fatty liver on ultrasound, as well as a diagnosis of type 2 diabetes, obesity, or at least two metabolic risk factors (increased waist circumference, dyslipidaemia, hypertension, insulin resistance, or metabolic syndrome findings).[11] Echocardiography measurements were performed by cardiologists with at least 10 years of experience using the ACUSON SC2000 PRIME (Siemens Medical Solutions USA) echocardiography device and 4V1c (Siemens Medical Solutions USA) probe.

2.2. Statistical analysis

All analyses were performed using the statistical software package SPSS 24.0 (Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess whether the distribution of continuous variables was normal. Continuous variables in group data were expressed as mean ± standard deviation. Categorical variables were expressed as numbers and percentages. The κ coefficient was used to examine the interobserver and intraobserver variability of USG measurements. Statistical significance level was accepted as $p<0.05$.

3. RESULTS

The mean age of the patients was 70.3± 11.7 years. 57.8% of the patients were male. The mean body mass index (BMI) was 30.1± 3.09. 37.95% of the patients had DM, 23.3% had CKD, 70.1% had HT, 49.7% had atrial fibrillation (AF), 23.9% had CAD, 57.2% had hyperlipidemia, and 59.2% had metabolic associated fatty liver disease (MASLD). The mean NTproBNP was 360.7± 13.7 and Fib-4 index was 1.09± 0.25. All other data in the study group are shown in table 1.

Table 1.

Demographic, clinical, laboratory, ultrasonography and electrocardiography findings of patients with heart failure preserved ejection fraction

Variables	Patient with HFpEF (n=348)
Age (year)	70.3 ± 11.7
Gender (F/M, %)	57.8 / 42.2
Systolic blood pressure (mmHg)	138.6 ± 16.0
Diastolic blood pressure (mmHg)	87.4 ± 10.5
Body mass index (kg/m2)	30.1 ± 3.09
Basal heart rate (pulse/minute)	91.8 ± 10.3
Smoking, %	51.4
Diabetes mellitus, %	37.6
Chronic kidney disease, %	23.3
Hypertension, %	70.1
Atrial fibrilasyon, %	49.7
Coronary artery disease, %	23.9
Stroke, %	11.8
Chronic pulmonary obstructive disease, %	8.3
Peripheral artery disease, %	10.1
Hyperlipidemia, %	57.2
US-confirmed MASLD diagnosis, %	59.2
Fasting plasma glucose, mg/dL	118.1 ± 29.1
White blood cell (10^3/ µL)	8.59 ± 2.08
Hemoglobin (g/dL)	12.3 ± 2.31
Platelet (10^3/ µL)	288.5 ± 106.5
e-GFR (mL/min)	58.4 ± 20.1
Sodium (mmol/L)	137.2 ± 4.43
Potassium (mmol/L)	4.28 ± 0.35
Albumin (g/dL)	3.83 ± 0.22
Aspartate aminotransferase (u/L)	24.3 ± 10.4
Alanine aminotransferase (u/L)	30.2 ± 11.4
Triglycerides, mg/dL	154.5 ± 31.9
HDL cholesterol, mg/dL	43.0 ± 10.2
LDL cholesterol, mg/dL	135.1 ± 28.5
CRP (mg/L)	2.94 ± 1.39
NTproBNP (pg/mL)	360.7 ± 113.7
Fib-4 index	1.09 ± 0.25
QTc duration, ms	410.6 ± 26.2
QRS duration, ms	90.8 ± 8.74

HDL: high density lipoprotein, LDL: low density lipoprotein, CRP: c reaktif protein, Fib-4: fibrosis-4, USG: ultrasonography, DM: diabetes mellitus, HFpEF: heart failure preserved ejection fraction, QTc: corrected QT

4. DISCUSSION

The main findings of our study are that patients diagnosed with HFpEF have a high prevalence of diseases called CRMD, mainly HT, MASLD, DM, CKD, hyperlipidemia. These findings indicate that HFpEF screening should be performed in patients with CRMD in outpatient clinics. While these patient groups are analyzed in detail for their own diseases in outpatient clinic examinations, they should also be screened for HFpEF clinically and with NT-proBNP and appropriate patients should be evaluated with TTE.

The total number of people with HFpEF continues to increase due to a the increasing prevalence of conditions that contribute to the pathophysiology. Growing and aging population and of HFpEF, such as obesity, HT and DM in high-income countries, it is estimated that approximately 50% of known HF patients have HFpEF. The number of prospective, population-based studies using natriuretic peptides and detailed echocardiography to assess the true prevalence of HFpEF is insufficient. It is possible that the prevalence of HFpEF is much higher than currently indicated. A meta-analysis of echocardiographic screening studies in the general population reported an 11.8% prevalence of overall HF in people aged 65 years and older in high-income countries. More than three-quarters of these cases are HFpEF.[12] Epidemiologic data show that the prevalence of HFpEF is increasing more frequently than HFrEF. These data make HFpEF the most common type of HF.[13]

Epidemiologic characteristics of HFpEF show an increasing prevalence with advancing age, female gender, and metabolic and inflammatory conditions that contribute to myocardial stiffness or comorbidities such as atrial fibrillation and valvular disease that worsen functional abnormality.[14] HFpEF is more common in women. In a study, HFpEF was found in 67% of cases in women with HF, whereas 42% of men with HF were shown to have HFpEF.[15] In our study, 57.8% of the patient group was female and the mean age was 70.3± 11.7 years. These data may suggest that gender may play a pathophysiologic role in this condition. The higher prevalence of HFpEF in women than men may be partly related to obesity and diabetes. Obesity is more common in women than men, and the association between obesity and incident HFpEF is greater in women. The fact that women have a longer life expectancy and develop comorbidities with advancing age may also explain why the prevalence of HFpEF increases with age and is higher in women. Low socioeconomic status is associated with a 62% higher risk of HF, including HFpEF.[16] In our study, we did not classify patients according to socioeconomic status. This may be related to the higher prevalence of negative behavioral risk factors such as physical inactivityin low socioeconomic societies, poor diet, smoking and medication nonadherence.

Cardiovascular and non-cardiovascular comorbidities are highly prevalent in patients with HFpEF and contribute significantly to the burden of morbidity and mortality in this population. The precise pathophysiologic mechanisms driving HF progression in HFpEF are still poorly understood. Current studies indicate that comorbidities such as obesity, HT, DM, chronic obstructive pulmonary disease and CKD contribute to a systemic proinflammatory state that increases endothelial dysfunction and HF progression. Since comorbidities disease progression may accelerate and contribute to functional intolerance in patients with HFpEF, systematic assessment and treatment of these comorbidities should be a fundamental treatment strategy.[17,18] Most patients with HFpEF have a history of HT. Lowering systolic blood pressure in patients with hypertension significantly and consistently reduces the incidence of HF. Uncontrolled HT may accelerate HF progression by exacerbating diastolic dysfunction, left ventricular hypertrophy, endothelial dysfunction and myocardial fibrosis.[18] In our study, the rate of HT in the patient group was 70.1%. In the PATENT-2 study conducted in Türkiye in 2012, the prevalence of HT was 30%. Above the age of 50 years, this rate reaches 50%.[19] Considering the increasing prevalence of hypertension in Turkey

and the high rate of HT in patients with HFpEF in our study as in other studies, we think that the awareness of internal medicine specialists on this issue should be increased.

Data from observational studies suggest that approximately 30% to 40% of patients with HFpEF have DM. Recent data from randomized trials suggest that prediabetes may be present in approximately one-third of patients without diabetes and insulin resistance in three-quarters of patients with HFpEF.[13,20] The rate of DM was 37.6% in our study. DM causes diabetic cardiomyopathy by causing changes in the myocardium independent of classical risk factors such as CAD, HT and valvular heart disease. Patients with DM have an increased risk of HF. HFpEF accounts for about half of the incidence of HF in DM. LVEF ≥50% and is characterized by exercise intolerance as the chief complaint. Due to the increased prevalence of HFpEF in patients with DM, it is recommended that NT-proBNP should be checked once a year in the follow-up of these patients.[21]

More than 80% of patients with HFpEF are overweight or obese. Compared with non-obese patients, obese HFpEF patients more right ventricular dysfunction, higher filling pressures and more congestion.[22] In our study, the BMI ratio of the patients was 30.1± 3.09. Because of the close association of obesity with all cardiovascular diseases and its increasing prevalence worldwide, all patients with a BMI of 30 and above who present to the internal medicine outpatient clinic should be evaluated for HFpEF. CKD increases the risk of developing HFpEF and may directly accelerate adverse cardiac remodelling (e.g. left ventricular hypertrophy, inflammation and myocardial fibrosis) and sodium/fluid retention, which contribute to the pathogenesis of HF. Patients with CKD tend to have more advanced symptoms, more impaired cardiac structure, fibrosis, and higher cardiac biomarker levels reflecting oxidative stress compared to those without CKD. A low estimated glomerular filtration rate and higher urinary albumin excretion are associated with an increased risk of developing HFpEF. This condition is also associated with an increased risk of adverse outcomes, including the severity of CKD, cardiovascular death, and hospitalisation due to HF. Lower estimated glomerular filtration rate and higher urinary albumin excretion are associated with a higher risk of developing HFpEF. It is also the severity of CKD and including cardiovascular death and hospitalization for HF associated with the risk of adverse outcomes.[23] In our study, 23.3% of patients had a diagnosis of CKD. Because of the increased frequency of HFpEF and cardiovascular events in patients with CKD, patients should definitely be evaluated in this respect.

Recent data have shown that approximately one third of the general adult population is affected by MASLD, making it one of the most common non-communicable diseases. Metabolic dysfunction is an important factor linking HFpEF and MASLD. MASLD triggers chronic inflammation and oxidative stress, leading to myocardial hypertrophy and stiffness. Up to 50% of patients with HFpEF are diagnosed with MASLD and this prevalence is much higher than in patients with HFrEF. This important association suggests that the pathophysiologic processes of HFpEF and MASLD are deeply intertwined, primarily through metabolic and inflammatory pathways.[24] In our study, the rate of MASLD in patients was 59.2%. The prevalence of MASLD is increasing worldwide, especially in DM patients. However, awareness of HFpEF in DM, which is one of the more well-known diseases, is low as well as awareness of MASLD screening. We think that it is important not to evaluate these diseases, which have similar physiopathologic processes, separately, but to screen for other conditions in patients with one of these diseases and to take a holistic approach. Our findings show that AF is highly prevalent in patients with HFpEF. The AF prevalence identified in our study is similar to the rates reported in previous studies. Large multicentre studies have reported AF prevalence rates ranging from 30% to 45%.[25] In our study, the AF rate was found to be 49.7%, which once again confirms the strong association between HFpEF and AF.

HFpEF refers to a cardiometabolic syndrome with multiple comorbidities and

accounts for more than 50% of all heart failure cases. Unlike HFrEF, HFpEF is strongly associated with metabolic disorders such as obesity, DM, HT and MASLD. Prevention and proper treatment of other risk factors such as HT, DM and obesity have been associated with lower risk or incident HF. Prevention of HT, obesity, DM and MASLD can significantly prolong survival, reduce heart failure-related morbidity and reduce the impact of heart failure on public health. CRMD is a set of clinical problems that is characterized by the interrelationships between obesity, DM, HT, CKD and cardiovascular disease. The CRMD approach is of increasing interest and these diseases are the most common patient groups encountered by internal medicine specialists. In the approach of DM, HT, obesity, HT and MASLD, which are diseases with similar physiopathologic processes and whose frequency is increasing day by day, patients should be evaluated and screened for HFpEF with NT-proBNP, clinical and, if necessary, TTE.

Our study had some limitations. Our study was single centered. Further studies with a larger number of patients and multicenter studies are needed. We did not classify the patients according to their medications, disease duration and TTE findings. We evaluated only HFpEF patients. New studies including HFrEF patients can be planned. Follow-up studies related to our study can be performed. Other limitations include its retrospective cross-sectional, the small number of parameters, and the fact that relationships are not statistically evaluated.

5. CONCLUSION

Given the increasing prevalence of CRMD, screening and awareness of HFpEF, which has a high prevalence in patients with CRMD, should be increased. We recommend clinical and NT-proBNP screening for HFpEF, which is associated with increased cardiovascular mortality and morbidity in patients with CRMD, and evaluation with TTE if necessary.

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The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

Adana City Training and Research Hospital Ethics Committee approved the study with decision number 318 dated 02.01.2025.

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

Copyright Statement

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Research Article

Morphological and Topographical Anatomy of the Nutrient Foramen on 176 Humeri and Current Literature Review

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Objective: The nutrient foramen of the humerus (NFH) is an important anatomical structure as it transports the nutrient artery that feeds the humerus. Our goal was to investigate morphological and morphometric features of the NFH.

Materials and Methods: In total, 176 (85 right, 91 left) dry adult human humeri were examined. We investigated the frequency, topographic position, and direction of NFHs. The distances of NFH to certain landmarks were also measured. Lastly, the foraminal index (FI) was determined.

Results: Humerus with one NFH and two NFHs were 151 (85.8%) and 22 (12.5%), respectively. NFHs were absent in 3 (1.7%) of humeri. All NFHs were downward. The mean shortest distances of the NFH to the most prominent point of the head of the humerus were found as 17.84±2.64 cm in the humerus with a single NFH and 17.32±2.76 cm in the humerus with a double NFH, respectively. The mean shortest distances of the NFH to the tip of the medial epicondyle were 11.39±1.89 cm in the humerus with a single NFH and 13.01±2.93 cm in the humerus with two NFHs. The overall average FI was 57%.

Conclusion: With this study, the distances of NFHs to certain landmarks were documented separately for single NFHs and double NFHs. Moreover, NFHs are most densely located in the middle third. We believe that this data may be helpful to orthopedic surgeons in terms of pre- and intraoperative planning and reaching NFHs more easily.

Keywords: Nutrient foramen of humerus, Nutrient artery, Topographic location, Foraminal index

1. INTRODUCTION

The humerus, the longest and largest bone of the upper extremity, is nourished mainly by the nutrient artery of the humerus (NAH). This artery reaches the humerus via the nutrient foramen of the humerus (NFH).[1]

Like other nutrient arteries, the NAH is important in bone development during the prenatal and postnatal phases. It also encourages the development of a callus structure at the site of the fracture.[2] Insufficient blood flow at the fracture site may result in malunion or nonunion of the humerus.[3,4]

Understanding the localization of NFH is crucial, as it can assist in optimizing invasive procedures involving NFH.[5] The NFH is located near the attachment of the coracobrachialis muscle, posterior to the deltoid tuberosity, directed downward near the medial margin of the humerus, just inferior to the middle.[1]

The anatomical features of the NFH are quite important in orthopedic surgery, bone grafting, and microsurgical bone transplantation on the humerus.[6] Since the nature of vascularized grafts requires arterial anastomoses, NFH also plays an important role in such grafts.[7]

In this study, considering the clinical significance of NFH, our goal was to analyze the number, direction, topographic location, and distances of NFH to certain landmarks and to present its possible clinical interest.

2. MATERIAL AND METHODS

For this cross-sectional study, a total of 176 (85 right, 91 left) dry adult human humeri were examined from the Department of Anatomy, Istanbul Faculty of Medicine, Istanbul University. The exclusion criteria included: Bones exhibiting pathological deformities or damage. Bones originating from infants or children. Information on the gender, age, and race of these bones was not

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accessible. The Clinical Research Ethical Committee of Istanbul Faculty of Medicine of Istanbul University approved the study (Date: 25/02/2022, number: 04).

2.1. Morphological properties

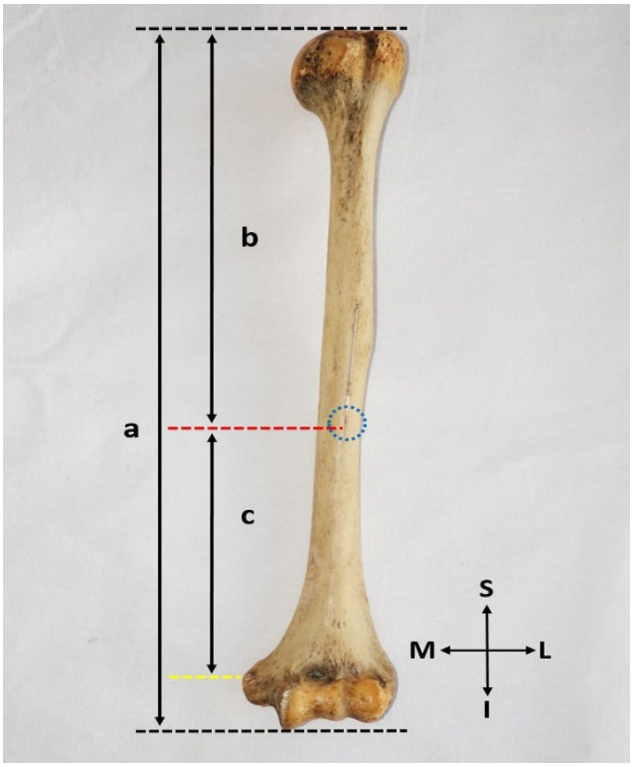
- The number of NFHs on the shaft of each sample was detected macroscopically.
- The patency and route of each NFH were explored by a 0.25 X 30 mm acupuncture needle. Foramina with diameters smaller than this needle were excluded from evaluation in the study.
- The topographic location of the NFHs was determined (On the border, surface, etc.).

2.2. Morphometric properties

- The perpendicular length between the highest point of the head of the humerus and its trochlea (Humerus length=**HL**) was evaluated (Figure 1).
- The perpendicular length from the highest point of the head of the humerus to the proximal margin of the NFH (**DHNF**) was measured (Figure 1).
- The minimum distance from the tip of the medial epicondyle to the distal edge of the NFH (**DMeNF**) was assessed (Figure 1).

Figure 1.

Demonstration of the measurement of the length of the humerus and distances of nutrient foramen to certain landmarks, anterior view, left. a: length of the humerus, b: the shortest distance of the nutrient foramen to the most proximal point of the head of the humerus, c: the shortest distance of the nutrient foramen to the tip of the medial epicondyle. The dotted black lines represent lines drawn parallel to the upper and lower ends of the humerus. The dotted yellow line represents the parallel line passing over the nutrient foramen. The dotted round blue line indicates the nutrient foramen.



S: Superior; I: Inferior; L: Lateral; M: Medial.

Lastly, we used the following calculation to obtain the foraminal index (FI): *FI= (DHNF/ HL) x 100*.[8]

According to the result of FI, the location of NF was classified into the following 3 groups:

Type 1: FI below 33.33%, proximal third of the humerus.

Type 2: FI between 33.33% and 66.66%, middle third of the humerus.

Type 3: FI above 66.66, distal third of the humerus.

The distances were measured with a digital caliper accurate to 0.01 mm (INSIZE Co., Ltd., Taiwan). Two independent researchers conducted

the measurements, and the final results were tabulated as the average value for each parameter.

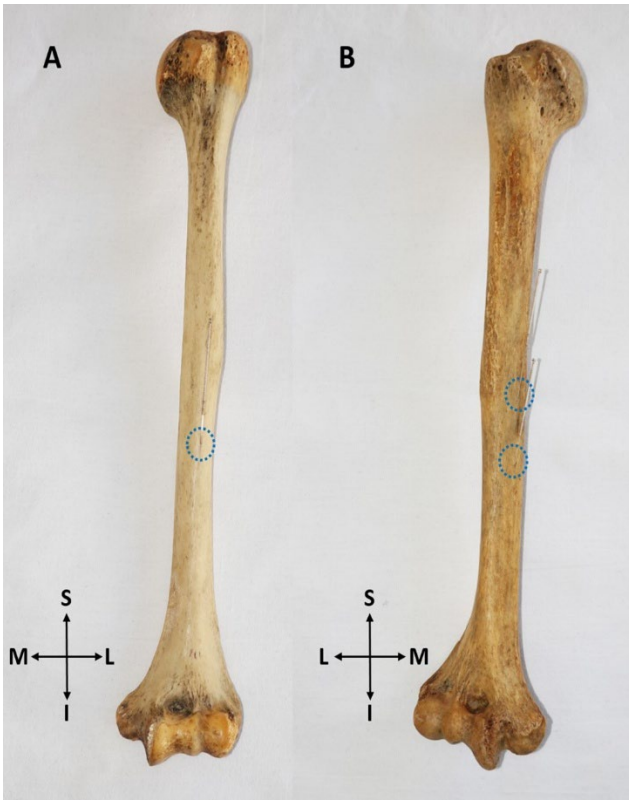
3. RESULTS

3.1. Morphological properties

In a total of 176 bones, we examined, 151 humeri (85.8%) with a single NFH (Figure 2A), 22 of them (12.5%) with double NFH (Figure 2B**),** whereas 3 (1.7%) of them had no NFH. All NFHs were towards the elbow (Figure 2). The detailed distribution of NFHs according to the side is shown in Table 1.

Figure 2.

Demonstration of the number of nutrient foramen on humeri. A Single nutrient foramen, anterior view, left. B double nutrient foramen, anterior view, right. The dotted round blue lines indicate the nutrient foramen



S: Superior; I: Inferior; L: Lateral; M: Medial.

Table 1.

Distribution of the nutrient foramen of the humerus in terms of side

Number of NFH	Right, n (%)	Left, n (%)	Total, n (%)
Absent	2 (2.4%)	1 (1.1%)	3 (1.7%)
Single	75 (88.2%)	76 (83.5%)	151 (85.8%)
Double	8 (9.4%)	14 (15.4%)	22 (12.5%)
Total	85 (100%)	91 (100%)	176 (100%)

NFH: Nutrient foramen of the humerus

Most of the NFHs (59.4%, 116 NFHs) were located on the anteromedial surface of the humerus (Figure 3A). This was followed by the medial border (25.7%, 50 NFHs) (Figure 3D), lateral border (6.7%, 13 NFHs) (Figure 3F), anterolateral surface (4.6%, 9 NFH) (Figure 3C), posterior surface (3.1%, 6 NFHs) (Figure 3B), and anterior border (0.5%, 1 NFH) (Figure 3E), respectively. The detailed topographic distribution of NFHs according to the side is shown in Table 2.

Table 2.

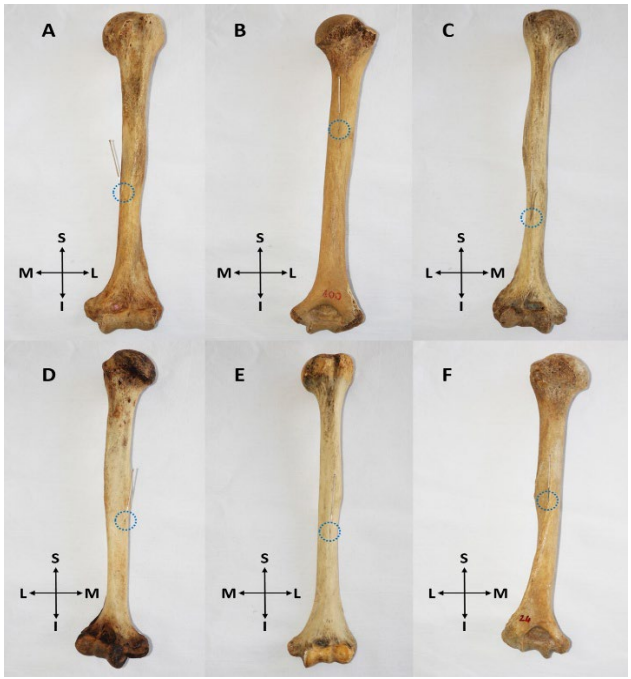
The topographic distribution of nutrient foramen of the humerus in terms of side

Location of NFH	Right, n (%)	Left, n (%)	Total, n (%)
AMS	52 (57.1%)	64 (61.6%)	116 (59.4%)
ALS	4 (4.4%)	5 (4.9%)	9 (4.6%)
PS	4 (4.4%)	2 (1.8%)	6 (3.1%)
AB	-	1 (0.9%)	1 (0.5%)
MB	24 (26.4%)	26 (25%)	50 (25.7%)
LB	7 (7.7%)	6 (5.8%)	13 (6.7%)
Total	91 (100%)	104 (100%)	195 (100%)

NFH: Nutrient foramen of the humerus, AMS: Anteromedial surface, ALS: Anterolateral surface, PS: Posterior surface, AB: Anterior border, MB: Medial border, LB: Lateral border.

Figure 3.

The illustration of nutrient foramen located in various topographic locations. A nutrient foramen on the anteromedial surface, anterior view, left. B, nutrient foramen on the posterior surface, posterior view, right. C, nutrient foramen on the anterolateral surface, anterior view, right. D, nutrient foramen on the medial border, anterior view, right. E, nutrient foramen on the anterior border, anterior view, left. F, nutrient foramen on the lateral border, posterior view, left. The dotted round blue lines indicate the nutrient foramen



S: Superior; I: Inferior; L: Lateral; M: Medial.

3.2. Morphometric properties

The HL was meanly 31.13±2.71 cm (ranging from 24.71 to 47.79 cm) and the mean DHNF was found as 17.84±2.64 cm in 151 humerus with single NFHs, while it was meanly 17.32±2.76 cm in 22 humerus with a double NFHs. Similarly, the mean DMeNF was 11.39±1.89 cm in 151 humerus with single NFHs, while it was meanly 13.01±2.93 cm in 22 humerus with double NFHs.

Lastly, the overall mean FI was 57%. Also, the average FI was 57.7% (151 NFHs) in the humeri with 1 NFH and 54.6% (22 NFHs) in those with 2 NFHs. Moreover, 1.2% (2 NFHs) of NFHs were obtained as Type 1, 95.9% (166 NFHs) of NFHs were Type 2, and 2.9% (5 NFHs) of NFHs were Type 3. The FI regarding the NFHs is shown in Table 3.

Table 3.

Classification of nutrient foramen of the humerus according to foraminal index

FI	Right (n=83), n (%)	Left (n=90), n (%)	Total (n=173), n (%)
Type I (<33.33%)	1 (1.2%)	1 (1.1%)	2 (1.2%)
Type II (33.33%-66.66%)	77 (92.8%)	89 (98.9%)	166 (95.9%)
Type III (>66.66)	5 (6%)	0 (0%)	5 (2.9%)

FI: Foraminal index

4. DISCUSSION

4.1. Morphological properties

For the number of NFHs, researchers reported different frequencies of NFHs. While studies report that there are no NFHs[9-11], there are also studies that have reported 1, 2, 3, 4, or even 5 NFHs.[9-13] A brief current literature review is shown in appendix. With the current paper, a total of 176 bones were examined, 151 of them (85.8%) with a single NFH (Figure 2a), 22 of them (12.5%) with double NFHs (Figure 2b), whereas 3 (1.7%) of them had no NFH. Our results are compatible with the results of Asharani and Ningaiah.[9]

Previous reports agree that the direction of NFHs was toward the elbow.[12, 14-16] Similarly, most of the NFHs observed in their study were on the anteromedial surface of the humerus. This rate was stated as the highest (90.83%, 109) in their research by Ukoha et al.[17] while the lowest (39.99%) was reported by Asharani and Ningaiah.[9] In our study, all NFHs were towards the elbow (Figure 2). In addition, most of the NFHs (59.4%, 116 NFHs) were on the anteromedial surface of the humerus. This was followed by the medial border (25.7%, 50 NFHs), lateral border (6.7%, 13 NFHs), anterolateral surface (4.6%, 9 NFHs), posterior surface (3.1%, 6 NFHs), and anterior border (0.5%, 1 NFH), respectively. The prevalence of NFHs on the anteromedial surface, recorded at 59.4% (116 NFHs), closely aligns with the findings of the studies conducted by Cihan and Toma.[13] Nevertheless, our findings regarding NFHs on the medial border (25.7%, 50 NFHs) do not align with those reported in previous studies.[9, 12, 17, 18] Our NFHs on the lateral border (6.7%, 13 NFHs) are inconsistent with the previous reports.[9, 12] Our NFHs on the anterolateral surface (4.6%, 9 NFHs), and posterior surface (3.1%, 6 NFHs) are almost the same as the studies of Mansur et al.[11] and Asharani and Ningaiah[9], respectively. The NFHs in this study located on the anterior border (0.5%, 1 NFHs) are the lowest rate in the literature tabulated in the appendix.

4.2. Morphometric properties

In their studies conducted on 100 (56 right and 44 left) humeri, Solanke et al.[7] reported that the mean HL was 28.77±1.77 cm (28.89±1.75 cm on the right side and 28.53±1.78 cm on the left side). They also stated that the mean DHNF was 17.70 ± 2.12 cm. Güner et al.[10] studied on 50 humeri. They found the mean HL was 310.2 mm and the mean DHNF was 175.5 mm. In addition, the FI was 55.7%. Mansur et al.[11] examined 253 (108 right and 145 left) humeri and they reported the mean HL was 270.22 mm (270.56 mm on the right side and 269.97 mm on the left side). The mean DHNF was 149.71 mm and the FI was 55.20% in their study. Ruthwik et al.[12] studied 80 humeri (42 right and 38 left). In their study, the mean HL was 299.5 mm (300.04 mm on the right side and 298.60 mm on the left side) and the mean DHNF was 154.24 mm (150.62 mm right and 157.66 mm on the left humeri). They also obtained an FI of 51.50%. In their observational study, Cihan and Toma[13] studied 103 humeri (52 right and 51 left) and stated that the mean HL was 304.39±20.04 mm on the right side and 303.54 ± 20.22 mm on the left side. Additionally, they reported that the mean DHNF was 172.49±23.17 mm on the right side and 166.68±25.26 mm on the left side. They calculated the mean FI as 55.77 and obtained no statistically significant difference in said values.

In our study, the mean HL was 31.13±2.71 cm (ranging from 24.71 to 47.79 cm). Additionally, the mean DHNF was 17.84±2.64 cm in 151

humerus with single NFHs and 17.32±2.76 cm in 22 humerus with double NFHs. Similarly, the mean DMeNF was 11.39±1.89 cm in 151 humerus with a single NFH and 13.01±2.93 cm in 22 humerus with double NFHs. Our FI was meanly 57% and the average FI was 57.7% (151 NFs) in the humeri with 1 NFH and 54.6% (22 NFHs) in those with 2 NFHs. Our results for HL and DHNF align well with the findings of Güner et al.[10] Regarding the DMeNF, Carroll[19] examined 71 humeri and they found this value 13.7 cm (range 8.1-20.2 cm). Our DMeNF with a single NFH is close to Carroll's study and our DMeNF with double NFHs is consistent with Carroll's study. The FI in the present study is slightly higher than the previous reports.[7, 10-13]

Solanke et al.[7] observed only Type 2 (90%) and Type 3 (6%) NFH. Asharani and Ningaiah[9] reported that 78.8% of the NFHs were located in the middle 1/3rd, 19.7% at the junction between the middle 1/3rd and lower 1/3rd, and 1.5 % in the lower 1/3rd. Mansur et al.[11] recorded that the NFHs were located at Zone II (middle 1/3rd=Type II) (94.84%), Zone III (lower 1/3rd=Type 1) (4.62%), and Zone I (upper 1/3rd=Type 3) (0.54%). Similar to Asharani and Ningaiah[9], Khandve and Verma[20] reported that 79% of the NFHs were in the middle 1/3rd, 19.3% at the junction between middle 1/3rd and lower 1/3rd and 1.7% in the lower 1/3rd. Rathwa and Chavda[16] stated that the NFHs were located at Zone II (middle 1/3rd=Type II) (86.11%), Zone I (upper 1/3rd=Type 1) (8.33%), and Zone III (lower 1/3rd=Type 3) (5.56%). Ruthwick et al.[12] observed that 90.09% of NFHs were in Zone 2 (middle 1/3rd=Type II), 8.08% in Zone 3 (lower 1/3rd=Type 3), and 1.01% in Zone 1 (upper 1/3rd=Type 1). A recent study by Cihan and Toma[13] reported that 89.3% and 10.6% of the NFHs were located at the middle 1/3rd (Type II) and lower 1/3rd (Type 3) of the humerus, respectively. In the current paper, 95.9% of NFHs were Type 2, 2.9% of NFHs were Type 3, and 1.2% of NFHs were obtained as Type 1. Only Type 1 value in our study is consistent with Ruthwick et al.'s study.[12] Type 2 and Type 3 are higher than the previous studies which may be caused by different sample sizes.

4.3. Clinical importance

The humerus is the bone that has the highest blood supply among the upper extremity bones. The NAH which mainly nourishes the humerus arises from the deep brachial artery, additionally, branches of the axillary, radial, and ulnar arteries supply the humerus.[21] Blood flow to the bones is crucial to their fracture healing. Despite optimal treatment, poor blood supply to the bone can lead to delayed fracture healing.[3,9] For this reason, comprehending the detailed anatomical attributes of the NFH is crucial, given that it is the location where the arteries that nourish the humerus penetrate the bone. In our study, the number and direction of NFHs are consistent with previous studies, however they differ in topographic location. Our NFHs on the medial border are lower than the previous reports and the NFHs on the lateral border are higher than the previous ones. Similarly, the NFHs in our research located on the anterior border are the lowest rate in the literature. According to our results, NFHs are more frequently localized on the lateral border of the humerus. We believe that knowing this information may be helpful to surgeons in terms of pre- and intraoperative planning and reaching NFH more easily. In addition, our morphometric values are almost the same as in previous studies. Type 2 (95.9%) and Type 3 (2.9%) are higher than the previous research. That is, NFHs are most densely located in the middle third (Type 2) and less densely located in the distal third (Type 3) of the humerus. We emphasize the importance of this information for orthopedic surgeons, as it may aid in achieving easier access to NFHs. Thus, NFHs may be reached without delay, and complications such as bleeding may be minimized. Due to our results being generally consistent with previous studies performed in different regions, we believe that regional differences (geographical differences) are not essential for NFHs of the humerus. Unlike previous studies, in this study, we calculated the values of the humerus with single NFH and double NFHs separately. In orthopedic surgery, knowledge of the anatomical features of NFHs during the surgery of humeral bone graft and microsurgical bone transplantation is very important.[6] In addition, knowing the exact

location of the NFH plays an important role in the success of vascularized bone grafts and joint allografts.[6,7] Collectively, we believe that our findings may be important in the related invasive procedures to NFHs.

This study has several limitations. Although the sample size has been relatively larger than most previous studies, comparison statistics could not be performed because the humeri did not belong same person. Additionally, since we did not have age and gender records of the humerus samples, detailed statistical analysis could not be performed.[22] Lastly, we did not have the clinical presentation of the said samples. Therefore, we did not make any comment on this topic.

5. Conclusion

It is essential to elucidate all anatomical aspects of NFHs. In this study, NFHs were analyzed anatomically. Many of our findings affirm previous studies and this study presents several additional findings regarding NFHs. Unlike earlier reports, in this study, morphometric values related to NFHs were documented separately for the humerus with single NFH and double NFHs. According to our results, NFHs were most densely located in the middle third and less densely in the distal third.

Article Information Form

Authors' Contribution

Conception: EB, LS, AE. Data collection: EB, ÖG, AE. Supervision: ÖG, LS, OC. Analysis or Interpretation: LS, EB, OC. Writer: LS, EB, OC. Critical Review: ÖG, OC.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

The study was approved by the Clinical Research Ethical Committee of Istanbul Faculty of Medicine of Istanbul University approved the study (Decision no: 04, Date: 25.02.2022).

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

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Research Article

Burden of Chronic Obstructive Pulmonary Disease Attributable to Air Pollution in Türkiye (1990–2021)

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Objective: Exposure to particulate matter and ozone has been linked to decreased lung capacity, hospitalizations, and mortality from Chronic Obstructive Pulmonary Disease (COPD). This study aims to evaluate the mortality rate attributed to air pollution-related Chronic Obstructive Pulmonary Disease (COPD) in Türkiye over the past 30 years.

Materials and Methods: This was a epidemiological study. Age-standardized mortality statistics for COPD caused by outdoor (Particulate Matter 2.5 and Ozone) and indoor (solid fuel) air pollution were obtained from the Global Burden of Disease (GBD) database. Changes in cause-specific death rate trends in Türkiye between 1990 and 2021 were assessed using Joinpoint regression analysis to calculate annual percentage changes (APC) and average annual percentage changes.

Results: Age-standardized mortality rates (ASMRs) declined from 48.41 (per 100,000) (95% CI: 39.31; 55.91) to 35.78 (95% CI: 24.03; 44.40) with an APC of -0.26 (95% CI: -0.46; -0.04) over the 1990-2021 period for both sexes. While there is a consistent downward trend in ASMRs attributed to household air pollution from solid fuels for both genders, different upward trends were observed over the years for ASMRs attributed to ambient particulate matter pollution and ambient ozone pollution.

Conclusion: Over the last 30 years in Türkiye, while the mortality rate linked with solid fuel consumption has generally decreased, the mortality rates associated with PM and ozone have fluctuated. This suggests that legislation addressing indoor air quality has been effective, but health risks associated with outdoor air quality have persisted in Türkiye over the past 30 years.

Keywords: Air pollution, Chronic Obstructive Pulmonary Disease, Trend analysis, Türkiye

1. INTRODUCTION

The consumption of fossil fuels to ensure the economic development of societies is a significant underlying factor contributing to air pollution[1]. Air pollution, defined by the World Health Organization (WHO) as the greatest environmental threat to human health, causes an annual prematüre death toll of 6.7 million. Nearly one-third of these deaths are attributed to household air pollution[2]. Ambient particulate matter (PM) is a mixture of solid and liquid particles in air, with variations in size, chemical composition, and properties due to natural or human-induced sources such as driving vehicles and operating manufacturing or power plants[3]. Ground level (trophospheric) ozone is not emitted directly; rather, it results from a photochemical process in which pollutants such as nitrogen oxides (NOx) and volatile organic compounds (VOCs) react in the presence of sunlight[4].

Air pollution is known to cause not only acute effects on human health, such as infections and asthma attacks but also chronic issues associated with atherosclerotic processes, leading to conditions like heart attacks, strokes, Chronic Obstructive Pulmonary Disease (COPD), and lung cancer[5-7]. Exposure to particulate matter and ozone has been linked to decreased lung capacity, hospitalizations, and mortality from Chronic Obstructive Pulmonary Disease (COPD)[8].Chronic Obstructive Pulmonary Disease (COPD) is generally associated with smoking, presenting as a progressive disease with components of chronic bronchitis and emphysema[9]. In the etiology of COPD, apart from genetic predisposition, factors such as indoor and outdoor air pollution, occupational exposure, exposure to substances irritating the respiratory tract, and recurrent respiratory infections can be considered[10]. In 2019, Chronic Obstructive Pulmonary Disease (COPD) ranked as the third leading cause of global

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mortality with 3.23 million deaths. While tobacco smoking accounts for over 70% of COPD cases in high-income countries, it constitutes 30-40% of cases in low and middle-income countries, where household air pollution emerges as a significant risk factor[11]. According to the guidelines set by the World Health Organization (WHO) in 2021, the annual average concentration limit for $PM_{2.5}$ is set at 5 μg m^{-3}. For PM_{10}, the annual average limit is 15 μg m^{-3}. The 8-hour average concentration limit for Ozone (O_3) is set at 100 μg m^{-3}.[12]. For existing pollutants, the EU limits are higher than those set by the WHO limits[13]. In Türkiye, according to the Black Report, the population affected by air pollution constitutes 9 out of every 10 individuals[5]. In Türkiye's national air quality legislation, PM_{10} limits with an annual average value of 40 μg m^{-3} while there is no specified limit for $PM_{2.5}$[14].

In the literature, there are numerous studies globally that utilize Global Burden of Disease (GBD) data to investigate the morbidity and mortality associated with air pollution[15,16]. Despite the existence of studies in Türkiye that investigate the trend of air pollution[17], there is currently no research specifically examining long time period of Chronic Obstructive Pulmonary Disease (COPD) mortality attributed to air pollution in the country. The purpose of this text is to examine the age-standardized mortality rate attributed to chronic obstructive pulmonary disease (COPD) due to air pollution in Türkiye between 1990 and 2021.

2.METHODOLOGY

2.1. Design and settings

The study has an epidemiological and descriptive design.

2.2. Data Sources and search parameters

This study focused on female and male patients in Türkiye who had been diagnosed with COPD due to a variety of risk factors. In the study, numbers, rates, age-standardized rates (adjusted to the WHO's standard population), and percentages of COPD fatalities attributed to risk factors were obtained from the Global Health Data Exchange (GHDx: http://ghdx.healthdata.org/). The age-standardized mortality rates from chronic obstructive pulmonary disease caused by air pollution (ambient particulate matter pollution, household air pollution from solid fuels, and ambient ozone pollution) were collected from the freely available GBD Results Tools repository [18]. The search parameters were "chronic obstructive pulmonary disease" and specific estimated risk factors for cause; "ambient particulate matter pollution", "ambient ozone pollution", "household air pollution from solid fuels" for risk; "deaths" for measurements; "1990-2021" for years; "Türkiye" for location; and "number, rate, and percent" for metrics. The Guidelines for Accurate and Transparent Health Estimates Reporting guidelines wre followed in this study.

2.3. GBD estimation framework

The GBD study's Cause of Death (COD) database is a collection of data from multiple primary source documents, such as vital registration, sample vital registration, and verbal autopsy reports. The incidence and mortality data go through a multi-step process that includes age-group adjustments and the aggregation of implausible and unspecified COD codes. The COPD estimates included the use of International Classification of Diseases (ICD) 10 codes (J40-J44)[18].

2.4. Ethical considerations

Because the data for the study was gathered from online open access databases, ethical approval and institutional permission were not obtained. Informed permission was not acquired because disease-specific mortality statistics were used in the study.

2.5. Statistical analyses

The study analyzed COPD mortality proportions over 30 years from 1990 to 2019, using Joinpoint software to assess trends. Joinpoint regression equation is as follows;

$$(x_1, y_1), \ldots, (x_n, y_n), x_1 \leq \ldots \leq x_n$$

$$E\,[y/x] = \beta_0 + \beta_1 x + \delta_1 (x-\tau_1)^+ + \ldots + \delta k\,(x-\tau k)^+$$

where x: independent variable (time), y: dependent variable, β0 ,β1 ,δ1 ,δk : regression

coefficients, τk: unknown joinpoint, δk = differences in slope.

The analysis included logarithmic transformation, homoscedasticity, and the weighted Bayesian Information Criterion. The Average Annual Percentage Change (AAPC) is a weighted average of annual percentage changes from Joinpoint trend analysis, with each segment's length as weight. The Average Annual Percentage Change (AAPC) and its associated 95% Confidence Interval were calculated to assess the scale and trajectory of recent trends. To examine mortality trends, we utilized Joinpoint software version 5.0.2.0, which is accessible at (https://surveillance.cancer.gov/joinpoint/)[19]. This software facilitates the fitting of consecutive linear segments to the trend in age-standardized rates. In our analysis, we specified options such as applying a logarithmic transformation to rates and percentages, ensuring consistent variance (homoscedasticity), and utilizing the weighted Bayesian Information Criterion (BIC) restricted with a maximum of 3 joinpoints. We presented the Annual Percentage Change (APC) by identifying breakpoints in the trend and calculating the APC's between these breakpoints. The study rejects the null hypothesis that the true AAPC is zero at a significance level of $\alpha<0.05$.

3.RESULTS

In Türkiye, in the year 1990, 72,320.07 (95% CI: 64,626.47; 80,148.87) new cases of chronic obstructive pulmonary disease (COPD) for both sex were observed, while this number increased to 210,198.95 (95% CI: 190,484.36; 230,494.14) in the year 2021.

According to mortality data, in the year 1990, there were 16,229.55 (95% CI: 12,848.83; 18,924.69) count of deaths, whereas by the year 2021, this number had risen to 34,044.47 (95% CI: 28,218.89; 40,618.51) deaths.

From 1990 to 2021, the percentage of deaths due to chronic obstructive pulmonary disease (COPD) among all-cause mortality increased from 5.41% (95% CI: 4.88; 5.79) to 5.48% (95% CI: 4.96; 5.92). On the other hand age-standardized mortality rates (ASMR's) were declined from 57.54 (per 100 thousand) (95%CI: 45.02; 67.31) to 40.77 (95%CI: 33.86; 48.52) with -0,29 (95%CI:-0,44; -0,03) APC in 1990-2021 time period for both sex. Between the same years, a decrease in ASMRs was observed, declining from 33.73 to 26.49 in females and from 88.48 to 59.18 in males.

Table 1 presents data on COPD mortality attributed to three types of pollution: ambient particulate matter pollution ($PM_{2.5}$), ambient ozone pollution (O_3), and household air pollution from solid fuels over the period from 1990 to 2021. The number of deaths, percentage of deaths, rates per 100,000 population, and disability-adjusted life years (DALY) are provided for each type of pollution. The findings reveal that the number of deaths attributed to $PM_{2.5}$ pollution increased from 315,191 in 1990 to 722,692 in 2021. During this period, the percentage of deaths remained stable at around 0.19% to 0.22%. Correspondingly, DALY associated with $PM_{2.5}$ pollution increased substantially from 74,362.21 to 160,222.59.

Table 1.

COPD mortality atributed to some pollutants between the years 1990 and 2021 in Türkiye

	Ambient particulate matter pollution ($PM_{2.5}$)			Ambient Ozone Pollution (O_3)			Household Air Pollution from Solid Fuels		
Year	Death Number	Rate*	DALY (year)	Death Number	Rate*	DALY (year)	Death Number	Rate*	DALY (year)
1990	3151,91	5,48	74362,21	1999,15	3,47	40282,04	963,77	1,67	22853,58
1991	3130,66	5,34	75668,52	1966,74	3,35	40340,97	880,72	1,50	21504,71
1992	3163,93	5,30	77220,23	1998,01	3,35	41153,61	820,04	1,37	20245,87
1993	3220,85	5,31	79048,51	2129,18	3,51	43882,27	766,42	1,26	19030,80
1994	3287,34	5,33	81047,89	2201,77	3,57	45389,44	717,24	1,16	17894,00
1995	3324,52	5,31	82288,90	2279,18	3,64	46914,72	664,05	1,06	16628,50
1996	3349,71	5,27	83146,10	2115,30	3,33	43379,77	607,71	0,95	15255,21
1997	3374,05	5,24	84026,00	2102,12	3,26	42928,31	551,55	0,85	13892,03
1998	3378,99	5,17	84621,35	1970,93	3,01	40115,98	494,29	0,75	12530,16
1999	3378,08	5,10	85232,60	1894,01	2,86	38477,58	443,85	0,67	11344,42
2000	3308,83	4,93	83776,19	1731,25	2,58	34787,18	395,45	0,58	10136,13
2001	3264,30	4,80	82773,75	1743,92	2,56	34667,99	360,24	0,53	9242,64
2002	3225,70	4,69	81899,46	1971,04	2,86	38794,57	330,85	0,48	8504,49
2003	3370,27	4,85	84696,72	2095,45	3,01	40902,58	320,53	0,46	8160,23
2004	3497,14	4,98	87072,78	2146,97	3,06	41521,07	307,39	0,43	7757,87
2005	3680,27	5,19	90723,25	2044,39	2,88	39188,54	293,63	0,41	7337,16
2006	3920,56	5,47	95590,20	2333,24	3,25	44229,55	271,14	0,37	6698,18
2007	4290,06	5,93	103041,33	2564,58	3,55	47920,68	246,89	0,34	5997,93
2008	4806,58	6,59	113159,57	2906,62	3,98	53489,40	224,91	0,30	5341,07
2009	5458,14	7,42	125827,94	2960,54	4,02	53897,91	206,52	0,28	4787,57
2010	5760,02	7,77	132138,98	2921,58	3,94	52996,12	179,15	0,24	4134,65
2011	5956,67	7,97	136142,10	3108,91	4,16	56233,24	153,50	0,20	3534,18
2012	6136,88	8,15	139013,17	3390,77	4,50	60835,78	128,37	0,17	2927,09
2013	6423,43	8,45	143328,88	3660,52	4,81	65009,90	106,71	0,14	2389,91
2014	6691,68	8,69	147499,19	3539,87	4,59	62325,03	88,05	0,11	1939,77
2015	6968,31	8,89	151745,75	3649,66	4,66	63610,74	73,80	0,09	1602,76
2016	7175,39	9,00	155393,01	3761,47	4,72	65236,57	62,52	0,07	1351,39
2017	7126,18	8,82	155115,36	3851,29	4,76	66777,03	50,81	0,06	1106,44
2018	6954,55	8,49	152861,03	3751,19	4,58	65160,04	40,74	0,04	897,18
2019	7089,45	8,57	154844,39	3879,23	4,69	66945,03	35,02	0,04	767,30
2020	6637,45	7,97	144792,28	3987,96	4,79	68761,40	31,53	0,03	689,73
2021	7226,92	8,64	160222,59	3925,36	4,69	68480,62	35,95	0,04	798,83

*Rate: Indicates per 100.000 population.

For ambient ozone pollution, the number of deaths ranged from 196,674 in 1991 to a peak of 398,796 in 2020. The percentage of deaths fluctuated slightly, remaining around 0.12% to 0.13%, before decreasing to 0.11% in recent years. The rate per 100,000 population varied, starting at 347 in 1991 and reaching up to 479 in 2020, before slightly decreasing. DALY associated with ozone pollution showed an increasing trend from 4,028,204 in 1990 to 6,876,140 in 2020.

Deaths due to household air pollution from solid fuels showed a marked decline from 96,377 in 1990 to 3,595 in 2021. The percentage of deaths attributed to this source of pollution dropped from 0.059% to 0.001%. Similarly, the rate per 100,000 population decreased from 167 to 4, and DALY significantly declined from 2,285,358 in 1990 to 79,883 in 2021.

The trend analysis of age-standardized mortality rates (ASMR) attributed to COPD was performed considering different independent variables, including gender, pollution type, and various time periods (Table 2, Figure 1). For females exposed to ambient ozone pollution, five breakpoints were identified: 1990-1995, 1995-2000, 2000-2005, 2005-2008, 2008-2015, and 2015-2021.

Table 2.

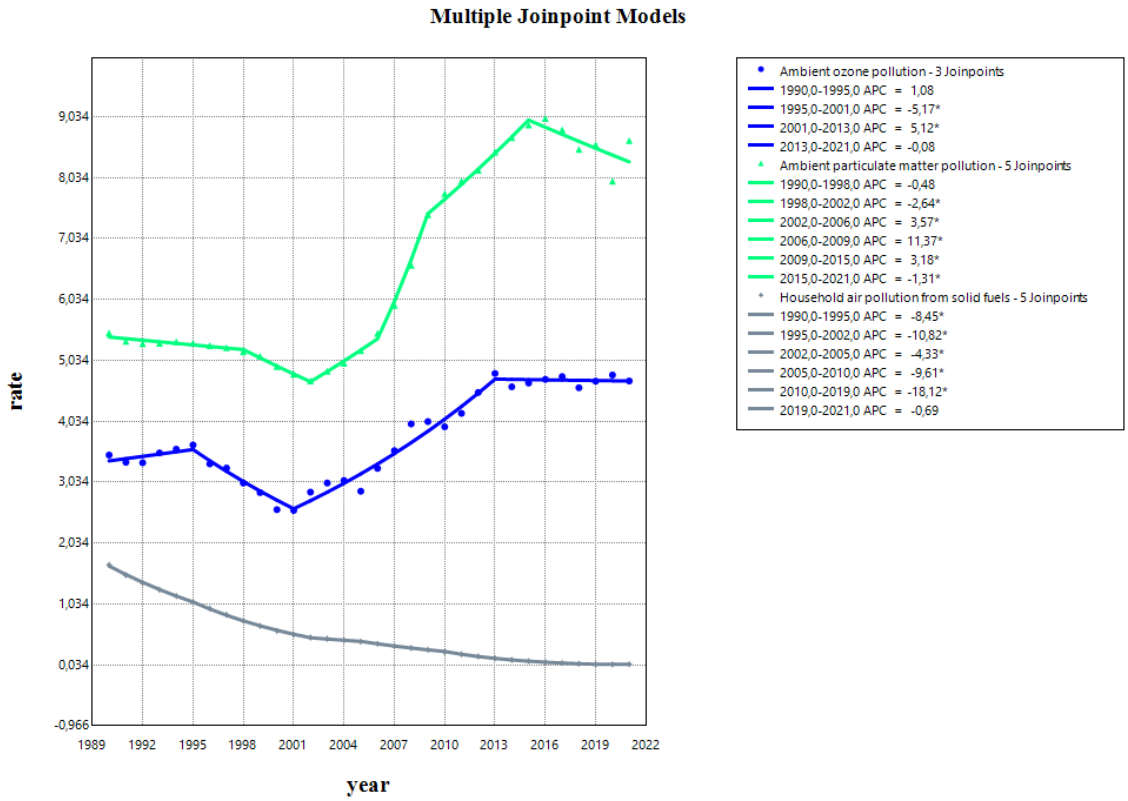
Trend analysis results of ASMR mortality rates attributed to COPD for some independent variables

Gender	Pollution Type	Breakpoint count	Breakpoint Period	APC between breaks (95% CI)	p	AAPC (95% CI)	p
Female	Ambient Ozone Pollution	5	1990-1995	0.91 (-4.20; 6.29)	0.361	1.52 (1.11; 1.89)	<0.001
			1995-2000	-4.48 (-8.87; 4.54)	0.127		
			2000-2005	1.88 (-6.09; 10.68)	0.318		
			2005-2008	10.71 (-0.21; 19.96)	0.059		
			2008-2015	3.96 (-4.51; 8.92)	0.121		
			2015-2021	-0.32 (-5.61; 4.92)	0.655		
	Ambient Particulate Matter$_{2.5}$	3	1990-2005	-0.35 (-0.68; -0.04)	0.023	1.84 (1.65; 1.99)	<0.001
			2005-2009	12.47 (10.17; 15.81)	<0.001		
			2009-2016	3.77 (2.65; 5.07)	<0.001		
			2016-2021	-2.16 (-4.30; -0.77)	0.004		
	Household air pollution from solid fuels	4	1990-2002	-9.26 (-10.02; -8.85)	<0.001	-10.89 (-11.12; -10.75)	<0.001
			2002-2009	-6.92 (-7.89; -4.58)	<0.001		
			2009-2016	-16.17 (-16.75; -14.48)	<0.001		
			2016-2019	-20.72 (-22.42; -18.53)	<0.001		
			2019-2021	1.22 (-3.32; 4.86)	0.473		
Male	Ambient Ozone Pollution	3	1990-1995	1.79 (-0.03; 4.06)	0.053	0.856 (0.63; 1.08)	<0.001
			1995-2000	-7.18 (-11.24; -5.41)	<0.001		
			2000-2013	4.44 (3.94; 5.14)	<0.001		
			2013-2021	-0.21 (-1.47; 0.73)	0.613		
	Ambient Particulate Matter$_{2.5}$	5	1990-1997	-0.40 (-0.99; 0.62)	0.0231	1.16 (1.02; 1.28)	<0.001
			1997-2002	-2.95 -5.13; -1.91)	0.025		
			2002-2006	4.45 (-0.15; 6.60)	0.055		
			2006-2010	8.63 (6.75; 10.58)	<0.001		
			2010-2015	2.03 (0.68; 3.71)	0.026		
			2015-2021	-1.14 (-2.49; 0.43)	0.019		
	Household air pollution from solid fuels	5	1990-1995	-8.36 (-9.50; -5.97)	<0.001	-11.48 (-11.70; -11.29)	<0.001
			1995-2002	-11.60 (-14.22; -10.92)	<0.001		
			2002-2005	-2.62 (-5.92; -0.98)	0.002		
			2005-2011	-11.72 (-13.03; -10.96)	<0.001		
			2011-2019	-18.93 (-19.93; -19.56)	<0.001		
			2019-2021	1.28 (-2.87;; 4.22)	0.288		
Total	Ambient Ozone Pollution	3	1990-1995	1.07 (-0.73; 4.21)	0.239	1.06 (0.82; 1.32)	<0.001
			1995-2001	-5.17 (-8.44; -3.61)	0.004		
			2001-2013	5.12 (4.48; 6.09)	0.002		
			2013-2021	-0.08 (-1.48; 0.92)	0.082		
	Ambient Particulate Matter$_{2.5}$	5	1990-1998	-0.48 (-0.97; 0.77)	0.194	1.38 (1.25; 1.51)	<0.001
			1998-2002	-2.63 (-4.47; -0.11)	0.049		
			2002-2006	3.57 (0.67; 8.79)	0.031		
			2006-2009	11.36 (3.93; 12.82)	<0.001		
			2009-2015	3.18 (1.75; 4.06)	0.034		
			2015-2021	-1.31 (-2.41; -0.44)	0.025		
	Household air pollution from solid fuels	5	1990-1995	-8.45 (-9.93; -4.36)	<0.001	-11.23 (-11.50; -11.01)	<0.001
			1995-2002	-10.82 (-14.09; -5.54)	<0.001		
			2002-2005	-4.32 (-9.75; -2.30)	<0.001		
			2005-2010	-9.61 (-19.28; -8.67)	<0.001		
			2010-2019	-18.12 (-19.03; -17.18)	<0.001		
			2019-2021	-0.69 (-5.79; 2.37)	<0.001		

APC: Annual Percentage Change; AAPC: Average Annual Percentage Change; 95%CI: 95% Confidence Interval.

Figure 1.

Trend of age-standard mortality rates for COPD attributed to various pollutants, between the years 1990 and 2021 inTürkiye



The annual percentage change (APC) varied significantly between these periods, with notable increases and decreases. The average annual percentage change (AAPC) for this group was 1.52 (95% CI: 1.11-1.89), indicating a significant trend (p<0.001). In the case of ambient particulate matter (PM2.5), three breakpoints were identified for females: 1990-2005, 2005-2009, and 2009-2016, 2016-2021. Significant APC increases were observed, particularly a 12.47% rise from 2005 to 2009. The AAPC was 1.84 (95% CI: 1.65-1.99), suggesting a significant upward trend (p<0.001). For household air pollution from solid fuels in females, four breakpoints were noted: 1990-2002, 2002-2009, 2009-2016, and 2016-2019, 2019-2021. The APC was generally negative, indicating a decline over these periods, with the most significant decrease being -20.72% from 2016 to 2019. The AAPC was -10.89 (95% CI: -11.12 to -10.75), (p<0.001) (Figure 2). Among males, three breakpoints were identified for ambient ozone pollution: 1990-1995, 1995-2000, 2000-2013, and 2013-2021. The APC showed both negative and positive values across different periods, with an AAPC of 0.856 (95% CI: 0.63-1.08), (p<0.001). For ambient particulate matter (PM2.5) in males, five breakpoints were found: 1990-1997, 1997-2002, 2002-2006, 2006-2010, 2010-2015, and 2015-2021. Significant APC changes were observed, such as an 8.63% increase from 2006 to 2010. The AAPC was 1.16 (95% CI: 1.02-1.28), (p<0.001). Regarding household air pollution from solid fuels in males, five breakpoints were identified: 1990-1995, 1995-2002, 2002-2005, 2005-2011, and 2011-2019, 2019-2021. The APC values were mostly negative, indicating declines, with the largest decrease being -18.93% from 2011 to 2019. The AAPC was -11.48 (95% CI: -11.70 to -11.29), (p<0.001) (Figure 3).

Figure 2.

JP Regression analysis of ASMRs attributed three risk factors in COPD for female gender

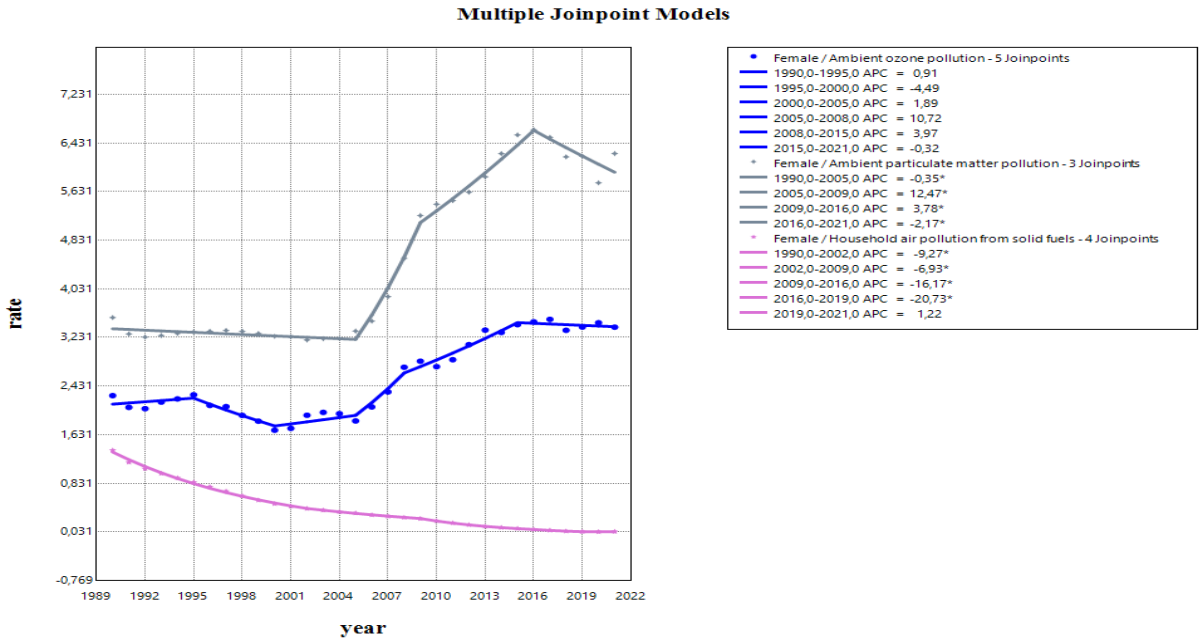
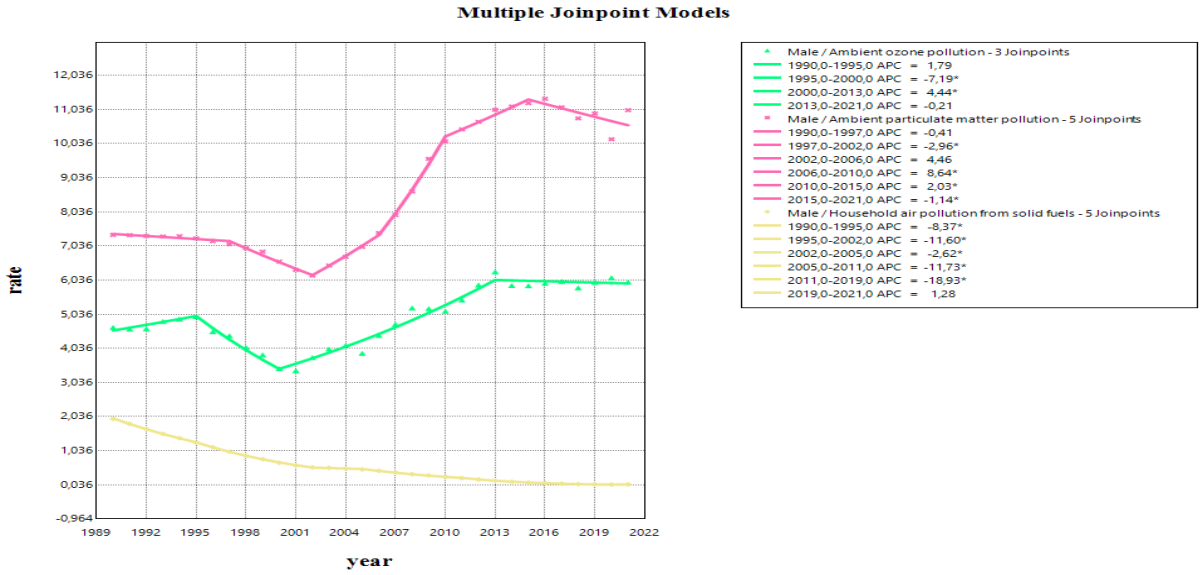


Figure 3.

JP Regression analysis of ASMRs attributed three risk factors in COPD for male gender



For the total population, ambient ozone pollution showed three breakpoints: 1990-1995, 1995-2001, 2001-2013, and 2013-2021. The APC indicated mixed trends, with the AAPC being 1.06 (95% CI: 0.82-1.32), indicating a significant overall trend ($p<0.001$). In terms of ambient particulate matter (PM2.5) for the total population, five breakpoints were identified: 1990-1998, 1998-2002, 2002-2006, 2006-2009, 2009-2015, and 2015-2021. The APC values varied, with significant increases in some periods. The AAPC was 1.38 (95% CI: 1.25-1.51), indicating a significant trend ($p<0.001$). Finally, for household air pollution from solid fuels in the total population, five breakpoints were observed: 1990-1995, 1995-2002, 2002-2005, 2005-2010,

2010-2019, and 2019-2021. The APC values were generally negative, indicating significant declines. The AAPC was -11.23 (95% CI: -11.50 to -11.01), reflecting a significant downward trend ($p<0.001$).

4.DISCUSSION

Air pollution continues to affect many people today. In this study, the trend of Chronic Obstructive Pulmonary Disease (COPD) mortality associated with outdoor and indoor air pollution in Türkiye over the past 30 years has been examined. In Türkiye, during the specified period, the number of new COPD cases increased approximately threefold from around 70,000 to 210,000, while the mortality data showed a twofold increase from around 16,000 to 30,000. Although, according to the Global Burden of Disease (GBD) data, the mortality rate attributed to COPD among all causes of death in Türkiye increased from 5.41% to 5.48% between 1990 and 2021. The age-standardized mortality rate related to ambient particulate matter and ambient ozone pollution has increased, while the rate related to household air pollution from solid fuels has decreased.

According to a research study examining the trend of Chronic Obstructive Pulmonary Disease (COPD) mortality attributed to ambient particulate matter (PM) and solid fuel consumption on a global scale from 1990 to 2021, the Age-Standardized Mortality Rate (ASMR) related to solid fuel consumption showed a decreasing trend, while the COPD mortality trend associated with ambient PM exhibited a fluctuating pattern. Additionally, the ASMRs were found to be higher in the male gender[20]. Our research findings are in line with the existing literature. Both in this study and in the literature, the higher prevalence of ASMR in men may contribute more to their employment[21], and indirectly, it can be associated with increased exposure to outdoor air pollution On the other hand, the transition from coal, which emits excessive amounts of carbon dioxide, to natural gas and renewable energy sources[22], as well as indoor air quality regulations in Türkiye and around the World, may have contributed to a reduction in COPD mortality rates caused by indoor air pollution. According to another research study examining respiratory diseases attributed to air pollution on a global scale over the past 30 years, it has been reported that the mortality rate attributed to Chronic Obstructive Pulmonary Disease (COPD) and lower respiratory tract infections shows a decreasing trend, while there is an increasing trend in the mortality rate of lung cancer[23]. Our research has focused on the impact of air pollution on COPD mortality, but it is necessary to conduct additional studies on different health effects.

In Türkiye, the transition to heating with natural gas is a positive development in reducing indoor air pollution. However, 85% of the country's energy needs are still met by fossil fuels[24]. Another improvement in indoor air quality is the implementation of smoke-free air policies under the Framework Convention on Tobacco Control[25]. Nevertheless, issues related to outdoor air quality persist. Moreover, there is no legally defined limit for $PM_{2.5}$ exposure, which is particularly concerning given its carcinogenic and chronic inflammatory effects[26,27]. Additionally, the "Black Report" regularly published by the Clean Air Right Platform highlights problems such as the insufficient number and poor positioning of outdoor air quality monitoring stations, which prevent a full representation of the air pollution situation in Türkiye[28]. COPD has various underlying etiological factors, with smoking being the most significant[29], Other determinants include occupational exposure, genetic factors such as alpha-1 antitrypsin deficiency, recurrent lung infections and chronic bronchitis[30]. This study focuses on COPD mortality attributed to air pollution.

In conclusion, the transition from solid fuel consumption for heating purposes to alternative sources is believed to have resulted in a significant decrease in Age-Standardized Mortality Rates (ASMRs) attributed to household air pollution from solid fuels. However, despite this decline, it can be argued that the increase in the number of people, distorted urbanization, and rural-to-urban migration, along with the growing traffic, have led to observed fluctuations in ASMRs attributed to ambient particulate matter pollution

and ambient ozone pollution during different periods. The lack of desired reductions in some intervals, along with identified increases in death rates during specific time intervals, is thought to be explainable by these factors.

Article Information Form

Authors' Contribution

Concept – AU, DHY; Supervision – DHY; Materials – AU; Data Collection and/or Processing – DHY; Analysis and/or Interpretation – AU, DHY; Writing –AU.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

Copyright Statement

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Research Article

The Clinical Role of the Thiol-Disulfide Balance as an Oxidative Stress Indicator in Patients with Obesity

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Objectives: Thiol-disulfide measurements will assess obesity-related oxidative stress.

Methods: A prospective observational study was done at two tertiary care centers. The participants were divided into three distinct categories based on their body mass index (BMI): The control group (Group 1) consisted of 116 individuals with a BMI ranging from 18 to 25 kg/m^2, while the overweight group (Group 2, n = 89) included those with a BMI between 25 and 30 kg/m^2. The obese group (Group 3, n = 39) comprised individuals with a BMI of 30 kg/m^2 or greater. This approach primarily utilizes the disulfide/native thiol ratio, disulfide/total thiol ratio, and native thiol/total thiol ratio as key metrics. All patients' demographics, waist circumference, hip circumference, height, weight, hemoglobin, hematocrit, white blood cell count, glucose, C-reactive protein, disulfide, native thiol (NT), total thiol (TT), lipid hydroperoxide radical (LOOH), and absolute ischemia-modified-albumin (ABSO) levels were recorded on calculations and records were made for disulfide to native and total thiol ratios.

Results: Thiol-disulfide equilibrium differed between the three groups. NT concentrations averaged 368.87 µmol/L across all individuals and were significantly higher in the normal-weight cohort (BMI 18-25 kg/m2) at 380.60 µmol/L, compared to overweight and obese populations (p<0.001). TT concentrations were higher in normal-weight individuals, with an average of 426.36±54.48 µmol/L, compared to 405.41±52.14 and 391.07±46.45 in overweight and obese individuals, respectively (p<0.001).

Conclusions: Reduced native and total thiol levels, along with altered disulfide concentrations in obese individuals, serve as indicators of oxidative stress.

Keywords: Thiol disulfide balance, Inflammatory markers, Oxidative stress, Obesity

1. INTRODUCTION

Obesity is characterized by an excessive accumulation of adipose tissue that negatively affects health, as defined by the World Health Organization (WHO).[1] This condition has escalated into a significant global public health challenge, with a rapidly increasing prevalence worldwide.[2] In the United States, obesity prevalence reached 42.4% during the period from 2017 to 2020, and this trend has been rising steadily.[3] Moreover, in 2019, approximately 5 million deaths globally were attributed to complications associated with obesity.[4] Projections indicate that by 2030, obesity could affect up to 50% of the global population.[5]

The assessment of obesity is predominantly determined by the Body Mass Index (BMI). Obesity is primarily evaluated using the BMI, which is calculated by dividing an individual's weight in kilograms by the square of their height in meters. The WHO classifies BMI as follows: A BMI ranging from 18.5 to 24.9 is deemed normal weight, 25 to 29.9 is defined as overweight (pre-obesity), and a BMI of 30 or more is categorized as obese.[6] However, BMI does not account for variations in body fat distribution and can be misleading, particularly in individuals with high muscle mass.[7]

Current guidelines suggest incorporating additional anthropometric measurements, such as

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waist circumference and waist-to-hip ratio, alongside BMI for a more comprehensive assessment of obesity. Waist circumference is particularly important for evaluating abdominal fat, which is a key indicator of metabolic risk associated with obesity. According to the 2020 guidelines from the American College of Cardiology and the American Heart Association (ACC/AHA), a waist circumference exceeding 102 cm in men and 88 cm in women is associated with an increased risk of cardiovascular disease and metabolic disorders.[8]

The accumulation of adipose tissue in obesity significantly elevates oxidative stress levels. Excessive adiposity induces increased generation of reactive oxygen species (ROS), causing cellular damage and inflammation.[9] This oxidative stress exacerbates insulin resistance and accelerates the onset of metabolic disorders related to obesity.[10] The chronic low-grade inflammation associated with obesity weakens antioxidant defense mechanisms, leading to the accumulation of oxidative damage.[11] Recent literature indicates that addressing obesity may reduce oxidative stress and enhance metabolic health.[12,13]

The thiol-disulfide system is essential for preserving cellular redox balance and controlling oxidative stress.[14] Thiol groups (-SH) are organic compounds containing a sulfur atom covalently bonded to a hydrogen atom, and are predominantly found in proteins. When these thiol groups encounter oxidative agents such as free radicals or ROS, they become oxidized, forming disulfide bonds (-S-S-) between two thiol groups.[15] This dynamic process helps maintain equilibrium and mitigate oxidative damage in both intracellular and extracellular spaces.[16]

The thiol-disulfide balance entails the oxidation of thiol groups into disulfide bonds under oxidative stress and their subsequent reduction back to thiol groups as oxidative stress subsides. This cycle reflects the cells' ability to manage oxidative stress and disruptions in this balance have been linked to metabolic disorders, inflammation and obesity.[17] Disruption of this balance results in heightened oxidative damage and inflammation, potentially contributing to the onset of various chronic diseases.[18]

Another oxidative stress biomarker, ischemia-modified albumin (IMA), forms through structural modifications in albumin molecules under ischemic conditions and holds a crucial role in assessing circulating oxidative stress levels.[19] Additionally, lipid hydroperoxides (LOOH) are lipid oxidation products resulting from oxidative stress, which compromise cell membrane integrity and negatively impact cellular functions.[20] These biomarkers are essential for identifying oxidative damage associated with obesity and for evaluating metabolic risks.[21]

The main objective of this study is to investigate the association between oxidative stress—evaluated through thiol-disulfide homeostasis, ischemia-modified albumin (IMA), and lipid hydroperoxides (LOOH)—and different Body Mass Index (BMI) categories in the context of obesity. Secondary outcomes include associations between thiol-disulfide homeostasis, IMA, and LOOH with waist circumference, waist-to-hip ratio, and waist-to-height ratio. This comprehensive approach will provide valuable insights into the oxidative mechanisms underlying obesity-related metabolic risks.

2. MATERIALS AND METHODS

The study was conducted as a prospective, multicenter observational investigation. The participating centers were Taksim Training and Research Hospital and Yıldırım Beyazıt University Hospital. Patients included in the study were enrolled over a six-month period, from November 2023 to April 2024. Approval from the Taksim Training and Research Hospital institution's ethics committee was obtained for the study (IRB date: 25.10.2023 no: 120).

2.1. Participants

The inclusion criteria were set as patients aged 18-99 without any chronic diseases. Patients who presented to the internal medicine outpatient clinic at Taksim Training and Research Hospital for routine check-ups, without any significant complaints and having fasted for 8-12 hours, were enrolled in the study. Patients with no findings of anemia, vitamin deficiency, or hormonal abnormalities in routine analyses were considered eligible. All patients were apprised

about the study and their informed consent was obtained. The exclusion criteria included pregnant women, those with a history of malignancy, patients who had undergone major surgery, and those with musculoskeletal deformities causing postural abnormalities.

Demographic data, waist circumference, hip circumference, height, weight, hemoglobin, hematocrit, white blood cell count, glucose, C-reactive protein, disulfide, native thiol (NT), total thiol (TT), lipid hydroperoxide radical (LOOH), and absolute ischemia-modified albumin (IMA_{ABSO}) levels of all patients were recorded on a data form. The ratios of disulfide to native thiol and disulfide to total thiol were also calculated and recorded. We categorized patients into three groups based on their BMI, following the guidelines established by the American Association of Clinical Endocrinologists: BMI categories include 18-25 kg/m^2, 25-29.9 kg/m^2, and over 30 kg/m^2.[22]

2.2. Sample collection and laboratory analysis

A 10 ml antecubital blood was taken following an 8-12 hour fasting period to evaluate thiol and disulfide levels. The samples underwent centrifugation at 1500 rpm for 10 minutes to isolate plasma and serum. Plasma samples were preserved at -80°C prior to analysis. The materials were thereafter transported through a cold route to the laboratory at XXX Hospital, in accordance with biological material transfer protocols. The thiol/disulfide measurement technique used in the study was developed by Erel et al. and is frequently cited in the current literature.[23] Thiol/disulfide levels were analyzed via Cobas 501, Roche analyzer and reported in micromoles per liter (µmol/L). This technique entails the conversion of dynamic disulfide bonds (-S-S-) into functional thiol groups (-SH) through reduction with sodium borohydride (NaBH4). Excess NaBH4 is neutralized with formaldehyde. Total thiol content is determined by modifying the Ellman reagent and measuring it spectrophotometrically at 415 nm. The concentration of native thiol is directly quantified using the modified Ellman substance, while the disparity between total thiol and native thiol is utilized to calculate the concentration of disulfide bonds (disulfide = [total thiol-native thiol] / 2). The key parameters obtained from this method are the ([-S-S-]/[-SH]), ([-S-S-]/ [total thiol]), and the ([-SH]/ [total thiol]).

IMA levels were measured using the albumin cobalt-binding (ACB) test, which assesses the reduced binding capacity of albumin to cobalt in ischemic conditions and were expressed in absorbance units (ABU).[24] LOOH concentrations were calculated with the ferrous oxidation-xylenol orange (FOX) test, a sensitive method for quantifying lipid hydroperoxides, and were expressed in micromoles per liter (µmol/L).[25]

2.3. Statistical analysis

Hypothesis tests were performed to compare variables among normal-weight, overweight, and obese groups. Categorical variables were expressed as frequencies and percentages. The Kolmogorov-Smirnov test was utilized to assess the normality of the data. Numerical variables following a normal distribution were reported as mean and standard deviation (SD), whereas those not normally distributed were presented as median and interquartile range (IQR). The Pearson Chi-square test was used to evaluate categorical variables. One-way ANOVA was applied for comparing normally distributed numerical variables. Post-hoc analyses were performed using either Dunnett or Tukey tests, depending on variance homogeneity. The Kruskal-Wallis test was employed for numerical variables that did not follow a normal distribution across the three groups, while the Mann-Whitney U test was used for pairwise comparisons. This study particularly examined the clinical significance of inflammatory biomarkers in obesity. Receiver operating characteristic (ROC) analysis was conducted to determine the sensitivity and specificity of inflammatory biomarkers in relation to obesity. The area under the curve (AUC) for each variable was assessed using ROC curves. All statistical analyses were performed at a 95% confidence interval with a significance level of 0.05. Data analysis was carried out using IBM SPSS Version 26 (IBM, Chicago, IL, USA).

3. RESULTS

A total of 244 patients were divided into three groups according to BMI: 116 patients between

18-25 kg/m^2 were classified as the control group (Group 1), 89 patients were overweight (Group 2), and those with a BMI of 30 kg/m^2 and above were classified as obese (Group 3, n=39). The average age of all study population was 36.95 (±12.78) years. A notable distinction was observed among the groups, with the average age of obese group 46.48 (±9.32) years, significantly higher than in other groups (p=0.001) (Table 1).

In the obese group (BMI ≥ 30), the average waist circumference was 101.64±11.72 cm, while it was 90.73±8.98 cm in group 2 and 75.32±8.34 cm in group 1 (p<0.001). Similarly, waist-to-hip and waist-to-height ratios also increased significantly with higher BMI. Fasting blood glucose levels were measured as 100.25±14.43 mg/dL across all patients (p=0.067). In terms of general inflammation markers, no significant differences in CRP or WBC levels were found among the groups (Table 1).

The average NT level across all patients was 368.87 μmol/L. In group, the NT level was significantly higher, at 380.60 μmol/L, compared to the overweight and obese groups (p<0.001). Similarly, TT values were higher in normal-weight individuals; the mean TT level in group 1 was 426.36±54.48 μmol/L, compared to 405.41±52.14 μmol/L in group 2 and 391.07±46.45 μmol/L in group 3 (p<0.001). Post-hoc analysis revealed that the TT level in the normal-weight group was significantly higher than in both the overweight and obese groups, although no difference was observed between the overweight and obese groups (Table 1).

Table 1.

Clinical characteristics, antropometric measurements, and oxidative biomarkers comparison of the study population

	Total N=244	**Group 1 n=116**	**Group 2 n=89**	**Group 3 n=39**	*P*
Age	36,95±12,78	31,07±11,23[2,3]	40,77±12,16[1,3]	46,48±9[1,2]	**0,001**
Female gender, n (%)	123 (50.4%)	59 (49.6%)	38 (44.2%)	26 (66.7%)	0,064
Weight, kg	72,95±16,52	61,86±9,66[2,3]	78,50±9,37[1,3]	94,53±18,04[1,2]	**<0.001**
Height, cm	168,51±9,61	168,71±9,15	168,72±9,49	165,51±10,95	0,162
Waistline, cm	84,96±13,61	75,32±8,34[2,3]	90,73±8,98[1,3]	101,64±11,72[1,2]	**<0.001**
Hip Circumference, cm	101,24±10,18	94,66±6,36[2,3]	103,91±5,61[1,3]	115,43±10,39[1,2]	**<0.001**
Waist/hip ratio	0,83±0,09	0,79±0,08	0,87±0,07	0,88±0,09	**<0.001**
Waist/height ratio	0,50±0,09	0,44±0,04	0,54±0,10	0,61±0,06	**<0.001**
Glucose, mg/dl	100,25±14,43	90,08±6,86	93,34±12,38	101,11±14,48	0,067
Hb, g/dl	13,61±1,70	13,54±1,80	13,89±1,63	13,40±1,50	0,218
CRP, mg/L	1,75 (1,83)	0,82 (1,41)	1,44 (1,53)	3,00 (2,56)	0,632*
WBC, 10^3/μL	7,37±1,93	7,30±2,17	7,39±1,75	7,56±1,50	0,757
NT, μmol/L	368,87±51,43	380,60±53,19[2,3]	360,84±48,22[1]	350,79±44,86[1]	**0,001**
TT, μmol/L	413,34±53,99	426,36±54,48[2,3]	405,41±52,14[1]	391,07±46,45[1]	**<0,001**
Disulfide, μmol/L	22,23±5,86	22,87±6,05[3]	22,28±5,67	20,14±5,39[1]	**0,040**
Disülfide/NT ratio	5,83±1,70	0,061±0,018	0,063±0,016	0,058±0,017	0,485
Disülfide/TT ratio	5,41±1,39	0,054±0,014	0,055±0,012	0,051±0,013	0,476
NT/TT ratio	89,16±2,78	0,89±0,29	0,88±0,25	0,89±0,27	0,475
IMA ABSO	0,90±0,22	0,94±0,21[3]	0,86±0,22	0,86±0,23[1]	**0,036**
LOOH	4,92±0,38	4,90±0,40	4,92±0,29	4,98±0,50	0,528

Hb: Hemoglobin; CRP: C reactive protein; WBC: white blood cell; NT: native thiol; TT: total thiol IMA ABSO: ischemia modified albümin absolute; LOOH: lipid hydroperoxides.

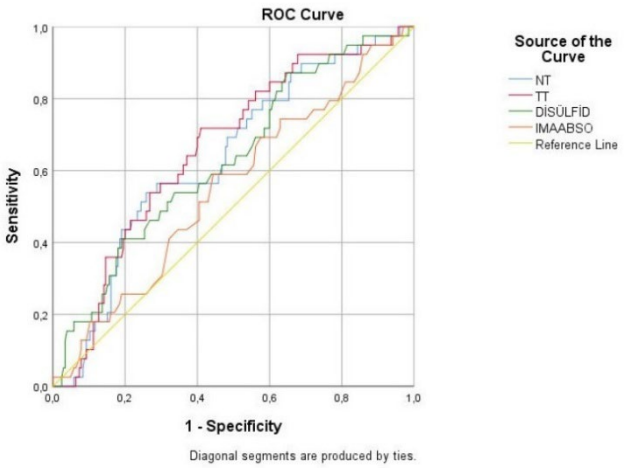
- * Kruskal-Wallis test was used to compare the group variables
- Other comparison were analysed with one-way ANOVA test
- [1]: Significant difference was detected with group 1 according to post-hoc tests
- [2]: Significant difference was detected with group 2 according to post-hoc tests
- [3]: Significant difference was detected with group 3 according to post-hoc tests

Disulfide levels were measured as 22.23±5.86 µmol/L across the study population. In group 1, the average disulfide level was 22.87±6.05 µmol/L, while it was 22.28±5.67 µmol/L in group 2 and 20.14±5.39 µmol/L in group 3. Significant differences in disulfide levels were found between the groups, with post-hoc analysis showing that the normal-weight group had significantly higher disulfide levels than the obese group (p=0.040). However, no significant differences were found between the groups regarding the disulfide/total thiol and disulfide/native thiol ratios.

Other biochemical markers, including IMA_{ABSO} and LOOH, were also examined. The average IMA ABSO value across all patients was 0.90±0.22, and the mean LOOH level was 4.92±0.38 µmol/L. IMA_{ABSO} levels differed significantly between the three groups, with values of 0.94±0.21, 0.86±0.22, and 0.86±0.23, respectively (p=0.036). However, no significant variations in LOOH levels were observed among the groups. ROC analysis supports these findings, with NT (AUC: 0.634, p=0.008), TT (AUC: 0.660, p=0.002), and disulfide (AUC: 0.629, p=0.010) values being significantly associated with obesity. Notably, lower NT, TT, and disulfide levels were more strongly related to obesity (Figure 1, Table 2).

Figure 1.

ROC curve and ROC analyses of the oxidative biomarkers



NT: Native Thiol, TT: Total Thiol, IMAABSO: Ischemia modified albümin

Table 2.

Area under curve of study variables

	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval Lower Bound	Upper Bound
NT	,634	,046	,008	,544	,725
TT	,660	,045	,002	,572	,747
Disulfide	,629	,048	,010	,536	,723
IMAabso	,550	,050	,319	,453	,648

The test result variable(s): NT: native thiol; TT: total thiol; IMA_{abso}: ischemia modified albümin.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

4. DISCUSSION

This study clearly demonstrates that oxidative stress increases in obesity. The key outcome of our study indicates that an imbalance in the thiol/disulfide system is linked to heightened oxidative stress and a reduction in antioxidant capacity among obese individuals.

Of the total patients, 50.4% were female, and 49.6% were male, indicating a balanced gender distribution across groups. A notable variation was observed among the groups, with the obese group having a mean age of 46.48 (±9.32) years, which was significantly higher compared to the other groups (p=0.001). This result underscores the link between obesity and aging, indicating that the likelihood of obesity rises with advancing age.

Oxidative stress plays a major role in the development of chronic diseases and is further aggravated by conditions like obesity.[26] Oklu et al. demonstrated that the thiol-disulfide balance is impaired in obese individuals, with this disruption

becoming more evident as BMI increases.[27] Likewise, studies have shown that the thiol-disulfide balance is impaired in obese children, with this imbalance being inversely correlated with BMI.[28] These results are consistent with studies emphasizing the link between obesity and elevated oxidative stress. Moreover, oxidative stress has been reported to be linked to heightened adipokine secretion, further disturbing the oxidative balance.[29] Our study revealed a significant decline in native and total thiol levels as BMI increased, reinforcing the evidence that oxidative stress levels are elevated in obese individuals. These results suggest that the thiol-disulfide balance could serve as an early indicator of chronic diseases associated with obesity.

CRP levels have been closely linked to obesity in the literature and are considered a marker of inflammation. A positive association has been identified between visceral adipose tissue and CRP levels in obese individuals, indicating a link to heightened inflammation.[30] Van Wijk et al. also demonstrated that CRP is a biomarker of the inflammatory processes related to obesity, which are linked to cardiovascular risks.[31] However, in our study, no significant differences in CRP levels were observed among the groups. This suggests that the participants in our study might be in a stage where chronic inflammation has not yet become clinically apparent. Moreover, the fact that all participants were healthy individuals without any health problems other than obesity could explain this. Individual differences and the impact of genetic factors on the inflammatory response may also have contributed to this outcome.[32]

In our study, disulfide levels—another marker of oxidative stress—were assessed and found to be lower in the obese group. Mengen et al. identified reduced disulfide levels in obese individuals as a sign of heightened oxidative stress.[33] Similarly, Elkan et al. indicated that the reduction in disulfide levels in obese individuals suggests that the antioxidant defense systems are insufficient.[34] These findings highlight that disulfide levels could be an early marker of oxidative stress related to obesity.

Numerous studies have highlighted the significance of anthropometric measurements, including waist circumference, waist-to-hip ratio, and waist-to-height ratio, in relation to obesity. A meta-analysis by De Koning et al. established that an increase in waist circumference serves as a strong predictor of cardiovascular events and has a direct association with oxidative stress.[35] These findings underscore that obesity is not merely an increase in weight but is also associated with fat accumulation and changes in the metabolic functions of adipose tissue.[36] Likewise, in our study, these anthropometric measurements were notably higher in individuals with elevated BMI, correlating with oxidative stress. The literature extensively documents that an increase in visceral fat tissue stimulates oxidative stress by promoting the release of free fatty acids and inflammatory cytokines.[37] These findings demonstrate the marked increase in abdominal obesity with rising BMI, highlighting potential health risks associated with central fat accumulation.

Ischemia-modified albumin (IMA) is a commonly utilized biomarker for assessing oxidative stress. Piva et al. demonstrated that elevated oxidative stress in obese individuals results in alterations in IMA levels.[38] The study demonstrated that IMA levels were significantly reduced in obese individuals, emphasizing the potential impact of oxidative stress on albumin structure. Mehmetoglu et al. also indicated that IMA levels are associated with obesity, and increased oxidative stress in these individuals results in changes in albumin structure.[39]

This study possesses multiple shortcomings that warrant acknowledgment. The observational approach restricts the capacity to deduce causality between oxidative stress and obesity. Longitudinal studies are needed to establish a clear temporal relationship. Second, the sample size, while adequate for preliminary analysis, may not fully represent the diverse population affected by obesity, potentially limiting the generalizability of the findings. Additionally, the exclusion of individuals with chronic diseases may have led to a selection bias, as the inflammatory responses in these patients could differ significantly from those without such conditions. Moreover, using BMI as

the sole indicator of obesity overlooks differences in body composition and fat distribution. Incorporating additional metrics, such as body fat percentage or bioelectrical impedance analysis, could offer a more comprehensive evaluation. Finally, while the study utilized established laboratory techniques for measuring thiol and disulfide levels, variations in laboratory protocols and individual biological variability could affect the reproducibility of the findings.

5. CONCLUSIONS

In conclusion, this study highlights a significant association between obesity and oxidative stress, as evidenced by the disruption of thiol-disulfide balance among different BMI categories. The results indicate that decreased native and total thiol levels, along with modifications in disulfide levels, serve as markers of heightened oxidative stress in obese individuals. This imbalance may play a role in the development of various metabolic disorders linked to obesity, highlighting the necessity for further research to investigate thiol-disulfide balance as a potential biomarker for oxidative stress and inflammation. Given the rising global obesity epidemic, strategies aimed at reducing oxidative stress may be beneficial in preventing and managing obesity-related health complications. Future studies should investigate the efficacy of interventions targeting oxidative stress in improving metabolic health and mitigating the risks associated with obesity.

Article Information Form

Authors' Contribution

All authors jointly conceived and designed the study. SY, OE, AS, and EFO contributed to data collection. SY, TD, NMH, EFO, and OE were involved in data analysis and interpretation. The manuscript draft was written by SY, TD, and NMH. Technical and material support was provided by SY, OE, AS, and OE. All authors critically revised the content. Literature review was conducted by SY, OE, and AS. All authors reviewed the final results and approved the final version of the manuscript.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

Approval from the Taksim Training and Research Hospital Ethics Committee was obtained for the study (IRB date: 25.10.2023, no: 120).

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

Copyright Statement

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Research Article

The Effect of Adherence to Mediterranean Diet on Quality of Life in Patients with Coronary Artery Disease

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Objective: The aim of this study was to evaluate the effect of Mediterranean diet adherence on quality of life in individuals with a history of coronary artery disease.

Materials and Methods: This cross-sectional study was conducted with the participation of 378 patients diagnosed with coronary artery disease between the ages of 18 and 65. Data were collected through face-to-face interviews using a questionnaire including questions on demographic characteristics, dietary habits, the Mediterranean Diet Adherence Scale (MEDAS), and the Cardiac Quality of Life Scale (HeartQoL). The IBM SPSS Statistics 26.0 program was used in the analysis of data.

Results: The mean HeartQoL score of the patients was 25.33±10.42, and the mean MEDAS score was 6.13±1.69. Diet quality was low in 62% of the participants. No significant effect of the level of adherence to the Mediterranean diet on blood pressure and lipid profile was detected ($p>0.05$). MEDAS score (B=3.04; 95% CI: 2.52–3.57; $p<0.001$) and hemoglobin A1c (HbA1c) level (B=–1.04; 95% CI: –1.68– –0.40; $p=0.002$) were found to be associated with HeartQoL score. Education level (B=0.23; 95% CI: 0.05–0.41; $p=0.013$) and waist circumference (B=–0.49; 95% CI: –0.08– –0.02; $p=0.002$) were found to be associated with MEDAS score.

Conclusion: Diet quality is generally low in coronary artery disease patients. High diet quality positively affects emotional and physical quality of life. On the other hand, high HbA1c levels negatively affect quality of life. Therefore, patients should be made aware of healthy nutrition, and the treatment process should include strategies to ensure glycemic control.

Keywords: Coronary artery disease, Mediterranean diet, Quality of life, Lifestyle, Glycemic control

1. INTRODUCTION

Coronary artery disease is a major health problem involving the development of atherosclerotic plaque and is among the leading causes of death worldwide. The plaque narrows the lumen of the artery and obstructs blood flow. If the plaque continues to grow in size, it leads to chest pain and the risk of heart attack.[1] Patients may experience symptoms such as shortness of breath, back pain, palpitations, and fatigue.[2] These symptoms significantly negatively affect both the psychological and physical health of the patients.[3,4] Lifestyle changes and medication are applied in the management of symptoms. Among these lifestyle changes, healthy eating, participation in regular physical activity, and smoking cessation are the most effective ones.[5]

The Mediterranean diet stands out as a potential gold standard in preventive medicine. This dietary model arises from a lifestyle specific to the Mediterranean region. It emphasizes moderation, frugality, seasonality, and tradition in food consumption.[6] The Mediterranean diet includes high amounts of fruits, vegetables, olive oil, and various herbs and spices, while red meat is limited. It has a metabolic and general health protective effect thanks to its antioxidant and anti-inflammatory components.[7] The Mediterranean diet is associated with cardioprotective effects. Positive effects on various cardiovascular risk factors, including lipid profile, blood pressure, and inflammatory markers, have been reported.[8]

Quality of life refers to the individual's perception of well-being in different areas of life. Health-related quality of life is the perception of well-being related to factors that are part of the

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individual's health (e.g., physical, mental, social, and functional health).[9] Individuals with coronary artery disease have difficulty in complying with treatment recommendations due to physical, psychological, and social problems caused by the disease. This situation negatively affects their life satisfaction and quality of life.[10] Assessment of health-related quality of life in coronary artery disease patients is important to measure the effectiveness of treatments and nutritional interventions.[11] The Mediterranean diet is known for its potential to reduce the risk of cardiovascular disease and disease burden. The best dietary model for heart patients is the Mediterranean diet due to its multifaceted health benefits. It is evidence-based recommended that patients adhere to this beneficial dietary pattern.[12,13]

In our study, we used a quality of life scale specific for coronary artery disease patients. We aimed to evaluate the effect of adherence to a Mediterranean diet on biochemical parameters and quality of life in patients. We hope to provide information to guide public health interventions aimed at reducing the burden of disease by determining the contribution of a sustainable and healthy diet in the effective management of coronary artery disease.

2. METHOD AND MATERIALS

2.1. Study design and participants

This cross-sectional study was conducted among patients with coronary artery disease visiting the outpatient clinic of Ankara Etlik City Hospital. G-power analysis was used to determine the sample size. The margin of error, power, and effect size were determined as 0.05, 0.95, and 0.5, respectively, and it was found that at least 176 people should be included in the study. To achieve more reliable results, the inclusion of a larger patient sample was planned, and the study was ultimately completed with 378 participants. Patients aged 18 to 65 years, diagnosed with coronary artery disease at least one year ago, followed up and were stable due to coronary artery disease, without any mental problem that prevented them from answering the questions, and who volunteered to participate in the study were included in the study. Patients with structural heart disease, hospitalization due to heart disease in the past six months, advanced cancer, chronic liver disease, and chronic kidney disease were excluded from the study.

2.2. Data collection tools and procedure

Data collection was conducted between January and February 2025 through face-to-face interviews by physician researchers trained in the study protocol. Each interview lasted approximately 20–30 minutes. The questionnaire included questions about demographic characteristics, nutritional habits, adherence to the Mediterranean diet scale, and cardiac quality of life scale. Furthermore, anthropometric measurements and biochemical findings of the patients were recorded in the questionnaire form.

2.3. Anthropometric measurements

Height, waist circumference, and hip circumference were measured with the help of an inflexible tape measure. Height was measured without shoes, with the head in an upright position and standing in the Frankfurt plane (ear canal and the lower border of the eye socket in the same line, gaze parallel to the ground). Waist circumference was measured while the individual was standing with the abdomen in a relaxed position, arms on both sides, feet side by side, and face to face with the researcher. Hip circumference was measured by the researcher standing on the side of the individual and from the widest part of the hip without compressing the tissue with the tape measure parallel to the ground. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2).[14]

2.4. Blood pressure and biochemical results

Blood pressure values obtained as a result of manual measurement from both arms were recorded by the physician, provided that no food, tea, coffee, or cigarettes were consumed in the last half hour and the patient rested for 10 minutes during the survey. The mean arterial pressure was calculated with the formula (SBP + (2XDBP))/3 using the recorded systolic (SBP) and diastolic blood pressure (DBP) values. Biochemical findings of the last month were obtained from the medical

files of the patients. Fasting blood glucose, HbA1C, triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, hemoglobin, hematocrit, ALT, AST, BUN, creatinine, sodium, and potassium values were recorded in the questionnaire form.

2.5. Mediterranean Diet Adherence Scale (MEDAS)

The scale provides a rapid assessment of adherence to the Mediterranean diet. It was developed by Schröder et al., and a Turkish validity and reliability study was conducted by Pehlivanoğlu et al.[15,16] The questionnaire consists of 14 questions and asks about the type of main fat used in meals, the amount of olive oil consumed daily, fruit and vegetable portions, margarine-butter, and red meat amount. Furthermore, it asks the amount of wine, pulses, fish-seafood, desserts, and dried nuts consumed on a weekly basis and whether white meat is preferred more than red meat. A score of 1 or 0 is obtained for each question asked according to the amount of consumption. A total score of 7 and above indicates an acceptable level of compliance with the Mediterranean diet, and a score of 9 and above indicates that individuals have strict compliance with the Mediterranean diet.[16]

2.6. Heart Quality of Life Scale for Coronary Artery Patients (HearthQoL)

The scale was developed to measure quality of life in individuals with ischemic heart disease.[17] A Turkish validity and reliability study was conducted by Duğan and Bektaş in 2020. It consists of 14 items and two sub-dimensions (physical and emotional characteristics). Each item is scored out of 0 to 3. The scale can be applied to individuals aged 18 years and over in clinical and community-based studies. The total scale score that can be obtained ranges from 0 to 52, and high scores indicate that there is no dysfunction and quality of life is high.[18]

2.7. Statistical analysis

The IBM SPSS (Statistical Package for Social Sciences) 26.0 package program was used to evaluate the data. Mean, standard deviation, number, and percentage values were used for descriptive statistics. Continuous variables were compared by a one-way ANOVA test, and categorical variables were compared by a Pearson chi-square test. Categorical variables were compared using the chi-square test with post-hoc pairwise comparisons; significant differences were indicated by different superscript letters (x, y, z). Continuous variables were analyzed using one-way ANOVA with Bonferroni post-hoc test; significant differences were indicated by different superscript letters (a, b, c). Individuals were divided into tertiles according to HeartQoL score, and a one-way ANOVA test was used to evaluate the differences between tertiles. Individuals with a HeartQoL score of ≤20.07 were included in the T1 group, individuals with a HeartQoL score of 20.07 < HeartQoL ≤ 31.0 were included in the T2 group, and individuals with a HeartQoL score of >31.0 were included in the T3 group. Pearson correlation analysis and a heat map were used to assess the relationship between two continuous quantitative variables. Multiple linear regression models were used to determine the factors affecting the HeartQoL and MEDAS scales. For all tests, $p<0.05$ was considered statistically significant.

2.8. Ethical approval

The study was conducted in accordance with the guidelines specified in the Helsinki Declaration. Ethical permission was obtained from the Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee to conduct the research (No:11.12.2024/AEŞH-BADEK-2024-1234). All participants provided written informed consent before participation. Patient anonymity was preserved by removing all identifiable personal information from the collected data and manuscript. Original consent forms are retained by the authors and are available for review upon journal request.

3. RESULTS

Table 1 presents the demographic characteristics, dietary habits, and scale scores of the patients according to the quality of life scale tertiles. The mean age of the individuals was 58.35±6.68 years, and they had cardiovascular disease for a mean of 4.34±4.76 years. According to post-hoc analysis, patients in the third tertile were significantly

younger (p=0.001). The duration of cardiovascular disease in patients in the second tertile is higher than in the third tertile (p=0.045). A higher male ratio was observed in conjunction with an increase in the quality of life tertile (p<0.001). Within the third tertile, the percentage of people who are married is higher than the percentage of people in the first tertile (p= 0.010). The percentages of patients who exercise regularly, who regularly consume 3 main meals, and patients without another chronic disease were significantly higher in the third tertile (p<0.05), as indicated by the post-hoc comparisons in the table (different superscript letters). The mean HeartQoL score was 25.33±10.42, and the mean MEDAS score was 6.13±1.69. As the quality of life increased, MEDAS scores also increased significantly (p<0.001), as demonstrated by the post-hoc comparisons.

Table 2 presents the anthropometric measurements, biochemical findings, and HearthQoL scores of the patients according to MEDAS classification. Body mass index, waist, and hip circumference were higher in patients with low adherence to the Mediterranean diet (p<0.05). While the level of adherence to the Mediterranean diet did not affect blood pressure, it affected hemoglobin and BUN values among biochemical findings. Hemoglobin values of patients with low adherence to the Mediterranean diet were statistically significantly lower than those with high adherence (p=0.012). BUN values of those with low adherence to the Mediterranean diet were statistically significantly higher than those with high adherence (p=0.045). As the level of adherence to the Mediterranean diet increased, the total score and sub-dimensions (emotional and physical quality of life) of the cardiac quality of life scale increased (p<0.001).

Table 3 presents the correlation analyses of the HeartQoL score, MEDAS score, anthropometric measurements, and biochemical findings of the patients. HeartQoL score and MEDAS score are positively correlated (r=0.554; p<0.001). There is a negative correlation between HeartQoL score and age, BMI and waist circumference (p<0.001). HeartQoL score is positively correlated with hemoglobin and hematocrit values among biochemical findings, while it is negatively correlated with HbA1c (p<0.05). While there is a negative correlation between MEDAS score and age, BMI, and waist circumference, a positive correlation has been found between hemoglobin and hematocrit values (p<0.05).

Figure 1 illustrates the results of multiple regression analysis showing the factors affecting patients' quality of life and adherence to the Mediterranean diet. According to the model, gender (B= -4.18, 95% CI: -6.96- -1.40, p=0.003), MEDAS score (B= 3.04, 95% CI: 2.52-3.57, p<0.001) and HbA1c level (B= -1.04, 95% CL: -1.68- -0.40, p=0.002) are associated with HeartQoL score after adjusting confounding factor. Education level (B= 0.23, 95% Cl: 0.05-0.41, p=0.013), HeartQoL score (B= 0.09, 95% CI: 0.07-0.010, p<0.001) and waist circumference (B= -0.49, 95% CL: -0.08- -0.02, p=0.002) are associated with MEDAS score after adjusting confounding factor.

Table 1.

Distribution of demographic characteristics, nutritional habits and scale scores of patients according to HeartQoL tertiles

		Total	Tertile			p value
			T1 [a] (n=125)	T2 [b] (n=133)	T3 [c] (n=120)	
Demographic Characteristics						
Age (year)		58.35±6.68	59.28±6.60	59.16±6.26	56.50±6.89	0.001* [a,b-c]
Duration of CVD (year)		4.34±4.76	4.32±4.41	5.05±5.59	3.56±3.95	0.045* [b-c]
Gender	**Female**	106 (28.0)	60 (48.0)	33 (24.8)	13 (10.8)	<0.001*
	Male	272 (72.0)	65 (52.0)	100 (75.2)	107 (89.2)	
Marital Status	**Single**	54 (14.3)	7 (21.6)	17 (12.8)	10 (8.3)	
	Married	324 (85.7)	98 (78.4)	116 (87.2)	110 (91.7)	0.010*
Education Status	**Literate**	51 (13.5)	30 (24.0)	15 (11.3)	6 (5.0)	
	Primary school	164 (43.4)	58 (46.4)	60 (45.1)	46 (38.3)	
	Middle school	110 (29.1)	26 (20.8)	35 (26.3)	49 (40.8)	<0.001*
	High school	37 (9.8)	8 (6.4)	16 (12.0)	13 (10.8)	
	University	16 (4.3)	3 (2.4)	7 (5.3)	6 (5.0)	
Place of Residence		49 (13.0)	20 (16.0)	19 (14.3)	10 (8.3)	
Village/District		329 (87.0)	105 (84.0)	114 (85.7)	110 (91.7)	0.173
	Province					
Smoking	**Yes**	93 (24.6)	31 (24.8)	26 (19.5)	36 (30.0)	
	No	131 (34.7)	60 (48.0)	40 (30.1)	31 (25.8)	<0.001*
	Quitting	154 (40.7)	34 (27.2)	67 (50.4)	53 (44.2)	
Alcohol	**Yes**	15 (4.0)	1 (0.8)	7 (5.3)	7 (5.8)	
	No	363 (96.0)	124 (99.2)	126 (94.7)	113 (94.2)	0.083
Presence of	**Yes**	306 (81.0)	107 (85.6)	111 (83.5)	88 (73.3)	
Chronic Disease	**No**	72 (19.0)	18 (14.4)	22 (16.5)	32 (26.7)	0.033*
Exercise status	**Yes**	55 (14.6)	10 (8.0)	18 (13.5)	27 (22.5)	0.005*
	≤2 days a week	16 (29.1)	2 (20.0)	7 (38.9)	7 (25.9)	0.504
	>2 days a week	39 (70.9)	8 (80.0)	11 (61.1)	20 (74.1)	
	No	323 (85.4)	115 (92.0)	115 (86.5)	93 (77.5)	
Nutritional Habits						
Meal	**2**	65 (17.2)	29 (23.2)	27 (20.3)	9 (7.5)	
	3	313 (82.8)	96 (76.8)	106 (79.7)	111 (92.5)	0.002*
Meal Skipping	**Yes**	65 (17.2)	29 (23.2)	65 (17.2)	29 (23.2)	0.002*
	No	313 (82.8)	96 (76.8)	313 (82.8)	96 (76.8)	
Water Consumption	**≤ 5 glasses**	17 (4.5)	7 (5.6)	5 (3.8)	5 (4.2)	0.428
	5-10 glasses	252 (66.7)	82 (65.6)	96 (72.2)	74 (61.7)	
	>10 glasses	109 (28.8)	36 (28.8)	32 (24.1)	41 (34.2)	
Cooking fat preference	**Butter**	4 (1.1)	2 (1.6)	1 (0.8)	1 (0.8)	<0.001*
	Sunflower oil	291 (77.0)	111 (88.8)	111 (83.5)	69 (57.5)	
	Olive oil	84 (22.0)	12 (9.6)	21 (15.8)	50 (41.7)	
Eating speed	**Slow**	9 (2.4)	6 (4.8)	1 (0.8)	2 (1.7)	0.203
	Moderate	129 (34.1)	45 (36.0)	42 (31.6)	42 (35.0)	
	Fast	240 (63.5)	74 (59.2)	90 (67.7)	76 (63.3)	
Salt consumption	**Salt-free**	11 (2.9)	6 (4.8)	4 (3.0)	1 (0.8)	0.481
Preference	**Lightly salted**	354 (93.7)	115 (92.0)	124 (93.2)	115 (95.8)	
	Salty	13 (3.4)	4 (3.2)	5 (3.8)	4 (3.3)	
Adding salt	**Yes**	6 (1.6)	2 (1.6)	2 (1.5)	2 (1.7)	0.995
without tasting	**No**	372 (98.4)	123 (98.4)	131 (98.5)	118 (98.3)	
Scale scores						
HeartQoL		25.33±10.42	13.07±4.63	26.18±3.23	37.16±3.19	<0.001* [a-b-c]
MEDAS		6.13±1.69	5.10±1.24	5.95±1.36	7.40±1.62	<0.001* [a-b-c]

One-way ANOVA and Chi-square analysis were used. Significance level, p<0.05 T1: HeartQoL ≤20.07; T2: 20.07 < HeartQoL ≤31.0; T3: HeartQoL >31.0

One-way ANOVA and Chi-square analysis were used. Significance level, p<0.05 T1: HeartQoL ≤20.07; T2: 20.07 < HeartQoL ≤31.0; T3: HeartQoL >31.0

CVD: Cardiovascular disease, MEDAS: Mediterranean Diet Adherence Screener, HeartQoL: Heart Quality of Life Scale

Table 2.

Anthropometric measurements, biochemical findings and HeartQoL scores of patients according to the MEDAS classification

	Total	<7 [a] (n=236)	7-8 [b] (n=102)	≥9 [c] (n=40)	*p value*
Anthropometric measurement					
BMI (kg/m²)	29.38±3.60	29.88±3.60	28.38±3.52	28.98±3.20	0.001* [a-b]
Waist circumference (cm)	99.11±6.29	100.0±5.98	97.74±7.03	97.40±5.12	0.002* [a-b,c]
Hip circumference (cm)	107.18±7.58	108.48±7.68	105.25±7.21	104.53±6.20	<0.001* [a-b,c]
WHR	0.93±0.04	0.92±0.04	0.93±0.04	0.93±0.03	0.246
Blood Pressure					
SBP (mm Hg)	130.78±16.07	132.06±17.14	128.46±13.68	128.70±14.56	0.117
DBP (mm Hg)	76.03±7.47	76.11±7.67	75.92±5.96	75.88±9.63	0.969
Arterial Pressure	94.27±9.18	94.77±9.72	93.43±6.91	93.48±10.85	0.407
Biochemical analysis					
FPG (mg/dl)	117.49±47.71	114.83±44.42	122.70±51.58	119.88±55.66	0.360
HbA1c (%)	6.18±1.31	6.12±1.27	6.22±1.35	6.43±1.40	0.368
Triglycerides (mg/dL)	171.74±118.41	164.35±94.83	190.47±165.85	167.63±94.05	0.172
Total cholesterol (mg/dL)	165.71±47.44	166.57±46.70	164.15±45.05	164.68±57.86	0.902
HDL (mg/dL)	42.73±10.97	43.07±11.17	41.55±10.18	43.73±11.78	0.420
LDL (mg/dL)	100.39±39.77	101.38±40.18	98.38±38.77	99.63±40.64	0.811
Hemoglobin (g/dL)	14.31±1.65	14.12±1.74	14.55±1.43	14.80±1.42	0.012* [a-c]
Hematocrit (%)	43.97±4.31	43.61±4.61	44.39±5.59	45.01±4.01	0.086
ALT (U/L)	23.74±18.10	22.94±12.94	25.94±27.91	22.80±11.07	0.356
AST (U/L)	20.99±10.14	20.28±7.14	22.29±14.96	21.28±10.01	0.279
BUN (mg/dL)	32.59±10.19	33.11±10.46	32.87±9.82	28.81±8.83	0.045* [a-c]
Creatinine (mg/dL)	1.06±3.11	1.15±3.94	0.91±0.20	0.90±0.16	0.762
Sodium (mEq/L)	140.20±2.53	140.28±2.60	140.0±2.44	140.23±2.41	0.651
Potassium (mEq/L)	6.04±2.47	6.41±3.0	4.49±3.0	7.75±2.1	0.725
CRP	3.61±6.34	3.60±5.41	3.75±8.30	3.26±5.84	0.918
HeartQoL	25.33±10.42	21.24±9.16	30.34±9.01	36.70±5.75	<0.001* [a-b-c]
EmotionalQoL	8.62±2.98	7.67±2.93	9.82±2.5	11.13±1.52	<0.001* [a-b-c]
PhysicalQoL	16.69±7.94	13.54±6.81	20.47±7.15	25.58±4.45	<0.001* [a-b-c]

One-way ANOVA was used. Significance level, p<0.05

BMI: Body mass index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, FBP: Fasting Plasma Glucose, HbA1c: glycated hemoglobin, HeartQoL: Heart Quality of Life Scale, EmotionalQoL: Emotional Quality of Life Scale, PhysicalQoL: Physical Quality of Life Scale

Table 3.

Correlation analysis of HeartQoL, MEDAS, anthropometric measurements and biochemical findings

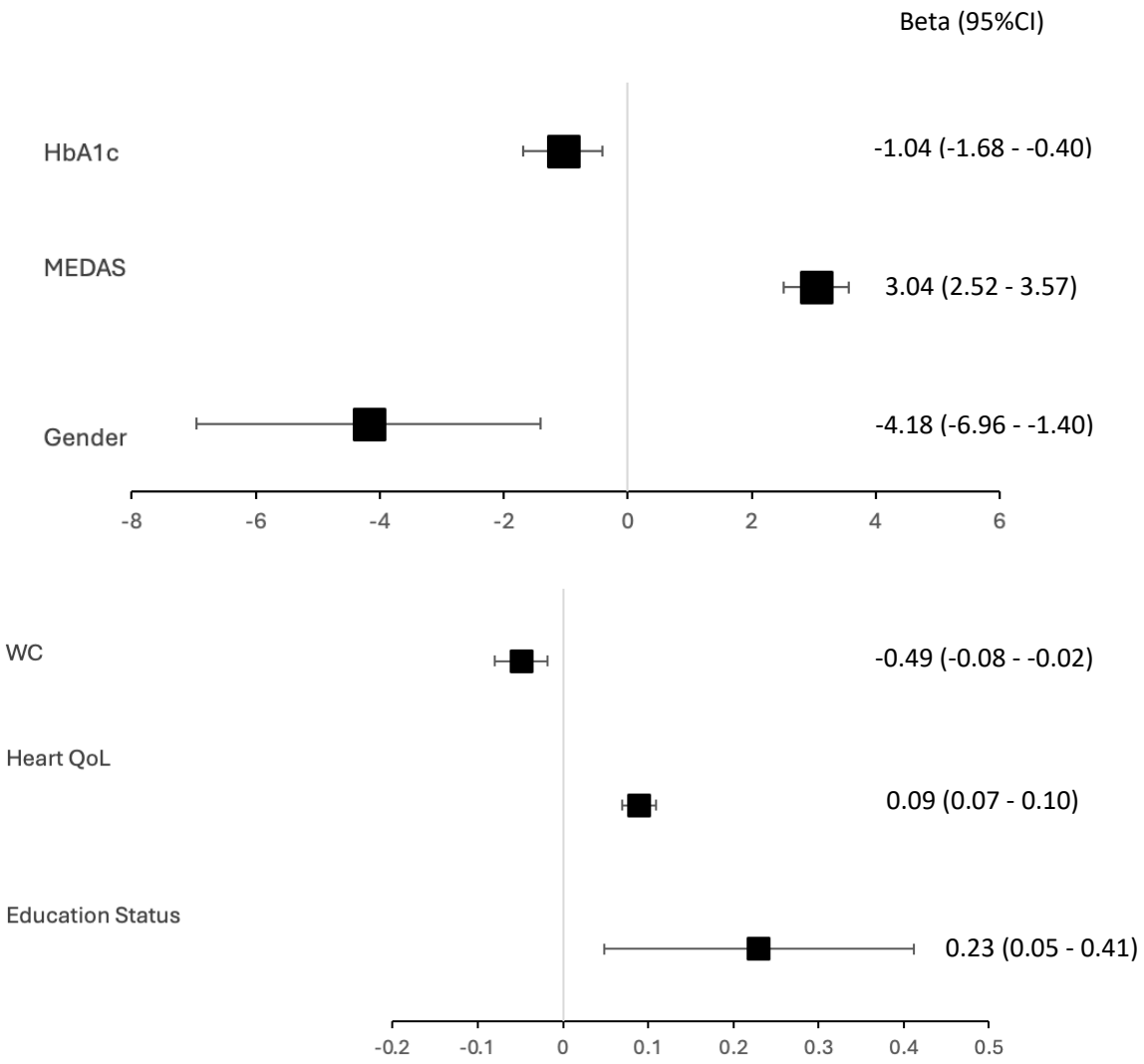
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1 HeartQoL	1.00																
2 MEDAS	0.554**	1.00															
3 Age	-0.181**	-0.180**	1.00														
4 Duration of CVD (y)	-0.090	-0.050	0.247**	1.00													
5 BMI (kg/m^2)	-0.237**	-0.120*	0.181**	0.085	1.00												
6 WC (cm)	-0.153**	-0.173**	0.136**	0.087	0.635**	1.00											
7 WHR	0.230**	0.090	-0.043	-0.023	-0.235**	0.222**	1.00										
8 SBP (mm Hg)	-0.090	-0.084	0.111*	0.160**	0.102*	0.094	0.029	1.00									
9 DBP (mm Hg)	-0.040	0.003	0.001	0.101*	0.033	0.029	-0.011	0.576**	1.00								
10 FPG (mg/dl)	-0.078	0.037	0.027	-0.014	-0.045	0.003	0.035	0.055	0.025	1.00							
11 HbA1c (%)	-0.107*	0.048	0.075	0.037	0.054	0.053	0.046	0.128*	0.073	0.694**	1.00						
12 Triglycerides (mg/dL)	-0.031	0.025	-0.170**	-0.015	-0.015	0.064	0.029	-0.003	-0.002	0.133**	0.100	1.00					
13 Cholesterol (mg/dL)	-0.060	-0.012	-0.052	0.074	0.038	0.090	-0.065	0.059	0.039	-0.001	-0.021	0.407**	1.00				
14 HDL (mg/dL)	-0.057	-0.006	0.225**	0.149**	0.166**	0.040	-0.213**	-0.001	-0.034	-0.076	-0.011	-0.316**	0.219**	1.00			
15 LDL (mg/dL)	-0.046	-0.014	-0.064	0.068	0.002	0.046	-0.050	0.042	0.040	-0.009	-0.061	0.228**	0.938**	0.130*	1.00		
16 Hemoglobin (g/dL)	0.263**	0.146*	-0.249**	-0.024	-0.289**	-0.084	0.205**	-0.018	0.080	-0.027	-0.062	0.161*	0.127*	-0.149**	0.131*	1.00	
17 Hematocrit (%)	0.212**	0.102*	-0.204**	0.005	-0.272**	-0.061	0.200**	-0.021	0.060	-0.045	-0.060	0.135**	0.122*	-0.129*	0.131*	0.950**	1.00

BMI, body mass index, WC, waist circumference, WHR, waist-hip ratio, HeartQoL: Heart Quality of Life Scale, MEDAS: Mediterranean Diet Adherence Screener, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, FBP: Fasting Plasma Glucose, HbA1c: glycated hemoglobin

*p<0,05; **p<0,01

Figure 1.

Evaluation of factors affecting HeartQoL and MEDAS with multiple linear regression models



Adjusted by age, gender, marital status, education status, residence place, and CVD duration.
HbA1c: glycated hemoglobin, MEDAS: Mediterranean Diet Adherence Screener, CVD: cardiovascular disease, HeartQoL: Heart Quality of Life Scale, WC: Waist circumference

4. DISCUSSION

Coronary artery disease is a serious problem, especially affecting adults over 35 years of age.[19] Research is ongoing to determine the most suitable treatment to prevent the development and progression of the disease. Treatment recommendations are largely based on the results of research to identify risk factors and protective factors.[20] This study investigated the effect of the Mediterranean diet, known as a protective factor, on the quality of life of adult coronary artery disease patients. Although MEDAS scores positively affected the scores of the quality of life scale, the majority of patients (62%) had low diet quality. The low diet quality of patients diagnosed with coronary artery disease has been confirmed in previous studies.[21,22] Patients are generally accustomed to a Western-style diet with high amounts of sugar, fat, and processed foods. [23] Their adaptation to the Mediterranean diet may not be easy, as it requires a lifestyle change. However, their adherence to a healthy diet can be improved by providing education and support. It has been reported that adherence to the Mediterranean diet is high even after the intervention is discontinued in patients who

follow a Mediterranean diet for a period of time with dietitian guidance.[24]

In this study, adherence to the Mediterranean diet positively affected the quality of life of the patients. Many previous studies have reported that Mediterranean diet components improve quality of life in patients with chronic diseases and healthy individuals with physical and mental health benefits.[25,26,27,28] The ability of the Mediterranean diet to modulate inflammation mediates the fight against chronic diseases and improves quality of life.[29] Another factor affecting the quality of life of patients, according to our study, is HbA1c level. Lower HbA1c levels are associated with higher quality of life. Diabetes was present in 34% of individuals with coronary artery disease, which could have influenced the findings. Nonetheless, while HbA1c is an important indicator of blood sugar control, high HbA1c levels have been associated with more severe disease and complications in patients who have non-diabetic coronary artery disease.[30] Consistent with our findings, a meta-analysis reported that glycemic control positively affects quality of life.[31] Furthermore, it is argued that glucose monitoring and glucose regulation in healthy individuals as well as patients may contribute to overall well-being.[32]

A diet rich in vegetables, fruits, olive oil, and legumes and limited in red meat is known to positively affect metabolic health and increase general well-being in heart patients.[7] Based on our results, adherence to the Mediterranean diet did not affect the blood pressure and lipid profile of the patients. However, previous studies have reported a vasoprotective effect of Mediterranean diet components on blood pressure and an association with an improved lipid profile.[33,34] The medications used by the patients may have prevented the detection of this effect of the Mediterranean diet. As an illustration, for lipid profiles, the potential advantages of the Mediterranean Diet may be obscured by statins, which are recognized to effectively reduce LDL cholesterol levels.[35,36] Based on our findings, hemoglobin values were higher in patients with high compliance with the Mediterranean diet. It has been previously reported that the Mediterranean diet increases iron absorption and retention.[37] Oleic acid, polyphenols, and vitamin C are dietary components that increase iron bioavailability.[38,39,40]

This study emphasizes the importance of a Mediterranean-style diet as a mediator of quality of life in coronary artery disease patients. However, it has some limitations. It does not explain causality because it has a cross-sectional design. Studies with longitudinal designs should be conducted to determine the direction of causality of the results. Being a single-center study limits the generalizability of the findings but increases the homogeneity of the sample. Especially due to the fact that all participants lived in the same geographical area, they are likely to have similar food accessibility. An additional weakness of the study is that there was no collection of data regarding the usage of medications. Antihypertensive, statin, and antidiabetic medicines can all have a direct impact on biochemical indicators like blood pressure, lipid profile, and HbA1c levels, as well as patient quality of life. This deficiency restricts the evaluation of dietary effects and hinders the management of possible confounding variables. Moreover, although the validated MEDAS scale was employed to evaluate adherence to the Mediterranean diet, a comprehensive analysis of dietary intake at the item level, concentrating on specific food components such as olive oil, seafood, legumes, and processed meats, was not conducted. This limits our capacity to identify which diet components most affect cardiovascular results and quality of life. Finally, the study contained self-reported outcomes, which could result in recollection and social desirability bias. However, collecting the data by face-to-face interviews by trained health professionals increased the accuracy of the information.

5. CONCLUSION

According to our results, adherence to a Mediterranean diet is associated with emotional and physical quality of life in coronary artery disease patients. Improvements in lipid profile and blood pressure regulation did not mediate this relationship. Further studies are needed to evaluate mediating factors. HbA1c levels

negatively affected quality of life. Glycemic control seems to be important for patients. Therefore, we recommend that glucose monitoring and control strategies be included in patients' treatment plans. Furthermore, patients should be made aware of the importance of a healthy diet to control disease progression and improve quality of life. In future studies, a more detailed assessment of dietary intake and analysis of individual nutrients will aid in determining which Mediterranean diet components have a greater impact on quality of life and contribute to the development of targeted nutritional recommendations in patients with coronary artery disease.

Article Information Form

Authors' Contribution

R.B, G.H., S.B and Y.E.Ö. designed the study. R.B and Y.E.Ö. collected the data. G.H. participated the manuscript writing. S.B. performed the statistical analysis. R.B., G.H, S.B. and Y.E.Ö. reviewed and edited the manuscript, approved the final version and agreed on the submission of the manuscript.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

The study was conducted in accordance with the guidelines specified in the Helsinki Declaration. Ethical permission was obtained from the Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee to conduct the research (No:11.12.2024/AEŞH-BADEK-2024-1234).

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

Copyright Statement

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Research Article

One-Year Retrospective Analysis of Adolescent Substance Use Treatment Clinic Cases

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Objective: This study aimed to examine the sociodemographic, clinical, psychosocial, and substance use characteristics of adolescents admitted to an outpatient Child and Adolescent Substance Addiction Treatment Center (ÇEMATEM) in Türkiye. It also compared adolescents who used a single substance with those who used multiple substances (polysubstance users).

Materials and Methods: The study retrospectively reviewed the medical records of 66 adolescents over a one-year period. Standardized assessment tools, including the Addiction Profile Index Adolescent Form (API-A) and the Substance Craving Scale (SCS), were used.

Results: The mean age of the sample was 15.97 ± 1.51 years. Polysubstance use was observed in 66.7% of the sample. Compared to monosubstance users, polysubstance users were more likely to be female, slightly older, and had significantly higher rates of prior hospitalization and suicide attempts. They also exhibited significantly higher levels of craving and addiction severity across all API-A domains. The most commonly used substances were alcohol, cannabinoids, stimulants, and methamphetamine. Half of the sample reported concurrent use of alcohol, stimulants, and cannabinoids.

Conclusions: Polysubstance use among adolescents is associated with greater psychosocial burden and clinical severity. These findings underscore the need for early identification and tailored interventions for this high-risk group.

Keywords: Suicide, Adolescent, Substance-related disorders, Risk factors, Cannabinoids, Polysubstance

1. INTRODUCTION

Adolescent substance use is a significant global public health concern. A large proportion of youth experiment with alcohol, tobacco, and illicit drugs during adolescence, and early initiation increases the risk of developing substance use disorders (SUDs) in adulthood.[1] In the United States, nearly one in ten adolescents meets criteria for a SUD annually,[2] while European surveys report that about 17% of 15–16-year-olds have used illicit drugs.[3] In Türkiye, national reports have noted a growing concern about adolescent substance use.[4,5] According to the 2019 Turkey Country Drug Report, the rate of cannabis use among young adults in the past year was 1.8%. The most commonly used illicit drug across the Turkish population was cannabis, followed by MDMA/ecstasy and cocaine. Illicit drug use was highest among males aged 15-34.[4] According to another national drug report from Türkiye, the first illicit substance that 85.6% of drug users tried was cannabis.[5] Studies surveying youth populations have found that the average age of first substance use falls between 13 and 15 years.[6]

One particularly high-risk pattern is polysubstance use, defined as the concurrent or sequential use of multiple substances. While less common than single-substance use, polysubstance use has been linked to more severe physical, psychological, and social consequences. A systematic review of latent class analyses found that adolescents in polysubstance use groups consistently reported higher levels of peer and parental substance use, academic problems, and psychiatric symptoms.[7] Longitudinal studies indicate that these adolescents are more likely to continue using substances into young adulthood and experience sustained impairment.[8]

Research also shows that polysubstance-using adolescents differ from their peers in several psychosocial domains. They often initiate use at an

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earlier age, experience more frequent psychiatric comorbidities, and have higher rates of trauma exposure and legal involvement.[9,10] Family-related factors, such as low parental monitoring, substance-using family members, and criminal behavior within the household, have been associated with increased risk.[11] Peer influence is powerful during adolescence and plays a central role in substance use behaviors.[11,12] Youth with substance-using peers are significantly more likely to engage in polysubstance use.[11] Conversely, high levels of parental disapproval and school engagement may serve as protective factors.[11,13]

Psychiatric comorbidities, particularly externalizing disorders like ADHD or conduct disorder, are prevalent among adolescents with substance use problems.[14] These conditions may increase impulsivity, emotional dysregulation, and risk-taking, all of which contribute to early and more hazardous patterns of use.[14,15] Studies from Türkiye report that a large proportion of treatment-seeking adolescents present with comorbid psychiatric symptoms, legal problems, school dropout, and family conflict.[16,17]

Despite increasing international evidence, research in treatment-seeking adolescent populations—particularly in low- and middle-income countries—remains limited. In Türkiye, outpatient clinics such as the Child and Adolescent Substance Addiction Treatment Centers (ÇEMATEM) provide specialized care for youth with substance-related problems. While a few clinical studies have examined the sociodemographic and clinical characteristics of ÇEMATEM patients, most have not differentiated between monosubstance and polysubstance users or examined their unique needs, such as treatment or psychosocial support.[16,18]

For example, a study of 1,969 participants found that more than 60% of adolescents in treatment engaged in polysubstance use. The study also reported that marijuana was the most commonly used substance.[18] More recent findings confirm that mixed-substance use disorders are the most frequent diagnosis among ÇEMATEM referrals, with significant psychosocial impairments reported across domains.[16] Similarly, another ÇEMATEM study found that 80% of hospitalized adolescents used multiple substances. Self-harm and conduct disorder were also highly prevalent.[17] Recent studies from different regions of Türkiye consistently highlight high rates of comorbid psychiatric conditions, early substance initiation, and poor school engagement.[16,19] However, despite this growing body of literature, comparative analyses between mono- and polysubstance users in outpatient-samples remain scarce.

The present study aims to address this gap by retrospectively examining one-year clinical data from adolescents admitted to a ÇEMATEM outpatient clinic in Türkiye. The study examines the sociodemographic, psychosocial, clinical, and substance use characteristics of this population and compares key variables between monosubstance and polysubstance users. We hypothesized that polysubstance users would show more severe addiction profiles and greater psychosocial burden than monosubstance users.

2. METHOD

2.1. Sample

The present study retrospectively reviewed the outpatient clinic records from a ÇEMATEM in Türkiye. One year of medical records from adolescents who presented to the ÇEMATEM outpatient clinic between June 2023 and May 2024 was included in the study. Information on the adolescents' sociodemographic characteristics, clinical data, and substance use profiles was systematically collected. The study was approved by the Scientific Research Ethics Committee of Sakarya University Faculty of Health Sciences (Approval No: 2024/75).

2.2. Measurements

Addiction Profile Index Adolescent Form (API-A): The Addiction Profile Index is a validated instrument designed to assess the extent and severity of addiction. The instrument consists of 25 items across five subscales and is administered to adolescents aged 15–18 with a history of alcohol or illicit substance use. It includes six subscores: substance use characteristics, diagnosis, impact on life, desires, motivation, and

a total score. The scale's Cronbach's alpha coefficient is 0.87.[20]

Substance Craving Scale (SAS): This scale is an adapted version of the Penn Alcohol Craving Scale for addictive substance users. The scale comprises five items, each scored from 0 to 6, yielding a total score ranging from 0 to 30. A Turkish adaptation of the scale has been developed. The Cronbach's alpha coefficient for the entire scale was 0.84. Corrected item-total correlation coefficients ranged from 0.75 to 0.82.[21]

2.3. ÇEMATEM procedures

There is a standardized assessment protocol for all adolescents presenting to the ÇEMATEM outpatient clinic. An addiction-trained psychologist (counselor) evaluates the adolescent. Sociodemographic information, individual and family psychiatric history, clinical status, history of suicide attempts, and characteristics related to substance use are recorded on a structured assessment form. The adolescent is interviewed individually using motivational interviewing techniques by a counselor. Following this process, the API-A and SCS, standard assessment tools for adolescent substance use, are administered. Family interviews are also conducted with the adolescent's parents and documented using standardized forms. Once these forms and assessment scales are completed, they are reviewed by the center's child and adolescent psychiatrist. The psychiatrist conducts semi-structured interviews and administers additional assessment tools to evaluate psychiatric comorbidities. All follow-up and motivational interviews are conducted by consultants under the supervision of the child and adolescent psychiatrist.

2.4. Statistical analysis

The normality of continuous variables was assessed based on skewness and kurtosis values. Descriptive statistics were presented as frequencies, percentages, means, and standard deviations. Group comparisons for normally distributed variables were conducted using the Student's t-test. Chi-square tests were employed to analyze relationships between categorical variables. Statistical significance was set at $p < 0.05$, and 95% confidence intervals were reported where appropriate. All analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (Released in 2020; IBM Corp., Armonk, NY, USA).

3. RESULTS

Over the course of one year, 66 adolescents presented to the ÇEMATEM outpatient clinic a total of 280 times. Regular outpatient follow-up was provided for all 66 patients included in the study. The average number of applications to the polyclinic in a year was 4.24±4.22, and the most frequently applied patient applied 18 times. The sample consisted of 66 adolescents with a mean age of 15.97 years (SD = 1.51). The mean age of first cigarette use was 11.87 years (SD = 2.14), and the average number of cigarettes smoked daily was 18.38 (SD = 12.40). The mean age of first substance use was 14.46 years (SD = 1.65), and participants had an average of 2.25 siblings (SD = 1.44).

Of the participants, 57.6% (n = 38) were male and 42.4% (n = 28) were female. In terms of education, 33.3% (n = 22) were primary school graduates and 66.7% (n = 44) were high school students. Clinically, 34.8% (n = 23) had been hospitalized for alcohol or substance use, 56.1% (n = 37) had a history of running away from home, and 43.9% (n = 29) had attempted suicide. Additionally, 22.7% (n = 15) had experienced institutional care under state protection, 48.5% (n = 32) had a criminal history, 53.0% (n = 35) had a family history of alcohol or substance use, and 40.9% (n = 27) had a family history of criminal behavior. Detailed sociodemographic and clinical variables are presented in Table 1.

Table 1.

Sociodemographic and clinical characteristics

Variables	Descriptive (n = 66)
	Mean (SD)
Age (year)	15.97 (1.51)
Age of first cigarette use (year)	11.87 (2.14)
Average number of cigarettes smoked daily	18.38 (12.40)
Age of first substance use (year)	14.46 (1.65)
Siblings	2.25 (1.44)
	n (%)
Gender	
Male adolescent	38 (57.6)
Female adolescent	28 (42.4)
Education	
Primary school graduate	22 (33.3)
High school student	44 (66.7)
Hospitalizations for alcohol/substance use	23 (34.8)
Running away from home	37 (56.1)
Suicide attempts	29 (43.9)
Institutional care under state protection	15 (22.7)
Criminal history	32 (48.5)
Family history of alcohol/substance use	35 (53.0)
Family history of criminal history	27 (40.9)

SD: Standard deviation.

Among the participants, methamphetamine was used by 53.0% (n = 31), with the majority (58.1%) using it once or more per week. Ecstasy was used by 42.4% (n = 28), though most of these individuals (75.0%) used it less than once per week. Stimulant use (any type) was reported by 57.6% (n = 38), with 60.5% of these using at least weekly. Cannabis use was highly prevalent at 74.7% (n = 49), with 42.9% of users reporting weekly or more frequent use. Synthetic cannabinoids were used by 60.6% (n = 40), and two-thirds of them (65.0%) used at least once per week. When considering any cannabinoid use (i.e., cannabis or synthetic cannabinoids), 75.8% (n = 50) reported use, evenly divided between low- and high-frequency users. Alcohol use was reported by 81.8% (n = 54), with 37.0% using weekly or more. Pregabalin was used by 24.2% (n = 16), equally divided between frequent and infrequent users. Volatile substance use (e.g., thinner, bally, lighter fluid) was less common at 34.8% (n = 23), with 78.3% using it less than once per week. Importantly, polysubstance use was observed in 66.7% (n = 44) of participants, and the majority of these (75.0%) reported using multiple substances at least once per week. Substance use characteristics in the last year are shown in Table 2.

Table 2.

Substance use characteristics in the last year

Variables	Less than once per week	Once or more per week	Total
	n (%)	**n (%)**	**n (%)**
Methamphetamine use	13 (41.9)	18 (58.1)	31 (53.0)
Ecstasy use	21 (75.0)	7 (25.0)	28 (42.4)
Stimulant use (any)	15 (39.5)	23 (60.5)	38 (57.6)
Cannabis use	28 (57.1)	21 (42.9)	49 (74.7)
Synthetic cannabinoid use	14 (35.0)	26 (65.0)	40 (60.6)
Any cannabinoid use	25 (50.0)	25 (50.0)	50 (75.8)
Alcohol use	34 (63.0)	20 (37.0)	54 (81.8)
Pregabalin use	8 (50.0)	8 (50.0)	16 (24.2)
Volatile substance use	18 (78.3)	5 (21.7)	23 (34.8)
Polysubstance use	11 (25.0)	33 (75.0)	44 (66.7)

[a] Thinner, bally, lighter fluid

Polysubstance users were significantly more likely to be female compared to monosubstance users (p = .022). Hospitalizations due to alcohol or substance use were significantly more frequent among polysubstance users (52.3%) than monosubstance users (13.6%) (p = .002). Suicide attempts were also more common in the polysubstance group (54.5%) compared to the monosubstance group (22.7%) (p = .014).

Although not reaching statistical significance, polysubstance users showed higher rates of running away from home (34.1% vs. 59.1%, p = .053), criminal history (43.2% vs. 68.2%, p = .055), and institutional care history (72.7% vs. 86.4%, p = .213) compared to monosubstance users. No significant group differences were observed in educational level, family history of substance use, or family criminal history (p > .05 for all). Table 3 presents a detailed comparison of clinical and psychosocial variables between the two groups.

Table 3.

Comparison of clinical and psychosocial variables between mono-substance and polysubstance users

Variables	**Monosubstance use (n = 22)**	**Polysubstance use (n = 44)**	***Statistics***	***p***
	n (%)	**n (%)**	χ^2	
Gender			5.242	**.022**
Male adolescent	17 (77.3)	21 (47.7)		
Female adolescent	5 (22.7)	23 (52.3)		
Education			.034	.854
Primary school graduate	7 (31.8)	15 (34.1)		
High school student	15 (68.2)	29 (65.9)		
Hospitalizations for alcohol/substance use			9.170	**.002**
Present	3 (13.6)	23 (52.3)		
No	19 (86.4)	21 (47.7)		
Running away from home			3.753	.053
Present	13 (59.1)	15 (34.1)		
No	9 (40.9)	29 (65.9)		
Suicide attempts			6.028	**.014**
Present	5 (22.7)	24 (54.5)		
No	17 (77.3)	20 (45.5)		
Institutional care under state protection			1.553	.213
Present	19 (86.4)	32 (72.7)		
No	3 (13.6)	12 (27.3)		
Criminal history			3.670	.055
Present	15 (68.2)	19 (43.2)		
No	7 (31.8)	25 (56.8)		
Family history of alcohol/substance use			1.507	.220
Present	12 (54.5)	17 (38.6)		
No	10 (45.5)	27 (61.4)		
Family history of criminal history			1.968	.161
Present	15 (68.2)	22 (50.0)		
No	7 (31.8)	22 (50.0)		

Group comparisons revealed several significant differences between adolescents who used a single substance and those who engaged in polysubstance use. The mean age of polysubstance users was significantly higher than that of monosubstance users (p = .041). Although no significant group differences were found in the age of first substance use (p = .079) or age of first cigarette use (p = .184), polysubstance users reported significantly higher craving levels as measured by the Substance Craving Scale (p = .012).

Regarding API-A subscales, polysubstance users scored significantly higher across all domains. Specifically, they reported higher scores in substance use characteristics ($p < .001$), number of diagnoses ($p < .001$), impact on life ($p < .001$), craving ($p < .001$), and motivation ($p = .024$). Furthermore, the total API-A score was significantly higher in the polysubstance group compared to the monosubstance group ($p = .004$). Although polysubstance users also reported a higher average number of cigarettes smoked per day, this variable was not statistically significant. Table 4 provides a detailed comparison of substance use profiles between groups.

Table 4.

Comparison of substance use profiles between monosubstance and polysubstance users

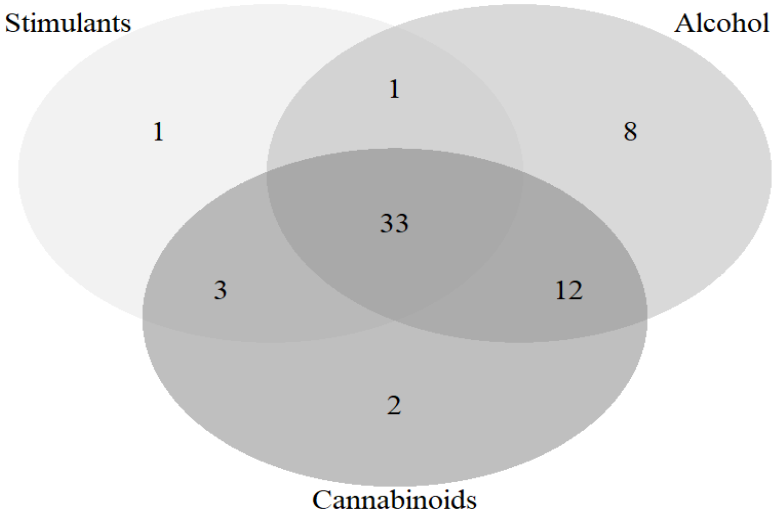
Variables	**Mono substance use**	**Poly substance use**	***Statistics***	***p***
	Mean (SD)	**Mean (SD)**	***t***	
Age (year)	15.43 (1.48)	16.23 (1.47)	-2.088	**.041**
Age of first substance use (year)	14.33 (3.06)	14.48 (1.50)	-0.140	.079
Average number of cigarettes smoked daily	17.05 (9.95)	19.00 (13.46)		
Age of first cigarette use (year)	12.40 (2.11)	11.62 (2.13)	1.344	.184
Substance craving scale	8.29 (5.31)	15.80 (8.80)	-2.141	**.012**
API-A				
Substance use characteristics	0.75 (0.67)	3.15 (1.34)	-6.453	**<.001**
Diagnosis	3.82 (3.71)	13.29 (5.06)	-5.714	**<.001**
Impact on life	5.09 (4.64)	15.76 (6.72)	-4.887	**<.001**
Craving	1.27 (1.42)	2.38 (1.35)	-2.342	**<.001**
Motivation	1.55 (1.69)	3.41 (0.92)	-3.488	**.024**
Total	4.81 (3.32)	12.66 (3.56)	-7.826	**.004**

SD: Standard deviation; API-A: Addiction Profile Index Adolescent Form.

Figure 1 illustrates the overlap between stimulant, alcohol, and cannabinoid users. Of the 66 adolescents, 38 reported using stimulants, 54 used alcohol, and 50 used cannabinoids within the past year. A substantial proportion reported overlapping use, with 34 individuals using both stimulants and alcohol, 36 using both stimulants and cannabinoids, and 45 using both alcohol and cannabinoids. Notably, 33 participants reported using all three substance categories, indicating a high level of polysubstance use within the sample.

Figure 1.

Distribution of alcohol and substance users



4. DISCUSSION

This study examined adolescents presenting to an outpatient ÇEMATEM clinic over one year, focusing on the differences between single and polysubstance users. The majority of the sample (66.7%) were polysubstance users. Compared to monosubstance users, polysubstance users were more likely to be female and slightly older. Polysubstance users also had significantly higher rates of prior hospitalizations and suicide attempts. Their substance craving and addiction severity scores were higher across all domains of the API-A. Although both groups started substance use at similar ages, polysubstance users showed more severe psychosocial profiles. The most commonly used substances were alcohol, cannabis, synthetic cannabinoids, and stimulants. Notably, 50% of the adolescents reported concurrent use of stimulants, alcohol, and cannabinoids within the past year.

Our findings align with international literature, which has consistently shown that polysubstance-using adolescents tend to experience worse outcomes than their monosubstance-using peers.[22] Previous studies have demonstrated that polysubstance use in youth is associated with earlier onset of substance use, greater psychiatric comorbidity, and a higher likelihood of continuing substance use into adulthood.[7,8] Similar to our results, these studies also found that polysubstance users are more likely to suffer from externalizing behaviors, legal issues, and mental health problems such as depression and anxiety.[23] In our cohort, polysubstance users had significantly higher rates of prior suicide attempts. This highlights the significant negative impact of co-occurring substance use on mental health. Our results also confirm previous research showing that polysubstance users tend to have higher craving levels, indicating a more entrenched addiction. [24]

In contrast to previous studies that frequently reported higher rates of polysubstance use among male adolescents[25,26], 52% of polysubstance users in our study were female adolescents. This finding is consistent with recent data from Türkiye and globally showing a narrowing gender gap.[10,27,28] A study in the ÇEMATEM sample found that 89.8% of females and 77.8% of males used more than one substance, indicating a relatively higher prevalence in females.[28] Similarly, another recent study reported that polysubstance use was statistically significantly more common in females (48.5%) than in males (27.8%).[29] In contrast, although one study reported a slightly lower prevalence (41%)[16], another found that all adolescents in the sample used more than one substance, with marijuana (72%) and methamphetamine (34%) being the most common[19]. This shift underscores the importance of incorporating gender-specific considerations into prevention and intervention strategies, as female adolescents may encounter unique psychosocial pressures related to substance use.

Locally, our findings support previous research from Türkiye indicating that polysubstance use is common among treatment-seeking adolescents. For example, previous studies have also found cannabis to be the most frequently used substance, a trend observed in our sample.[16,18] This trend is mirrored in other national studies reporting high rates of polysubstance use among both genders: 81.5%[28], 80%[17], and 60.2%[18]. Furthermore, our finding that 60% of polysubstance users had a family history of substance use and 49% had a criminal history is consistent with previous national studies showing that familial and environmental factors play a significant role in adolescent substance use.

In line with these findings, our study observed significantly higher API-A and SAS scores among polysubstance users, reflecting more severe addiction profiles and greater psychosocial burden. These results underscore the clinical necessity of distinguishing between mono- and polysubstance users in treatment planning, particularly given the elevated levels of craving, impairment, and comorbidities in the latter group.

4.1. Strengths and limitations

A major strength of this study is its comprehensive assessment of adolescents using standardized tools in a clinical setting. The inclusion of both male and female participants, as well as a range of substance types, enhances the study's generalizability. Distinguishing between mono-

and polysubstance users also enabled the identification of specific clinical needs.

However, the study has limitations. The retrospective design prevents causal conclusions. As the data were drawn from a single clinical site, findings may not be generalizable to national populations. The small sample size limits generalizability. Self-report and chart-based data are subject to reporting bias. Additionally, psychosocial variables such as socioeconomic status, peer influence, and trauma history were not included. Polysubstance use was defined based on past-year use, which may have overlooked the frequency and context of substance consumption.

4.2. Future directions

Future research should focus on longitudinal studies to track the long-term outcomes of adolescents with polysubstance use. Understanding how these adolescents fare in terms of mental health, educational attainment, and social integration over time would provide valuable insights into the persistence of substance use and related impairments. In addition, qualitative studies exploring the experiences and motivations of adolescents who engage in polysubstance use could inform more targeted prevention and intervention strategies.

5. CONCLUSION

This study highlights the significant psychosocial and clinical burden experienced by adolescents engaged in polysubstance use. Polysubstance users tend to have more severe addiction profiles and greater psychosocial impairment compared to their monosubstance-using peers. These findings underscore the need for integrated, intensive interventions that address both substance use and co-occurring mental health issues. Policymakers and clinicians should prioritize early identification and tailored interventions for polysubstance-using adolescents to mitigate the long-term impact of substance use on their lives.

Article Information Form

Authors' Contribution

Conception: MTT; Design: MTT; Supervision: MTT, ES; Materials: MTT, ES; Data collection: MTT, ES; Analysis: MTT; Literature Review: MTT; Writing: MTT; Critical Review: MTT, ES.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

The study was approved by the Scientific Research Ethics Committee of Sakarya University Faculty of Health Sciences on April 14, 2024 (Approval No: 2024/75).

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

Copyright Statement

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Research Article

Comparison of PPD and IGST Sensitivity in Latent Tuberculosis Assessment (Cross-sectional Study)

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Objective: Purified Protein Derivative (PPD) and Interferon Gamma Release Assay (IGRA) were performed on patients with ankylosing spondylitis and rheumatoid arthritis who were planned to initiate immunosuppressive treatment. The aim was to determine which test would be more appropriate for diagnosing latent tuberculosis (TB) and to evaluate the sensitivity and specificity of PPD and IGRA tests in latent TB diagnosis.

Materials and Methods: Forty-seven patients with rheumatoid arthritis and 27 patients with ankylosing spondylitis were included in the study. All patients underwent both PPD and QuantiFERON-TB Gold Plus testing. Latent TB was defined as close contact with active tuberculosis infection and/or presence of suspicious fibrotic/calcified lesions on chest radiography without active tuberculosis infection.

Results: The QuantiFERON-TB Gold Plus test demonstrated a specificity of 96.6% and sensitivity of 73.3%, while the tuberculin skin test (TST) showed a specificity of 25.4% and sensitivity of 93.3%. A significant correlation was found between the QuantiFERON-TB Gold Plus test and latent tuberculosis criteria ($p<0.001$, $r=0.562$), whereas no statistically significant correlation existed between TST and latent tuberculosis criteria ($p=0.309$, $r=0.120$).

Conclusion: The IGRA test demonstrated higher specificity and sensitivity compared to TST. Given the lower specificity of TST observed in our study compared to other studies, the IGRA test may be recommended for patients planned to receive prophylactic treatment.

Keywords: PPD, BCG, IGRA, Latent tuberculosis, Prophylaxis

1. INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*M.tuberculosis*) that can manifest at any stage of life. While it predominantly affects the pulmonary system, it has the potential to involve all bodily organs and systems. The World Health Organization (WHO) has documented tuberculosis incidence and prevalence rates in Türkiye as 18 per 100,000 and 22 per 100,000 individuals, respectively.[1]

Tumor necrosis factor-alpha (TNF-α) serves as a critical proinflammatory cytokine that significantly contributes to the immunological response against *Mycobacterium tuberculosis*, maintaining the structural integrity of granulomas following infection.[2] Disease-modifying antirheumatic drugs (DMARDs) such as infliximab, etanercept, and adalimumab function as TNF-α antagonists used in the therapeutic management of rheumatic diseases.[3] The administration of anti-TNF agents may precipitate active tuberculosis following organism invasion or incite reactivation of latent bacilli within granulomas.[4] Similarly, conventional DMARDs used in rheumatic conditions, including methotrexate, sulfasalazine, and leflunomide, can also induce tuberculosis reactivation.[5]

The tuberculin skin test (TST/PPD) has served as an established immunological diagnostic approach for many years. It measures the diameter of induration resulting from a delayed-type hypersensitivity response to mycobacterial protein derivatives in subjects previously exposed to the bacillus. This test is administered on the inner forearm and evaluated after 72 hours. PPD is widely used globally due to its ease of application and low cost. Mycobacteria

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are potent inducers of interferon-gamma secretion from Th1 cells. The interferon-gamma release assay (IGRA), which has emerged as a pivotal diagnostic instrument in contemporary practice, quantifies interferon-gamma specifically secreted in response to *M. tuberculosis* antigens in vitro. Unlike PPD, IGRA employs ESAT-6 (early secretory antigenic target-6) and CFP-10 (culture filtrate protein-10) antigens.[6–8]

PPD may cross-react with the Bacillus Calmette-Guérin (BCG) vaccine and is affected by non-tuberculous mycobacteria, producing false-positive results that diminish diagnostic specificity.[2] IGRA can largely differentiate true tuberculosis infection from vaccine effects in BCG-vaccinated individuals and non-tuberculous mycobacterial infections.

Latent TB screening should be performed in patients for whom DMARD therapy is planned. No universally accepted gold standard test exists for identifying latent TB. PPD and IGRA are used to determine whether patients should receive TB prophylaxis (isoniazid 300 mg for 9 months) based on test results. However, it remains unclear which test provides better prediction for latent TB. While some studies have shown no significant difference, others have demonstrated that IGRA detects latent TB better than TST in psoriasis patients.[9,10]

This research assessed the sensitivity and specificity of PPD and IGRA for detecting latent TB in ankylosing spondylitis and rheumatoid arthritis patients to determine which test would be more appropriate for these diseases where DMARD therapy is planned.

2. MATERIALS AND METHODS

Forty-seven patients with rheumatoid arthritis and 27 patients with ankylosing spondylitis for whom DMARD therapy was planned were included in the study. Routine posteroanterior (PA) chest X-rays and PPD tests were performed on all patients. Additionally, IGRA was conducted in the laboratory environment for this study. Age, gender, number of BCG scars, documented history of contact with active tuberculosis infection, presence of suspicious fibrotic or calcified lesions on chest radiography, TST results, and IGRA results were recorded for all patients.

Exclusion criteria included age parameters (individuals younger than 18 years or older than 70 years), pregnancy, active tuberculosis infection, and history of prior anti-tuberculosis treatment. Written informed consent was obtained, and the research protocol received approval from the Ethics Committee of the Faculty of Medicine at Balıkesir University (2017/67).

Latent tuberculosis was defined as a history of close contact with individuals exhibiting active tuberculosis infection and/or presence of fibrotic or calcified lesions on chest X-ray indicative of prior infection, without signs of active tuberculosis. The identification of at least one of these criteria was considered positive.

For the Tuberculin Skin Test (TST), purified protein derivative (0.1 mL) was administered using the Mantoux technique. Induration measurement at the TST site was conducted 72 hours post-administration. An induration measurement of ≥5 mm was classified as positive.[11]

The QuantiFERON-TB Gold Plus Test was employed as the IGRA. This test utilized 4 tubes with 1 mL of blood drawn into each: Nil tube (gray cap, white ring), TB1 tube (green cap, white ring), TB2 tube (yellow cap, white ring), and Mitogen tube (purple cap, white ring). All tubes underwent incubation at 37°C for 16-24 hours. Following incubation, samples were centrifuged at 2000-3000 Relative Centrifuge Force (RCF) for 15 minutes. Optical density values were computed using a primary wavelength of 450 nm and reference wavelength of 620-650 nm to determine Interferon Gamma (IFN-γ) concentrations. Results were considered positive (M. tuberculosis infection likely) when IFN-γ level was ≥0.35 IU/mL, and negative when IFN-γ level was <0.35 IU/mL based on the Mitogen-Nil difference value. The study was conducted in accordance with ethical principles outlined in the Declaration of Helsinki.

Ethical Approval in the conducted research, informed consent was acquired from all participants involved in the study, adhering to the

principles articulated in the Declaration of Helsinki. Authorization from the Ethics Committee was secured from the Clinical Research Ethics Committee of Balıkesir University Medical Faculty, with the resolution dated 26.07.2017 and assigned the number 67.

2.1. Statistical analysis

Data were analyzed using SPSS version 23.0. Normal distribution assessment was conducted using the Kolmogorov-Smirnov test. Chi-square and Pearson correlation tests were implemented for statistical evaluation. Interrelationships among tests were assessed using Pearson correlation coefficient. Sensitivity and specificity for both IGRA test and TST were computed. Categorical variables were represented as percentages with total patient numbers (n). A p-value <0.05 was considered statistically significant.

3. RESULTS

A total of 47 cases with rheumatoid arthritis and 27 patients with ankylosing spondylitis were included in the study. Twenty-one patients (28.4%) were male and 53 (71.6%) were female, with a mean age of 49.82±13.16 years.

The demographic attributes of the patient cohort are delineated in Table 1. A weak positive relationship was detected between BCG scar number and TST results (p=0.02, r=0.271). The Quantiferon-TB Gold Plus assay was positive in 9 of 44 patients (20.5%) with 1 BCG scar and in 3 of 18 patients (16.6%) with 2 BCG scars. Conversely, it returned negative results for all 9 individuals with 3 BCG scars. No statistically significant association was identified between BCG scar number and Quantiferon-TB Gold assay results (p=0.128). The results of the testing are presented in Table 2.

Table 1.

Demographic characteristics of the patients included in the study

Demographic characteristics	n (%)
Gender, Male/Female	21 (28.4) / 53 (71.6)
Age, mean years	49.82±13.16
Rheumatoid Arthritis	47 (63.5)
Ankylosing Spondylitis	27 (36.5)
BCG Scar	
Present	71 (96)
Absent	3 (4)
Latent Tb¶	15(20.3)
Non-Latent Tb	59(79.7)

¶Patient diagnosed with latent Tb according to clinical criteria.

Table 2.

Distribution of patients based on BCG scar count in IGRA and TST

		BCG Scar Count				
		Absent n (%)	1 n (%)	2 n (%)	3 n (%)	Total n (%)
TST	positive	2 (3.5)	30 (51.7)	17 (29.3)	9 (15.5)	58 (100)
	negative	1 (6.25)	14 (87.5)	1 (6.25)	0 (0)	16 (100)
IGRA	positive	1 (7.7)	9 (69.3)	3 (23)	0 (0)	13 (100)
	negative	2 (3.3)	35 (57.4)	15 (24.6)	9 (14.7)	61 (100)

The Quantiferon-TB Gold Plus assay yielded negative results in 12 of 16 subjects with negative TST results (<5 mm) and positive results in 9 of 58 individuals with positive TST results (≥5 mm) (refer to Table 3). Statistical analysis revealed no significant correlation between TST and Quantiferon-TB Gold Plus assay (p=0.547). Moreover, no significant correlation was established between TST and latent tuberculosis criteria (p=0.309, r=0.120). Conversely, a moderate correlation was identified between Quantiferon-TB Gold Plus assay and latent tuberculosis criteria (p<0.001, r=0.562).

Table 3.

Distribution of IGRA test and TST results in all patients

		IGRA		
		Positive	Negative	Total
TST, n (%)	Positive	9 (69.2)	49 (80.3)	58 (78.4)
	Negative	4 (30.8)	12 (19.7)	16 (21.6)
Total, n (%)		13 (100)	61 (100)	74 (100)

In our study, 15 (20.3%) patients had latent TB findings. In the present study, according to the latent tuberculosis criteria, the specificity of the Quantiferon-TB Gold Plus assay was determined to be 96.6%, while its sensitivity was recorded at 73.3%. In contrast, the specificity of the Tuberculin Skin Test (TST) was found to be 25.4%, with a sensitivity of 93.3%. The sensitivity and specificity metrics for both the TST and the Quantiferon-TB Gold Plus test across all patients are detailed in Table 4.

Table 4.

Specificity and sensitivity of the Quantiferon-TB Gold test and TST in all patients

		Latent TB Present	Latent TB Absent
TST	Positive	14	44
	Negative	1	15
		Sensitivity 93.3%	Specificity 25.4%
IGRA	Positive	11	2
	Negative	4	57
		Sensitivity 73.3%	Specificity 96.6%

Latent TB criteria: Patients without active tuberculosis infection, recent close contact with an active tuberculosis infection in the past year, or suspicious fibrotic/calcified lesions on chest X-ray. (The presence of at least one of these criteria was considered positive.)

4. DISCUSSION

TST specificity in our study was lower than in other studies. Consistent with other research, Quantiferon-TB Gold assay specificity and sensitivity were higher than TST. The Quantiferon-TB Gold assay may be recommended instead of TST for patients planned to start prophylactic treatment.

In Türkiye, IGRA is recommended for patients suspected of tuberculosis infection or those who are immunosuppressed or planning immunosuppressive therapy with negative TST (rapel).[12] A positive TST result may lead to misdiagnosis of latent tuberculosis infection, resulting in unwarranted treatment regimens. Consequently, in countries where BCG vaccine is routinely recommended, especially for low-risk pediatric populations, it is advisable to corroborate positive TST findings with interferon-gamma release assays (IGRA) to reduce false-positive results.[13]

IGRA test results may yield negative outcomes in individuals with positive TST. This can be attributed to exposure to non-tuberculous mycobacteria.[14] Lewinsohn et al. indicated that BCG vaccination does not influence IFN-gamma response.[15] Brock et al. determined that prior vaccination does not impact Quantiferon-TB Gold Plus test results.[10] In our study, no statistically significant correlation was identified between BCG scar quantity and Quantiferon-TB Plus test results. Consequently, we propose that Quantiferon-TB Gold Plus test can be employed confidently in rheumatic disease patients preparing to initiate TNF-alpha blocking agents, as no relationship exists between test outcomes and BCG scar number.

A cross-sectional study revealed poor concordance between Quantiferon-TB Gold Plus and TST.[16] Another study documented significant agreement between TST and Quantiferon-TB Gold Plus assay.[17] Among 150 individuals with rheumatic conditions, positive results for TST and

Quantiferon-TB Gold Plus assay were observed in 27 (18%) and 14 (9.8%) participants, respectively.[18] Chang et al. assessed Quantiferon-TB Gold Plus assay, TST, and chest radiography in 107 patients (61 with AS, 46 with RA) receiving TNF-α inhibitors for latent tuberculosis infection identification. Correlation was found between tests. Additionally, 34% of patients had positive TST results, while 66% had negative results.[19]

In our study, TST was positive in 58 patients and negative in 16 patients, while IGRA was positive in 13 patients and negative in 61 patients. No notable correlation was detected between TST and Quantiferon-TB Gold Plus assay. The lack of relationship between TST and Quantiferon-TB Gold Plus assay may be due to our small study population. Inconsistency between latent tuberculosis infection screening test results in rheumatic patients has been detected. The reason for this inconsistency varies depending on country endemic status and underlying disease.[20]

In our study, TST was positive in 58 patients and negative in 16 patients, while IGRA was positive in 13 patients and negative in 61 patients. No notable correlation was detected between the Tuberculin Skin Test (TST) and the Quantiferon-TB Gold Plus assay. The lack of relationship between TST and Quantiferon-TB Gold Plus assay may be due to the small size of our study population. Inconsistency between the screening test results for latent tuberculosis infection in rheumatic patients has been detected. The reason for this inconsistency varies depending on country endemic status and underlying disease.[20]

Different sensitivity and specificity rates for TST have been reported in literature. Mrozek et al. demonstrated that Quantiferon-TB Gold Plus test had better sensitivity compared to TST (79% vs. 69%)[6]. Quantiferon-TB Gold Plus test specificity and sensitivity for tuberculosis infection were found to be 98% and 90%, respectively.[21] In a separate prospective investigation, Quantiferon-TB Gold Plus assay specificity was 91%, whereas TST specificity was 78.6%.[22]

Assessing sensitivity and specificity in latent tuberculosis infection diagnosis presents significant challenges due to the absence of a definitive gold standard. In another Turkish study on the same patient group, Quantiferon-TB Gold Plus specificity was 85.7% and sensitivity 73.9%, while TST specificity and sensitivity were 60.3% and 47.8%, respectively.[23] Similarly, Mrozek et al. demonstrated that the Quantiferon-TB Gold Plus assay showed superior sensitivity compared to the TST.[6] In a similar context, our investigation demonstrated that Quantiferon-TB Gold Plus assay displayed enhanced specificity compared to TST (96.6% vs. 25.4%). It has been emphasized that antigens used in IGRA tests are almost exclusively expressed by the *M. tuberculosis* complex, with exceptions of *Mycobacterium kansasii*, *Mycobacterium szulgai*, *Mycobacterium marinum*, and *Mycobacterium riyadhense*, making IGRA less likely to be confused with prior BCG vaccination and/or exposure to non-tuberculous mycobacteria (NTM).[24] For these reasons, TST test specificity in our study may have been low.

In a contemporary meta-analysis, IGRAs demonstrated superior specificity compared to TST. The negative predictive value (NPV) of IGRA tests in patients with active tuberculosis who had latent tuberculosis infection was high, and IGRA tests ability to predict that individuals with negative test results would not develop disease was better. Furthermore, IGRA assessments demonstrated superior predictive capability for progression to active disease compared to TST.[24]

In immunosuppressed RA patients, sensitivity for latent tuberculosis infection diagnosis was higher with Quantiferon-TB Gold Plus test compared to TST.[24]

A limitation of our research is the lack of a definitive gold standard assay for latent tuberculosis detection.

In this study, latent tuberculosis was defined as a history of close contact with individuals exhibiting active tuberculosis infection and/or the presence of fibrotic or calcified lesions on chest X-ray indicative of prior infection, without signs of active tuberculosis. This definition was made based on previous

studies.[23,25] To date, no test can directly identify viable *Mycobacterium tuberculosis* presence in humans. Latent tuberculosis infection diagnosis remains indirect and is based on detecting host immune responses to *Mycobacterium tuberculosis*-specific antigens, assuming such responses indicate prior bacterial exposure. The TST and IGRA tests are primary tools for LTBI diagnosis. However, both methods are immunological and do not provide direct evidence of *Mycobacterium tuberculosis* bacilli presence or viability. Therefore, latent tuberculosis evaluation should be performed together with clinical and radiological assessment.[25]

5. CONCLUSION

The implementation of tuberculosis screening is obligatory for individuals diagnosed with rheumatic disorders who are intending to undergo therapy involving TNF-α blockers. In our study, the IGRA test showed higher specificity and sensitivity compared to TST, consistent with other studies. As the specificity of the TST in our study was found to be lower than in other studies, despite the higher cost, we recommend the use of the IGRA test for patients in whom prophylactic treatment is planned. In Türkiye, prophylactic treatment is initiated based on TST results. Therefore, we believe that by reducing false positives, the number of patients receiving prophylaxis could also decrease. New prospective studies may show that prophylaxis is not necessary for patients with false-positive TST diagnoses.

Article Information Form

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Authors' Contribution

Concept (FE, NS, NŞ), Design (FE, NS), Data Collection and/or Processing (FE, NS, MÇ, HÇ, KBB), Analysis and/or Interpretation (FE, NS).

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

Ethics Committee permission (without specifying the institution from which it was obtained) was obtained from Balıkesir University Medical Faculty Clinical Research Ethics Committee with the decision number 67 on 26.07.2017.

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

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Research Article

Prognosis Symptoms, Quality of Life and Comorbidity Relationship with Cough in Patients with Idiopathic Pulmonary Fibrosis

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Objective: Cough is one of the most frequent symptoms in patients with idiopathic pulmonary fibrosis (IPF). The aim of this study was to investigate whether there was any difference with respect to quality of life, depression, sleep disturbance and reflux symptoms between IPF patients with and without cough symptom.

Study Design: Cross-sectional study

Materials and Methods: Patients with IPF who were admitted to outpatient clinic were divided into two groups according to the Visual Analog Scale (VAS) scores as cough group and non- cough group. In each group, Leicester cough questionnaire, reflux questionnaire, Beck depression questionnaire, St George's quality of life questionnaire (SGRQ) and Sleep Quality index were evaluated to determine whether there were any differences between groups.

Results: It was shown that the Leicester cough questionnaire score was lower in the cough group (86±24.9 vs 111±18.9) (p 0,02). Beck depression score revealed moderate level of depression in both groups (22±10.74 in cough group vs 18±11.86 in non-cough group) (p 0,4). SGRQ symptom score was significantly higher in the cough dominant group (p 0,04).

Conclusion: It is found that presence of cough in patients with IPF negatively affected the quality of life and was associated with the sleep disorders and depression. Leicester cough questionnaire can be used to assess whether the cough symptom affects patients' quality of life in routine clinical evaluation of patients with IPF. This evaluation is thought to improve quality of life and treatment compliance by increasing cough palliation in IPF patients.

Keywords: Idiopathic pulmonary fibrosis, Cough, Leicester cough questionnaire, Quality of life

1. INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is the most common type of interstitial pneumonia and is a chronic, progressive interstitial pneumonia of unknown origin. It is common in adults and is limited only to the lungs.

Progressive fibrosis in IPF leads to impaired gas exchange, reduced functional capacity, exercise intolerance and impaired quality of life.[1] The prognosis of the disease is poor and the average life expectancy is two to five years after diagnosis.[2] However treatment with antifibrotic agents reduced the decline of functional capacity, increased the survival and improved the quality of life in patients with IPF.[3-6] The most important treatment goal is to increase survival but improvement of quality of life and palliation of symptoms are also important, especially in patient's perspective.

It's been shown that severity of dyspnea is associated with anxiety, depression and decreased quality of life in patients with IPF however it is not clear whether presence of cough also related to these conditions.[7]

Technological advances in diagnostic methods, increase in human life expectancy, especially the development of radiological diagnostic methods and the emergence of new treatment options in the treatment of IPF in the recent past have both increased the diagnosis rate in IPF cases and led to more IPF cases in the clinical practice of chest diseases. Although the emergence of new treatment options such as antifibrotic therapies in

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IPF is an important development, improving the quality of life is still important.

The aim of this study was to investigate whether there is any difference in quality of life parameters, presence of depression, sleep disturbances, and reflux symptoms among patients with IPF with and without cough.

2. MATERIALS AND METHODS

1.1. Study population

Twenty patients diagnosed with IPF who were admitted to Kocaeli University Medical Faculty Hospital Chest Diseases Clinic between February 2017 and July 2017 were included in the study. The study was approved by Kocaeli University Ethics Committee (Project No: 201/367). The study is planned according to the International Declaration of Helsinki. The patients were informed about the aim and methods of the study and written informed consent was obtained.

Inclusion and exclusion criteria are presented in Table 1.

Table 1.

Inclusion and exclusion criteria

Inclusion Criteria	Exclusion criteria
Age older than 18 years	Previous diagnosis of chronic airway disease such as COPD and asthma, and use of
IPF diagnosis according to ATS/ERS criteria without any exacerbation in the last three months,	Presence of active malignancy
No respiratory tract infection in the last month	Use of antitussive medication
No need for long-term oxygen therapy at home.	Use of gastric acid suppressant such as antacids, proton pump inhibitors, H2 receptor blockers in the last three months
	Angiotensin Converting Enzyme (ACE) inhibitors and beta-blockers in the last month.

2.2. Study plan

Demographic characteristics (age, gender, occupation, education level, smoking habits, history of comorbidities, occupational exposures, family history, symptom questioning, vaccine applications, diagnostic and therapeutic procedures) and anthropometric measurements (height, weight, body mass index) of patients who met the inclusion criteria (Table 1) and agreed to participate in the study by signing an informed consent form were evaluated. Detailed physical examinations were performed, and pathological findings, especially the presence of clubbed toe and fibrotic rale, were recorded. Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m2).

Visual Analogue Scale (VAS) was used to evaluate the presence of cough symptom. The patients were asked to mark level of cough disturbance on a 100 mm scale; markings of 40 mm or less were classified as non-cough group whereas markings higher than 40 mm was defined as cough group.

Leicester Cough Questionnaire (LCQ), reflux symptom questionnaire, Beck depression questionnaire, St. George quality of life questionnaire (SGRQ) and sleep quality index were compared between the groups. In addition, GAP scores (Gender, Age, Physiological evaluation) were used as indicator of disease severity and risk of mortality.

2. Measurements

2.3.1. Pulmonary function tests

Pulmonary function test was performed according to ATS/ERS criteria and forced vital capacity (FVC), forced expiratory volume in 1

second (FEV1) and FEV1 / FVC levels were measured via a spirometer (ZAN™, Germany). After resting for 15 minutes, at least 3 tests were performed in the sitting position. The test was repeated for a maximum of eight maneuvers until three technically acceptable results were obtained. It was terminated if acceptable results could not be achieved despite 8 attemps or if the patient got tired. Diffusing capacity for carbonmonoxide (DLCO) was measured using the single-breath manuever.

2.3.2. Visual analog scale

The VAS scale is used to evaluate symptoms such as cough and pain that can not be measured numerically. The straight horizontal line with the length of 100 mm was used in this study. The two ends were defined as no-cough and the worst cough and the level for the presence of clinically significant cough was accepted as 40 mm.

2.3.3. Leicester cough questionnaire

Leicester cough questionnaire is a short, easy-to-perform questionnaire that is developed to investigate the effect of chronic cough on quality of life.[8]

2.3.4. Sleep, depression, reflux and quality of life surveys

Pittsburgh Sleep Quality Index (PSQI): It is a self-report questionnaire to assess sleep quality over one month period and consists of 19 items and 7 components which are subjective sleep quality, sleep latency, sleep time, habitual sleep efficiency, sleep disturbances, sleep medication use and daytime functions.[9]

Beck Depression Scale (BDS): It is a self-assessment inventory consisting of 21 questions developed to measure physical, emotional, cognitive and motivational symptoms of depression.[10]

St. George's Respiratory Questionnaire (SGRQ): The SGRQ consists of 50 items, within three sections representing the symptom, activity and impact domains.[11]

Reflux questionnaire (GERDQ): It is a self-administered tool that scores the frequency of six items (heartburn, regurgitation, dyspepsia, nausea, need for treatment and sleep disturbance) during the past 7 days according to a 4-point scale.[12]

2.3.5. GAP score

The GAP (Gender, Age, Physiology) model measures clinical and physiological variables to predict mortality in patients with IPF. There are four clinical variables; gender (woman: 0 points, man: 1 point), age (0–2 points), FVC (%) (0–2 points), and DLCO (%) (0–3 points) and three stages to predict mortality in GAP model. In the study of Ley et al, 1-year mortality of of GAP stage I, II and III were 6%, 16%, and 39%, respectively.[13]

2.4. Statistical analysis

Statistical analysis was performed with IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) package program. Normal distribution was assessed by Kolmogorov-Smirnov Test. Numerical variables with normal distribution were presented as mean ± standard deviation, numerical variables not showing normal distribution were given as median (25th - 75th percentile) and categorical variables as frequency (%). The difference between the groups was tested by independent samples t test for numerical variables with normal distribution, and with Mann Whitney U Test for numerical variables without normal distribution, and FisherExactkikare and Monte Carlo chi-square test for categorical variables. For the testing of bidirectional hypotheses, $p < 0.05$ was considered sufficient for statistical significance.

3. RESULTS

Totally 20 patients, 5 female (25%) and 15 male (75%), diagnosed as IPF according to ATS/ERS criteria were included in the study.[14] Patients were divided into two categories according to VAS scores as cough and non-cough groups. Cough group consisted of 11 patients (%55) who had a VAS score of 40 mm or higher. Demographic data and pulmonary function test parameters of the patients are shown in Table2. Gender distribution was similar between the groups.

Table 2.

Demographic data and pulmonary function test parameters of the patients

Gender	Female	5 (%25)
	Male	15 (%75)
Education level	Primary education	14 (%70)
	Middle School	-
	High school	1 (%5)
	University / College	1 (%5)
Smoking history	Current smoker	0
	Ex smoker	15 (%75)
	Non smoker	5 (%25)
Occupational exposure	(+)	20 (%100)
Family history	(+)	1 (%5)
Comorbidities	(+)	14 (%70)
Symptoms	Dyspnea	17 (%85)
	Cough	11 (%55)
	Gastro esophageal reflux	6 (%30)
Physical examination	Velcro crackles	20 (%100)
	Clubbing	7 (%35)
m MRC dyspnea score	1	4 (%20)
	2	8 (%40)
	3	8 (%40)
	4	-
Diagnostic assesment	Fiberoptic bronchoscopy	12 (%60)
	Surgical lung biopsy	4 (%20)
Treatment	Follow up without treatment	10 (%50)
	Pirfenidone	6 (%30)
	Nintedanib	4 (%20)

In cough group DLCO, FVC and FEV1 values were lower than the non-cough group however the difference was not statistically significant (Table 3).

Table 3.

Pulmonary function test parameters of the cases

Pulmonary function test	**VAS<40**	**VAS≥40**	**p**
FVC, L	2,24 ± 0,75	2,08 ± 0,58	0,6
FVC, %	66,17 ± 20,3	62,31 ± 11,43	0,6
FEV_1, L	1,98 ± 0,65	1,83 ± 0,44	0,5
FEV_1, %	71,43 ± 20,81	70,19 ± 12,68	0,9
FEV_1/FVC, %	87,80 ± 7,86	85,87 ± 8,03	0,6
DLCO, %	43,01 ± 15,39	34,73 ± 7,27	0,2

Leicester Cough Questionnaire, Gastroesophageal Reflux Questionnaire, Pittsburgh Sleep Quality Questionnaire, St. George Respiratory Questionnaire (SGRQ) and Beck Depression Questionnaire were applied to all patients who were divided into two groups according to VAS score (Group-1 VAS<40, Group-2 VAS≥40). The Leicester Cough Questionnaire score was higher in the non-cough group (111 ± 18.9 vs 86 ± 24.9). There was a correlation between VAS score and Leicester Cough Questionnaire (p=0.02). Apart from this, there was no statistically significant difference between the scores of the Beck Depression Questionnaire and the Pitsburgh Sleep Quality Questionnaire of the two groups (Table 4)

Table 4.

LCQ, BDI and Pittsburgh SQI results according to VAS

	VAS<40	**VAS≥40**	**p**
Leicester Cough Questionnaire	111,63 ± 18,87	86,11 ± 24,87	**0,02**
Beck Depression Questionnaire	18 ± 11,86	22 ± 10,74	0,4
Pitsburgh Sleep Quality Questionnaire	5,81 ± 6,27	10 ± 4,74	0,1

Patients were asked whether they had reflux symptoms and six of them (30%) responded positively. Patients also fulfilled the GERDQ and again no difference was found between the two groups (Table 4).

SGRQ symptom score was significantly higher in cough group. However activity, effect and total scores were not statistically significant between the two groups. (Table 5).

Table 5.

Reflux questionnaire and SGRQ results

	Median (25.-75. percentil)	**P value**
Reflux questionnaire	2,5 (0- 9,75)	0,9
SGRQ activity	874,1 (465,82-956,7)	0,8
SGRQ effect	872,6 (412,65 – 1299,15)	0,5
SGRQ symptom	344,8 (270,8 – 487,63)	**0,04**
SGRQ total scores	2106,5 (1214,85 – 2683,33)	0,6

There was no significant difference between the groups in terms of GAP scores. In the dominant cough group, 1 patient was evaluated as stage-1, 3 patients as stage-2 and 3 patients as stage-3. In the non-cough group, 3 patients were evaluated as stage-1, 3 patients as stage-2 and 3 patients as stage-3.

4. DISCUSSION

In this study, the presence of cough in IPF patients correlated with the Leicester Cough Questionnaire and the symptom domain of the SGRQ. In the cough group, pulmonary functions were lower, Beck depression scores were higher and sleep quality was lower but these differences did not reach statistical significance level.

Interstitial lung diseases consist of several diseases, ranging from simple inflammation to fibrosis, affecting lung parenchyma and airways. IPF is the most common subgroup among idiopathic interstitial pneumonias.[15] The most common symptoms are shortness of breath and dry cough and 70 to 85% of patients have cough at the time of diagnosis.[16,17]

In IPF patients, cough is generally dry and increases during exercise and speech and generally does not respond the treatment. In a previous study, the frequency of cough in patients with IPF was found to be 9.4 times per hour and frequent in daytime.[18] In this study 11 out of 20 (55%) patients had severe cough with a VAS score above 40 mm.

Since cough is a common symptom in the community, it is also important to identify pathologies that may cause of cough in IPF patients. Previous study by Madison JM et al. reported that half of the patients had additional factors that may be cause of cough symptom such as reflux, cough variant asthma, upper airway cough syndrome and medication.[19] Since we aimed to investigate cough associated with IPF, patients who had a history of comorbid disease

and/or medication that could cause cough were excluded from this study.

The Leicester Cough Cuestionnaire is a short, easy to apply and valid questionnaire developed to investigate the effect of chronic cough on quality of life.[8] In a study involving 19 patients investigating the frequency of cough and its effect on quality of life in IPF patients, it was shown that cough was a common symptom in IPF patients and VAS score and Leicester Cough Questionnaire were effective in determining the frequency of cough in these patients.[18] In our country, it was validated by Havlucu et al. with 100 patients and its validity and reliability in our language was shown.[20] In our study, patients were divided into two groups according to VAS score in terms of the presence of cough and Leicester Cough Questionnaire scores were found to be significantly different between the groups. It is thought that the Leicester questionnaire, which can be considered as a cough-specific quality of life questionnaire to show the effect of cough on quality of life in IPF, can be included in the routine clinical evaluation of these patients. It is thought that the use of this short, easy-to-administer and patient-administered questionnaire in the evaluation of cough will provide additional information in terms of the severity of this symptom and increase the physician's awareness of cough symptoms, leading to symptom palliation and thus improvement in the patient's quality of life indicators.

Gastroesophageal reflux is more common in IPF patients than in the normal population.[21] It is thought that there is a relationship between microaspirations caused by reflux and disease development. In a case-control study, erosive esophagitis secondary to reflux was reported to be associated with pulmonary fibrosis.[22] Although the mechanism of action has not been determined, there are several studies reported stable pulmonary function, lower number of attacks and prolonged survival in patients with IPF receiving proton-pump inhibitor (PPI).[21,23] However there are other studies reported no favorable effects in disease course with PPI moreover it is associated with increased frequency of lung infection.[24] Therefore routine use of PPI in patients with IPF is not recommended. In this study we have excluded patients with anti-reflux therapy considering this may affect cough frequency. Still %30 of the patients stated they had reflux symptoms and GERDQ scores showed impact of reflux in study population however there was no difference between the groups.

Since there is no quality of life questionnaire specific to IPF patients therefore we used SGRQ, a questionnaire designed to measure impact on overall health, daily life, and perceived well-being in patients with respiratory disease. Dyspnea has been shown to be the most important symptom associated with deterioration of quality of life in patients with IPF.[11,25] According to the data obtained from the meta-analysis in which 60 studies were included in the literature, it was shown that there was a relationship between the decrease in quality of life and the severity of the disease in patients followed up with the diagnosis of interstitial lung disease. It was revealed that SGRQ scores increased as the severity of the disease increased.[26] In our study, it was seen that the symptom score of the SGRQ questionnaire was significantly higher in the group with cough than in the other group. However no differences were found in other domains.

Panic, anxiety and fear were reported to be common in patients with IPF. Studies related to depression and anxiety in these patients have shown that the Hospital Anxiety Depression (HADS) scale is significantly higher than the control group.[27,28] The frequency of long-term anxiety and depression was found to be higher in symptomatic IPF patients. In a study included 102 participants in Australia, patients were assessed by the Hospital Anxiety and Depression Scale and 20 of them (21%) had long-term anxiety.[29] Prolonged anxiety was associated with initial dyspnea, need for additional oxygen, presence of comorbidities and severe cough. Anxiety-related increase in HADS score was detected in 13% of the patients and this deterioration was attributed to an increase in cough severity and shortness of breath at 12-month follow-up. Prolonged depression was detected in 14 patients and multivariate analysis indicated that the increase in initial cough severity could be an independent

marker for depression. It was reported that a 10 mm increase in cough severity during follow-up increases the risk of long-term depression by 45%.[29] In our study, the mean Beck Depression Scale score was high in both groups suggesting moderate depression in the study population. Although there was no significant difference between the two groups, depression scores were higher in the group with cough symptoms. In IPF, especially in patients with higher symptom burden, depression and anxiety questioning is thought to be important in terms of increasing the compliance of patients to the treatment.

Mortality and morbidity in IPF is high and the average survival is between 2.3 and 3.5 years. Clinical course and prognosis may vary between individuals.[30] This causes difficulties in predicting prognosis and planning treatment. Therefore, prognostic factors such as age, sex and radiological evaluation have been tried to predict the clinical course of the disease.[31] Ley et al. developed a 4-parameter GAP score (Gender, Age, Physiological evaluation) in 2012 to predict disease prognosis.[32] In the study, which included 1262 patients the survival of patients in Group-3 was significantly lower than in Group-1 and Group-2. However, this study did not find any significant difference between cough and non-cough group which may be related to relatively low number of patients included in the study.

The study has some limitations. First, the study was a single centered and the number of patients was low. Second, the fact that some of the patients were on antifibrotic therapy might have affected the frequency of cough. However, since half of the patients were not receiving treatment and there was no difference between the groups in terms of treatment used, it was thought that treatment did not significantly affect the study findings.

As a result, it is found that presence of cough in patients with IPF negatively affected the quality of life and was associated with the sleep disorders and depression. Leicester cough questionnaire can be used to assess whether the cough symptom affects patients' quality of life in routine clinical evaluation of patients with IPF. This evaluation is thought to improve quality of life and treatment compliance by increasing cough palliation in IPF patients. There is a need for multicentre studies involving more patients.

Article Information Form

Authors' Contribution

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Salih Küçük, İlknur Başyiğit, Serap Argun Barış and Haşim Boyacı. The first draft of the manuscript was written by Salih Küçük, İlknur Başyiğit, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

The study was approved by Kocaeli University Ethics Committee (Project No: 201/367).

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

Copyright Statement

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Araştırma Makalesi / Research Article

Öğrenme Güçlüklerinin Ötesinde: Özgül Öğrenme Bozukluğu Olan Çocuklarda Dikkat Eksikliği Hiperaktivite Bozukluğu ve Otistik Özelliklerin Öz Kavramı Üzerindeki Etkisinin Çok Değişkenli Analizi

Beyond Learning Difficulties: A Multivariate Analysis of Self-Concept in Children with Specific Learning Disorder, Attention-Deficit/Hyperactivity Disorder, and Autistic Traits

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Giriş: Bu çalışma Özgül Öğrenme Bozukluğu (ÖÖB) tanılı çocuk ve ergenlerde Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) eş tanısının ve otistik özelliklerin öz kavramı üzerindeki etkisini incelemeyi amaçlamaktadır. Literatürde bu komorbidite ve özelliklerin öz kavramı üzerindeki etkisini değerlendiren özgül çalışmalar sınırlıdır.

Materyal ve Yöntem: Kesitsel desenle yürütülen çalışmaya, 9–17 yaş arası 172 çocuk ve ergen dahil edilmiştir. Öz kavramı düzeyi Piers-Harris Öz Kavramı Ölçeği ile, DEHB semptom şiddeti Turgay DSM-IV Ölçeği ile, otistik özellikler ise Otizm Spektrum Anketi ile değerlendirilmiştir. Veriler bağımsız örneklem t-testleri, korelasyon ve çoklu regresyon analizleriyle analiz edilmiştir.

Bulgular: DEHB eş tanılı grup, DEHB olmayan gruba kıyasla daha düşük öz kavramı puanlarına ve daha yüksek otistik özellik düzeylerine sahiptir. DEHB semptom şiddeti ile öz kavramı arasında negatif, otistik özellikler ile pozitif yönde anlamlı ilişkiler saptanmıştır. Regresyon analizi otistik özelliklerin, DEHB semptom şiddeti ve demografik değişkenlerden bağımsız olarak öz kavramını anlamlı şekilde yordadığını göstermiştir.

Sonuç: DEHB eş tanısı ve otistik özellikler, ÖÖB'li çocuklarda sadece akademik değil, sosyal ve duygusal alanlarda da ek riskler oluşturmaktadır. Bu nedenle öz kavramı ve sosyal becerileri hedefleyen bütüncül klinik değerlendirme ve müdahale yaklaşımları geliştirmek yerinde olacaktır.

Anahtar Kelimeler: Özgül Öğrenme Bozukluğu, Dikkat Eksikliği Hiperaktivite Bozukluğu, Öz Kavramı, Otistik özellikler

Introduction: This study aims to examine the impact of comorbid Attention Deficit Hyperactivity Disorder (ADHD) and autistic traits on self-concept in children and adolescents diagnosed with Specific Learning Disorder (SLD). In the literature, research specifically addressing the effects of ADHD and autistic traits on self-concept remains limited.

Materials and Methods: This cross-sectional study included 172 children and adolescents aged 9–17 years. Self-concept was assessed using the Piers-Harris Children's Self-Concept Scale, ADHD symptom severity was measured with the Turgay DSM-IV Disruptive Behavior Disorders Rating Scale, and autistic traits were evaluated with the Autism Spectrum Quotient. Statistical analyses were performed using independent samples t-tests, correlation analyses, and multiple regression analyses.

Results: The group with comorbid ADHD exhibited lower self-concept scores and higher levels of autistic traits compared to the non-ADHD group. ADHD symptom severity was negatively associated with self-concept. In addition, autistic traits were positively correlated with ADHD symptom severity. Regression analysis demonstrated that autistic traits significantly predicted self-concept, even after controlling for ADHD symptom severity and demographic variables.

Conclusion: ADHD comorbidity and autistic traits pose additional risks for children with Specific Learning Disorder, not only in academic functioning but also in social and emotional domains. These findings highlight the need for developing comprehensive clinical assessment and intervention approaches that specifically target self-concept and social skills.

Keywords: Specific Learning Disorder, Attention Deficit Hyperactivity Disorder, Self-Concept, Autistic traits

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EXTENDED ABSTRACT

Introduction:

Specific Learning Disorder (SLD) is a neurodevelopmental condition characterized by persistent difficulties in reading, writing, arithmetic, and other academic domains despite adequate intelligence and education. SLD frequently co-occurs with other psychiatric and developmental disorders, most notably Attention-Deficit/Hyperactivity Disorder (ADHD), with comorbidity rates ranging from 30% to 82% in SLD populations. In addition, children with SLD may exhibit autistic traits such as impaired social cognition, reduced theory of mind capacities, and limited empathy, even in the absence of a formal Autism Spectrum Disorder (ASD) diagnosis. Self-concept, a person's perception and evaluation of their own abilities, appearance, and worth, is a multidimensional construct shaped by both internal and external factors. In children with SLD, especially those with comorbid psychiatric disorders, self-concept tends to be more negatively affected due to academic failures, social rejection, and low self-efficacy. However, there is a lack of studies investigating how ADHD comorbidity and autistic traits jointly or independently influence self-concept in children diagnosed with SLD. This study aims to address this gap by exploring the impact of both ADHD and autistic traits on the self-concept of children and adolescents with SLD.

Materials and Methods:

This cross-sectional study included 172 children and adolescents (aged 9–17) who were diagnosed with SLD and referred to the Child and Adolescent Psychiatry Clinic of a tertiary hospital between February 2023 and February 2024. Participants were grouped based on the presence (n=126) or absence (n=46) of a comorbid ADHD diagnosis. Inclusion criteria required participants to be actively enrolled in formal education, have a Full-Scale IQ score of 80 or above (as assessed by WISC-R or WISC-IV), and meet DSM-5 criteria for SLD. Children with additional psychiatric diagnoses apart from ADHD were excluded. Self-concept was assessed using the Piers-Harris Children's Self-Concept Scale, which evaluates six domains: happiness and satisfaction, anxiety, popularity, behavioral adjustment, physical appearance, and intellectual/school status. ADHD symptoms were measured using both parent and teacher-reported versions of the Turgay DSM-IV-Based Rating Scale. Autistic traits were assessed using the Adolescent Version of the Autism Spectrum Quotient (AQ), validated for Turkish populations. Statistical analyses included independent samples t-tests, Pearson correlation analyses, and linear regression models to assess the predictive roles of ADHD symptom severity and autistic traits on self-concept scores.

Results:

The group with comorbid ADHD (ADHD+) demonstrated significantly lower total self-concept scores than the SLD-only group (ADHD–) ($t=3.12$, $p=0.002$, Cohen's $d=0.537$). Additionally, the ADHD+ group exhibited significantly higher total scores on the Autism Spectrum Quotient ($t=-3.25$, $p=0.002$, Cohen's $d=0.555$). In terms of subscales, the ADHD+ group had lower scores in happiness, anxiety, behavioral adjustment, and physical appearance, but no significant differences were found in popularity or intellectual/school domains. These findings suggest that ADHD comorbidity impacts emotional and social aspects of self-concept more than academic-related domains. Correlation analyses revealed that ADHD symptom severity, as rated by both parents and teachers, was moderately and negatively correlated with self-concept scores and positively associated with autistic traits. Furthermore, simple linear regression showed that autistic traits significantly predicted self-concept scores ($R^2=0.106$, $F(1,171)=21.25$, $p<0.001$). This relationship remained statistically significant in a multiple regression model controlling for ADHD symptom severity, age, and gender ($\beta=-0.212$, $p=0.007$), indicating that autistic traits independently contribute to lower self-concept. No significant differences in self-concept or AQ scores were found between ADHD subtypes (inattentive vs. combined presentation).

Conclusion:

This study demonstrates that children with SLD who also have comorbid ADHD are at greater risk

for low self-concept and elevated autistic traits. Autistic traits appear to be a significant predictor of reduced self-concept, even when controlling for ADHD severity and demographic factors. These findings underscore the need for comprehensive, multidimensional clinical evaluations for SLD populations, particularly those with multiple neurodevelopmental features. Given that self-concept is closely linked to emotional well-being, academic motivation, and social adjustment, early identification and intervention are essential. Clinical programs for SLD should therefore include not only academic support but also structured interventions that target social cognition, emotion regulation, and self-perception. Addressing these areas may improve long-term psychosocial outcomes and promote resilience in children with complex developmental profiles.

1. GİRİŞ

Özgül öğrenme bozukluğu (ÖÖB); okuma, anlama, konuşma, dinleme, matematiksel mantık kurabilme, aritmetik hesapları yapabilme, yazılı anlatım becerilerinin kazanılması ve kullanılabilmesinde gecikme ya da bozulmanın olması olarak tanımlanan nörogelişimsel bir bozukluktur.[1] ÖÖB'nin yaygınlığının okul çağı çocuklarındaki sıklığının %5-15 arasında değiştiği anlaşılmaktadır. Bununla uyumlu olarak, Türkiye'de yapılan yakın zamanlı bir çalışmada ÖÖB prevalansı %6,6 olarak saptanmıştır.[2] ÖÖB, erken çocukluk döneminde başlamakta ve değişken klinik görünümlerle yaşam boyu devam etmektedir.

Öz kavramı; kişinin kendi hakkındaki hislerini, diğerleri tarafından kendisine yöneltilen içselleştirdiği düşünceleri, genel ve özel kabiliyetleri ve fiziksel olarak kendisine yönelik algısını ifade etmektedir.[3] Aynı zamanda kişinin kendisine ilişkin ve sosyal çevresinden edindiği algılar doğrultusunda yeteneklerine dair geliştirdiği inanç ve beklentileri öz kavramı olarak tanımlanmaktadır. Öz kavramı, içsel faktörlerden etkileneceği gibi; sosyal ilişkiler, yaşam deneyimleri, ebeveyn tutumları gibi dışsal faktörlerle de ilişkili olabilmektedir.[4] ÖÖB'nin kronik doğası gereği çocuklarda zaman içinde düşük benlik algısı gelişebilmekte, kişinin kendisine dönük atıflarında ve çevresine yönelik algılarında olumsuz gidişat izlenebilmektedir. Bu durumun, öz kavramı üzerindeki etkileri çeşitli çalışmalarda farklı biçimlerde ele alınmıştır.[5] Literatürde öz kavramı ve ÖÖB arasındaki ilişkiyi inceleyen öncül derlemede akademik öz kavramı başta olmak üzere, genel öz kavramının ÖÖB'li çocuklarda özel gereksinimi olmayan çocuklara göre daha düşük olduğu bulunmuştur. Çalışmacılar üçüncü sınıfta başlayan öz kavramındaki bu düşüşün lise yıllarına değin stabil seyrettiğini söylemektedir.[6] Öz kavramı ve ÖÖB arasındaki çalışmaları içeren bir başka meta-analiz çalışmasında öğrencilerin hangi konumda eğitim aldıkları fark etmeksizin öz kavramında düşüklük gösterdiği bulunmuştur.[7] Bir diğer meta-analizde ise ÖÖB ve öz kavramı sadece akademik alanda ilişkili bulunmuş, öz kavramının diğer alanlarında etkilenme olmadığı sonucuna ulaşılmıştır.[8] En güncel meta-analiz çalışmasında ise ÖÖB'li çocuklarda öz kavramının alt grup ayırt etmeksizin normal gelişim gösteren çocuklardan daha düşük seyrettiği ifade edilmektedir.[9] Bu çalışmalar arasındaki bulgu farkları, öz kavramının çok boyutlu yapısı ve kullanılan ölçme araçlarının çeşitliliğiyle açıklanabilir. Öz kavramının sadece akademik alanda kalmayıp işlevselliğin tüm alanlarına etki edişine işaret eden bir çalışmada ÖÖB'li ergenlerde, öz kavramının kişilik güçleri ve psikolojik iyi oluş arasında aracı rol oynadığı gösterilmiştir.[10] Akranlar ve aile ile sürdürülen iyi sosyal ilişkilerin ise negatif öz algısına karşı koruyucu bir faktör olabileceği öne sürülmüştür.[11] Dolayısıyla, öz kavramını yalnızca akademik yeterliliklerle sınırlı bir yapı olarak değil; sosyal beceriler, duygusal işleyiş ve genel psikopatolojik yük ile dinamik bir ilişki içinde değerlendirmek gerekir.

ÖÖB, Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) başta olmak üzere birçok ruhsal bozuklukla birlikte görülebilmektedir. DEHB'nin ÖÖB'ye en sık eşlik eden ruhsal bozukluk olduğu ifade edilmektedir.[12] ÖÖB tanılı olgularda DEHB eş tanı oranı %30-%82,3 arasında değişmekteyken, DEHB tanılı olgularda ÖÖB eş tanı oranı %27-%31 oranında değişmektedir. [12–14] ÖÖB tanılı çocuk ve ergenlerde, DEHB eş tanısının yanı sıra, diğer bir nörogelişimsel bozukluk olan otizm spektrum

bozukluğunun (OSB) bazı belirtilerinin görülebildiği ifade edilmiştir. OSB tanılı çocuk ve ergenlere benzer şekilde, ÖÖB tanılı çocuk ve ergenlerin sosyal biliş, zihin kuramı ve empati yapma yetilerinin tipik gelişim gösteren çocuklara göre geri olduğu belirtilmiştir. [15–17] ÖÖB tanılı çocukların; mitleri, metaforları, şakaları ve atasözlerini kavramakta zorlandıkları bilinmektedir.[18,19] ÖÖB tanılı çocuk ve ergenler tipik gelişim gösteren çocuklara kıyasla zihin kuramı testinde daha düşük performans sergilemişlerdir.[17,20] Bir başka çalışma ÖÖB tanılı çocukların sağlıklı kontrollere göre başkalarının duygu ve düşüncelerini anlamada zorluk yaşadıklarını bildirmiştir.[15] Sosyal ipuçlarını anlama, başkalarının duygularını yorumlama ve uygun sosyal tepkiler geliştirme gibi sosyal bilişsel becerilerdeki bu zorluklar, DEHB belirtileriyle birleştiğinde, bireyin sosyal çevresinden aldığı geri bildirimleri sağlıklı bir şekilde değerlendirmesini zorlaştırabilir ve duygusal regülasyon süreçlerini olumsuz yönde etkileyebilir.

Bu tür sosyal ve davranışsal zorlukların, özellikle gelişimsel dönemde öz kavramı üzerinde olumsuz bir etkiyle ilişkili olabileceği düşünülmektedir.

Tüm bu bulgular, ÖÖB tanılı çocuk ve ergenlerde öz kavramının yalnızca akademik yeterliliklerle sınırlı olmadığını; sosyal ilişkiler, eş tanılar ve bilişsel-duygusal işleyiş gibi çok sayıda faktörden etkilendiğini ortaya koymaktadır. Ancak, DEHB komorbiditesi ve otistik özelliklerin bu etkiyi nasıl şekillendirdiği halen yeterince araştırılmamıştır. Bu bağlamda, bu çalışmada özgül öğrenme bozukluğu tanısı almış çocuklarda öz kavramının, DEHB ve otistik özelliklerle ilişkisi incelenmektedir. Özellikle DEHB'nin eşlik ettiği durumlarda dikkat, dürtüsellik ve davranış regülasyonundaki güçlüklerin, çocuğun akademik ve sosyal başarısını olumsuz etkileyerek daha düşük bir öz kavramına yol açabileceği öngörülmektedir. Benzer şekilde, otistik özelliklerin sosyal etkileşim, iletişim ve empati alanlarındaki zorlukları pekiştirerek bireyin kendilik algısı üzerinde olumsuz bir etkiye sahip olabileceği düşünülmektedir. Bu doğrultuda çalışmanın iki temel hipotezi bulunmaktadır: (1) ÖÖB'ye DEHB eşlik ettiğinde çocukların öz kavramları daha olumsuz olacaktır; (2) ÖÖB tanılı çocuklarda gözlenen otistik özellikler, negatif öz kavramını anlamlı düzeyde yordayacaktır. Bu araştırmanın, öğrenme güçlüğü yaşayan çocukların psikososyal gelişimini daha iyi anlamaya katkı sunması ve çoklu tanılı çocuklara yönelik erken dönemde bütüncül müdahalelerin geliştirilmesine zemin hazırlaması beklenmektedir.

2. GEREÇ VE YÖNTEM

2.1. Katılımcılar

Bu çalışma kesitsel bir çalışmadır. Çalışma örneklemi, İstanbul'da bir eğitim ve araştırma hastanesi çocuk ve ergen psikiyatrisi kliniğine 01.02.2023-01.02.2024 tarihleri arasında başvuran ÖÖB tanısı olan hastalardan oluşmaktadır. Çalışma örneklemindeki katılımcılar ve ebeveynleri, çalışma prosedürü hakkında ayrıntılı olarak bilgilendirilmiştir ve aydınlatılmış onamları alınmıştır. Çalışma protokolü aynı hastanenin etik kurulu tarafından onaylanmıştır. Çalışmaya dahil etme kriterleri; 9-17 yaş arasında olmak, en az 1 yıl örgün eğitime devam etmiş olmak, DSM-5'e göre ÖÖB tanısının bulunması, WISC-R veya WISC-4 üzerinden yapılan değerlendirmede tüm ölçek zekâ puanından 80 ve üstü almak şeklinde belirlenmiştir. Dışlama kriterlerinde ise DEHB dışında ek bir psikopatoloji varlığı, kronik herhangi bir hastalığın olması bulunmaktadır. Çalışmanın örneklem büyüklüğü G Power programı 3.1.9.7 sürümü ile gerçekleştirilen *a priori* güç analizi ile belirlenmiştir. Örneklem büyüklüğü için Araz Altay ve Görker'in çalışması esas alınmıştır.[13] Etki büyüklüğü 0,28, alfa hata değeri 0,05 ve çalışmanın gücü %80-95 aralığında alındığında 108 ila 176 arası toplam katılımcının yeterli olacağı saptanmıştır. Çalışmamızda ise dahil edilme kriterlerini karşılayıp hariç tutma kriterlerinden dışlanmış toplam 172 katılımcı çalışma şartlarını tamamlamış ve çalışmaya dahil edilmiştir. Çalışma kapsamında alınan katılımcılar DSM-5 kriterlerine göre değerlendirilmiş olup 12 çocuk Otizm Spektrum Bozukluğu, 10 çocuk anksiyete bozuklukları, 3 çocuk Sosyal İletişim Bozukluğu, 5 çocuk depresif bozukluklar nedeniyle dışlanmıştır. WISC-R veya WISC-4 ile yapılan zekâ değerlendirmesinde tüm ölçek zeka

puanından 70-80 arası alan 7 çocuk çalışmaya katılmamıştır. 5 çocuk ise çeşitli kronik hastalıkları (epilepsi, diyabetes mellitus) nedeniyle çalışmanın dışında tutulmuştur. Ek olarak 13 adet çocuğun verisine, ailelerine sonrasında ulaşılamadığından dolayı erişilememiştir.

2.2. Ölçekler

a. Piers-Harris öz kavramı ölçeği

1964 yılında Piers ve Harris tarafından Amerika Birleşik Devletleri'nde geliştirilmiş 80 maddeden oluşan öz bildirim ölçeğidir. Mutluluk ve doyum, kaygı, popülarite ve sosyal beğeni, davranış ve uyum, fiziksel görünüm, zihinsel durum ve okul durumu olmak üzere altı faktörden oluşur. Ölçekte sorulan sorulara evet ya da hayır diye cevap verilmektedir. Bu ölçekten alınabilecek en yüksek puan 80, en düşük puan ise 0'dır. Yüksek puan olumlu benlik saygısını, düşük puan ise olumsuz benlik saygısını ifade eder. Ölçeğin Türkçe geçerlilik ve güvenirlik çalışması Öner tarafından 1996 yılında yapılmıştır.[21] Ölçeğin güvenirlik katsayısı alt ölçekleri için ,78 ile ,93 arasında değişmektedir. Altı faktör toplam puan değişiminin %42'sini açıklamaktadır. Türkçe formun iç tutarlık katsayıları ,81 ile ,89 arasında değişmektedir.

b. Turgay Çocuk ve Ergenlerde Davranış Bozuklukları için DSM-IV'e dayalı tarama ve değerlendirme ölçeği

Turgay tarafından 1994 yılında geliştirilmiş olan, yıkıcı davranış bozukluklarını tarayan bir ölçektir. Ölçekte dikkat eksikliği, hiperaktivite/dürtüsellik, karşıt olma karşı gelme bozukluğu ve davranım bozukluğunu sorgulayan dört bölüm mevcuttur. Bu çalışmada ölçeğin dikkat eksikliği ve hiperaktivite/dürtüselliği sorgulayan bölümleri çalışmaya dahil edilmiştir. Eşik puanı geçmek için dikkat eksikliğini sorgulayan 9 maddenin en az 6'sının, hiperaktivite/dürtüselliği sorgulayan 9 maddenin en az 6'sının 2 ya da 3 olarak puanlanması gerekmektedir. Her bir maddenin şiddeti dörtlü Likert tipi puanlama ile ölçülmektedir. Ölçeğin Türkçe geçerlilik güvenilirlik çalışması 2001 yılında Ercan ve arkadaşları tarafından yapılmıştır. Çalışma sonucunda alt ölçekler düzeyinde yapılan analizler yeterli ölçüde geçerli, güvenilir olarak bildirilmiş ve tanı ve tarama amaçlı kullanılabilecek ayrıntılı bir ölçek olduğu belirtilmiştir.[22] Ölçek, ebeveyn ve öğretmen tarafından puanlanmaktadır. Bu çalışmada hem ebeveyn hem de öğretmen tarafından uygulanan ölçekler çalışmaya dahil edilmiştir.

c. Otizm spektrum anketi-ergen versiyonu

Simon Baron-Cohen ve arkadaşları tarafından 9-16 yaşları arasındaki çocuk ve ergenler için geliştirilmiş,[23] Çetinoğlu ve Aras tarafından Türkçe geçerlilik güvenilirlik çalışması yapılmıştır.[24] Ölçek, çocuklardaki otizm spektrumunu nicel olarak ölçen ve eşik altı otistik özelliklerin derecesini belirleyen ebeveyn bildirimli bir tarama aracıdır. Dikkati değiştirme, hayal etme, iletişim, detaylara dikkat ve sosyal beceriler olmak üzere beş alt ölçekten oluşan ölçekte her maddeye Likert tipi olarak 0-3 arasında değişen puanlar verilmektedir. Yüksek puan otistik özelliklere yatkınlık olarak değerlendirilmektedir. Ölçeğin Türkçe versiyonunda Cronbach α değeri 0,829, ordinal alfa değeri 0,90 olarak bulunmuştur.

2.3. İstatistiksel analiz

Veriler, Sosyal Bilimler için İstatistik Paketi (*Statistical Package for the Social Sciences*; SPSS Inc., Chicago, IL) sürüm 22.0 kullanılarak analiz edilmiştir. Analizlere başlanmadan önce veri seti kayıp değerler, uç değerler ve normallik açısından incelenmiştir. Verilerin normal dağılıma uygunluğu çarpıklık ve basıklık değerleri üzerinden değerlendirilmiştir. Çarpıklık ve basıklık katsayılarının −1,5 ile +1,5 aralığında bulunması, normal dağılıma uygunluk ölçütü olarak kabul edilmiştir.[25] Normal dağılıma uyan sürekli değişkenler **ortalama ± standart sapma** değerleriyle, normal dağılıma uymayan sürekli değişkenler ise **ortanca (medyan) ve çeyrekler arası aralık (IQR)** değerleriyle sunulmuştur. Normal dağılıma sahip sürekli değişkenlerin iki grup arasında karşılaştırılmasında **bağımsız örneklemler t testi** kullanılmış ve etki büyüklüğü olarak **Cohen's d** değeri raporlanmıştır. Normal dağılıma uymayan sürekli değişkenlerin grup karşılaştırmalarında ise **Mann–Whitney U testi**

uygulanmış, etki büyüklüğü ölçütü olarak **rank-biserial korelasyon (r)** değeri verilmiştir.

Sürekli değişkenler arasındaki ilişkiler **Pearson korelasyon analizi** ile incelenmiştir. Bir veya birden çok sürekli bağımsız değişkenin, sürekli bir bağımlı değişken üzerindeki yordayıcı etkisini belirlemek amacıyla **basit ve çoklu doğrusal regresyon analizleri** yapılmıştır. Çoklu karşılaştırmalarda Tip I hata oranını azaltmak için **False Discovery Rate (FDR) düzeltmesi** uygulanmış ve düzeltilmiş p değerleri ayrıca raporlanmıştır.

3. BULGULAR

Mevcut çalışma ÖÖB tanısına sahip 172 katılımcıdan oluşmaktadır. Bu katılımcıların 126'sı DEHB tanısına sahip iken, 46 katılımcı DEHB tanı kriterlerini karşılamamaktadır (DEHB-). DEHB tanılı gruptaki (DEHB +) 70 katılımcı dikkat eksikliği (DE) görünümündeyken, 4 katılımcı hiperaktivite (HA) ve 52 katılımcı ise karma görünüme sahiptir. Buna göre iki grup arasında yaş ve cinsiyet yönüyle anlamlı bir farklılık saptanmamıştır. DEHB+ ve DEHB– gruplarının sosyodemografik bilgilerinin karşılaştırılmasına ait veriler Tablo 1'de sunulmuştur.

Tablo 1.

Sosyodemografik verilerin karşılaştırılması (n=172)

Değişkenler	DEHB + (n=126), Ort ± SD,	DEHB – (n=46), Ort ± SD	İstatistik	Etki Büyüklüğü	p
Yaş (yıl)	10,52 ± 2,61	10,86 ± 2,67	t=0,76	Cohen's d=0,129	0,450
Cinsiyet (E:K)	80:46	22:24	X^2=3,43	Cramer's V=0,141	0,064

Ort: Ortalama, SD: Standart sapma, t: Bağımsız örneklemlerde t testi, X^2: ki-kare testi

DEHB+ grubun Piers Harris Öz Kavramı Ölçeği Toplam Puanları, DEHB– gruba göre daha düşük bulunmuştur (t=3,12, p=0,002, Cohen's d=0,537). Ayrıca DEHB+ grubun Otizm Spektrum Anketi toplam ölçek puanı, DEHB- gruba göre daha yüksek bulunmuştur (t=-3,25, p=0,002, Cohen's d=0,555). Katılımcıların adı geçen ölçeklerin alt ölçek puanlarına göre karşılaştırılmasına ait bilgiler ise Ek Tablo 1'de sunulmuştur. Buna göre Piers Harris Öz Kavramı Ölçeği mutluluk, kaygı, davranışsal uyum ve fiziksel görünüm alt ölçek puanları DEHB+ grup lehine daha düşük bulunurken; popülarite ve zihinsel durum okul alt ölçek puanları iki grup arasında anlamlı farklılık göstermemiştir. Katılımcıların toplam ölçek puanlarının karşılaştırılmasına ait veriler Tablo 2'de sunulmuştur.

Tablo 2.

Toplam ölçek puanlarının DEHB olan ve olmayan karşılaştırılması(n=172)

Toplam Ölçek Puanları	DEHB+ (n=126), Ort ± SD,	DEHB– (n=46), Ort ± SD,	İstatistik	Etki Büyüklüğü/Cohen's d	p
Piers Harris Öz Kavramı Ölçeği	51,45 ± 11.32	57,41 ± 10.45	t=3,12	0,537	**0,002**
Otizm Spektrum Anketi	60,71 ± 13,64	53,24 ± 12,95	t=-3,25	0,555	**0,002**

Ort: Ortalama, SD: Standart sapma, t: Bağımsız örneklemlerde t testi, Med: Ortanca, IQR: Çeyrekler arası aralık (1. Ve 3. Çeyrek değerleri sunulmuştur).

Turgay Çocuk ve Ergenlerde Davranış Bozuklukları için DSM-IV'e Dayalı Tarama ve Değerlendirme Ölçeği-Ebeveyn formu dikkat eksikliği ve hiperaktivite puanları ile Piers Harris toplam puanları arasında negatif yönlü, orta düzeyde anlamlı ilişki saptanmıştır. Turgay Çocuk ve Ergenlerde Davranış Bozuklukları için DSM-IV'e Dayalı Tarama ve Değerlendirme Ölçeği-Öğretmen formu dikkat eksikliği ve hiperaktivite puanları ile Piers Harris Öz Kavramı Ölçeği toplam puanları arasında ise negatif yönlü düşük düzeyde anlamlı ilişki saptanmıştır. Ayrıca Turgay Ebeveyn dikkat eksikliği ve hiperaktivite puanları ile Otizm Spektrum Anketi toplam puanları arasında pozitif yönlü, orta düzeyde anlamlı ilişki saptanmıştır. Turgay Öğretmen formu dikkat eksikliği ve hiperaktivite puanları ile Otizm Spektrum Anketi toplam puanları arasında ise pozitif yönlü düşük düzeyde anlamlı ilişki saptanmıştır. Katılımcıların ebeveynleri ve öğretmenleri tarafından bildirilen dikkat eksikliği ve hiperaktivite semptom şiddeti ile (Turgay Çocuk ve Ergenlerde Davranış Bozuklukları için DSM-IV'e Dayalı Tarama ve Değerlendirme Ölçeği-Ebeveyn ve Öğretmen formu) Piers Harris Öz Kavramı Ölçeği ve Otizm Spektrum Anketi ölçek puanları arasındaki ilişkiye ait veriler Tablo 3'te sunulmuştur.

Tablo 3.

DEHB semptom şiddeti ile ölçek puanları arasındaki korelasyonlar (n=126)

Toplam Ölçek Puanları	Turgay-Ebeveyn		Turgay-Öğretmen	
	Dikkat Eksikliği	Hiperaktivite	Dikkat Eksikliği	Hiperaktivite
Piers Harris Öz Kavramı Ölçeği [a]	**r=-0,346, p<0,001, düz.p<0,001**	**r=-0,306, p<0,001, düz.p=0,001**	**r=-0,234, p=0,002, düz.p=0,005**	**r=-0,186, p=0,015, düz. p=0,015**
Otizm Spektrum Anketi [a]	**r=0,453, p<0,001, düz.p<0,001**	**r=0,316, p<0,001, düz.p=0,001**	**r=0,192, p=0,012, düz.p=0,014**	**r=0,210, p=0,006, düz.p=0,008**

a. Pearson Korelasyon Analizi

düz.p= düzeltilmiş p değeri (Benjamini-Hochberg FDR yöntemiyle düzeltilmiş)

DEHB görünümüne göre gruplar arasında Piers Harris Öz Kavramı Ölçeği ve Otizm Spektrum Anketi açısından anlamlı bir farklılık saptanmamıştır (p>0,05). HA görünümündeki katılımcılar, sayıca çok az olduğundan (n=4) analiz dışı bırakılmış ve karşılaştırma DE ve Karma görünüm arasında gerçekleştirilmiştir. DEHB+ gruptaki katılımcıların DEHB görünümüne göre ölçek puanlarının karşılaştırılmasına ait veriler Tablo 4'te sunulmuştur.

Tablo 4.

DEHB görünümüne göre toplam ölçek puanlarının karşılaştırılması (n=122)

Toplam Ölçek Puanları	DE (n=70), Ort ± SD,	Karma (n=52), Ort ± SD,	İstatistik/t	Etki Büyüklüğü/Cohen's d	p
Piers Harris Öz Kavramı Ölçeği	53,13 ± 11,69	49,85 ± 10.27	1,62	0,295	0,109
Otizm Spektrum Anketi	58,93 ± 15,18	63,12 ± 10,62	-1,79	0,312	0,076

Ort: Ortalama, SD: Standart sapma, t: Bağımsız örneklemlerde t testi

DEHB+ grupta Otizm Spektrum Anketi toplam ölçek puanının Piers Harris Öz Kavramı Ölçeği toplam puanını yordayıp yordamadığını tespit etmek için kurulan basit lineer regresyon analizi sonucunda Otizm Spektrum Anketi toplam ölçek puanlarının Piers Harris Öz Kavramı Ölçeği toplam

puanını anlamlı bir şekilde yordadığı saptanmıştır ($F_{(1,170)}$=21,25, p<0,001, düzeltilmiş R^2=0,106). Otizm Spektrum Anketi toplam puanlarının Piers Harris Öz Kavramı Ölçeği toplam puanı üzerine olan etkisinin Turgay-DE, Turgay-HA puanları, yaş ve cinsiyet değişkenlerinin kontrol edilerek yeniden incelenmesi için çoklu lineer regresyon modeli kurulmuştur (Tablo 5). Buna göre Dikkat Eksikliği semptom şiddeti (Turgay-DE), hiperaktivite semptom şiddeti (Turgay-HA), yaş ve cinsiyet değişkenleri kontrol edildiğinde dahi Otizm Spektrum Anketi toplam puanı, Piers Harris Öz Kavramı Ölçeği toplam puanını halen anlamlı bir şekilde yordamaktadır (p=0,007). Otizm Spektrum Anketi puanındaki artış, Piers Harris Öz Kavramı Ölçeği puanlarında azalmaya neden olmaktadır (β=-0,212).

Tablo 5.

Çoklu doğrusal regresyon analizi

Bağımsız Değişkenler	B	S.E	β	t	p	%95 G.A	VIF
Otizm Spektrum Anketi	-0,174	0,064	-0,212	-2,73	**0,007**	-0,300- -0,048	1,221
Turgay-DE	-0,365	0,189	-0,189	-1,93	0,055	-0,738-0,008	1,939
Turgay-HA	-0,199	0,162	-0,118	-1,23	0,222	-0,519-0,121	1,874
Yaş (yıl)	-0,431	0,324	-0,099	-1,33	0,186	-1,071-0,210	1,134
Cinsiyet (referans: erkek)	0,826	1,743	0,036	0,474	0,636	-2,616-4,268	1,425

B: Unstandardize regresyon katsayısı, β: Standardize regresyon katsayısı, S.E: Standart hata

*Modele ait bilgiler: Bağımlı değişken= Piers Harris Toplam Puanı, $F_{(5,166)}$=7,37, p<0,001, Düzeltilmiş R^2=0,157, G.A: Güven Aralığı, VIF: Varyans Inflasyon Faktör

Ek Tablo 1.

Katılımcıların ölçek alt puanlarının karşılaştırılması(n=172)

Toplam Ölçek Puanları		DEHB+ (n=126), Ort± SD, Med (IQR)	DEHB – (n=46), Ort± SD, Med (IQR)	İstatistik	Etki Büyüklüğü/ Cohen's d/Rank biserial korelasyon	p	Düz.p
Piers Harris Öz Kavramı Ölçeği	Mutluluk	9,00 (7,00-12,00)	11,00 (9,75-12,00)	Z=-2,84	0,473	**0,005**	**0,015**
	Kaygı	6,52 ± 2,57	7,65 ± 3,02	t=2,45	0,422	**0,015**	**0,030**
	Popülarite	7,57 ± 2,54	7,52 ± 2,68	t=-0,11	0,019	0,911	0,911
	Davranış Uyum	10,00 (7,00-14,00)	13,00 (10,75-14,00)	Z=-3,53	0,598	**<0,001**	**0,003**
	Fiziksel Görünüm	7,00 (6,00-9,00)	8,00 (7,00-9,00)	Z=-2,29	0,327	**0,022**	**0,033**
	Zihin ve Okul Durumu	3,84 ± 1,66	4,22 ± 1,56	t=1,34	0,230	0,184	0,221

Ek Tablo 1 (Devamı)

Otizm Spektrum Anketi	Sosyal	10,00 (6,00-13,00)	8,00 (5,00-11,25)	Z=-1,71	0,193	0,087	0,109
	Dikkat Değiştirme	13,21 ± 4,14	10,17 ± 3,73	t=-4,37	0753	**<0,001**	**<0,001**
	Detay	11,60 ± 3,94	12,54 ± 3,89	t=1,40	0,242	0,163	0,163
	İletişim	12,40 ± 5.80	9,76 ± 5.50	t=-2,68	0,462	**0,008**	**0,013**
	Hayal	12,09 ± 4,29	10,11 ± 3,61	t=-2,79	0,481	**0,006**	**0,013**

Ort: Ortalama, SD: Standart sapma, t: Bağımsız örneklemlerde t testi, Med: Ortanca, IQR: Çeyrekler arası aralık (1. ve 3. Çeyrek değerleri sunulmuştur), düz.p= düzeltilmiş p değeri (Benjamini-Hochberg FDR yöntemiyle düzeltilmiş)

4. TARTIŞMA

Çalışmamızda ÖÖB tanılı çocuk ve ergenlerde DEHB eş tanısı ile bu olgulardaki otistik özellikler, öz kavramı ilişkisi incelenmiştir. Bu bağlamda ÖÖB tanılı çocuklarda DEHB eş hastalanımı varlığı ve yokluğu durumlarında öz kavramındaki farklılık ortaya konmaya çalışılmıştır. Çalışmamızın bir diğer amacı da ÖÖB ve DEHB eş hastalanımı olan çocuklarda otistik özelliklerin öz kavramı ile olan ilişkisini ortaya koymaktır. Bulgularımızdan elde ettiğimiz sonuçlara göre DEHB komorbiditesinin öz kavramı üzerinde olumsuz bir etkiye sahip olduğu; ÖÖB tanılı çocuklarda DEHB komorbid grupta DEHB belirti düzeyi, yaş ve cinsiyetten bağımsız bir biçimde otistik özelliklerin öz kavramını yordayabileceği gösterilmiştir.

DEHB, ÖÖB'ye en sık eşlik eden nörogelişimsel bozukluktur.[2,26] Literatürde, DEHB tanılı çocuklarda öz kavramının yaşla birlikte ve içe atım sorunlarının artışıyla birlikte değişim gösterdiği,[27] dikkat becerileri ve yürütücü işlevlerdeki güçlüklerin öz kavramı üzerinde olumsuz etkide bulunabildiği,[28] DEHB'ye eşlik eden anksiyete belirtilerinin, dikkat becerileri ile öz kavram arasındaki ilişkide aracılık rolü oynayabileceği[29] belirtilmektedir. ÖÖB ile öz kavramı ilişkisini inceleyen sistematik derleme, [6] meta-analizler [7–9] incelendiğinde ise ÖÖB ve DEHB birlikteliğinde öz kavramını ele alan çalışmaların oldukça sınırlı olduğu görülmektedir. Nitekim güncel araştırmalarda, karıştırıcı değişkenlerin etkisini minimize etmek amacıyla ÖÖB genellikle eş hastalık olmaksızın ele alınmakta, komorbiditeler çalışmalardan dışlanmaktadır.[30] Çalışmamız bu literatüre, DEHB komorbiditesi ve otistik özelliklerin birlikte değerlendirildiği daha güncel, çok boyutlu bir katkı sunma çabasındadır. Mevcut bilgimize göre bugüne dek yalnızca bir çalışma doğrudan ÖÖB ve DEHB komorbiditesi durumunda öz kavramını incelemiştir.[9] Tabassam ve ark.[31] yaş grubu bizim çalışmamıza benzer ÖÖB tanılı çocuklarla yürüttükleri araştırmada, akademik öz kavramı ile akademik olmayan öz kavramı arasında farklılık bulmuştur. Komorbid durumda çocukların akademik öz kavram puanları sayısal olarak daha düşük olsa da, bu fark istatistiksel olarak anlamlı değildir. Buna karşılık, akademik olmayan öz kavram puanları anlamlı düzeyde düşük bulunmuştur. Bizim çalışmamızda da benzer şekilde öz kavramı içindeki zihin/okul durumu alt ölçeğinde bir farklılık bulunmazken, davranış/uyum, mutluluk ve kaygı etmenlerinde anlamlı farklılık gözlenmiştir. Ayrıca çalışmamızda, DEHB şiddeti hem ebeveyn hem de öğretmen değerlendirme formları aracılığıyla ölçülmüş; öz kavramı ile DEHB şiddeti arasında olumsuz bir ilişki olduğu bulunmuştur. Bununla birlikte, DEHB'nin dikkat eksikliği baskın ve karma görünüm alt türleri arasında öz kavramı düzeyi açısından anlamlı bir fark saptanmamıştır. ÖÖB'ye DEHB'nin eşlik ettiği durumlarda fonemik farkındalık, sözel akıl yürütme, hızlı otomatize isimlendirme ve çalışma belleği gibi alanların daha olumsuz seyredebileceği bildirilmektedir.[32] Bu komorbiditenin daha ağır bir nörofizyolojik zayıflık ve artmış bir genetik yük ile ilişkili olabileceği düşünülmektedir.[33] Ayrıca bu eş hastalanım; okul başarısı, okul devamlılığı ve mesleki edinim açısından da daha olumsuz bir yaşam sürecini öngörmektedir.[34] Buna ek olarak,

ÖÖB ve DEHB eş hastalanımında hem içe atım hem de dışa atım bozuklukları sıklığında artış gözlenmekte, arkadaşları tarafından reddedilme, yalnızlık gibi alanlarda sosyal işlevsellik daha belirgin etkilenmektedir.[35] Nitekim bir çalışmada, ÖÖB tanılı çocuklarda sosyal işlevsellikle ilişkili olarak bu durumun yalnızca DEHB komorbiditesi varlığında söz konusu olduğu da bildirilmiştir.[36] Mevcut literatür bilgileri çalışmamızda gösterilen mutluluk, kaygı, davranış/uyum parametrelerine dair öz kavramının DEHB komorbid grupta düşük bulunmasını açıklar gözükmektedir. Çalışmamızdan elde ettiğimiz bir diğer sonuç ise fiziksel görünüm parametresinin DEHB tanılı grupta daha düşük seyretmesi olmuştur. DEHB tanılı çocuklarda artmış bir motor gelişim sorunu olduğu bilinmekte,[37] gelişimsel koordinasyon bozukluğu ile birlikte görülme sıklığı yüksek oranda seyretmektedir.[38] Bu birliktelik daha düşük yaşam kalitesi ve daha kötü akran ilişkileriyle de ilintili bulunmaktadır.[39] Disgrafi gibi motor becerilerin daha ön planda olduğu alanlarda sorunlar ile koordinasyon bozukluğu kendini gösterebilmektedir.[40] Dolayısıyla, DEHB'nin eşlik ettiği ÖÖB tanılı çocuklarda görülebilecek motor kabiliyet eksiklikleri, bedenleri üzerindeki yetkinlik algılarını öznel yetersizlik düşünce ve duyguları veya akranlarının muhtemel negatif söylem ve eylemleri aracılığıyla etkilemiş olabilir. Tüm bu bulgular değerlendirildiğinde hem nöropsikolojik ve genetik etmenler gibi doğrudan faktörler ve hem de DEHB'nin eşlik etmesiyle birlikte bozulabilecek akran ilişkileri, aile dinamikleri ve zaman içinde ortaya çıkabilecek anksiyete ve depresyon gibi içe atım bozukluklarının öz kavramı ile ilişkili olabileceği söylenebilir. İlgili etmenlerle öz kavramının neden sonuç ilişkisini inceleyebilmek adına ileri boylamsal çalışmaların yapılmasına ihtiyaç duyulmaktadır.

ÖÖB diğer bir nörogelişimsel sorun olan bazı otistik özelliklerle birlikte seyredebilmektedir. ÖÖB tanılı çocukların; dilin pragmatik alanında zorluk yaşadığı,[18,19] zihin kuramında daha düşük performans sergilediği,[17,20] emosyon tanıma ve niyet okuma açısından güçlük çektiği bildirilmiştir.[15] DEHB tanılı çocukların tipik gelişen çocuklara göre de daha yüksek oranda otistik özellikler gösterdiği ortaya konmuştur [41,42]. Ayrıca, DEHB eş tanılı ÖÖB'li çocukları sosyal biliş ve otistik özellikler açısından sağlıklı kontrol grubu ile kıyaslayan bir başka çalışmada, araştırmacılar DEHB eş tanılı ÖÖB'li çocukların sosyal bilişlerinin normal gelişim gösteren kontrol grubuna kıyasla daha olumsuz göründüğünü ve otizm spektrum özelliklerinin daha fazla olduğunu saptamışlardır.[43] Ancak, bildiğimiz kadarıyla ÖÖB tanılı çocuk ve ergenlerde DEHB eş tanısı varlığı ve yokluğunun otizm spektrum bozukluğu özelliklerine özgül katkısını araştıran bir çalışma bulunmamaktadır. Çalışmamızda DEHB eş tanısı olan ÖÖB'lilerin DEHB eş tanısı olmayan ÖÖB'lilere kıyasla otizm spektrum özelliklerinin daha belirgin olduğu sonucuna ulaşılmıştır. Ek olarak DEHB semptom şiddeti ile otistik özelliklerin ilişkisi incelenmiş, DEHB semptom şiddeti arttıkça otistik özelliklerin de arttığı bulunmuştur. Çalışmamızın temel odağı olan öz kavramı açısından bakıldığında ise DEHB eş tanısı varlığında DEHB belirti şiddetinden bağımsız bir biçimde otistik özelliklerin daha düşük öz kavramını yordadığı gösterilmiştir. DEHB eş tanısının varlığı yukarıda belirtilen literatür ışığında artmış sosyal iletişim defisitleri, kısıtlı pragmatik beceriler ve düşük sosyal kognisyon yetileri aracılığıyla ÖÖB'li çocuklarda öz kavramını etkileyebilir. Tipik gelişim gösteren çocuklara göre halihazırda düşük öz kavramı gösteren ÖÖB tanılı çocuklar [9,44,45] DEHB komorbiditesinin varlığında artan sosyal zorluklarla[35] mutsuzluk ve kaygı parametreleri açısından kendilerine dönük algılarında olumsuz etkilenme yaşamış olabilir. Bir diğer açıdan bakıldığında öğrenme bozukluğunda otistik özelliklerin daha ağır belirtilerle seyrettiği gözlenmiştir.[46] Çalışmamızda her ne kadar ÖÖB şiddeti değerlendirilmemişse de otistik özelliklerle öz kavramı arasındaki bu ilişkinin bir açıklaması da bu bağlamda ÖÖB şiddetindeki artış olabilir.

Çalışmamız, DEHB eş tanılı ÖÖB olgularında otizm spektrum özellikleri ve öz kavramı ilişkisi hakkında literatüre önemli katkılar sağlamasına karşın bazı sınırlılıklar da içermektedir. İlk olarak çalışmamızın örneklem grubu az sayıda olgudan oluşan bir klinik popülasyonundan elde edilmiştir

ve genellenebilirliği kısıtlıdır. Ebeveynlerin sosyoekonomik durumları, eğitim düzeyleri ve öz kavramını etkileyebilecek ebeveyn-çocuk ilişkileri değerlendirilmeye katılmamıştır. ÖÖB tanılı çocuklar alt grup ve klinik şiddet açısından değerlendirilmemiştir. Çalışmamızda OSB özelliklerinin ebeveyn görüşünü baz alan bir ölçekle değerlendirilmesi de bir kısıtlılık olarak görülebilir. Ek olarak, çalışmamızın kesitsel deseni neden sonuç ilişkilerini kurmak açısından elverişli değildir. Bununla beraber çalışmamızın bazı güçlü yönleri bulunmaktadır. DEHB dışı psikopatolojileri olan olgular çalışmaya dahil edilmemiş ve bu sayede ek tanıların etkisi ortadan kaldırılıp homojen bir grup ortaya çıkarılmıştır. Bu çalışmanın ÖÖB ve DEHB eş tanılı çocuklarda otistik özellikler ile öz kavramı arasındaki ilişkiyi inceleyen ilk çalışma olması literatüre önemli bir katkı gibi görünmektedir.

5. SONUÇ

Sonuç olarak, ÖÖB tanılı çocuk ve ergenlerde DEHB eş tanısının varlığı, öz kavramını olumsuz yönde etkilemekte ve otistik özelliklerde artışa yol açmaktadır. Bu eş hastalanım durumunda otistik özelliklerin öz kavramı üzerinde anlamlı bir yordayıcı etkisinin bulunduğu görülmektedir. Bu bulgular, çocuk ve ergen ruh sağlığı ve hastalıkları kliniklerinde DEHB eş tanılı ÖÖB'li olguların otistik özellikler ve öz kavramı açısından daha ayrıntılı değerlendirilmesinin önemini ortaya koymaktadır. Ayrıca, bu çocuk ve ergenlerde yalnızca akademik desteğe odaklanmak yerine, sosyal becerileri ve öz kavramını güçlendirmeye yönelik müdahalelerin de dahil edildiği bütüncül bir tedavi yaklaşımının geliştirilmesi gerektiği anlaşılmaktadır.

Makale Bilgi Formu

Teşekkür

Yazarlar çalışmaya katılan çocuklara ve ailelerine şükranlarını sunar.

Yazarların Katkısı

Çalışma dizaynı: İA, ÖE İSG; Veri Toplanması: İA, RSK, HE, OBK, İSG; Veri Analizi: İA, OBK, HE, TS; Çalışma Süpervizyonu: İA, ÖE, TS, OBK; Metin Yazımı; TS, İA, HE, RSK; Eleştirel Revizyonlar: İA, ÖE, TS, HE.

Çıkar Çatışması / Ortak Çıkar Beyanı

Yazarlar tarafından herhangi bir çıkar çatışması veya ortak çıkar beyan edilmemiştir.

Etik Kurul Onay Beyanı

Çalışma protokolü Sağlık Bilimleri Üniversitesi Erenköy Ruh ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi etik kurulu tarafından 17.06.2019 tarihinde onaylanmıştır.

Yapay Zeka Beyanı

Bu makale yazılırken hiçbir yapay zeka aracı kullanılmamıştır.

Telif Hakkı Beyanı

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Research Article

Real-World Impact of SGLT2 Inhibitors on Systemic Inflammation in Type 2 Diabetes: A Composite Biomarker-Based Evaluation

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Background: Chronic low-grade inflammation is increasingly recognized as a key contributor to the pathophysiology and complications of type 2 diabetes mellitus (T2DM). Although sodium-glucose co-transporter 2 (SGLT2) inhibitors offer established metabolic and cardiovascular benefits, their real-world impact on systemic inflammation remains unclear. In this study, we investigated the effects of SGLT2 inhibitor therapy on composite inflammation indices over six months in patients with T2DM and explored the differences across clinical subgroups and drug types.

Methods: In this retrospective observational study, 163 adults with T2DM who were prescribed either empagliflozin or dapagliflozin were followed up for six months. Inflammatory burden was assessed using the pan-immune-inflammation value (PIV) and systemic immune-inflammation index (SII), which were calculated from the complete blood count parameters. Paired comparisons were performed using Wilcoxon signed-rank tests, and subgroup differences in ΔPIV and ΔSII were analyzed using the Mann–Whitney U-test.

Results: At the sixth month, significant reductions were observed in both PIV (335.0 ± 287.4 to 282.6 ± 189.3; p=0.014) and SII (579.1 ± 332.8 to 496.0 ± 224.0; p<0.001). Empagliflozin led to greater improvements in ΔPIV (p=0.011) and ΔSII (p<0.001) than those with dapagliflozin. Subgroup analysis revealed that patients aged ≥55 years and those with a baseline SII >600 exhibited the most pronounced reductions in inflammatory indices. No significant differences were observed according to sex, BMI, or smoking status of the patients.

Conclusion: SGLT2 inhibitors significantly reduce the systemic inflammatory burden in patients with T2DM, with empagliflozin demonstrating superior anti-inflammatory efficacy. The benefits are particularly evident in individuals with elevated baseline inflammation and older age, supporting the integration of inflammation-based biomarkers, such as PIV and SII, into future personalized therapeutic approaches.

Keywords: SGLT2 inhibitors, Systemic inflammation, Type 2 diabetes mellitus, PIV, SII, Inflammatory biomarkers

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance, β-cell dysfunction, and chronic hyperglycemia.[1] In addition to impaired glucose metabolism, T2DM is frequently accompanied by a constellation of metabolic and inflammatory abnormalities, including dyslipidemia, central obesity, low-grade systemic inflammation, and increased cardiovascular risk.[2] Therefore, there is growing clinical interest in therapeutic approaches that extend beyond glycemic control to target these interconnected comorbidities.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors have emerged as an innovative class of antihyperglycemic agents that reduce blood glucose levels by enhancing urinary glucose excretion.[1,3] In addition to their glucose-lowering effects, accumulating evidence suggests that SGLT2 inhibitors confer a range of pleiotropic benefits, including reductions in body weight, blood pressure, and systemic inflammatory markers, as well as improvements in cardiovascular and renal outcomes.[4]

Dapagliflozin, one of the most extensively studied agents in this class, has demonstrated robust efficacy in improving glycemic control and reducing cardiovascular events in large-scale randomized trials. However, real-world data evaluating the effects of empagliflozin on systemic

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inflammation and broader metabolic profiles in patients with T2DM are scarce. Recently, composite inflammatory indices, such as the pan-immune-inflammation value (PIV) and the systemic immune-inflammation index (SII), derived from neutrophil, platelet, lymphocyte, and monocyte counts, have emerged as novel biomarkers of systemic inflammatory burden and have been associated with cardiovascular and metabolic outcomes in various populations.[5,6]

In this study, we aimed to investigate the effects of SGLT2 inhibitor therapy on systemic inflammation in patients with T2DM over a six-month period. We evaluated composite inflammatory markers, including PIV and SII, to better characterize the changes in the inflammatory burden. Thus, we aimed to provide real-world evidence of the broader immunometabolic effects of SGLT2 inhibitors beyond glycemic control.

2. METHODS

2.1. Study design and population

This retrospective observational study included adult patients with T2DM who were initiated on SGLT2 inhibitor therapy and were followed up for at least six months. Patients were enrolled from a single tertiary care center.

Exclusion criteria:

- Age <18 years
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2)
- Active malignancy
- Pregnancy or lactation
- Introduction of new antidiabetic or antihyperlipidemic agents during the follow-up period
- Patients who stopped or interrupted treatment
- Patients who consume alcohol
- Patients who are active smokers
- Acute or chronic viral hepatitis
- Patients with active infection or those who have received treatment for infection within the last month
- Patients with autoimmune diseases
- Patients receiving steroid therapy
- Patients who have had surgery within the last month

2.2. Ethical considerations

The study was approved by the Institutional Review Board Approval Date: August 21, 2024; Decision No: 2024-13/2 and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

2.3. Data collection

Demographic characteristics (age, sex, and smoking status), anthropometric measurements (height, weight, and BMI), and laboratory data, including complete blood count parameters, were collected at baseline and 6 months after SGLT2 inhibitor therapy initiation.

The following systemic inflammation indices were calculated at both time points:

- **Pan-Immune-Inflammation Value (PIV)** = (Neutrophil × Platelet × Monocyte) ÷ Lymphocyte
- **Systemic Immune-Inflammation Index (SII)** = (Neutrophil × Platelet) ÷ Lymphocyte

Changes in inflammatory markers were computed as delta values (Δ), defined as the difference between the 6-month and baseline measurements.

2.4. Subgroup definitions

Patients were stratified according to the following criteria:

- SGLT2 inhibitor type (empagliflozin vs dapagliflozin),
- Gender (female vs male),
- Smoking status (smoker vs non-smoker),
- BMI group (obese [≥30 kg/m^2] vs non-obese),

- Age group (<55 vs ≥55 years),
- Baseline inflammatory burden (SII >600 vs. SII ≤600). A baseline SII cutoff of 600 was used to define high versus low inflammatory burden, consistent with previous studies and aligned with the median SII value observed in our study population.

2.5. Statistical analysis

Data distribution was assessed using the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation (SD) for normally distributed data and as median with interquartile range (IQR) for non-normally distributed data. Paired comparisons between baseline and 6-month values were performed using the Wilcoxon signed-rank test. Between-group differences (empagliflozin vs. dapagliflozin) were analyzed using the Mann–Whitney U test. Statistical significance was set at $p < 0.05$.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (Armonk, NY: IBM Corp.).

3. RESULTS

3.1. Baseline characteristics

A total of 163 patients were included in the analysis. The mean age was 56.96 ± 9.74 years, with an almost equal distribution of females (n=82, 50.3%) and males (n=81, 49.7%). Most of the participants were non-smokers (62.0%). The mean BMI at baseline was 30.84 ± 4.51 kg/m^2, which decreased to 29.61 ± 4.14 kg/m^2 at the sixth month. The detailed demographic and clinical characteristics are presented in Table 1.

Table 1.

Baseline demographic and clinical characteristics of the study population

Variable	n (%)	Mean ± SD	Median (IQR)
Age (years)		56.96 ± 9.74	57.0 (49.0–64.0)
Gender			
Female	82 (50.3)		
Male	81 (49.7)		
Smoking status			
Non-smoker	101 (62.0)		
Smoker	62 (38.0)		
Height (cm)		166.4 ± 9.4	165.0 (158.0–175.0)
Weight at baseline (kg)		85.04 ± 11.81	83.0 (76.5–92.0)
Weight at 6th months (kg)		81.57 ± 10.02	82.0 (74.0–88.5)
BMI at baseline (kg/m^2)		30.84 ± 4.51	31.1 (27.7–33.4)
BMI at 6th months (kg/m^2)		29.61 ± 4.14	29.6 (26.9–32.0)

BMI: body mass index

Continuous variables are presented as mean ± standard deviation (SD) and median (interquartile range [IQR]), depending on distribution. Categorical variables are expressed as frequencies and percentages. Data reflect baseline measurements prior to initiation of SGLT2 inhibitor therapy.

3.2. Overall changes in inflammatory indices

Both PIV and SII showed statistically significant reductions after six months of SGLT2 inhibitor therapy. The mean PIV decreased from 335.0 ± 287.4 to 282.6 ± 189.3, with a median change of 16.9 (IQR: −53.8 to 87.7; p =0.014). The mean SII declined from 579.1 ± 332.8 to 496.0 ± 224.0, with a median reduction of −59.5 (IQR: −195.5 to 76.5; p<0.001) (Table 2, Figure 1).

Table 2.

Change in inflammatory indices following 6 Months of SGLT2 inhibitor therapy

Parameter	Baseline (mean ± SD)	6th Months (mean ± SD)	Median Change (IQR)	p-value
PIV	335.0 ± 287.4	282.6 ± 189.3	16.9 (-53.8–87.7)	0.014
SII	579.1 ± 332.8	496.0 ± 224.0	-59.5 (-195.5–76.5)	<0.001

PIV: pan immune value, SII: Systemic Immune-Inflammation Index
Data are presented as mean ± standard deviation (SD) for normally distributed variables and as median (interquartile range [IQR]) for non-normally distributed variables. Statistical significance was evaluated using the Wilcoxon signed-rank test for paired comparisons. A two-sided p-value <0.05 was considered statistically significant. Mean percentage change from baseline to 6 months was 2.3% ± 51.1 for PIV and –0.5% ± 50.9 for SII, indicating considerable interindividual variability in inflammatory response to SGLT2 inhibitor therapy.

3.3. Drug-based subgroup analysis

In subgroup analyses based on drug type, patients receiving empagliflozin (n=111) exhibited a significant reduction in both PIV and SII, whereas those receiving dapagliflozin (n=52) showed no meaningful change in PIV and a paradoxical increase in SII. The difference in the median ΔPIV and ΔSII values between the two groups was statistically significant (p=0.011 and p<0.001, respectively) (Table 3).

3.4. Additional subgroup comparisons

Subgroup analyses by sex, smoking status, obesity, age, and baseline SII levels revealed several noteworthy patterns.

- No significant differences were observed in the ΔPIV or ΔSII between male and female participants.
- Non-smokers showed a trend toward greater reductions in the SII than smokers, although this did not reach statistical significance.
- Both obese and non-obese individuals experienced comparable reductions.
- Notably, patients aged ≥55 years exhibited significantly greater reductions in both PIV (p=0.044) and SII (p=0.020) than those aged < 55 years.
- The most pronounced improvements were observed in patients with a baseline SII >600, with median ΔPIV and ΔSII of 102.3 and –250.1, respectively (both p<0.001), indicating a stronger anti-inflammatory response in individuals with higher baseline inflammation (Table 3 and Figure 2).

Figure 1.

Comparative changes in the Pan-Immune-Inflammation Value (PIV) and Systemic Immune-Inflammation Index (SII) from baseline to 6 months following SGLT2 inhibitor

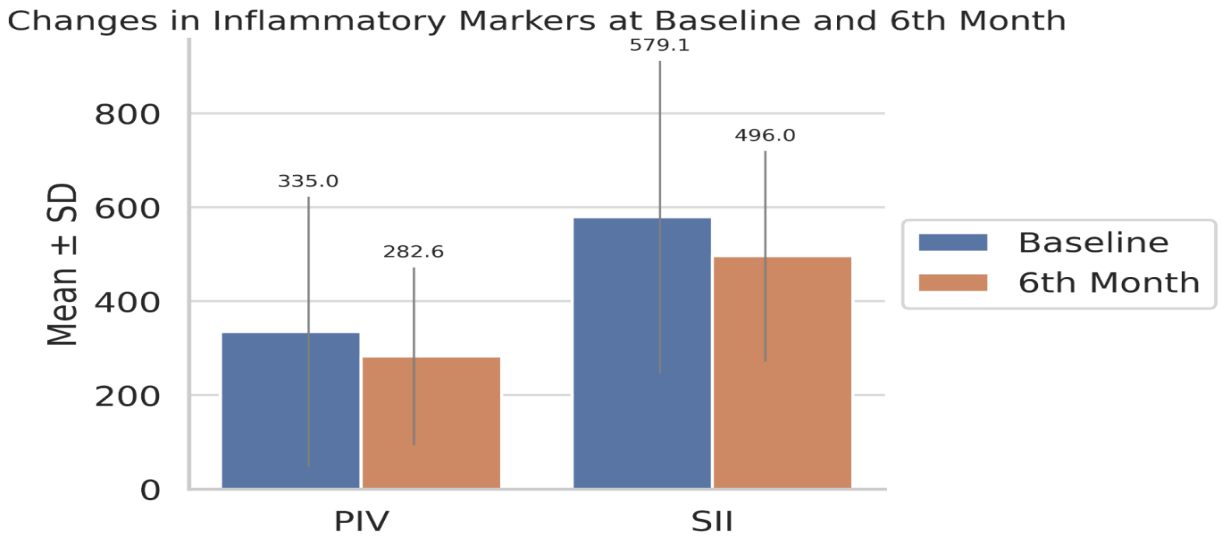

Table 3.

Integrated subgroup analysis of PIV and SII changes

Subgroup	n	PIV Baseline (mean ± SD)	PIV 6 Mo (mean ± SD)	PIV Δ (median, IQR)	PIV Δ p-value	SII Baseline (mean ± SD)	SII 6 Mo (mean ± SD)	SII Δ (median, IQR)	SII Δ p-value
Empagliflozin	111	342.5 ± 272.5	276.3 ± 176.6	27.7 (-37.7–93.1)	0.000	603.0 ± 335.9	455.9 ± 187.8	-86.1 (-203.5–31.3)	0.000
Dapagliflozin	52	319.0 ± 319.0	295.8 ± 215.2	-18.5 (-90.6–53.5)	0.554	528.1 ± 323.3	581.7 ± 269.0	83.9 (-84.9–252.7)	0.038
Sex: Female	82			21.6 (-49.8–93.0)	0.869			-71.8 (-203.6–60.1)	0.851
Sex: Male	81			8.6 (-60.7–78.0)	0.869			-54.5 (-194.0–85.0)	0.851
Smoking: No	101			21.9 (-50.6–94.4)	0.230			-76.2 (-193.7–41.3)	0.118
Smoking: Yes	62			7.5 (-57.8–72.8)	0.230			-16.7 (-136.8–103.4)	0.118
Obese	90			10.2 (-53.0–73.4)	0.420			-63.7 (-174.8–47.4)	0.760
Non-obese	73			18.9 (-55.9–93.6)	0.420			-56.2 (-221.8–109.5)	0.760
Age <55	69			1.7 (-69.9–73.2)	0.044			-18.1 (-142.2–106.0)	0.020
Age ≥55	94			26.4 (-55.7–108.4)	0.044			-78.9 (-202.1–44.2)	0.020
SII >600	59			102.3 (-18.4–223.1)	0.000			-250.1 (-408.5–-91.8)	0.000
SII ≤600	104			-9.0 (-53.2–35.2)	0.000			6.4 (-95.2–108.0)	0.000

PIV: pan immune value, SII: Systemic Immune-Inflammation Index

Values are expressed as mean ± SD or median (IQR), depending on data distribution. Within-group comparisons (baseline vs. 6th month) were conducted using the Wilcoxon signed-rank test. Between-group comparisons of delta values (ΔPIV and ΔSII) were performed using the Mann–Whitney U test. Statistical significance was defined as a two-tailed p-value <0.05

4. DISCUSSION

In this real-world cohort of 163 T2DM patients, six months of SGLT2 inhibitor therapy yielded robust anti-inflammatory effects, as evidenced by significant reductions in both PIV and SII. Notably, empagliflozin demonstrated superior efficacy compared with dapagliflozin (ΔPIV $p = 0.011$; ΔSII $p < 0.001$). Stratified analyses revealed that older individuals (≥55 years) and those with markedly elevated baseline inflammation (SII >600) experienced the most profound declines in inflammatory markers, whereas sex, BMI, and smoking status did not affect inflammatory response.

4.1. Mechanistic insights and alignment with literature

Our findings support the growing body of preclinical and clinical evidence indicating that SGLT2 inhibitors possess intrinsic anti-inflammatory properties. Empagliflozin has been shown to attenuate macrophage-mediated inflammation by downregulating TLR4/NF-κB, ERK1/2-MAPK, and JAK/STAT signaling, leading to the suppression of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, in cellular and animal models.[7,8] Dapagliflozin similarly reduces NLRP3 inflammasome activation by preserving mitochondrial respiratory capacity and decreasing ROS-mediated immune activation.[9] These mechanistic insights may partly explain the more pronounced reductions in PIV and SII observed in the empagliflozin group of our study, as empagliflozin has been shown to attenuate LPS-induced pro-inflammatory macrophage activation by inhibiting the IKK/NF-κB, JNK/MAPK, and JAK2/STAT1 signaling pathways.[10]

The link between metabolic dysregulation and low-grade systemic inflammation is largely driven by mechanisms such as adipose tissue dysfunction, excess glucose levels and lipid overload. These disturbances trigger key inflammatory pathways, including the activation of NF-κB, the NLRP3 inflammasome, and oxidative stress cascades, which sustain a proinflammatory state.[11] Chronic hyperglycemia is known to promote the release of cytokines, such as IL-6, TNF-α, and IL-1β, both directly and via the generation of reactive oxygen species.[12] By improving glycemic control and reducing oxidative stress, SGLT2 inhibitors may help interrupt this cycle, leading to a gradual reduction in systemic inflammation.

4.2. Significance of composite indices (PIV and SII)

By integrating multiple immune cell lineages, SII and PIV outperformed single-cell measures in reflecting the systemic inflammatory burden. Elevated SII levels have a predictive value for diabetic complications and cardiovascular risk in various populations. Our study extends this understanding by showing that SII reductions, particularly in patients with a baseline SII >600, mirror the anti-inflammatory efficacy of SGLT2 inhibitors in clinical settings.

The PIV and SII are composite biomarkers derived from peripheral blood parameters, including neutrophils, lymphocytes, platelets, and monocytes (for PIV). These indices offer an integrative view of the immune-inflammatory burden and have shown superior prognostic performance compared to isolated leukocyte counts in predicting major adverse cardiovascular events, heart failure outcomes, and all-cause mortality.[6,13,14] Our results not only support their clinical utility but also demonstrate their responsiveness to SGLT2 inhibition, particularly in patients with high baseline inflammatory loads. However, the mean percentage change was relatively modest (2.3% increase for PIV and 0.5% decrease for SII), with wide standard deviations (±51.1 and ±50.9, respectively), reflecting substantial interindividual variability in inflammatory response. This variation may be attributed to the baseline metabolic status, differential drug effects, or unmeasured confounders such as adherence or undiagnosed inflammatory conditions.

4.3. Subgroup-based insights

Subgroup analysis revealed that older individuals and patients with a baseline SII >600 exhibited significantly greater improvements in inflammatory marker levels. This finding supports previous findings in cardiovascular and metabolic populations, in which high baseline inflammation

predicts a greater therapeutic response.[6] These results may have important implications for personalized antidiabetic treatment strategies, in which the anti-inflammatory potential can guide the selection of agents.

4.4. Empagliflozin vs. Dapagliflozin: A class effect or a distinct signature?

Although both empagliflozin and dapagliflozin are approved SGLT2 inhibitors, head-to-head comparison data on their modulation of inflammation are limited. Our findings add to the emerging evidence suggesting that empagliflozin exerts broader immunomodulatory effects.[7,10] Although this difference could stem from pharmacodynamic properties, further prospective randomized studies are needed to determine whether this represents a consistent class effect gradient.

4.5. Strengths and limitations

The strengths of this study include the use of real-world data, validated composite inflammation indices, and comprehensive subgroup analysis. However, it is limited by its retrospective design, single-center setting, and potential confounding factors from unrecorded concomitant therapies such as statins or RAS blockers. In addition, causality cannot be inferred without a randomized controlled trial.

4.6. Future directions

Future research should aim to address the following issues.

1. Conduct randomized controlled trials comparing empagliflozin and dapagliflozin in a head-to-head comparison.
2. Exploration of longitudinal outcomes related to cardiovascular and renal events in relation to inflammatory indices.
3. Elucidate the molecular pathways underlying SGLT2 inhibitor–mediated modulation of immune cell activation, particularly in high-inflammation cohorts.

5. CONCLUSION

SGLT2 inhibitor therapy significantly reduces the systemic inflammatory burden in patients with T2DM, with empagliflozin demonstrating greater efficacy than dapagliflozin. Patients with a high baseline SII and those aged ≥55 years derived the most pronounced benefit. These findings suggest that PIV and SII may serve as valuable tools for evaluating the immunometabolic impact of antidiabetic therapy, supporting their integration into future personalized treatment models.

Article Information Form

Authors' Contribution

All authors contributed to the article. Study design: NY, NK; Data collection: NY; Data analysis: NY, NK; Study supervision: NK; Manuscript writing: NY, NK; Critical revisions: NK

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

The study was approved by the Institutional Review Board (Approval Date: August 21, 2024; Decision No: 2024-13/2) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

Copyright Statement

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Research Article

Emergent Hemodialysis Access: Balloon Venoplasty and Tunneled Catheter Placement in Patients with Exhausted Venous Access – Evaluation of Safety and Patency Determinants

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Background/Objectives: Central venous occlusion (CVO) presents a significant challenge in providing emergency hemodialysis to patients with end-stage renal disease (ESRD). This study evaluated the feasibility, safety, and effectiveness of percutaneous transluminal balloon venoplasty to restore central venous patency and enable tunneled hemodialysis catheter placement in patients with complete CVO. This study specifically focused on patients with complete occlusion of all central venous pathways, a rare and underreported scenario in the literature.

Methods: This retrospective, single-center observational study included 50 dialysis patients with confirmed occlusion of all central veins between November 2015 and September 2024. Balloon venoplasty was performed to recanalize the occluded veins, followed by the placement of a catheter. Patients were monitored for catheter patency and complications, and predictors of catheter dysfunction were analyzed.

Results: A 100% technical success rate was achieved. The mean primary patency duration was 4 months (range: 1–37 months). Catheter dysfunction occurred in 11 patients (22%), primarily due to infection or occlusion. Multivariable analysis identified catheter distal tip location as the sole predictor of dysfunction (OR: 0.146, 95% CI: 0.026–0.816, p = 0.028). Catheters with tips in the right atrium demonstrated better patency than those in the inferior vena cava. Minor complications included hematomas (11.3%) and arrhythmias (16.1%).

Conclusions: Balloon venoplasty is a safe and effective technique for managing patients with exhausted central venous access, providing emergency hemodialysis, and acting as a bridge to definitive solutions such as AV fistulas, peritoneal dialysis, or renal transplantation. To optimize patency and reduce the risk of dysfunction, catheter tips are recommended to be placed in the right atrium. Further research is needed to refine this approach and extend access longevity.

Keywords: Central venous occlusion, Balloon venoplasty, Tunneled dialysis catheter, Emergency hemodialysis, Vascular access, Central vein recanalization

1. INTRODUCTION

Long-term dialysis catheter use can cause vascular injury, endoluminal occlusion due to thrombus formation, extrinsic compression from musculoskeletal (e.g., costoclavicular or sternal) or vascular (e.g., aortic ectasia) sources, or hemodynamic abnormalities that promote neointimal hyperplasia. Several factors may cause bilateral occlusion of central veins, necessitating catheter placement in the femoral vein.[1,2] Emergency hemodialysis becomes a significant challenge when all viable access routes are blocked, requiring innovative approaches to restore central venous patency.

Percutaneous transluminal balloon venoplasty (PTBV) recanalizes occluded central venous (OCV) pathways to enable tunneled dialysis catheter (TDC) placement through PTBV.[2-4] With this technique, patients can initiate hemodialysis promptly and transition to more definitive treatment options, such as renal transplantation, preparation for peritoneal dialysis, or the creation of arteriovenous fistulas (AVF).

In addition to PTVB, sharp recanalization has been demonstrated to restore central venous patency, allowing TDC to be placed in challenging situations.[5,6] TDC placement can also be achieved

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via alternative methods, including femoral vein access and mediastinal tunneling. However, each has specific limitations and risks.[7, 8]

This study aimed to evaluate the feasibility, safety, and effectiveness of PTBV in restoring central venous patency in patients with complete OCV pathways who require emergency hemodialysis. The research also looked into the duration of hemodialysis possible after recanalization of the pathway using this method and the functional duration of this intervention before transitioning to more permanent solutions.

2. MATERIALS AND METHODS

2.1. Patients

This study was designed as a retrospective, single-center observational study. A total of 54 patients with an urgent need for hemodialysis and who underwent central venous occlusion treatment followed by tunneled hemodialysis catheter placement were identified from hospital records between November 2015 and September 2024. Among these, 50 patients met the specific inclusion criteria and were included in the study. Four patients were excluded as they did not meet the required criteria.

This study was approved by the Başkent University Medical and Health Sciences Research Committee (Project No. KA 25/17) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki**.** Written informed consent was obtained from all patients prior to the procedure.

The included patients were those with complete occlusion of all central veins, including the right and left brachiocephalic veins (BCVs) or superior vena cava (SVC), and the right and left iliac veins or inferior vena cava (IVC), resulting in no remaining vascular access for hemodialysis.

2.2. Inclusion criteria

Patients were included in the study if they met the following criteria:

1. Angiographic imaging confirmed the Complete occlusion of all four central venous systems (right and left BCVs or SVC, and right and left iliac veins or IVC).
2. Acute need for hemodialysis at the time of presentation.
3. Placement of a tunneled hemodialysis catheter following central venous intervention.
4. Availability of complete clinical and procedural records.

Patients who did not meet these criteria were excluded from the study.

The patients were selected based on clinical examination and duplex ultrasound (DUS) findings of both the upper and lower limbs. The occlusion of all central veins was confirmed by angiography.

2.3. Technical aspects

Written informed consent was obtained before the procedure, and potential drawbacks were explained to the patients in simple language. Patients were transferred to the angiography suite (*GE Innova™ 3100 angio system*, *GE HealthCare*, USA) and positioned supine on the angiography table. Interventional radiologists performed all procedures with at least 10 years of experience in central venous interventions. Local anesthesia was administered for all angioplasty procedures, supplemented with sedation and analgesia as needed. Throughout the procedure, patients were continuously monitored for blood pressure, oxygen saturation, and ECG changes.

Venograms were initially performed via the right subclavian or right internal jugular vein, followed by the left subclavian or left internal jugular vein, respectively. If direct access to these veins was not feasible under USG guidance, their occlusion was confirmed, and tunneling catheter placement was deemed unfeasible due to the inability to visualize the veins in both upper extremities.

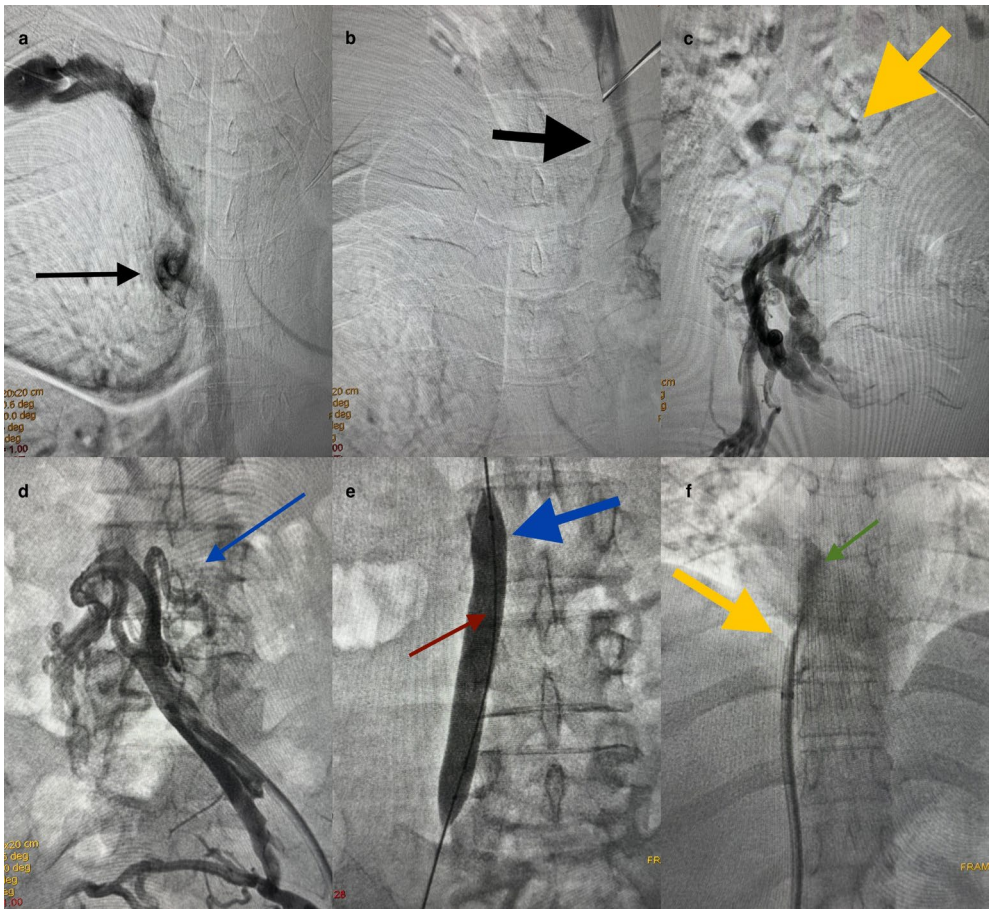
Upon confirming occlusion of the upper extremity central veins (right and left brachiocephalic veins or superior vena cava [SVC]), the right and left femoral veins were cannulated to assess the lower extremity central veins. The occlusion of the right and left iliac veins or inferior vena cava (IVC) was confirmed. The location and length of the occlusion, as well as the presence of collaterals, were identified during the procedure.

All vascular punctures were performed under USG guidance to ensure accuracy and minimize complications.

Figure 1 illustrates the imaging findings and interventional steps involved in treating a complete central venous occlusion with balloon venoplasty.

Figure 1.

Imaging and interventional steps in the treatment of complete central venous occlusion with balloon venoplasty



Caption:
(a) Fluoroscopic venography via the right subclavian vein demonstrates an occluded superior vena cava. The arrow identifies the azygos vein, which functions as a collateral pathway.
(b) Venography from the left internal jugular vein reveals occlusion of the left subclavian vein, with the arrow indicating the presence of collateral veins.
(c) Imaging via the right common femoral vein illustrates occlusion of the right common iliac vein and the inferior vena cava, with the arrow pointing to dense pelvic collateral vessels.
(d) Venograms acquired from a dysfunctional temporary dialysis catheter demonstrate proximal occlusion of the left common iliac vein as well as the inferior vena cava. The arrow highlights the presence of collateral venous pathways.
(e) The balloon venoplasty procedure is depicted, with the thick blue arrow marking the balloon and the thin red arrow designating the stiff guidewire.
(f) Post-venoplasty venography confirms proper placement of a tunneled catheter. The thick yellow arrow indicates the catheter tip positioned at the atriocaval junction, while the thin green arrow shows the flow of contrast material into the atrium.

2.4. Access technique

The decision on which vein to recanalize was based on the patient's clinical condition, urgent dialysis requirement, anatomical features, and imaging findings. The operator's experience and technical preference significantly affected this process.

Under ultrasonography (USG) guidance, the most appropriate entry site was determined to enable access to the OCV and facilitate the placement of a tunneled catheter. Access was achieved using the

Micropuncture Set (Merit MAK™ Mini Access Kit, Merit® Medical Systems, South Jordan, Utah, USA), followed by the introduction of a 6F or 8F vascular sheath (Cordis® Introducer Sheath, Cordis Corporation, Miami Lakes, Florida, USA) at the selected site. After visualizing the occluded segments, a 0.035-inch hydrophilic guidewire (*Radiofocus® Guide Wire-Angled*, *Terumo Corporation*, Hanoi City, Vietnam) and a vertebral catheter were used to navigate through the central vein occlusion. When needed, a 0.035-inch hydrophilic rigid guidewire (*Radiofocus® Guide Wire, Straight-Stiff Type or Angled Type*, *Terumo Corporation*, Tokyo, Japan) was employed for further support.

If the occlusion could not be crossed despite various guidewire and catheter manipulations, a 0.018-inch angled guidewire (*Radiofocus™ Glidewire Advantage™, *Terumo Corporation*, Fujinomiya City, Japan) was utilized. For cases where this approach was unsuccessful, sharp recanalization was performed using the hard posterior part of the guidewire to overcome the occlusion.[9]

A balloon catheter (Sterling™ PTA Balloon Dilatation Catheter, Boston Scientific, Marlborough, MA, USA, monorail, 0.018-inch system) or Mustang™ PTA Balloon Catheter (Boston Scientific, Marlborough, MA, USA, over-the-wire, 0.035-inch system) was advanced over the guidewire and centered on the occluded segment. The choice of balloon was based on operator preference and the type of guidewire that successfully crossed the occlusion. In cases recanalized with a 0.035-inch guidewire, the Mustang™ balloon was used, whereas in cases requiring 0.018-inch wires, the Sterling™ balloon was preferred. No additional balloon types were required in this series. Inflation was conducted for 60–90 seconds and repeated as necessary to ensure adequate dilatation.

Following the reopening of the central vein, the guidewire was replaced with a stiff guidewire (*Amplatz Super Stiff™ Guidewire*, *Boston Scientific*, Marlborough, Massachusetts, USA), further dilatations were performed, and a peel-away sheath was inserted. The hemodialysis catheter was then tunneled to the infraclavicular region to optimize patient mobility.

The same catheter placement technique was applied for upper extremity interventions (right and left subclavian veins and left and right internal jugular veins). For femoral vein interventions, the cuffed catheter was tunneled into the anterolateral region of the thigh to ensure optimal positioning and patient comfort.

2.5. Follow-up and reinterventions

Each patient was monitored for complications related to endovascular access site problems and catheter patency during the first three months following the procedure. During hemodialysis sessions, nursing staff assessed the catheter exit site and pathway for signs of infection, dialysis adequacy, pressure and suctioning, facial or arm edema, clot aspiration, and blood flow. When problems were identified, the patient was instructed to consult our unit.

Catheter kinks or misalignment of the tip were evaluated using chest X-rays. If a mechanical malfunction was identified, the catheter was repositioned or replaced. If no mechanical problem was detected, a thrombolytic solution was infused into both lumens and clot removal was attempted overnight. If these methods failed, DUS followed by CT venography was performed to exclude central vein thrombosis.

If the central vein was re-occluded, the catheter was left in place, and the occluded vein was accessed with a guidewire. When necessary, the sharp posterior end of the guidewire was used to cross the occlusion site. After the new catheter was successfully placed, the old catheter was removed. If resistance was encountered during catheter passage, a 10F vascular sheath was placed, and vein dilatation was performed using a balloon of appropriate diameter. The new catheter was then advanced over the wire.

If the occluded vein was narrow or could not be fully dilated, a longer catheter was used, and its tip was directed towards the right atrium to mitigate the risk of failure if the catheter remained in the stenotic vein.

2.6. Definitions of primary patency/technical success and identification of complications

Primary patency was defined as maintaining catheter functionality from placement until treatment completion, with no failure or need for replacement. Technical success meant restoring patency in the OCV and successfully placing the TDC. Complications were classified as major or minor according to the CIRSE guidelines [10]. Major complications included prolonged hospital stays, required additional or surgical treatment, or led to permanent damage or death. Minor complications were transient and clinically insignificant, and were managed conservatively. These criteria were recorded and evaluated for all events that occurred during or after the procedure.

2.7. Statistical analysis

Data was analyzed using SPSS software version 21.0 (SPSS Inc., Chicago, Illinois). The Kolmogorov-Smirnov test was applied to assess the normality of continuous variables. Descriptive statistics of the normally distributed data were expressed as mean ± standard deviation, while non-normally distributed data were presented as median (interquartile range). Categorical variables were defined using frequencies and percentages. Non-normally distributed data of the continuous variables between groups were compared using the Mann-Whitney U test, and Fisher's exact Chi-squared test was applied to compare categorical variables. The Independent Samples t-test was utilized for continuous variables with a normal distribution. A p-value <0.05 was defined as statistically significant. Correlation analyses of the normally distributed variables were performed using the Pearson correlation coefficient, and Spearman's rank correlation coefficient was used for the non-normally distributed variables. Multivariable logistic regression analysis was used to determine the independent predictors of catheter dysfunction after the PTBV.

3. RESULT

A total of 50 patients were included in the analysis. The mean age was 60.8 ± 18.3 years, with 70% of the participants being female, and the mean maintenance dialysis duration before the procedure was 53.6 ± 35.8 months (Table 1). A 100% technical success rate was achieved in recanalizing OCV and placing a TDC for emergency dialysis. The mean primary patency was 4 months (1–37 months). Fifty patients were divided into two groups based on catheter dysfunction: those with dysfunction (n = 11) and those without (n = 39). Baseline characteristics, laboratory values, angiographic data, primary patency duration, and total hemodialysis duration are shown in Table 2. No significant differences were observed between the groups except for total cholesterol levels (164.7 ± 35.2 vs. 143.1 ± 29.1, p = 0.043). While technical data, such as complication rates, stent implantation, and venous access sites, were similar between groups, catheter dysfunction was associated with the distal tip position. Dysfunction occurred more frequently when the catheter tip was placed in the inferior vena cava (7 [63.6%] vs. 8 [20.5%], p = 0.010).

Multivariable logistic regression, including age, heart failure, balloon diameter, and catheter tip position, showed that only the tip location was associated with dysfunction (OR: 0.146, 95% CI: 0.026–0.816, p = 0.028) (Table 3 and Figure 2). No major complications were observed. Minor complications included small hematomas (11.3%), transient arrhythmias (16.1%), and minor vein perforations (2.4%). As shown in Figure 3 and Table 1, the most common reasons for catheter removal were mortality (36%), transition to peritoneal dialysis (22%), and occlusion (16%), while infection accounted for 6% of the removals. Additionally, 42% of patients eventually transitioned to more permanent solutions.

Table 1.

Indications for hemodialysis catheter removal

n (%)	
Mortality	18 (36)
Renal transplantation	4 (8)
Peritoneal dialysis	11 (22)
Occlusion	8 (16)
Catheter infection	3 (6)
Fistula creation	6 (12)

Table 2.

Patient characteristics according to catheter dysfunction status

	Catheter dysfunction present (n = 11)	Catheter dysfunction absent (n = 39)	Total (n = 50)	p value
Age	60.6±13.8	60.9±19.5	60.8±18.3	0.967
Gender (Female), n (%)	10 (90.9)	25 (64.1)	35 (70)	0.139
Smoking, n (%)	4 (36.4)	12 (30.8)	16 (32)	0.728
Diabetes mellitus, n (%)	6 (54.5)	22 (56.4)	28 (56)	0.589
Hypertension, n (%)	7 (63.6)	27 (69.2)	34 (68)	0.728
Dyslipidemia, n (%)	1 (9.1)	1 (2.6)	2 (4)	0.395
Heart failure, n (%)	5 (45.5	13 (33.3)	18 (36)	0.494
Fasting blood glucose, mg/dL	116 (74-208)	101 (62-370)	104.5 (62-370)	0.461
ALT, units/liter	12 (8-30)	14 (6-57)	13.5 (6-57)	0.532
AST, units/liter	17.5±8.1	22±9.8	21±9.6	0.175
Total cholesterol, mg/dl	164.7±35.2	143.1±29.1	147.8±31.5	0.043
LDL-C, mg/dl	109.1±30.3	99.1±21.9	101.3±24	0.230
HDL-C, mg/dl	34±8.7	38.4±6.9	37.4±7.5	0.074
Triglyceride, mg/dl	140 (85-216)	125 (85-404)	126 (85-404)	0.379
Hemoglobin, g/dl	10.1±1.5	10.5±1.3	10.4±1.3	0.394
Albumin, g/dl	3.6±0.5	3.5±0.5	3.6±0.5	0.744
Balloon diameter, mm	11.4±2.8	12.6±2.1	12.4±2.3	0.127
Stent implantation, n (%)	1 (9.1)	2 (5.1)	3 (6)	0.534
Complications, n (%)	1 (9.1)	6 (15.4)	7 (14)	0.513
Catheter distal tip location (IVC), n (%)	7 (63.6)	8 (20.5)	15 (30)	0.010
Venous access sites, n (%)				
Right internal jugular vein	2 (18.2)	11 (28.2)	13 (26)	0.188
Left internal jugular vein	0 (0)	10 (25.6)	10 (20)	
Right subclavian vein	0 (0)	2 (5.1)	2 (4)	
Left subclavian vein	1 (9.1)	3 (7.7)	4 (8)	
Right femoral vein	6 (54.5)	8 (20.5)	14 (28)	
Left femoral vein	2 (18.2)	5 (12.8)	7 (14)	
Total hemodialysis duration, months	64±42.2	50.7±33.8	53.6±35.8	0.282
Primer patency duration, months	4 (1-14)	4 (1-37)	4 (1-37)	0.637

ALT: Alanine transaminase, AST: Aspartate transaminase, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, IVC: Inferior vena cava.

Table 3.

Univariate and multivariable regression analysis for the catheter dysfunction after the percutaneous transluminal angioplasty

Univariate	p value	OR	95% CI		Multivariate	p value	OR	95% CI	
			Lower	Upper				Lower	Upper
Age	0.966	1.001	0.965	1.038	Age	-	-	-	-
Heart failure	0.462	1.667	0.427	6.499	Heart failure	-	-	-	-
Balloon diameter	0.133	1.238	0.937	1.634	Balloon diameter	-	-	-	-
Catheter distal tip location	0.010	0.147	0.034	0.631	Catheter distal tip location	0.028	0.146	0.026	0.816

OR: Odds ratio

Figure 2.

Regression analysis

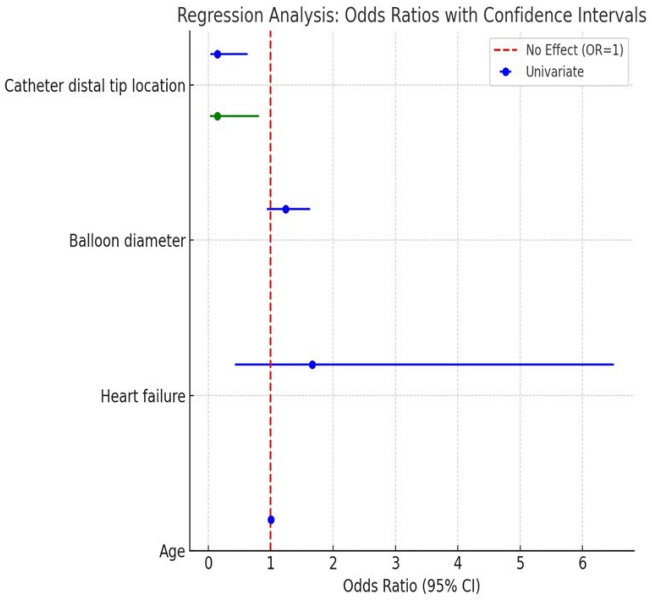
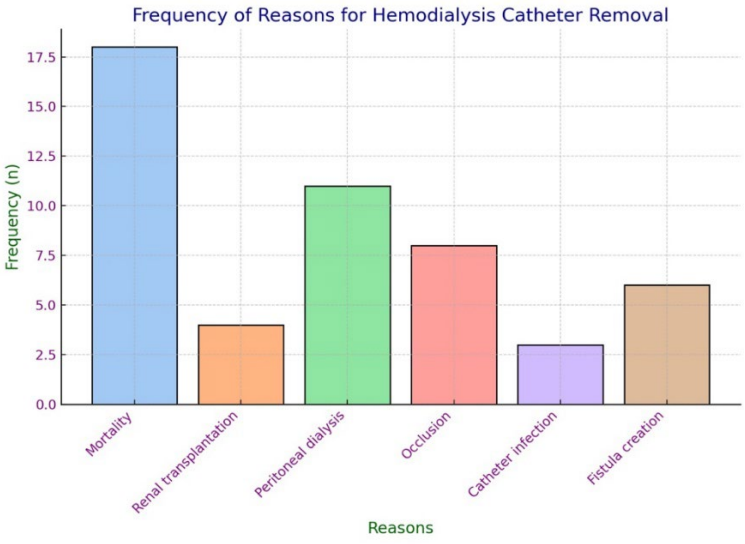


Figure 3.

Frequency of reasons for catheter removal



4. DISCUSSION

Complete central venous occlusion creates a significant access challenge in emergency hemodialysis. This condition requires rapid and effective vascular access, as it can lead to life-threatening complications. Our study evaluated patients with complete OCV pathways in both the upper and lower extremities, thereby addressing a scenario not comprehensively investigated in the literature.

Existing literature has shown that innovative methods, such as PTBV, can effectively restore central venous patency and facilitate the placement of a TDC. However, most studies have primarily focused on upper limb venous occlusions and have not adequately addressed the application of these techniques in more complex cases where all central venous pathways are entirely blocked. Additionally, there is limited knowledge about the factors contributing to catheter dysfunction and strategies to enhance long-term catheter patency. Addressing these knowledge gaps is crucial for improving care standards for high-risk patient populations.

In our series, the balloon venoplasty method proved effective in high-risk patients requiring hemodialysis access, achieving 100% technical success with no major complications. During follow-up, four patients underwent kidney transplantation, 11 transitioned to peritoneal dialysis, and six arteriovenous fistulas were created.

Although open surgical bypass procedures are available to treat central venous occlusions, endovascular therapy has emerged as the primary method for restoring central venous patency, with reported success rates ranging from 80% to 100% [11-13]. Our study reached a 100% technical success rate in line with these findings. The effectiveness of venoplasty in restoring patency in OCD is well-documented, particularly in thoracic central vein occlusions.[14,15] This intervention provides a crucial window of opportunity to allow preparation for and transition to more permanent access methods such as AVF creation or peritoneal dialysis.

However, data on patients requiring hemodialysis where all central venous pathways are completely occluded remain limited. Falk et al.[5] demonstrated a 93% technical success rate in placing TDC across stenotic or OCV, emphasizing the feasibility and safety of endovascular recanalization in preserving central venous access for future use.[5] However, their study primarily focused on upper extremity venous occlusions and did not address the more complex scenarios where all central venous pathways are entirely occluded. Similarly, Frampton et al. [16] explored the use of femoral artery access as an emergency method for hemodialysis in patients with no other viable access options. In contrast to our approach, their study involved surgical interventions when endovascular techniques failed, resulting in higher complication rates.[16]

The study by Lotfy et al.[17] included patients with central venous stenosis or partial occlusion, some of whom had alternative vascular access routes, such as the subclavian or jugular veins. In contrast, our study focused exclusively on patients who had exhausted all central venous access options and had no alternative vascular access. In this patient group, a 100% technical success rate was achieved. Lotfy et al.[17] reported a 79% technical success rate in patients with complete central venous occlusion. The higher success rate in our study (100%) may be attributed to factors such as the advanced techniques employed, operator experience, patient selection, and study design.

Furthermore, when comparing primary patency durations, we observed that catheters with the tip placed in the right atrium maintained functionality for a more extended period and had a significantly lower dysfunction rate than those placed in the inferior vena cava. Our multivariate analysis demonstrated that right atrial catheter tip placement had a direct positive impact on patency duration. In contrast, catheters placed in the inferior vena cava had a significantly higher risk of dysfunction (OR: 0.146, 95% CI: 0.026–0.816, p = 0.028). Although Lotfy et al. [17] did not provide a detailed analysis of primary patency duration, they reported a decline to 70% at one year and 5% at four years.[17] In contrast, our study demonstrated that catheters placed in the right

atrium had significantly longer patency durations. These findings underscore the crucial role of catheter tip location in maintaining long-term catheter functionality.

In our study, complications associated with PTBV were generally minor. The recorded issues included access site hematoma (11.3%), accidental arterial puncture (3.2%), arrhythmias (16.1%), and small vein perforations in three cases of central vein occlusion (2.4%). None of these events required prolonged hospitalization or additional surgical intervention. However, more severe complications have been reported in the literature during central venous recanalization procedures, including extraluminal perforations of large veins, which can result in massive bleeding into the pleural or pericardial space or even pneumothorax[14]. Despite the low complication rate observed in our study, potential risks such as re-occlusion, infection, and catheter dysfunction remain concerns.[15,18] To mitigate these risks, adjunctive treatments, including anticoagulants and antibiotic lock solutions, are recommended to prolong the patency of the recanalized track and improve patient outcomes.

According to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, native arteriovenous fistulas (AVFs) remain the preferred long-term vascular access for hemodialysis.[19] Endovascular treatment is well established in the management of thrombosed or dysfunctional AVFs, with percutaneous transluminal angioplasty (PTA) demonstrating high technical success (≈89%) and acceptable short- to mid-term patency (≈60–79% at 6–12 months).[19] Larger series have confirmed these findings, reporting primary patency rates exceeding 90% and mean patency durations approaching two years when repeat interventions were performed.[20] Our study addresses the most advanced stage of vascular access failure, in which all central venous pathways were completely occluded and no option for AVF salvage or creation was immediately feasible. In this setting, balloon venoplasty allowed 100% technical success in recanalizing occluded veins and placing tunneled dialysis catheters, thereby ensuring urgent dialysis and providing a bridge to definitive access options (AVF creation, peritoneal dialysis, or transplantation). Thus, while AVF salvage procedures aim to preserve native access and reduce catheter dependence, our findings demonstrate that the same principle—timely endovascular intervention—can be extended to the central venous system when conventional access is entirely exhausted.

This study has several limitations. First, it was a retrospective, single-center study with a relatively small sample size, which may limit the generalizability of the findings. Second, the follow-up duration varied among patients, potentially affecting the assessment of patency outcomes. Third, the study did not include a comparison group treated with alternative interventional or surgical approaches. Finally, although the procedures were performed by experienced operators, operator-dependent variability in technical approaches may have influenced outcomes.

5. CONCLUSION

This study demonstrates that PTBV of a total OCV, combined with PTBV and placement of a TDC, is a safe and effective method for dialysis patients with a depleted vascular bed. This approach provides not only emergency hemodialysis access but also serves as a critical bridge, facilitating the transition to more permanent vascular access methods. Our findings demonstrated that the distal tip location of the catheter is a determining factor in long-term patency, revealing that catheters placed in the right atrium have a lower risk of dysfunction than those placed in the inferior vena cava. In this critical scenario, which has not been extensively addressed in the literature, the success of endovascular treatment approaches offers an important treatment option for this patient group. Our study demonstrates that individualized endovascular strategies can increase treatment success and improve current standards for patients with exhausted central venous access.

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Authors' Contribution

Conceptualization, M.M. and I.K.; methodology, M.M. and I.K.; software, I.K.; validation, M.M. and I.K.; formal analysis, M.M.; investigation, I.K.; resources, M.M. and I.K.; data curation, M.M. and I.K.; writing—original draft preparation, M.M. and I.K.; writing—review and editing, M.M. and I.K.; visualization, I.K.; supervision, M.M.; project administration, M.M. and I.K.; All authors have read and agreed to the published version of the manuscript.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Baskent University Faculty of Medicine (protocol code KA25/17, approved on January 29, 2025).

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

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Case Report

47 Year Old Female with a Recurrent Abdominal Perivascular Epithelioid Cell Tumor: Case Report and Literature Review

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Abstract: Perivascular epithelioid cell tumors (PEComas) are rare mesenchymal neoplasms characterized by histologically and immunohistochemically distinctive epithelioid or spindle cells. These tumors express both smooth muscle markers and melanocytic markers. They can arise in various anatomical locations throughout the body, including the gastrointestinal tract, genitourinary system, retroperitoneum, and soft tissues. The exact cell of origin for these tumors remains unidentified. Clinical outcomes vary widely, spanning benign to malignant behavior, with the potential for local recurrence and metastasis. The management of PEComas typically involves surgical resection, though use of adjuvant chemotherapy and immunotherapy has been reported. The high recurrence rate of PEComas highlights the necessity for long-term surveillance and a multidisciplinary approach to treatment. We present the case of a 47-year-old female with a previous abdominal PEComa, who presented to our clinic with an enlarged recurrent abdominal tumor. Confirmation of recurrence was obtained through ultrasound and PET-CT imaging. Additionally, post-operative pathology findings supported the diagnosis.

Keywords: Perivascular epithelioid cell neoplasms, Recurrence, Mesenchymal neoplasms

1. INTRODUCTION

Perivascular epithelioid cell tumors (PEComas), are mesenchymal neoplasms made up of distinctive epithelioid or spindle-shaped cells. These tumors are identified by their unique histological and immunohistochemical features, with the cells testing positive for markers associated with both smooth muscle (e.g., actin and desmin) and melanocytic cells (e.g., HMB-45 and Melan-A).[1,2] These are rare tumours that can develop in various parts of the body, including but not limited to the gastrointestinal tract, genitourinary system, retroperitoneum, and soft tissues.[3] The specific cell type that gives rise to these tumors is unknown. Perivascular epithelioid cells are not typically found, and the name describes the tumor's appearance when examined under a microscope, it is thought to originate from a unique perivascular cell type that exhibits myomelanocytic differentiation.[4] The most common tumors within the PEComa group are renal angiomyolipoma and pulmonary lymphangioleiomyomatosis, both of which occur more frequently in individuals with tuberous sclerosis complex.[5] Additionally, many types of PEComas show a higher incidence in females.

The clinical behavior of these tumors is variable, ranging from benign to malignant, with potential for local recurrence and metastasis.[6] The management of PEComas often involves surgical resection, surgical resection with clear margins remains is the prefered manegment.[7] For lesions exhibiting malignant features not amenable to operative removal, use of adjuvant chemotherapy and immunotherapy has been reported but there is still limited data involving these therapies, though targeted therapies, such as mTOR inhibitors, have shown promise in some cases. Prognosis depends on several factors, including tumor size, location, and histological features indicative of aggressive behavior.[8]

2. CASE REPORT

A 47 year woman came to the outaptient clinic complaning from abdominal pain, fatigue, changes in bowel habits and weight gain for the last few

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months. The patient has a history of PEComa, an abdominal mass diagnosed at another hospital two years ago. At that time, Informed consent was obtained from the patient and surgery was performed to remove the mass, and the procedure also included the removal of the uterus and ovaries.

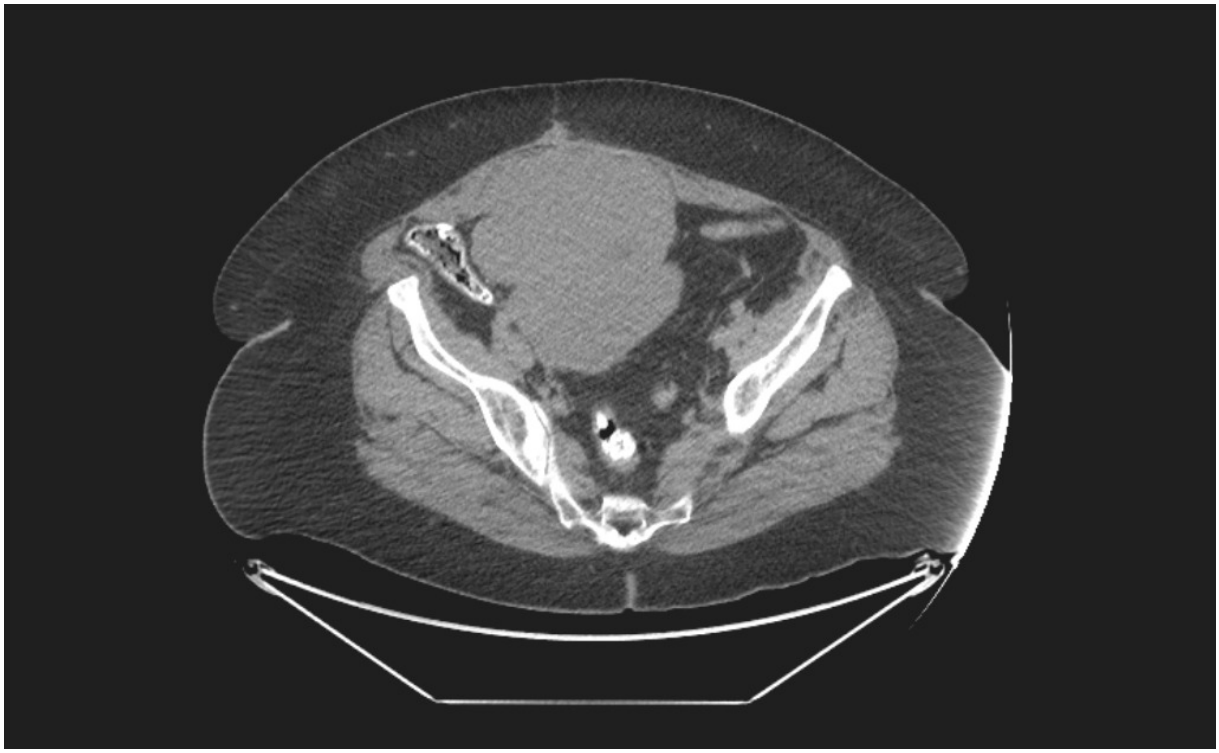
The patient had a recurrence of the tumor one month prior to her visit to our hospital. This recurrence was initially recognized by the urology department at a different hospital following an abdominal ultrasongraphy (USG) performed due to a urinary tract infection (UTI) the patient had at that time.

The USG report describes a heterogeneous hypoechoic solid mass with a bilobed appearance, measuring 138x75x110 mm in total size, located adjacent to the right side of the bladder.

The patient has also undergone a PET-CT scan, which identified a mass with irregular borders and lobulated contours measuring approximately 13x10 cm in the axial plane and up to 17 cm obliquely in the craniocaudal axis. The mass starts superiorly to the bladder in the pelvis and extends to the level of the umbilicus in the abdominal midline. The scan showed heterogeneously increased FDG metabolism, compatible with the recurrence of the primary lesion (Figure1).

Figure 1.

A Pre - Op transverse plane CT showing the mass in the abdomen



In our clinic the physical examination findings indicated presentation of asymmetry on the right side of the abdomen, hepatomegaly and an abdominal palpable mass in the right lower quadrant was dedected while palpating the abdomen.

Based on the patient's history and the results of our examinations, informed consent was obtained, and an operation was planned for the patient, who was diagnosed with a recurrent intra-abdominal mass.

2.1. Surgery

A laparotomy procedure resulted in the removal of two soft tissue tumors measuring 20 cm and 25 cm from the right lower quadrant of the abdomen. These tumors were attached to the bowel loops but showed no signs of invasion. The tumors were successfully dissected and removed from the abdomen without any major bleeding.

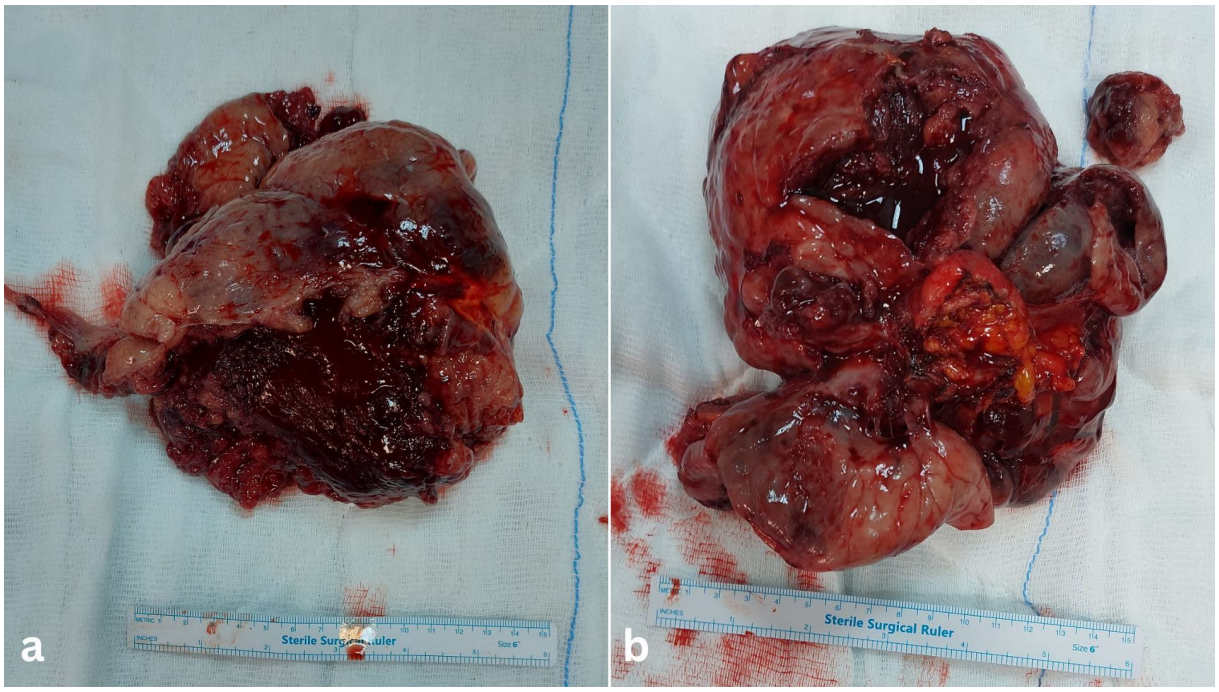
Post operative follow up was uneventful and the patient was discharged on third post operative

day. On post operative 7th day, abdominal ultrasonography revealed no fluid collection.

The post-operative pathology report confirmed the diagnosis of PEComa (perivascular epithelioid cell tumor). The tumor exhibited irregular borders and a characteristic fleshy consistency. Notably, sections of the mass showed areas of bleeding and a necrotic appearance over a wide region, indicating significant tissue breakdown and hemorrhage within the tumor. Immunohistochemical staining was performed to further characterize the tumor and confirm the diagnosis. The results were positive for HMB45, Melan A, SMA (Smooth Muscle Actin), and Desmin. These markers are commonly associated with PEComa and help distinguish it from other types of tumors. The positive staining for these markers supported the diagnosis of PEComa and provided valuable information for determining the tumor's origin and potential behavior (Figure2).

Figure 2a – b.

The tumour (from each side) after it was excised from the patient



One year after the operation, the patient experienced a second recurrence of the tumor four months post-surgery. Following this recurrence, she underwent chemotherapy at another hospital. Currently, she is receiving only anti-cancer medications.

3. DISCUSSION

PEComas, a rare group of mesenchymal tumors, present significant diagnostic and therapeutic challenges due to their diverse clinical presentations and histopathological features. According to the literature, these tumors are characterized by the expression of melanocytic and smooth muscle markers such as HMB45, Melan A, SMA, and occasionally Desmin, findings which were also observed in our patient's immunohistochemical profile.[1,2,9]

Several studies have noted that PEComas often occur in patients with tuberous sclerosis, where abnormalities in the TSC1/TSC2 genes lead to cell proliferation via activation of the mTOR pathway. There is also interest in TFE3 gene fusions and their correlation with the family of perivascular epithelioid cell tumors.[9,10,11]

Surgical resection remains the primary treatment for PEComas, as demonstrated in our patient, leading to an improvement in symptoms. Adjuvant therapies like chemotherapy have shown varied outcomes, particularly in high-risk patients. This underscores the importance of personalized treatment approaches based on factors such as tumor size, location, and molecular characteristics.[7,8]

Regarding targeted therapy, mTOR inhibitors have been shown to reduce the rate of progression in patients with metastatic disease (For Example: rapamycin or everolimus). The recurrence rate of PEComas underscores the importance of long-term surveillance and a multidisciplinary management strategy, as seen in our patient who had two reoccurrences in the span of three years.[8]

Given the rarity of PEComas, further research is essential to better understand their pathogenesis and identify new therapeutic targets. In conclusion, while advances in diagnostic techniques and treatment options have led to improved outcomes, ongoing research remains vital to enhance our understanding and management of PEComas.

4. CONCLUSİON

PEComas, a rare group of mesenchymal tumors, present significant diagnostic and therapeutic challenges because of their diverse clinical presentations and histopathological characteristics.

We report a 47-year-old female with a history of abdominal PEComa who presented to our clinic with an abdominal tumor recurrence that had increased in size. The treatment included surgical removal of the tumor and regular follow-ups to monitor for any further recurrences. Subsequent follow-ups revealed a second recurrence, after which the patient received chemotherapy at another facility.

Although advances in diagnostic techniques and treatment options have improved outcomes, continued research is crucial to deepen our understanding and improve the management of PEComas.

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Authors' Contribution

Conception/ Design: A.Y, U.D, M.E, B.E, Data Collection: A.Y, U.D, M.E, Data Analysis/Interpretation: A.Y, U.D, M.E, B.E, Writing: A.Y, U.D, B.E, Technical Support/ Material Support: A.Y, U.D, M.E, Critical Review of Content: U.D, M.E, Literature Review: A.Y.

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No conflict of interest or common interest has been declared by authors.

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

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Letter to the Editor

The Impact of Loneliness in Older Adults Presenting with Memory Impairment: A Single-Center Experience

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Dear Editor,

I am writing regarding the article titled "The Impact of Loneliness in Older Adults Presenting with Memory Impairment: A Single-Center Experience" published in the Sakarya Medical Journal.[1] As a geriatrician, I would like to thank the authors for addressing this topic in a well-structured way.

I would, however, like to highlight a few additional considerations on behalf of this study that could enhance the interpretation of the findings and inform future research.

Forgetfulness is a common symptom observed in older adults, and it is crucial to identify all potential causes to determine treatable factors and implement interventions to reverse it. As the authors have noted in the article, psychological, social, and metabolic conditions can contribute to the development of cognitive impairment through various mechanisms. In this study, while examining the relationship between loneliness and mild cognitive impairment in the elderly, individuals already diagnosed with Alzheimer's disease, those with central vascular diseases, metabolic disorders such as diabetes and thyroid diseases, as well as those with psychiatric and oncological conditions, were excluded from the analysis. However, some other important conditions in older adults that can cause cognitive impairment and potentially affect the results may not have been fully addressed. One of this condition is presence of sleep disturbances or insomnia. Sleep disturbances can reduce the clearance of metabolites such as amyloid-beta, a

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lipoprotein, which may lead to tau aggregation and, over the long term, neurodegeneration.[2] The relationship between sleep disturbances and cognitive impairment has been demonstrated in several studies involving older adults.[3,4] Furthermore, sleep disturbances contribute to systemic inflammation, oxidative stress, and changes in the neurovascular unit, all of which exacerbate cognitive decline over time.

Another issue is that, as readers, we are not provided with information about the medications that participants routinely use. Medications with anticholinergic effects, such as those prescribed for common conditions among older adults—like urinary incontinence, depression, anxiety, or insomnia—are known to have detrimental effects on memory. Although the direct cause-and-effect mechanism is not yet clear, it is well-known that drugs with anticholinergic properties can cause cognitive decline in older adults.[5] This may occur through cholinergic depletion, as acetylcholine plays a crucial role in memory and cognitive function. Its depletion can exacerbate neurodegenerative processes and promote brain atrophy.

Finally, in studies of this nature, considering the high prevalence of comorbidities in older adults—as highlighted in this study, where at least 76.7% of participants had at least one comorbidity—it may be more appropriate to use a parameter that reflects the overall comorbidity burden and its severity, such as the Charlson Comorbidity Index, rather than categorizing participants simply as having or not having chronic diseases. This approach would provide readers with a clearer understanding of participants' overall health status. Moreover, given the varying systemic impact and severity of chronic diseases, evaluating the total disease burden could provide a more meaningful metric in analysis.

Once again, I commend the authors for their valuable contribution to geriatric/neurologic care.

Thank you for the opportunity to provide feedback.

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