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Original Articles

The European Research Journal 2025;11(3):436-448 Original Article

DOI: https://doi.org/10.18621/eurj.1537714 *Medical Biochemistry*

The relationship between visfatin, resistin and CRP parameters and insulin resistance in obese and non-obese type 2 diabetic individuals

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ABSTRACT

Objectives: Inflammation caused by adipokines such as adiponectin, leptin, resistin, visfatin, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) released by fat cells and immune cells within fat tissue is a significant factor in the onset of insulin resistance and Type 2 diabetes mellitus (T2DM). This study explores the relationship among these adipokines and insulin resistance in T2DM patients, focusing on the impact of abdominal obesity.

Methods: The study involved 73 adult T2DM patients who were seperated into two groups based on their body mass index (BMI): 47 were classified as obese (BMI ≥30 kg/m²), and 26 were classified as non-obese (BMI <25 kg/m²). Additionally, 42 healthy controls were included, comprising 18 obese and 24 non-obese individuals. Adipokine concentrations (resistin, leptin, adiponectin, visfatin, IL-6 and TNF-α) were measured with the ELISA method.

Results: The concentrations of adiponectin were substantially lower in T2DM patients relative to the control group (P<0.0125). Leptin concentrations did not show significant differences between the groups, but there was a notable increase in obese controls compared to non-obese controls (P<0.0125). TNF-α concentrations were significantly higher in obese controls than in non-obese controls (P<0.001). Resistin concentrations were significantly correlated with C-reactive protein (CRP) and IL-6 in both groups, independent of BMI (P=0.001 and P<0.0125, respectively). We found that CRP levels were significantly higher in both obese diabetics compared to non-obese diabetics and in obese controls compared to non-obese controls (P<0.0001).

Conclusions: Adipose tissue is a crucial determinant of circulating inflammation markers. Elevated CRP concentrations in obesity may result from insulin resistance rather than being a cause. Further research is required to comprehend the connection between fatty tissue, insulin resistance, and elevated inflammatory markers.

Keywords: Obesity, Type 2 diabetes mellitus, resistin, visfatin, adiponectin, leptin

Diabetes is stated that affects more than 463 million people worldwide today and type 2 diabetes mellitus (T2DM) represents 90-95% of the total instances [1]. T2DM is associated with microvascular issues like retinopathy, nephropathy, and neuropathy, in addition to macrovascular problems in-

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cluding myocardial infarction, stroke, and peripheral vascular disease [2]. Conditions associated with obesity, including hypertension, elevated cholesterol levels, T2DM, fatty liver disease, heart disease, and certain cancers, resulted in roughly 3.4 million adult fatalities in 2016, as reported by the WHO [3].

tissue is an important organ that helps regulate glucose and lipid metabolism by producing adipokines [4]. Adipokines, create a low-grade chronic inflammatory state believed to lead to insulin resistance and T2DM [5]. Among these adipokines, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are cytokines that promote inflammation. Specifically, IL-6 is crucial in the liver by regulating the production of inflammatory proteins like C-reactive protein (CRP) [5]. TNF-α is a homotrimer protein composed of 157 amino acids that is primarily synthesized by activated macrophages, natural killer cells and T-lymphocytes [6]. Many autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, psoriasis, non-infectious uveitis and inflammatory bowel disease, are triggered by abnormal secretion of TNF-α [6]. Leptin is present in the bloodstream in both its free and protein-bound states. The biologically active form is the free leptin, and the balance between free and bound forms regulates leptin bioavailability [3].

Adiponectin plays an important role in regulating lipid and carbohydrate metabolism and promotes the breakdown of fatty acids and the use of carbohydrates to reduce lipids and blood glucose levels [7]. Individuals suffering from DM, coronary heart disease and obesity have been observed to have significantly lower serum adiponectin concentrations compared to healthy individuals, suggesting that adiponectin levels are closely related to these diseases [7]. A hormone secreted from adipose tissue, Resistin leads to the development of T2DM by increasing insulin resistance and disrupting glucose homeostasis [8]. Resistin appears to be a link between visceral obesity and diabetes. Visfatin has been shown to be strongly associated with visceral adiposity [9]. Despite ongoing uncertainty regarding the connections among visfatin, lipid profiles, and glucose metabolism, meta-analysis findings continue to indicate that elevated visfatin levels are more common in individuals with obesity, T2DM, cardiovascular disease, and metabolic syndrome [10].

In this research, to contribute to the discussion on whether the relationship between insulin resistance, T2DM, and inflammation markers is independent of increased adipose tissue or is caused by obesity, we examined the relationship between adipokines such as resistin, leptin, adiponectin, visfatin, IL-6, TNF-α, and insulin resistance.

METHODS

This study follows the principles of the Declaration of Helsinki. The study was conducted with approval from Istanbul University Faculty of Medicine Clinical Research Ethics Committee dated 28.08.2006 and numbered 1745. All participants provided their informed consent.

The research took place between January 10, 2007, and September 15, 2007. Patients meeting the ADA criteria for type 2 diabetes and attending the Diabetes Polyclinic at Istanbul University Medicine Faculty, Endocrinology and Metabolic Diseases Department, were included in the study. These patients were divided into two groups based on their body mass index (BMI): obese (BMI ≥30 kg/m², 23 men and 24 women) and non-obese (BMI <25 kg/m², 18 men and 8 women). Additionally, 42 non-diabetic individuals were included as the control group (obese: BMI ≥30 kg/m², 7 men and 11 women; non-obese: BMI <25 kg/m², 9 men and 15 women).

Height, weight, waist and hip circumference measurements were taken for both patient and control groups. Patients using insulin and TZD as antidiabetic medications were excluded. Data on age, gender, medication history, diet, smoking, alcohol consumption, and any existing diseases other than diabetes were also collected for both groups.

Blood samples were collected after a fasting period of 8-12 hours to measure glucose, BUN, creatinine, triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, ALT, AST, HbA1c, fructosamine, insulin, hs-CRP, and C-peptide concentrations. Serum samples were prepared by centrifuging blood at 2500 rpm at +4 degrees Celsius for 10 minutes. Adiponectin, IL-6, leptin, resistin, TNF-α, and visfatin concentrations were determined using the ELISA method from serum samples stored at -80 degrees Celsius until the analysis day. Insulin resistance was as-

sessed using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) formula, which is derived from fasting glucose and insulin levels.

Data Collection and Analysis

Glucose, cholesterol and triglyceride levels were measured by colorimetric enzymatic methods. BUN concentrations were determined using the kinetic UV method, while LDL-cholesterol and HDL-cholesterol were measured using homogeneous enzymatic colorimetric methods. Creatinine concentrations were measured using the kinetic colorimetric method, and AST and ALT concentrations were determined using the kinetic UV method. Fructosamine was analyzed colorimetrically on the Modular System DPP Autoanalyzer (Roche Diagnostics, Indianapolis, USA). HsCRP concentrations were measured using the immunoturbidimetric method on the Cobas Integra 800 (Roche Diagnostics, Indianapolis, USA, reference range; 0.5-5 mg/L) analyzer in the hospital central laboratory.

HbA1c concentrations were measured in whole blood hemolyzed with detergent using the turbidimetric inhibition immunoassay (TINIA) method on the Modular System P module (Roche Diagnostics, Indianapolis, USA). C-peptide concentrations were determined with the electrochemiluminescence immunoassay (ECLIA) method on the Modular System E170 module (Roche Diagnostics, Indianapolis, USA), and insulin levels were measured using the chemiluminescence microparticle immunoassay (CMIA) method on the Architect System i2000 (Abbott Diagnostics, USA) module. Serum resistin, adiponectin and leptin levels were determined by sandwich ELISA (Enzyme-linked immunosorbent assay) method using a commercial kit (ImmunAssayPro, Missouri, USA). TNF-α and IL-6 determination in serum was performed by sandwich ELISA (Enzyme Linked Immunosorbent Assay) method using a commercial kit (Biosource International, Inc., Human TNF-α and Human IL-6, California, USA), and visfatin determination in serum was performed by sandwich ELISA (Enzyme Linked Immunosorbent Assay) method using a commercial kit (Alpco Diagnostics, USA).

Statistical Analysis

In the study, the data distribution of the evaluated parameters was assessed, and skewness and kurtosis values were found to exceed 2. Consequently, statistical comparisons between groups were performed using the non-parametric Mann-Whitney U test. Given that four groups were compared, the Bonferroni correction was applied, and the significance level was set at $P< 0.0125$. The relationships between the evaluated parameters were assessed using Spearman's correlation analysis.

RESULTS

Table 1 presents the physical characteristics of the patient and control groups. The groups included 47 obese

Table 1. Age, body mass index, waist/hip ratio and HOMA-IR values of the patient and control groups.

	Obese DM (n=47)	Obese Control (n=18)	Non-Obese DM (n=26)	Non-Obese Control (n=24)
Age (years)	57.5 (38-70)	58 (36-65)	57 (42-70)	55.1 (35-60)
BMI (kg/m^2)	32.4 (30-58.8)	32.3 (30.2-35.8)	24.25 (21-24.9)	23.4 (19-24.9)
Waist-Hip Ratio	0.91 (0.74-1.14)	0.88 (0.72-0.99)	0.90 (0.75-0.95)	0.78 (0.68-0.91)
HOMA-IR	3.89 (0.97-17)	2.01 (0.66-4.58)	2.02 (0.76-8.6)	1.34 (0.63-3.2)

Data are shown as median (minimum-maximum). DM=Diabetes Mellitus, BMI=Body Mass Index, HOMA-IR= Homeostatic Model Assessment for Insulin Resistance

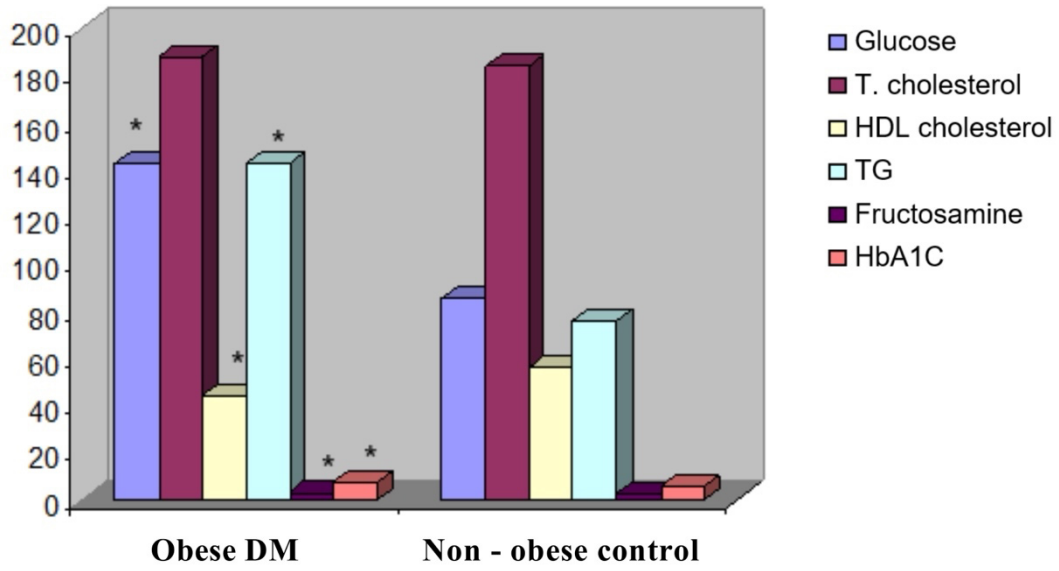

Fig. 1. Glucose, total cholesterol, HDL cholesterol, triglyceride, fructosamine and HbA1C values in obese diabetic and non-obese control groups (median), *P<0.001.

diabetic patients (24 women and 23 men), 26 non-obese diabetic patients (8 women and 18 men), 18 obese controls (11 women and 7 men), and 24 non-obese controls (15 women and 9 men). These groups were compared based on median (distribution range) values for age, BMI, HOMA-IR, and waist/hip ratio.

There was no statistical difference between the patient and control groups in terms of age. Significant differences were observed in waist/hip ratio. Particularly in the comparisons between the obese diabetic group and the obese control group and the obese diabetic group and the non-obese diabetic group, P values were found to be less than 0.0125. When the biochemical parameters of the obese diabetic group and the non-obese control group, the non-obese diabetic group and the non-obese control group, and the obese control group and the non-obese diabetic group were compared, the results were also found to be significant

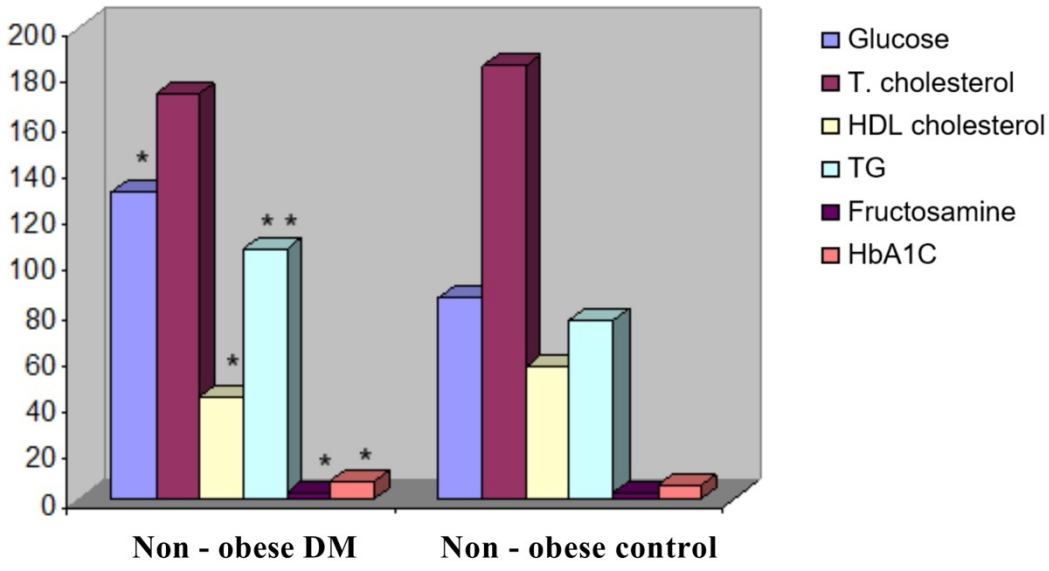

Fig. 2. Glucose, total cholesterol, HDL cholesterol, triglyceride, fructosamine and HbA1C values in non-obese diabetic and non-obese control groups (median), * P<0.001, **P<0.0125.

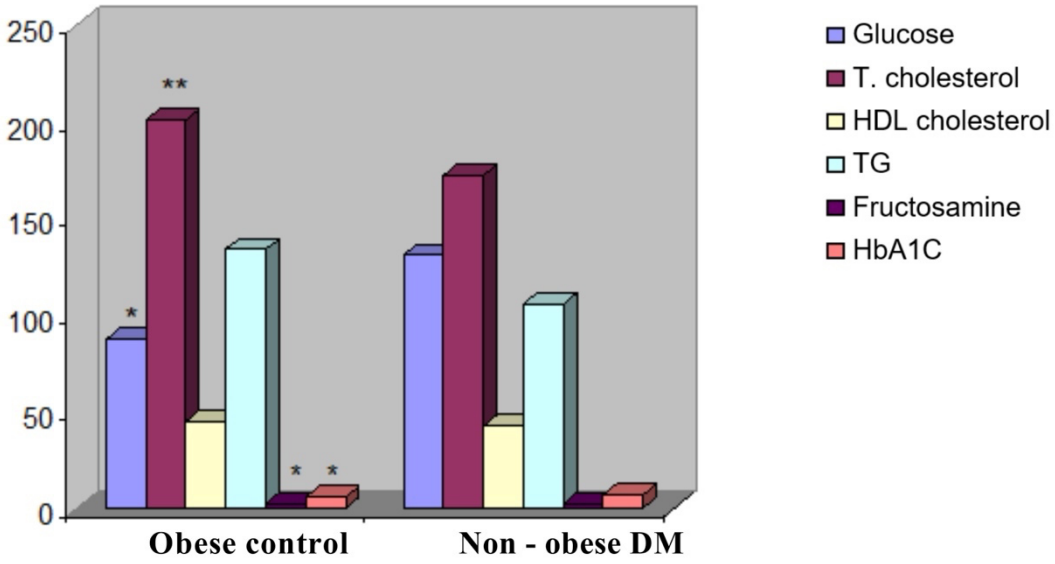

Fig. 3. Glucose, total cholesterol, HDL cholesterol, triglyceride, fructosamine and HbA1C values in non-obese diabetic and obese control groups (median), *P<0.001, **P<0.0125.

(Figs 1, 2 and 3).

Routine biochemical parameters of control groups and the patients are described in Table 2. Resistin, adiponectin, leptin, visfatin, Tnf-α, IL-6 and hsCRP values of patients and group controls are in Table 3 (Figs. 4, 5, 6, 7, 8 and 9). Correlations of resistin and vistatin with other parameters in the patient and control groups are in Tables 4 and 5.

DISCUSSION

Type 2 diabetes (T2DM) is a metabolic condition associated with obesity and impaired fat tissue storage. Insulin resistance (IR), which is considered to be a relative pancreatic β-cell deficiency with a disturbed balance between abnormal cellular response and insulin actions, is one of the leading causes of T2DM [11].

Table 2. Glucose, total cholesterol, HDL cholesterol, triglyceride, fructosamine and HbA1c values of the patient and control groups

	Obese DM	Obese Control	Non-Obese DM	Non-Obese Control
Glucose (mg/dL)	143 (83-341)	87.5 (72-100)	131 (79-287)	86 (73-98)
Total cholesterol (mg/dL)	188.3 (82-281)	201.5 (164-256)	172.5 (121-243)	184.5 (134-245)
HDL cholesterol (mg/dL)	44 (30-71)	45 (27-66)	43 (33-70)	56 (35-73)
Triglyceride (mg/dL)	143 (53-400)	134 (86-374)	106 (49-284)	76 (34-223)
Fructosamine (mmol/L)	2.99 (2.19-4.44)	2.32 (2.1-2.52)	2.88 (2.18-4.61)	2.38 (1.94-2.97)
HbA1C (%Hb)	7.2 (5.4-10.8)	5.75 (5.5-6.2)	6.8 (5.5-11.4)	5.6 (5-6.1)

Data are shown as median (minimum-maximum). DM=Diabetes Mellitus, HDL=High-density lipoprotein, HbA1c=Glycated Hemoglobin

Table 3. Resistin, adiponectin, leptin, visfatin, TNF-α, IL-6 and hsCRP values of patient and control groups

	Obese DM (n=47)	Obese Control (n=18)	Non-Obese DM (n=26)	Non-Obese Control (n=24)
Resistin (ng/mL)	9.72 (4.86-19.63)	12.4 (5.39-19.68)	8.22 (3.6-18.5)	10.33 (5.38-18.84)
Adinopectin (µg/mL)	6.8 (3.9-32.4)	9 (3.4-40.6)	5.7 (2.7-12.6)	8.99 (3-44.6)
Leptin (ng/mL)	55.5 (4.6-436.8)	78.99 (24.6-316)	46.94 (5.84-214.7)	49.31 (8.86-147.2)
Visfatin (ng/mL)	3.37 (1.35-24)	3.83 (0.75-10.8)	3.78 (0.25-11)	3.62 (0.83-17.25)
TNF-α (ρg/mL)	15.69 (6.32-73.74)	34.96 (11.09-153.6)	17.7 (3.31-67.43)	14.04 (0.6-60.67)
IL-6 (ρg/mL)	14 (10.2-25.35)	14.45 (10.2-19.97)	14.8 (9.18-30.66)	17.38 (10-33.6)
HsCRP (mg/L)	2.95 (0.7-78.5)	3.25 (0.73-13.4)	0.955 (0.12-7.6)	0.8 (0.3-4.1)

Data are shown as median (minimum-maximum). DM=Diabetes Mellitus, TNF=Tumor Necrosis Factor, IL=Interleukin, HsCRP= High-sensitivity C-reactive protein

Additionally, IR is closely linked to other metabolic conditions such as hypertension, hyperinsulinemia, dyslipidemia, obesity and fatty liver disease, which are key components of metabolic syndrome. Overweight and obese individuals exhibit a range of oxidative stress, metabolic abnormalities, immune dysfunction, mitochondrial dysfunction, and chronic low-grade inflammation [12].

Recent studies suggest that triglycerides accumulated in muscle tissue and impaired mitochondrial ox-

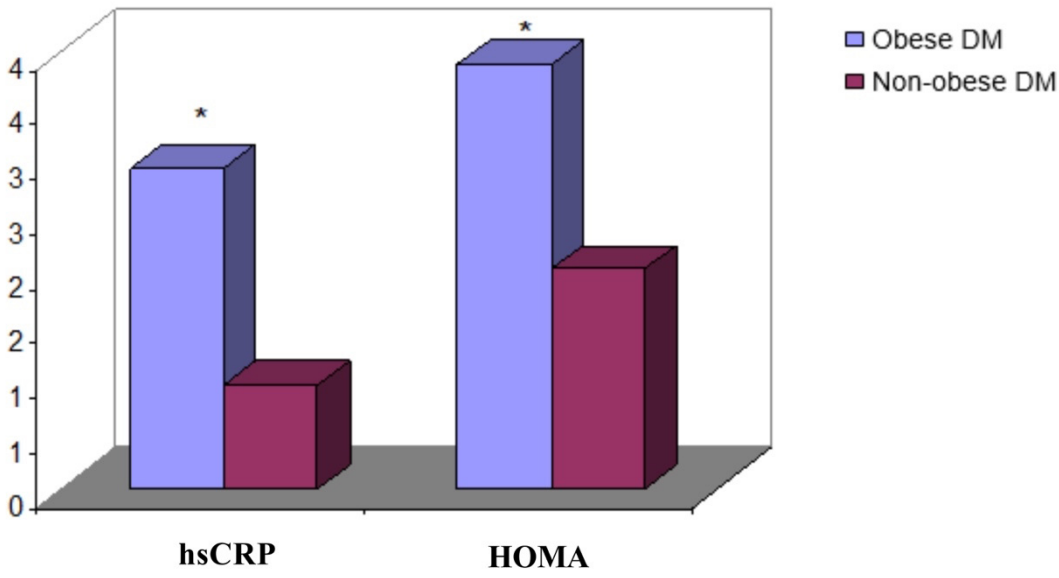

Fig. 2. HsCRP and HOMA-IR values in obese diabetic and non-obese diabetic groups (median), *P<0.001.

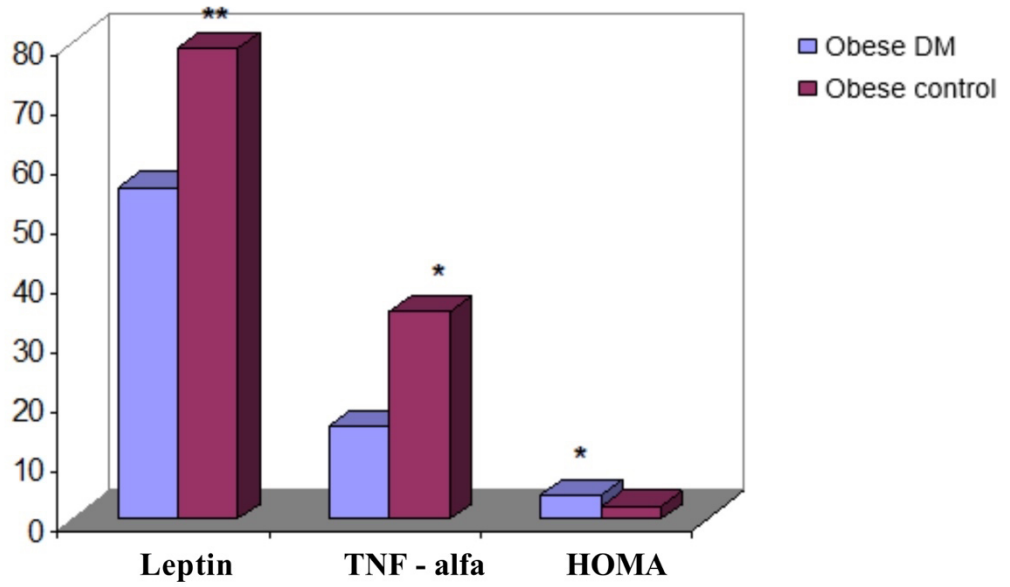

Fig. 5. Leptin, TNF-α and HOMA-IR values in obese diabetic and obese control groups (median), *P<0.001, ** P<0.0125.

idative phosphorylation in genetically predisposed individuals contribute to insulin resistance [13]. Adipose tissue, the primary source of circulating fatty acids, has been linked to impaired insulin action when there is an increase in abdominal fat tissue, as opposed to peripheral or gluteofemoral fat tissue [14,15].

Inflammation, particularly CRP, is regarded as a key contributor to the pathogenesis of glucose intolerance, insulin resistance, and T2DM [16,17]. Numerous studies have reported a strong relationship

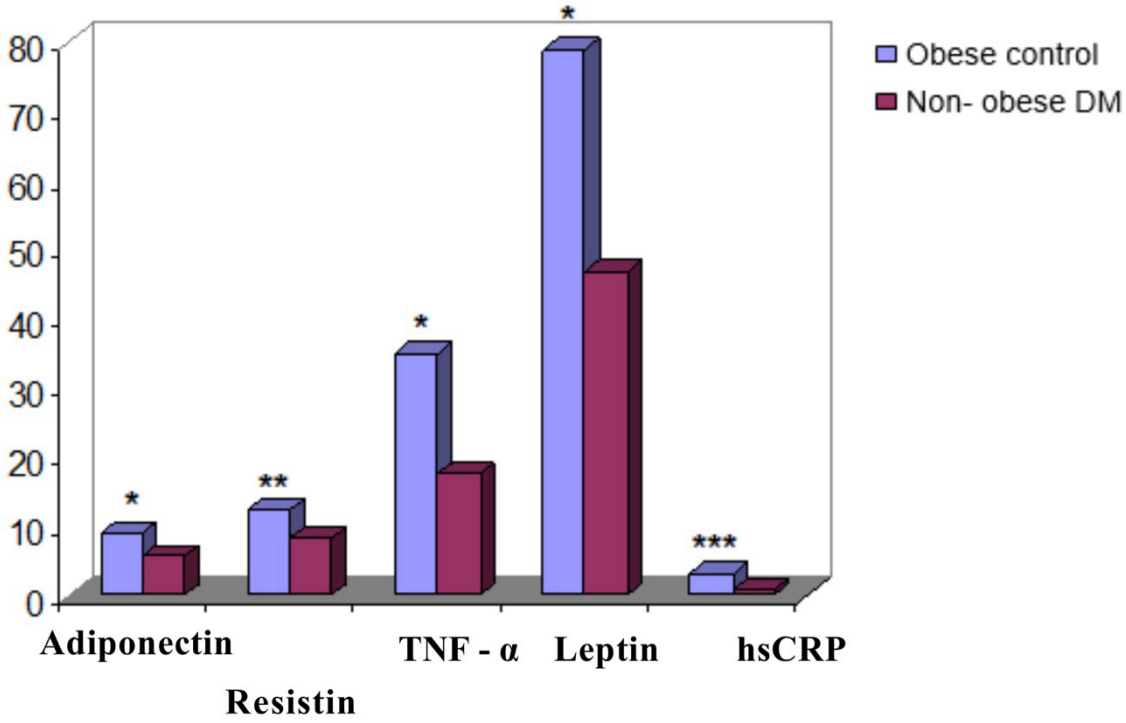

Fig. 6. Adiponectin, resistin, TNF-α, leptin and hsCRP values in obese control and non-obese diabetic groups (median), *P<0.01, **P<0.0125, ***P<0.001.

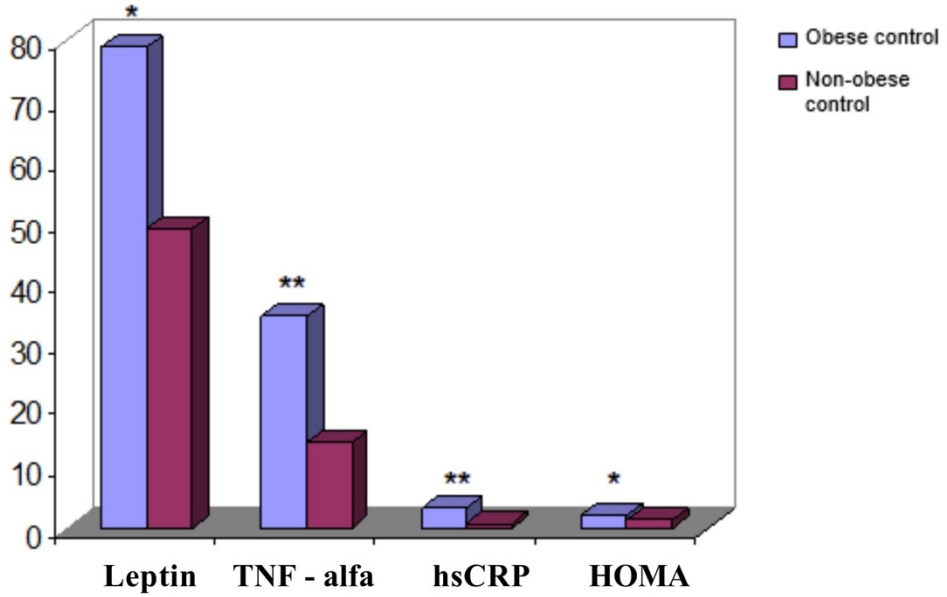

Fig. 7. Leptin, TNF-α, hsCRP and HOMA-IR values in obese control and non-obese control groups (median), *P<0.0125, ** P<0.001.

between circulating inflammatory markers and the development of T2DM [18-19]. Different markers, such as cytokines, chemokines, IL-6, and fibrinogen, have been examined, but results have been inconsistent.

Adipose tissue, traditionally known for storage and heat insulation, plays an active role in maintaining energy balance and in immune and inflammatory processes. Weight gain and obesity cause phenotypic changes in white adipose tissue characterized by the infiltration of inflammatory, dysfunctional fat cells into the stromal vascular fraction, and these inflammatory fat cells secrete proinflammatory cytokines that impair the function of adipose tissue and distant organs, both locally and systemically [12]. These adipokines affect insulin sensitivity and are vital in developing inflammation, insulin resistance, diabetes,

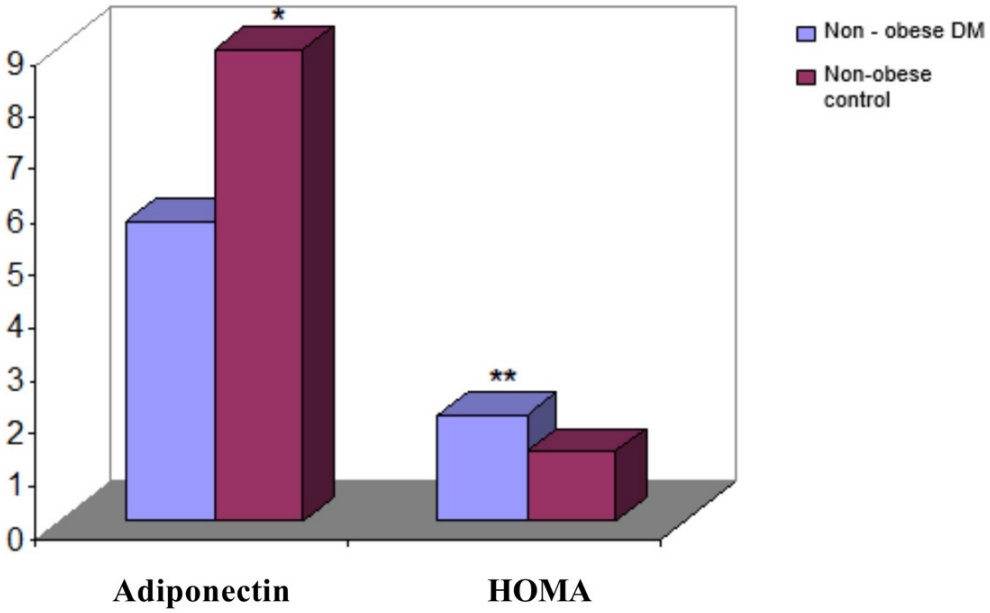

Fig. 8. Adiponectin and HOMA-IR values in non-obese diabetic and non-obese control groups (median) *P<0.0125, **P<0.01.

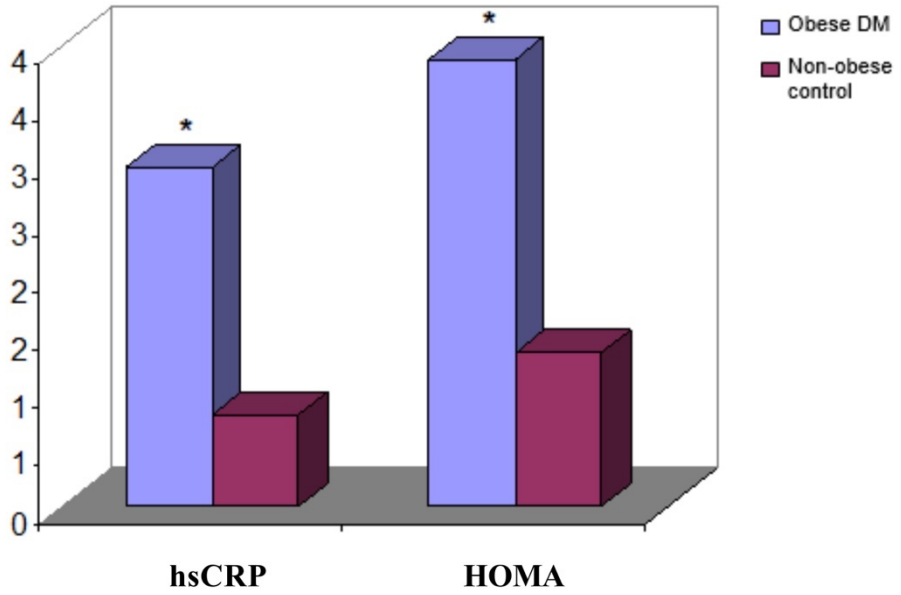

Fig. 9. HsCRP and HOMA-IR values in obese diabetic and non-obese control groups (median), *P<0.001.

dyslipidemia, and atherosclerosis [20].

While there is ongoing debate about whether the connection between T2DM and inflammatory markers is independent of increased adipose tissue or mediated by obesity, some studies argue that this debate is partly due to the indirect assessment of the amount and distribution of adipose tissue using anthropometric measures such as BMI and waist/hip ratio [21].

Our study analyzed T2DM patients diagnosed with the ADA criteria. Patients were divided into two groups according to BMI: obese (n=47) and non-obese (n=26). We investigated serum adipokine concentrations (leptin, adiponectin, resistin, visfatin, TNF-α, IL-6) and hs-CRP and their correlations with HOMA-IR-calculated insulin resistance. Additionally, we studied 42 healthy individuals with similar BMIs for comparison.

We found that, despite similar body mass indexes,

Table 4. Correlation of resistin with other parameters in patient and control groups.

Resistn	Obese DM		Obese Control		Non-Obese DM		Non-Obese Control	
	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value
Adiponectin	-0.218	0.147	0.297	0.232	-0.002	0.993	-0.07	0.743
Leptin	0.045	0.766	0.301	0.226	-0.205	0.315	0.282	0.182
Visfatin	-0.085	0.574	0.439	0.068	0.614	**0.0008***	0.495	**0.014**
TNF-α	0.11	0.459	0.27	0.277	0.528	**0.006***	0.106	0.623
Il-6	0.235	0.112	0.245	0.328	0.398	**0.044**	-0.115	0.592
HsCRP	0.036	0.814	0.327	0.185	0.046	0.825	0.252	0.234
Homa-IR	-0.007	0.96	-0.458	0.055	-0.054	0.793	0.234	0.272
BMI	0.203	0.177	-0.145	0.567	0.202	0.322	0.217	0.308

DM=Diabetes Mellitus, TNF=Tumor Necrosis Factor, IL=Interleukin, HsCRP= High-sensitivity C-reactive protein, BMI=Body Mass Index, HOMA-IR= Homeostatic Model Assessment for Insulin Resistance

*P<0.0125

Table 5. Correlation of visfatin with other inflammatory parameters in patient and control groups

Visfatin	Obese DM		Obese Control		Non-Obese DM		Non-Obese Control	
	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value
TNF-α	0.03	0.836	0.05	0.845	0.132	0.522	0.111	0.606
Il-6	0.148	0.314	0.486	**0.04**	0.274	0.176	-0.179	0.401
HsCRP	0.189	0.198	-0.331	0.179	-0.014	0.945	0.406	**0.04**
Homa-IR	0.239	0.101	-0.218	0.385	0.101	0.623	0.576	**0.0032***
BMI	-0.112	0.448	-0.056	0.826	-0.043	0.835	0.346	0.097

DM=Diabetes Mellitus, TNF=Tumor Necrosis Factor, IL=Interleukin, HsCRP= High-sensitivity C-reactive protein, BMI=Body Mass Index, HOMA-IR= Homeostatic Model Assessment for Insulin Resistance

*P<0.0125

the waist-hip ratios of diabetics in both groups were significantly higher than their controls, indicating abdominal obesity (P<0.0125 and P<0.0001, respectively). Studies have demonstrated that plasma concentrations of adiponectin, produced by specialized fat cells, are reduced in T2DM [22-23]. Our study also observed an important decrease in adiponectin concentrations in T2DM patients compared to the control group, with this significant difference persisting in non-obese diabetics (P<0.0125). However, adiponectin concentrations were not different between obese diabetics and their controls. The amount of food consumed, overall body fat, and various hormones all contribute to regulating leptin secretion [3]. Insulin is the main factor in regulating the production of leptin. Prolonged elevated insulin levels in the blood result in an increased concentration of leptin in the plasma, whereas short-term elevated insulin levels do not cause this change [24]. The effects of leptin resemble those of other acute-phase reactants; it stimulates the secretion of various inflammatory cytokines (e.g., IL-12, IL-6 and TNF-α) [25]. An increase in fat mass leads to higher concentrations of leptin in the blood, directly related to obesity [26]. Our study found higher leptin concentrations in obese T2DM patients than in non-obese T2DM patients, though the difference was insignificant. In the non-diabetic group, obese individuals had higher leptin concentrations than non-obese individuals (P<0.0125).

IL-6, which is secreted by some cells, endothelial cells, monocytes, including fibroblasts, and adipocytes, is crucial in regulating the production of inflammatory proteins like CRP in the liver [27]. There is a positive correlation among circulating IL-6 and CRP levels in adipose tissue [28]. Studies have shown that IL-6 may be linked to insulin resistance and complications [29]. However, our study found no significant differences in IL-6 levels among groups.

TNF-α is suspected to play a role in obesity-related insulin resistance, with increased expression in the adipose tissue of obese individuals [30]. Studies have found conflicting results regarding the relationship between TNF-α concentrations and human insulin resistance [31,32]. However, a study conducted between 1998 and 2001 in 2356 individuals (children of Framingham Study participants) showed that TNF-α has an association with insulin resistance [33]. In our study, TNF-α concentrations of obese controls were significantly higher than lean controls (P<0.001). Although non-obese diabetics had higher TNF-α concentrations than non-obese controls, the difference was insignificant. TNF-α concentrations in obese controls exceeded those in obese diabetics (P<0.001).

Resistin functions through autocrine, paracrine, and endocrine modes of action, affecting various cell types and tissues [34]. Circulating resistin levels positively correlate with common inflammatory and fibrinolytic biomarkers such as CRP, IL-6 and TNF-α in conditions including type 2 diabetes, chronic kidney disease, rheumatoid arthritis, coronary atherosclerosis and sepsis [34]. Inconsistent results have been obtained from human studies. Macrophages that infiltrate adipose tissue are believed to be humans' primary source of resistin [35]. Circulating resistin is positively

associated with adiposity and may have a role in pro-inflammatory signaling [5]. Our study found no difference in resistin concentrations among obese or non-obese diabetics or control groups. Furthermore, no significant correlation was found between resistin and insulin resistance. But there was a correlation between resistin concentrations and CRP concentrations in T2DM patients, independent of BMI (P<0.001). Visfatin, recently identified and synthesized primarily by visceral adipose tissue, has metabolic effects similar to insulin and shows a strong relationship with adipose tissue mass [36]. Although plasma visfatin concentrations are high in type 2 diabetes in some studies, no relationship between circulating visfatin and insulin resistance has been shown [37,38]. Our study found no significant difference in visfatin concentrations between type 2 diabetic patients and no relationship between visfatin and insulin resistance, BMI, or insulin concentrations.

CRP, typically produced by the liver in reaction to cytokines like IL-6, has also been found to have its mRNA expressed in adipose tissue [39]. This suggests that adiposity may be an important source of inflammatory cytokines in healthy individuals. The increased CRP concentrations detected in the presence of insulin resistance might be attributed to an increase in adipose tissue [40]. In our study, hs-CRP concentrations were significantly higher in obese diabetics than in non-obese diabetics, and in obese controls compared to non-obese controls (P<0.0001). This supports the hypothesis that increased adipose tissue mediates the slightly elevated CRP concentrations. It remains unclear whether inflammation triggers insulin resistance in obesity or if pro-inflammatory cytokines and inflammation markers like IL-6 and CRP are elevated in obese individuals as a result of insulin resistance. Our study found higher hs-CRP concentrations in non-obese diabetics than their controls, but the difference was not significant.

CONCLUSION

To sum up, our findings indicate that insulin resistance in the absence of obesity may not be associated with known inflammatory processes. It is clear that there is a link between obesity and insulin resistance, and that adipokines probably contribute to lipid and carbohydrate metabolism. Although new studies have made significant progress, more detailed studies on insulin resistance and obesity are needed.

Ethical Statement

This study follows the principles of the Declaration of Helsinki. The study was conducted with approval from Istanbul University Faculty of Medicine Clinical Research Ethics Committee dated 28.08.2006 and numbered 1745. All participants provided their informed consent.

Authors' Contribution

Study Conception: AT, AGST; Study Design: AY, AGST; Supervision: AY, AGST, AKÜ; Funding: N/A; Materials: AY, AKÜ; Data Collection and/or Processing: AY, AKÜ; Statistical Analysis and/or Data Interpretation: AY, AGST, AKÜ; Literature Review: AY, AGST; Manuscript Preparation: AY and Critical Review: AY, AGST.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Editor's note

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Investigation of the effect of SGLT-2 inhibitors on the triglyceride/glucose index in diabetic patients: a cross-sectional study

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ABSTRACT

Objectives: The aim of this study is to estimate the change in the Triglyceride Glucose Index (TyG index), in patients with type 2 Diabetes Mellitus who are using a sodium-glucose cotransporter-2 (SGLT2) inhibitor, and to evaluate the effect of these drugs on triglyceride glucose index.

Methods: This is a cross-sectional study of 55 diabetic patients in our internal medicine clinic in Turkey. Triglyceride, glucose, and glycosylated hemoglobin (HbA1c) values were measured at the beginning of the treatment and the 3rd-month follow-up. The TyG index of the patients before starting SGLT-2 inhibitor treatment and at the end of 3 months of treatment was calculated by the researchers using the data in the hospital digital records.

Results: The mean age of 55 patients (56.4% male) was 62.7±10.2 years. The number of patients using dapagliflozin 10 mg was 15 (27.3%) and the number of patients using empagliflozin was 41 (72.8%). It was determined that fasting plasma glucose, TyG index, and HbA1c values before starting SGLT-2 inhibitor treatment and in the 3rd month of treatment decreased significantly (P<0.001, P=0.002 and P<0.001, respectively). According to the correlation analysis results between TyG index and HbA1c, it was determined that the values both before treatment and in the 3rd month of treatment showed a correlation (r=0.516, P<0.001 and r=0.448, P=0.001, respectively).

Conclusions: SGLT-2 inhibitor usage significantly reduces TyG index in diabetic patients, and new studies are needed to investigate the effect of these drugs on triglyceride index among pre-diabetic patients.

Keywords: Triglyceride glucose index, SGLT-2 inhibitor, dapagliflozin, empagliflozin, diabetes mellitus

The Triglyceride Glucose Index (TyG index) was first proposed in Mexico in 2008 as a marker for insulin resistance [1]. The formula for its calculation is "ln [Fasting triglyceride (mg/dL) × fasting glucose (mg/dL)]/2". The initial cut-off for the TyG index was Ln 4.65 to diagnose insulin resistance, with an initial sensitivity of 84.0% and specificity of 45.0% [1]. Subsequent research validated its effectiveness, showing a higher sensitivity when compared to the gold standard test [2]. Later studies have indicated that the TyG index is more accurate than the Homeostatic Model Assessment for In-

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sulin Resistance (HOMA-IR) in predicting metabolic syndrome (MetS) [3] and is uniquely effective in predicting the onset of MetS [3].

The relationship between the TyG index and atherosclerotic cardiovascular disease has been the subject of extensive research. A notable study involving two large cohorts found that rising values of the TyG index were linked to an elevated risk of heart failure. Specifically, those in the maximum one-fourth of the TyG index had an adjusted increased risk significantly when compared to the lowest (P<0.001) [4]. In another study, the investigators found that a higher TyG index was an independent predictive factor for coronary artery disease (CAD) severity among patients with glucose intolerance or impaired fasting glucose [5]. This study found that individuals in the highest TyG index group (≥7.38) had an approximately 1.5 times elevated risk of multivessel CAD compared to those in the lowest group (<6.87) [5]. Additionally, a high TyG index was associated with a greater risk of atrial fibrillation in non-diabetic individuals [6].

Lee *et al*. [7] examined the relationship of the TyG index with coronary stenosis in a cohort of 888 diabetic patients with no previous CAD. Their findings indicated that elevated levels of TyG index were linked to a greater risk of coronary artery stenosis, alongside factors such as advanced age, male gender, poor glycemic control, longer diabetes duration, and non-use of statins. The study further established that a higher TyG index independently contributed to CAD risk (OR: 3.19, 95% CI: 1.371-7.424) [7].

Additional research has reinforced the positive association between elevated TyG index levels and atherosclerotic cardiovascular disease events, even after adjusting for confounding variables, in a population with a 10-year median follow-up period [8].

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, including dapagliflozin and empagliflozin, represent newer treatment options for Type 2 Diabetes Mellitus (T2DM) due to their glycosuric effects. Extensive research has demonstrated that these drugs not only enhance blood glucose control but also reduce mortality in heart failure patients [9, 10]. Several large studies have shown that SGLT-2 inhibitors can significantly lower the risk of cardiovascular morbidity and mortality, including heart attacks, strokes, and hospitalizations for heart failure, compared to placebo in people with a diagnosis of T2DM who have established cardiovascular disease or at high risk for cardiovascular disease. The mechanisms by which SGLT-2 inhibitors provide cardiovascular protection are not entirely clear but may be related to their ability to reduce blood glucose levels, blood pressure, and body weight, as well as improve cardiac function and metabolic parameters such as lipid profiles and kidney function. Recent studies also suggest that SGLT-2 inhibitors have protective effects against kidney failure and albuminuria [11, 12]. The mechanisms underlying their beneficial impact on endothelial function include increased nitric oxide production, reduced oxidative stress, improved microvascular function, and decreased inflammation [13].

Our study aims to assess changes in the TyG index among patients with a diagnosis of T2DM following the initiation of SGLT-2 inhibitor treatment.

METHODS

This cross-sectional study involved 55 patients over 18 years old, diagnosed with Type 2 Diabetes Mellitus, who were seen at the Internal Medicine outpatient clinic of Samsun Training and Research Hospital in Turkey. The data of patients who began SGLT-2 inhibitor treatment (dapagliflozin 10 mg, empagliflozin 10 mg, or empagliflozin 25 mg) and were monitored for at least 3 months from January 1, 2022, to December 31, 2022, were analyzed through a retrospective file review. The study adhered to the Declaration of Helsinki and was approved by the Samsun University Ethics Committee, with protocol number SUKAEK-2023 7/20. This study is also registered in Clinical Trials System with the protocol number NCT05915884. Exclusions were made for patients with insufficient follow-up, missing data, those receiving dyslipidemia treatment, or those who started other antidiabetic drugs during the study period. The patient selection is illustrated in Fig. 1.

All demographical and biochemical findings were collected anonymously from medical records, including age, gender, diabetes duration, SGLT-2 inhibitor usage duration, medical history, all medications for glucose control, dyslipidemia status, hypothyroidism status, and laboratory test results. Triglyceride, glucose, and glycosylated hemoglobin (HbA1c) levels were measured at the start of treatment and after 3

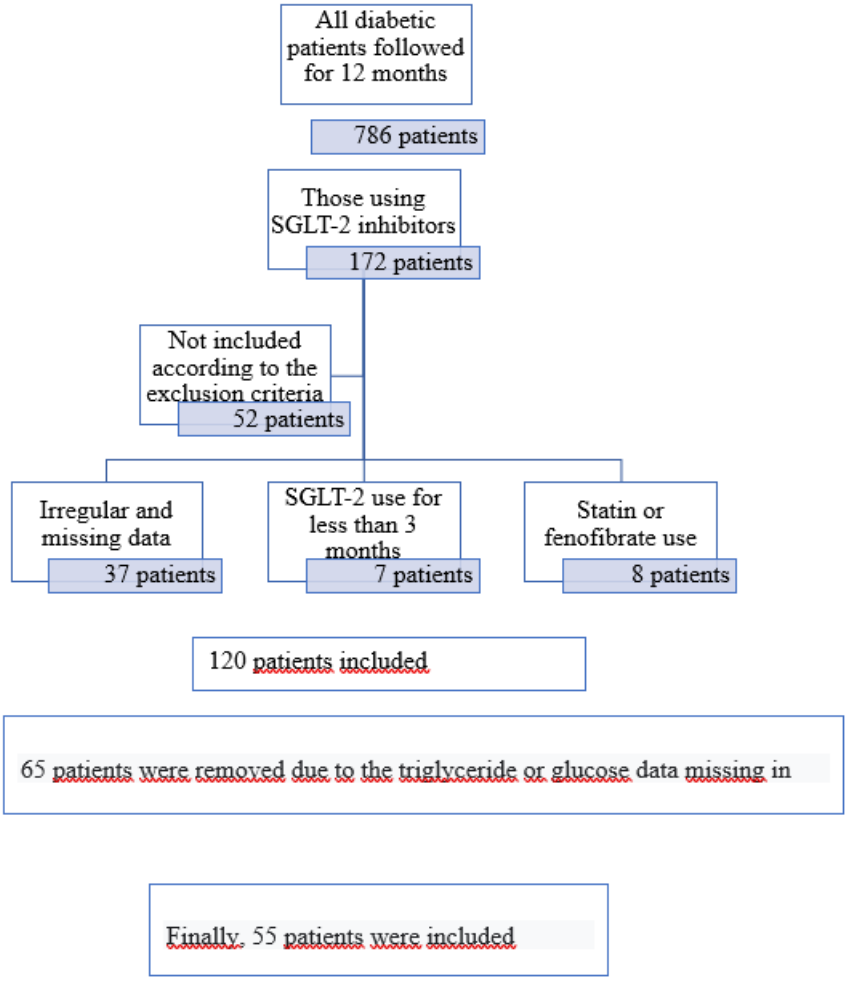

Fig. 1. Patient selection for inclusion.

months. The calculation of the TyG index was done according to the aforementioned formula [1]. No additional blood tests or laboratory analyses were conducted.

Statistical Analysis

The analyses were conducted using SPSS 21.0.0.1 for Windows (Statistical Package for the Social Sciences; IBM). The Kolmogorov-Smirnov test was employed to assess data distribution. Continuous variables were presented as either mean or median depending on their distribution pattern. Categorical variables were reported as frequencies (n) and percentages (%). The paired sample t-test and the Wilcoxon signed-rank test assessed group differences. A P value of less than 0.05 was deemed statistically significant. Pearson correlation test was conducted to explore the relationships between variables.

RESULTS

The data of 786 diabetic patients followed for 12-month periods in our internal medicine clinic were searched and 55 patients were included for the last analysis (Fig. 1).

The mean age of 55 patients (56.4% male) was 62.7±10.2 years and the median duration of SGLT-2 inhibitor use was 18 (3-60) months. The number of patients using dapagliflozin 10 mg was 15 (27.3%) and the number of patients using empagliflozin was 41 (72.8%). Forty-nine (89.1%) patients had a diagnosis of diabetes for more than 5 years. Demographical properties are shown in Table 1.

It was determined that fasting plasma glucose, triglyceride index, and HbA1c values before starting SGLT-2 inhibitor treatment and in the 3rd month of treatment decreased significantly (P<0.001, P=0.002,

and P<0.001, respectively) (Table 2). According to the correlation analysis results between triglyceride index and HbA1c, it was determined that the values both before treatment and in the 3rd month of treatment showed a correlation (r=0.516, P<0.001 and r=0.448; P=0.001, respectively).

Subgroup analyses were done according to the nephropathy status and CAD status of the patients. While the change in the TyG index was found to be significant in those without CAD (n=40, 95% CI: 0.087-0.299; P=0.001), the index change was not found to be significant in those with an established CAD (n=14, 95% CI: -0.157-0.365; P=0.403). Similarly, while the change in triglyceride glucose index was not found to be significant in patients with nephropathy (n=15), 95% CI: -0.21-0.19; P=0.940], the index change was found to be significant in patients without nephropathy (n=39, 95% CI: 0.11- 0.34; P<0.001).

Table 1. The general features the study population

Variables	Data
Demographics	
Age (years)	62.7±10.2
Gender, male	31 (56.4)
SGLT-2 inhibitor, n (%)	
Dapagliflozin 10 mg	15 (27.3)
Empagliflozin 10 mg	37 (67.3)
Empagliflozin 25 mg	3 (5.5)
Other antidiabetic treatments, n (%)	
DPP4 inhibitor	37 (67.3)
Long acting insulin analogue	21 (38.2)
Preprandial insulin analogue	6 (10.9)
Sulphonylurea	10 (18.2)
Pioglitazone	6 (10.9)
Complications and comorbidities, n (%)	
Retinopathy	12 (21.8)
Nephropathy	15 (27.3)
Neuropathy	16 (29.1)
Hypertension	39 (70.9)
Coronary artery disease	14 (25.1)
Cerebrovasculary disease	2 (3.6)

Data are shown as mean±standard deviation or n (%) where appropriate

DISCUSSION

In our study, we observed a notable reduction in fasting plasma glucose, LDL cholesterol, HbA1c, and the TyG index following three months of treatment with empagliflozin or dapagliflozin in patients with T2DM. As previously mentioned in the introduction section existing research has highlighted a strong correlation between higher TyG index levels and an elevated adverse cardiovascular event risk [4-6].

A large-scale prospective study with 62,443 participants evaluated the TyG index at four-year intervals. After a median observation period of 7.01 years, cardiovascular disease incidence was 4.05%. This study revealed that higher quartiles of change in the index were related to a higher risk of experiencing new cardiovascular events. Specifically, after adjusting for various confounding factors, the hazard ratios for the biggest quartile (Q4) compared to the smallest quartile (Q1) were approximately 1,4 for overall cardiovascular disease, stroke, and myocardial infarction [14]. Another investigation found a significant relationship between elevated TyG index levels and carotid atherosclerosis, assessed by common carotid artery intima-media thickness in patients who had suffered ischemic strokes, suggesting that this index could be a promising indicator for atherosclerosis [15]. Moreover, a large prospective study from China involving 138,620 participants found that an increment in the TyG index was linked to an elevated risk of heart failure [16]. An analysis of patients with premature onset CAD showed that those with major adverse cardiovascular events had significantly higher TyG index values compared to those without such events (8.94±0.52 vs. 8.72±0.57, P<0.001) [17]. A recent metaanalysis also supported the link between elevated TyG index levels and cerebrovascular disease [18].

Our research indicates that SGLT-2 inhibitor therapy is associated with a reduction in the TyG index. However, the impact of this reduction on cardiovascular event risk was not evaluated in our study due to its cross-sectional design and the absence of long-term

Table 2. Biochemical properties before and after SGLT-2 inhibitor treatment

Variable	Before SGLT-2 inhibitor treatment (n=55)	3rd month of SGLT-2 inhibitor treatment (n=55)	P value
Fasting glucose median (mg/dL)	180 (74.00-600.00)	152 (48.97-140.00)	**<0.001**
Triglyceride (mg/dL)	163 (62.00-433.00)	162 (52.00-441.00)	0.265
Low density lipoprotein (mg/dL)	99.50 (0.34)	91.00 (31.15)	0.051
Triglyceride glucose index	5.18 (0.34)	5.01 (0.32)	**0.002**
Glycosylated hemoglobin (%)	8.93 (1.98)	7.69 (1.10)	**<0.001**

Data are shown as mean±standard deviation or median (minimum-maximum) where appropriate

follow-up data.

The evidence supporting the TyG index as a predictor of insulin resistance and metabolic syndrome, combined with its association with cardiovascular disease risk, suggests it may be valuable for assessing cardiovascular risk in diabetic patients. Previous studies have demonstrated that SGLT-2 inhibitors reduce the atherosclerotic cardiovascular disease risk regardless of diabetes diagnosis, and have a positive effect on mortality and hospitalization rate [9-12].

The EMPA-REG OUTCOME trial showed that adding empagliflozin to standard therapy resulted in a 14% reduction in 3-point major adverse cardiac events, a 38% decrement in cardiovascular mortality, a 32% decrement in all-cause mortality, and a 35% decrement in heart failure hospitalization compared to placebo [9]. Additionally, empagliflozin improved diabetic nephropathy and reduced albuminuria [9]. In our study, SGLT-2 inhibitor usage was divided into 72.8% for empagliflozin and 27.2% for dapagliflozin. We believe that the lack of another new antidiabetic drug except SGLT-2 inhibitor or lipid-lowering medication between the initial and follow-up laboratory tests was sufficient to discover the impact of SGLT-2 inhibitors on these parameters. A strength of our study was the consideration of various confounding factors affecting biochemical metabolic parameters in our inclusion and exclusion criteria, though this led to a significant reduction in the number of participants in the final analysis, which is a notable limitation.

In two comparable studies conducted in our country, the influences of these drugs on metabolic parameters were evaluated with similar sample sizes to ours [19, 20]. One study reported significant reductions in weight, body mass index, waist circumference, and hip circumference after six months of empagliflozin use [19]. The other study also found significant decreases in body mass index and weight in patients treated with empagliflozin compared to pre-treatment levels and the control group [20].

In our study, the change in triglyceride index was not found to be significant among patients with a history of CAD and those who already developed nephropathy, while a significant decrease was observed in the opposite cases. This result shows that starting SGLT-2 inhibitors early, before complications develop, is metabolically important. However, studies with larger numbers of participants are needed to generalize the results.

SGLT-2 inhibitor treatment may change during follow-up period. For example, a patient may start dapagliflozin treatment than changed into empagliflozin, vice versa. That's why, we could not perform drug specific analysis. We think that new prospective studies are needed to investigate the effect of each molecule on TyG index, seperately.

CONCLUSION

The results we obtained in our study showed that treatment of diabetic patients with SGLT-2 inhibitors reduces the TyG index. We think that new studies should be conducted to research the impact of these drugs on the TyG index and the risk of developing MetS in non-diabetic individuals.

Ethical Statement

The study adhered to the Declaration of Helsinki

and was approved by the Samsun University Clinical Research Ethics Committee (Decision no: SUKAEK-2023 7/20 and date: 12.04.2023)

Authors' Contribution

Study Conception: DSKÖ, AK; Study Design: DSKÖ, AK; Supervision: DSKÖ, AK; Funding: N/A; Materials: N/A; Data Collection and/or Processing: DSKÖ, AK, RİV; Statistical Analysis and/or Data Interpretation: DSKÖ, AK, RİV; Literature Review: DSKÖ, AK, RİV; Manuscript Preparation: DSKÖ, AK, RİV, MDD; and Critical Review: DSKÖ, MDD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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This study is also registered in Clinical Trials System with the protocol number NCT05915884.

Editor's note

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Renal shear wave elastography in familial Mediterranean fever patients without nephropathy

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ABSTRACT

Objectives: Due to its lethal effects, early diagnosis of high risk patient groups for renal involvement especially amyloidosis is critical for Familial Mediterranean Fever (FMF). Amyloidosis, defined by the accumulation of extracellular amyloid protein material in the kidney, can reduce the elasticity of the renal parenchyma. Shear wave elastography (SWE) is a new ultrasonographic imaging modality that evaluates tissue elasticity. This pilot study assessed the renal parenchyma of FMF patients using SWE.

Methods: Fifty-three FMF patients and 51 age- and sex-matched healthy control participants were included in this study. Participants with amyloidosis, estimated glomerular filtration rate (eGFR) less than 60 mL/min and/or signs of nephropathy (proteinuria, hematuria, renal tubular acidosis) were excluded. Routine history, physical, laboratory examinations (blood urea nitrogen, creatinine, C-reactive protein, urine dipstick test, spot proteinuria) and renal ultrasound were performed. SWE imaging was performed to measure renal parenchymal stiffness.

Results: There was no significant correlation between SWE values (elasticity and velocity) and age, eGFR, serum blood urea nitrogen, and creatinine in the comparison of SWE findings of FMF patients and control groups. SWE values were statistically higher in FMF patients than in the control group ($P=0.002$ and $P< 0.001$ for elasticity and velocity, respectively).

Conclusions: Increased renal stiffness in FMF patients may indicate early renal involvement (especially amyloidosis), suggesting SWE as a potential non-invasive diagnostic tool for early detection.

Keywords: Familial Mediterranean fever, nephropathy, amyloidosis, shear wave elastography, renal cortical stiffness

Familial Mediterranean Fever (FMF) represents an autosomal recessive, autoinflammatory disorder distinguished by recurrent, self-limiting episodes of fever, concomitant with aseptic inflammation in serosal cavities, joints, and the skin [1, 2]. Acute attacks usually last 1 to 3 days and resolve spontaneously. Nevertheless, in certain individuals, these episodes may extend beyond the typical timeframe, lasting more than one week, with an occasional occurrence of up to one month. However, instances of even longer durations are exceedingly rare [3]. Despite being self-limiting, some FMF patients develop sec-

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ondary amyloidosis, particularly AA type, which is the most severe complication of FMF [4].

Before colchicine therapy, renal amyloidosis was the main cause of death in those under the age of 40 years. In addition, according to more recent studies, 11-13% of FMF patients develop still amyloidosis despite receiving colchicine therapy [5]. This disease typically presents with heavy proteinuria, nephrotic syndrome, and eventually progresses to end-stage renal failure. Early diagnosis of renal amyloidosis is challenging because its symptoms become apparent only in the later stages, marked by significant amyloid deposition [6]. Currently, the diagnosis requires biopsy to show amyloid deposition. Therefore, many studies have concentrated on early identifying FMF patients at risk of amyloidosis.

In the past, conventional methods have been utilized to detect and evaluate renal disorders. These methods include computed tomography (CT) scans, magnetic resonance imaging (MRI), conventional ultrasound (USG), and biochemical analysis of blood samples. However, each method carries its own risks, such as radiation exposure and the administration of iodinated contrast medium in CT scans. Conventional renal USG is often used for initial evaluation because it is safe, easy, and inexpensive to perform. Renal USG can easily assess features such as increased parenchymal echogenicity and decreased renal size and parenchymal thickness. Parenchymal echogenicity is a commonly used marker for nephropathy. However, this marker is subjective, not quantitative, and often fails to detect renal abnormalities [7]. Elastography is a non-invasive, objective and cost-effective ultra-sonographic imaging modality that evaluates tissue elasticity [8]. Strain wave elastography, acoustic radiation force impulse imaging, shear wave elastography (SWE) and transient elastography are the different elastography techniques. The advantage of SWE over other USG elastography techniques is that it shows the true quantitative elasticity values of the tissues (kPa). It also does not require external compression and therefore allows to investigate the elasticity of the abdominal organs [7, 9]. Variations of SWE have been used to study many organs, including breast, thyroid, prostate, renal allografts and CKD [10-13]. Renal cortical stiffness, as assessed by SWE, exhibits a correlation with renal parenchymal disease and fibrosis. Importantly, this parameter remains unaffected by systemic and demographic variables [2].

In the kidney, amyloid can accumulate in the vascular space, glomeruli and interstitial space. The glomerulus is the most common and most severely involved renal compartment, but as mentioned above, it can be asymptomatic until the late stage [14]. Therefore, amyloid deposit in the renal parenchyma can be detected by SWE without any symptoms. As a matter of fact, in a few limited and small-scale studies on this subject, SWE values were found to be higher in FMF patients [15, 16]. This study aimed to evaluate renal elasticity in FMF patients with SWE

METHODS

Patient Population

In this cross-sectional pilot study, 53 FMF patients were recruited from the Department of Rheumatology at the Health Sciences University Antalya Training and Research Hospital, and 51 age- and sex-matched healthy control participants were enrolled in the study between June 2022 and June 2023.

The FMF diagnosis was made according to Tel-Hashomer criteria and all FMF patients were on colchicine treatment (1.5 mg/day) [17]. International severity scoring system for FMF (ISSF) was used to assess severity [18]. In this scoring system, parameters such as chronic sequelae, organ involvement and failure, and attack frequency are scored to determine the severity of the disease. A detailed history of the disease (duration of treatment, disease severity, etc.) was obtained from each patient, routine physical examination, laboratory examinations (blood urea nitrogen [BUN], creatinine, C-reactive protein [CRP], dipstick, spot urine protein/creatinine ratio) and conventional and doppler USG was performed followed by SWE imaging to measure renal stiffness. All participants in the healthy control group had normal laboratory parameters and no abnormal findings (echogenicity, kidney size, cortical blood flow, etc) on conventional doppler USG.

The exclusion criteria were as follows; participants with FMF-associated renal involvement, participants with diseases affecting the kidney other than FMF (such as chronic kidney disease [CKD], diabetes

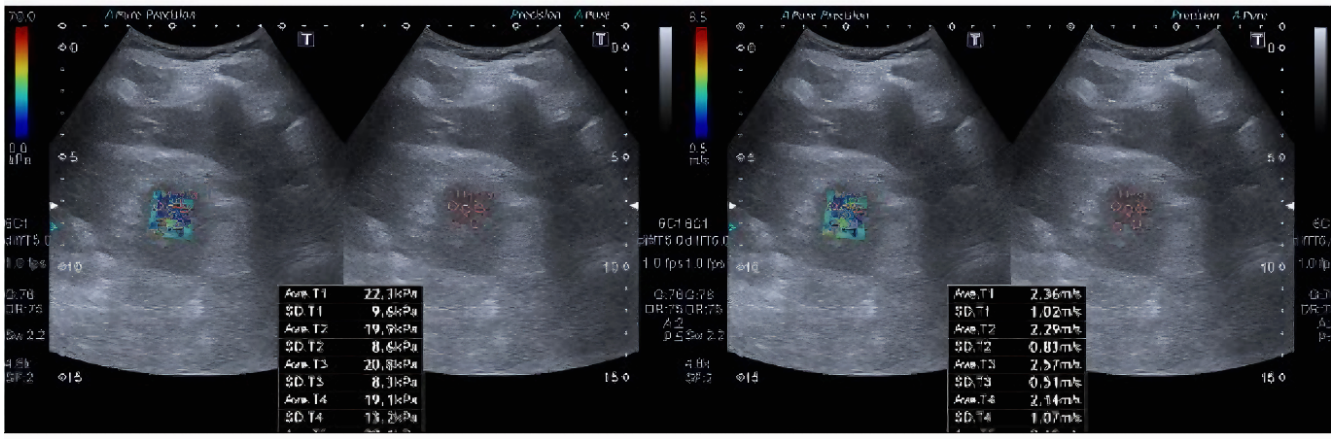

Fig. 1. Elasticity (kPa) and velocity (m/s) values in measurements obtained in the transverse plane from the lower pole parenchyma of the kidney in a FMD patient.

mellitus, hypertension, cardiovascular diseases, etc.), participants using nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs, antibiotics in the past three months, participants with estimated glomerular filtration rate (eGFR) < 60 mL/min (It was calculated eGFR using KD-EPI Creatinine 2009) or markers of kidney damage such as haematuria and proteinuria), smokers, participants with CKD any findings on conventional and doppler USG, participants with body mass index (BMI) over 35 kg/m2, participants with pregnancy or nursing status, any condition that prevents visualization of the kidney by ultrasound. Participants over 18 years of age who did not fulfill any of the exclusion criteria were included in the study. This study was approved by the Clinical Research Ethics Committee of Health Sciences University Antalya Training and Research Hospital (Approval number: 8/9 and date: 08.06.2023) and was conducted in accordance with the ethical standards defined in the 1964 Helsinki Declaration. During the study execution, patients were informed about the study, and their written consents were obtained. All participants gave written informed consent before enrolment.

Shear Wave Elastography

SWE assessment was conducted using a convex abdominal probe operating at a frequency range of 5-1 MHz, utilizing the Toshiba Applio 500 ultrasound system based in Tokyo, Japan. SWE measurements were assessed from the left kidney while the patients

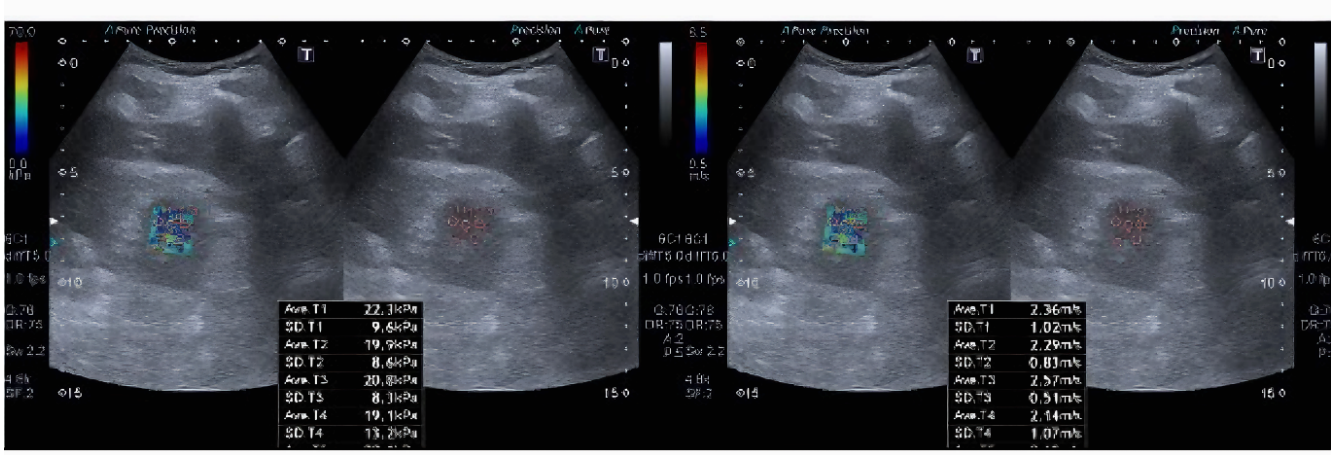

Fig. 2. Elasticity (kPa) and velocity (m/s) values in measurements obtained in the transverse plane from the pole parenchyma of the kidney in a healthy individual.

were lying in the lateral decubitus position. If the left kidney was deep or the acoustic window was deemed inadequate by the radiologist, measurements were taken from the right kidney. To minimize external pressure on the kidney, measurements were performed at the end-expiration. SWE evaluation was obtained at the lower renal pole, where the acoustic window was optimum. The measurement was performed in the transverse axis of the kidney so that the medulla segments do not enter the image area from the lower pole. Measurements were acquired subsequent to defining a region of interest (ROI) on specified targets within conventional renal USG images. ROI was positioned vertically within a renal cortex region devoid of vessels or cysts. The primary axis of the ROI was aligned in parallel with the axis of the renal pyramid, oriented vertically to the kidney surface. The maximum ROI target distance was 8 cm, and the ROI constant box size was 1-0.5 cm. We obtained five valid measurements from kidney and calculated the mean value. SWE stiffness values were presented as kPa, velocity values as m/sec (Figs. 1 and 2). Participants were assessed by a single radiologist with 5 years of experience in SWE. The radiologist was blinded to the groups.

Statistical Analysis

Descriptive analyses were depicted with measures such as mean ± standard deviation, median (minimum-maximum), or n (%), as deemed suitable. The normality of the data was assessed using the Shapiro–Wilk test, while categorical data were subjected to analysis using the Pearson chi-square test. The Mann-Whitney U test and Student's t-test were employed for the analysis of numerical data with non-normal and normal distributions, respectively. Receiver Operating Characteristic (ROC) curve analysis was utilized to ascertain the optimal cut-off point for elasticity and velocity in predicting FMF. The Area Under the Curve (AUC), sensitivity, and specificity were calculated and reported with 95% confidence intervals. The optimal threshold for measurements was identified as the value associated with the maximum Youden index. To explore relationships between variables, Spearman's correlation coefficient was computed. Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). A two-tailed p-value less than 0.05 was deemed statistically significant.

RESULTS

A cohort comprising 53 FMF patients (28 females) and 51 healthy participants (31 females) were included in this study. The average age among FMF patients was 39.98±11.56 years, while healthy participants had an average age of 41.63±16.07 years. There was no statistically significant age and BMI difference between the patient and control groups (Table 1).

We found that SWE values were statistically higher in FMF patients than in the control group. The mean values for elasticity were 17.66±3.77 kPa, 15.49±3.15 kPa, respectively (P= 0.002). The mean values for velocity were 2.31±0.25 m/sec and 2.12±0.26 m/sec, respectively (P<0.001) (Table 1).

Table 1. Demographic features and shear wave elastography imaging parameters in participants

Variables	FMF (n=53)	Control (n=51)	P value
Age (years)	39.98±11.56	41.63±16.07	0.551
Gender, n (%)			
Female	28(52.8)	31(60.8)	0.413
Male	25(47.2)	20(39.2)	
BMI (kg/m^2)	28±2.57	28±2.15	0.563
Elasticity (kPa)	17.66±3.77	15.49±3.15	**0.002**
Velocity (m/sec)	2.31±0.25	2.12±0.26	**<0.001**

Data are shown as mean±standard deviation or n (%). FMF=familial mediterranean fever BMI= body mass index

Table 2. Correlation of elastography findings with age and laboratory findings of FMF patients

Variables	Elasticity		Velocity	
	r	P value	r	P value
Age	-0.173	0.215	-0.067	0.631
BUN	0.036	0.806	-0.043	0.770
Creatinine	0.117	0.427	0.148	0.317
GFR	-0.064	0.667	-0.176	0.231
CRP	-0,008	0.959	-0.072	0.640

BUN=blood urea nitrogen, CRP=C-reactive protein, eGFR=estimated glomerular filtration rate, FMF=familial mediterranean fever

r=relationship coefficient

There is no significant correlation between SWE values and age, eGFR, BUN and creatinine (Table 2). Upon analyzing the correlation coefficients of mean elasticity and mean velocity values in relation to treatment duration and disease severity, it was observed that the correlation coefficients for both mean elasticity and velocity values with treatment duration were neither significant nor high (P>0.05). Conversely, a strong, direct, and significant correlation was identified between SWE value and disease severity (ISSF score) (elasticity: r=0.853, P<0.001; velocity: r =0.801, P<0.001,) (Table 3).

Using a cut-off value >15.8 kPa for mean values for elasticity, the area under the ROC curve to diagnose FMF was 0.674 (95%CI: 0.575-0.763, P=0.001) with a sensitivity and specificity of 67.92 and 62.75, respectively (Fig. 3). These values indicate that the test has a certain accuracy, although not perfect, in showing renal involvement, and that velocity has a slightly higher accuracy than elasticity. Using optimal cut-off value > 2.25 m/s for velocity, the area under the ROC curve was found 0.707 to diagnose FMF (95%CI: 0.609-0.792, P<0.001) with a sensitivity and specificity of 67.92% and 74.51, respectively (Fig. 4).

DISCUSSION

Early detection of amyloidosis in high-risk FMF patients is crucial due to its lethal consequences. In this preliminary study, we conducted an assessment of the renal parenchyma in FMF patients using SWE early. Our findings revealed that the recorded SWE values exhibited a higher magnitude within the patient group as compared to the control group. Moreover a strong, direct and significant correlation was found between mean elasticity and velocity and disease severity.

SWE values, like conventional USG, may be affected by age and laboratory parameters such as urea, creatinine, and BUN. Yu *et al*. [19] and Hassan *et al*. [20] and Leong *et al*. [21] founded significantly correlated with age and this laboratory parameters. This may be due to the development of glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis as the kidneys age. However, Samir *et al*. [10] reported no significant correlation between elastography values and age. Much like the findings of Samir *et al*. [10] our study also did not reveal any significant correlation between these parameters. This lack of correlation could potentially be attributed to variations in

Table 3. Correlation of elastography findings with treatment duration and disease severity score

Variables	Treatment duration		Disease severity score	
	r	P value	r	P value
Elasticity (kPa)	0.083	0.531	0.853	**<0.001**
Velocity (m/sec)	0.142	0.278	0.801	**<0.001**

r=relationship coefficient

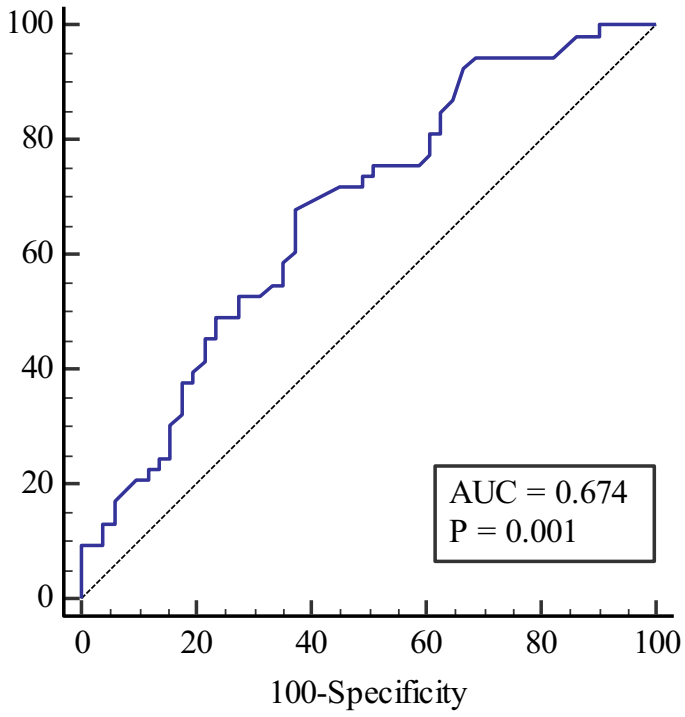

Fig. 3. ROC analysis for elasticity in predicting diagnosis of FMF. In the ROC analysis with a cut-off value of >15.8 kPa for elasticity, the AUC was 0.674. The sensitivity and specificity of the elasticity parameter was 67.92% and 62.75%, respectively.

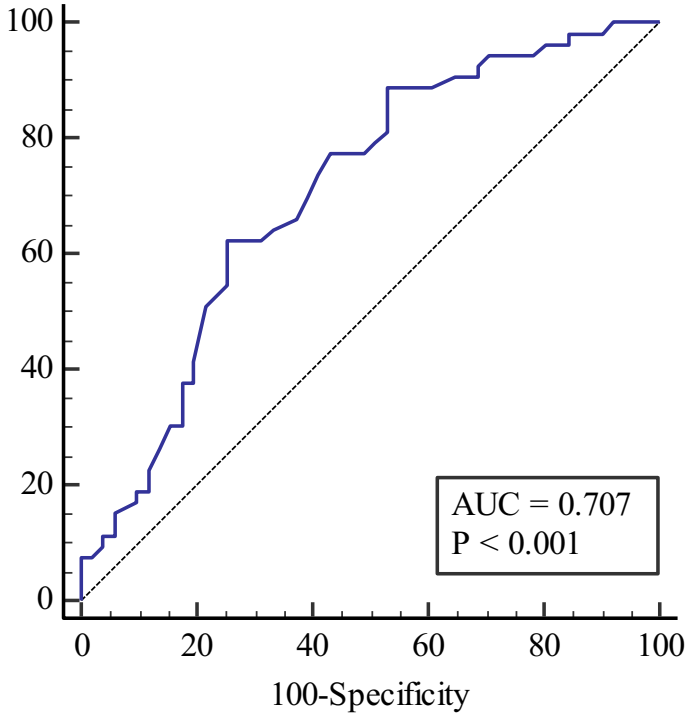

Fig. 4. ROC analysis for velocity in predicting diagnosis of FMF. In the ROC analysis performed with a cut-off value of >2.25 m/s for velocity, the AUC was calculated as 0.707. The sensitivity and specificity of the velocity parameter was 67.92% and 74.51, respectively.

the sample type and sample size we selected. Participants with renal dysfunction were not included in our study. Intrarenal fibrosis represents the ultimate shared pathway across all CKD, and the degree of fibrosis has been observed to correlate with the severity of the disease [22, 23] . As of the present clinical practices, renal biopsy stands as the sole method available for the assessment of renal fibrosis. Since renal biopsy is an invasive and expensive method, new methods such as elastography are being investigated. For instance, Leong *et al*. [21] and Samir *et al*. [10] evaluated renal parenchymal stiffness with SWE in adults with CKD, they reported that the patient group had higher SWE values than the control group. In addition, Hu *et al*. [24] investigated the relationship between SWE scores and renal biopsy scores in CKD patients. In this study, it was determined that as the fibrosis score increased in the biopsy and the elasticity score also increased. As a result of these studies, it has been shown that SWE is a cost-effective and non-invasive method that provides additional diagnostic information in the diagnosis and follow-up of CKD [24].

CKD incidence and prevalence are increasing, particularly diabetes and hypertension-related nephropathies [25]. It is crucial to ascertain alterations in mesangial, endothelial, and epithelial cells during the early stages of fibrosis, preceding the onset of nephropathy. In studies conducted for this purpose, the SWE values of patients with primary hypertension or diabetes mellitus without signs of nephropathy were observed to be greater than the control groups [26, 27]. In addition, increased SWE levels in patients with diabetic nephropathy correlated with BUN, creatinine, eGFR, urinary albumin/creatinine ratio, and urinary micro albumin level in these studies [18, 19, 28]. Similar to these studies, we found SWE values were higher in patients with FMF without nephropathy. However, we did not detect significant correlation between SWE values and eGFR, BUN, creatinine. It may result from exclusion of patients with eGFR <60 mL/min and/or those with signs of nephropathy such as microalbuminuria. In conclusion, SWE can be em-

ployed as a new method in the early diagnosis and follow-up of nephropathy.

There are few studies in the literature investigatıng renal elastography in FMF patients Bayramoğlu *et al*. [15] compared the changes in lung, spleen, pancreas and kidney elasticity in prediatric FMF patients with and without amyloidosis with healthy control group. They found that liver, spleen, kidney and pancreas elasticity values were significantly higher in the amyloidosis group compared to the control group. SWE values were significantly higher in the FMF group with or without amyloidosis compared to control subjects. In this study, the age range of the participants was very wide. Factors that may affect SWE values such as BMI, hypertension, diabetes mellitus and smoking were not excluded. In addition, participants were not evaluated for other renal pathologies such as cysts and lipomas before elastography. In a study conducted by Özmen *et al*. [16] in children with FMF, SWE values were found to be higher in FMF patients compared to healthy control group. However, in this study, the participants were not evaluated in terms of nephropathy (hematuria, proteinuria, creatinine). Additionally, the relationship between disease severity, duration of treatment, treatment regimen, age at diagnosis, and SWE values was not examined. Albayrak *et al*. [29] compared the renal elasticity value of adult FMF patients with and without proteinuria with the control group. They found that SWE values of FMF patients were higher than the control group. In addition, SWE values of patients with proteinuria were higher than the control group and FMF patients without proteinuria. However, although FMF patients with proteinuria were included in the study, biopsy was not performed in these patients, so the cause of proteinuria may be due to causes other than amyloidosis. In the study conducted by Kayalı *et al*. [30] on adult FMF patients, higher SWE values were also found compared to healthy control group. However, this study included a small number of patients, some of whom had nephropathy (e.g., proteinuria). Morover, factors that may affect SWE values, such as BMI, smoking, hypertension and diabetes, have not been excluded. In our current study, similar to previous research, we found higher SWE values in FMF patients. Unlike other studies, our research included a larger number of adult patients and excluded volunteers with any evidence of nephropathy to ensure a more objective and homogeneous sample.

Currently, there are no standardized renal SWE values available for FMF patients. In their comparison of renal velocity and elasticity values between FMF patients and the control group, Kayalı *et al*. [30] established cut-off values of 7.37 kPa for elasticity (sensitivity=76%, specificity=93%) and 1.42 m/s for velocity (sensitivity=70%, specificity=89%) [30]. In our study we have suggested that a cut-off value 15.8 kPa for mean values for elasticity (sensitivity and specificity of 67.92 and 62.75, respectively) and cut-off value 2.25 m/s for velocity (sensitivity and specificity of 67.92% and 74.51, respectively). While these values may not be adequate for diagnosing FMF patients, they indicate that SWE could serve as a valuable method for monitoring renal involvement in FMF patients. Extensive studies in this area may contribute to the standardization of SWE values and further augment their diagnostic utility.

Amyloidosis is characterized by the deposition of extracellular protein material known as amyloid in various organs, including the heart and kidneys. This condition can result in a gradual decline in organ function, potentially culminating in a fatal outcome. The clinical and imaging characteristics of the disease are not pathognomonic. Currently, a biopsy is needed to demonstrate the deposition of amyloid. Elastography is a novel imaging technique for assessing tissue elasticity. Elestosonographic findings have been demonstrated that amyloid material increases the tissue stiffness of the affected organ [28]. For instance, numerous case reports have demonstrated elevated liver stiffness in patients with hepatic amyloidosis [31-33]. Amyloidosis is seen more often in patients in the severe disease group. ISSF is the most commonly used scoring system to determine the severity of the disease in the follow-up of FMF patients. Kayalı *et al*. [30] found that as ISSF scores increased, SWE values also increased, but this positive correlation was not statistically significant. In our study, we observed a strong correlation was found between SWE values and disease severity score. Long-term prospective studies with larger cohorts are necessary to understand the future implications of these results for FMF patients.

Limitations

This study has same limitations: (1) The number

of patients enrolled in this study was low and further studies with larger number patients are required. (2) In our study, there are two groups of individuals with normal kidney function with or without FMF. We recommend further studies including FMF patients with amyloidosis as a third group. (3) Since kidney biopsy is not clinically indicated for patients with FMF, no biopsy data were included for histological measurement. (4) We did not measure the variance between observations as all SWE studies were performed by a single radiologist.

CONCLUSION

We observed that the SWE values were higher in the patient group than in the control group. In additon, a strong correlation was found between elasticity and velocity and disease severity. Recently, SWE has been found to be a useful method in the early diagnosis and follow-up of renal involvement (especially amyloidosis). SWE may be also a cost-effective, non-invasive method to diagnose and follow up renal involvement (especially amyloidosis) in FMF patients.

Ethical Statement

This study was approved by the Clinical Research Ethics Committee of Health Sciences University Antalya Training and Research Hospital (Approval number: 8/9 and date: 08.06.2023) and was conducted in accordance with the ethical standards defined in the 1964 Helsinki Declaration. During the study execution, patients were informed about the study, and their written consents were obtained.

Authors' Contribution

Study Conception: MK, ABA; Study Design: MK, ABA, SÜ; Supervision MK, ABA; Funding: MK, SÜ; Materials: MK, ABA, SÜ; Data Collection and/or Processing: MK, ABA, SÜ; Statistical Analysis and/or Data Interpretation: MK, ABA; Literature Review: MK, ABA; Manuscript Preparation: MK, ABA, SÜ and Critical Review: MK, ABA, SÜ

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Comparative analysis of pain outcomes in operative versus diagnostic hysteroscopy: the role of menopausal status

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ABSTRACT

Objectives: The study investigates the differential pain outcomes associated with operative and diagnostic hysteroscopy, with a focus on the influence of menopausal status on pain perception. This research aims to refine pain management strategies tailored to patient demographics in gynecological practices.

Methods: A total of 200 patients undergoing hysteroscopy were systematically evaluated. Pain intensity was assessed using the Visual Analog Scale (VAS). The study distinguished between operative and diagnostic procedures, with particular attention to the effect of menopausal status on pain scores. Compliance with CONSORT guidelines was ensured, and relevant clinical trial registration numbers were included.

Results: Pain scores did not significantly differ between operative and diagnostic hysteroscopies, suggesting that the invasiveness of the procedure might not directly correlate with pain perception. However, menopausal women reported significantly higher pain scores, indicating a possible increased sensitivity or decreased pain tolerance related to hormonal changes.

Conclusions: The results affirm that existing pain management protocols effectively mitigate discomfort across different hysteroscopic procedures. Nonetheless, the distinct pain profiles of menopausal women warrant the development of customized pain management strategies. Enhancing analgesic approaches for this subgroup could improve patient care and outcomes in gynecological settings.

Keywords: Hysteroscopy, pain perception, menopause, visual analog scale, patient outcomes, gynecological surgery

Hysteroscopy has become an integral component of contemporary gynecological practice, revolutionizing the diagnosis and treatment of intrauterine conditions with its minimally invasive approach. This technique allows for direct visualization of the uterine cavity and is instrumental in both diagnostic and therapeutic interventions, ranging from the evaluation of abnormal uterine bleeding to the precise removal of submucosal fibroids and polyps. As hysteroscopy has evolved, it has significantly improved in terms of patient comfort and procedural efficiency, reflecting broader trends in medical technology that prioritize patient-centered care [1, 2].

Despite these advancements, one of the enduring

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challenges in hysteroscopic procedures is the management of pain, a critical aspect that can significantly affect patient experiences and outcomes. Research indicates that pain perception varies significantly among patients undergoing hysteroscopic procedures, influenced by a variety of factors including procedural technique, the type of hysteroscopy (operative vs. diagnostic), and individual patient characteristics such as age, hormonal status, and particularly menopausal status. The menopausal transition, characterized by hormonal changes, can alter pain thresholds and tissue response, thereby potentially intensifying discomfort during and after the procedure [3, 4].

Addressing these challenges, the current study proposes a comparative analysis focusing on pain outcomes associated with operative and diagnostic hysteroscopy, with a special emphasis on the influence of menopausal status on pain perception. This approach is rooted in a comprehensive review of the literature that highlights both the advancements and ongoing challenges in the field. By integrating robust empirical data with a systematic review of existing studies, this research aims to deepen the understanding of pain dynamics in hysteroscopy and to develop targeted pain management strategies that can be customized to patient demographics [5, 6].

Furthermore, this study not only explores the clinical aspects of hysteroscopy but also considers the procedural innovations that have been developed to enhance its safety and effectiveness. These include the use of advanced imaging technologies, improved instrument design, and refined surgical techniques, all of which contribute to reducing patient discomfort and improving clinical outcomes. Additionally, the study examines the role of pre-procedural counseling and patient education in managing expectations and reducing anxiety, which are closely linked to pain perception [7, 8].

In summary, this research endeavors to provide a comprehensive overview of the current state of hysteroscopic practice, with a specific focus on optimizing pain management for enhancing patient care. The outcomes of this study are anticipated to offer significant contributions to gynecological practices, influencing both clinical guidelines and procedural standards to better accommodate the needs of diverse patient populations, particularly those undergoing the menopausal transition. It is hoped that the findings will not only advance the scientific understanding of pain management in hysteroscopy but also lead to more effective and empathetic patient care protocols.

METHODS

Research Design

Our study was structured as a prospective observational study within a controlled clinical setting to adhere strictly to the highest standards of academic rigor. Approval was obtained from the University of Health Sciences, İstanbul Bağcılar Health Research Center Clinical Research Ethics Committee with the ethical approval code issued for conducting research involving human participants (Ethics Approval No: 2023/248). This approval ensured that all study procedures complied with ethical standards and regulations pertinent to human research.

Participant Selection

The participant selection process was critical to the validity and reliability of the study outcomes. We included a total of 200 patients between the ages of 18 and 65 who presented with indications for hysteroscopy, such as abnormal uterine bleeding or suspected intrauterine pathologies. Exclusion criteria were stringently defined to rule out any potential confounding variables that could impact the study's results or patient safety. Excluded were patients who were pregnant, had pelvic infections, known malignancies, or severe psychiatric disorders at the time of the study.

Additionally, informed consent, in the form of the Informed Voluntary Consent Form was obtained from all participants prior to their inclusion in the study. This process was conducted under the oversight of the institution's ethics committee, which monitored adherence to ethical standards throughout the study's duration.

Data Collection

Data collection was meticulously carried out by experienced practitioners utilizing the state-of-the-art B.I.O.H.® Bettocchi® Integrated Office Hysteroscope from Karl Storz, Germany. This equipment was chosen for its precision and reliability, ensuring consistency and high-quality data across all procedures. The procedures were performed using a standardized ap-

proach that involved no cervical preparation or dilation, employing the vaginoscopic technique to significantly reduce patient discomfort. All collected data were anonymized and managed according to the principles of confidentiality and data protection. The datasets generated during this study are scheduled to be deposited in a publicly accessible database, ensuring that the data will be available for replication and further research by the academic community. Accession numbers for the database will be provided during the review process and included in the final published manuscript. In line with ethical standards, all participants were provided with detailed information about the study and its potential risks and benefits. Informed consent was obtained from all participants prior to their inclusion in the study. This consent process was conducted according to the guidelines of the Declaration of Helsinki and under the oversight of the institution's ethics committee, which also monitored the study's adherence to ethical standards throughout its duration.

Statistical Analysis

Data were analyzed using SPSS software, version 25.0. Descriptive statistics were employed to summarize patient characteristics and procedural outcomes. Inferential statistics, including t-tests and chi-squared

Table 1. Comparison of patient characteristics between operative and diagnostic hysteroscopy

Characteristics	Operative Hysteroscopy (n=100)	Diagnostic Hysteroscopy (n=100)	P value
Age (years)			
Mean±SD	44±10	44±10	0.477
Median (min-max)	45 (25-71)	44 (24-69)	
BMI (kg/m²)			
Mean±SD	29±5	29±5	0.548
Median (min-max)	29.3 (18.0-43.5)	29.3 (19.5-44.9)	
Parity			
Mean±SD	2.6±2	2.2±2	0.761
Median (min-max)	2 (0-15)	2 (0-8)	
Number of uterine operations			
Mean±SD	0.6±0.9	0.7±1	0.440
Median (min-max)	0 (0-4)	0 (0-4)	
Menopause status, n (%)			
No	78 (78%)	80 (80%)	0.728
Yes	22 (22%)	20 (20%)	
Normal spontaneous delivery, n (%)			
No	27 (27%)	37 (37%)	0.130
Yes	73 (73%)	63 (63%)	
Cesarean section birth, n (%)			
No	65 (65%)	63 (63%)	0.768
Yes	35 (35%)	37 (37%)	
Prior uterine operations, n (%)			
No	63 (63%)	59 (59%)	0.562
Yes	37 (37%)	41 (41%)	

BMI=body mass index, SD=standard deviation

Table 2. Comparison of cervical canal passage vas score, post-procedure vas score, and procedure duration

Description	Operative hysteroscopy (n=100)	Diagnostic hysteroscopy (n=100)	P value
VAS for cervical canal passage	1.45±1.58	1.73±1.80	0.381
VAS at end of procedure	1.59±1.96	1.25±1.59	0.356
Procedure duration (seconds)	240.46±222.74	80.80±61.42	**<0.001**

tests, were utilized to compare pain scores between diagnostic and operative hysteroscopy groups. A P-value of less than 0.05 was considered statistically significant, ensuring the robustness of our analytical methods.

RESULTS

This section provides a detailed description of the findings from the comparative analysis of operative and diagnostic hysteroscopy, focusing on patient demographics, clinical characteristics, pain scores, and procedural duration.

Patient Demographics and Clinical Characteristics

This section presents a comprehensive analysis of such characteristics to confirm that any differences in outcomes can be attributed to the type of hysteroscopy rather than underlying patient differences (Table 1). Table 1 demonstrates that there are no significant differences in demographic and clinical characteristics between patients undergoing operative and diagnostic hysteroscopy. Age, BMI, parity, and menopausal status are similarly distributed across both groups, indicating that the cohorts are well-matched and suitable for comparing the outcomes of the two types of hysteroscopy.

Pain Scores and Procedure Duration

We examine the Visual Analog Scale (VAS) pain scores during cervical canal passage, at the end of the procedure, and the overall duration of the hysteroscopy to understand differences in patient experience and procedural efficiency (Table 2). The data from Table 2 provides insights into the pain management effectiveness and procedural efficiency between operative and diagnostic hysteroscopy. Pain levels, as measured by the VAS during and after the procedures, show no significant difference between the two groups, indicating effective pain management across both procedural types. However, the duration of the procedures significantly differs, with operative hysteroscopy taking longer due to the more complex nature of the interventions required.

Distribution of Pain Scores

We assess the distribution of pain scores to further dissect the nuances of patient experiences during these procedures (Table 3). Table 3 highlights that the majority of patients experienced mild pain (VAS < 4) during the cervical canal passage, emphasizing the effectiveness of current hysteroscopic techniques and pain management protocols. A smaller subset of patients experienced moderate to severe pain (VAS ≥ 4), which may indicate specific patient factors or procedural variables that necessitate additional management strategies.

These structured findings provide a comprehensive overview of the study's results, facilitating a clear understanding of the differences and similarities in patient outcomes for operative versus diagnostic hysteroscopy.

Table 3. Distribution of all patients' cervical canal passage VAS scores being <4 and ≥4

VAS Score	Number of Patients	Percentage
<4	169	84.5%
≥4	31	15.5%

DISCUSSION

In analyzing the results of our study, we integrate our findings with a broad spectrum of prior research to delineate their significance within the domain of gynecological practice, specifically focusing on the experiences of patients undergoing both operative and diagnostic hysteroscopy.

Our study's findings on pain management, particularly with the use of the Visual Analog Scale (VAS) for both types of hysteroscopy, revealed that the advancement in procedural techniques and analgesic strategies are significantly enhancing patient comfort. This is in alignment with Buzzaccarini *et al*. [9], who highlighted the effectiveness of modern pain management protocols that are adept at mitigating discomfort across various hysteroscopic procedures. Despite the longer durations associated with operative hysteroscopies, these procedures did not result in higher pain scores, which suggests a substantial improvement in analgesic methods, a sentiment also supported by Centini *et al*. [10].

A crucial insight from our study is the impact of menopausal status on pain perception. Menopausal women tended to report higher VAS scores, which may be attributed to physiological changes such as decreased cervical elasticity and lubrication, as detailed by Almeida *et al*. [3]. This finding underscores the need for specialized pain management strategies for this demographic, supporting the recommendations by Al-Fozan *et al*. [2] for tailored preoperative preparations and analgesic protocols.

Interestingly, our study noted that parity and previous uterine operations did not significantly influence pain scores, which may suggest that the standardized pain management protocols are effectively addressing these factors. This notion is corroborated by the findings of Aas-Eng *et al*. [1], who observed that an individualized approach to pain management can effectively neutralize the potential discomfort caused by varied patient histories.

Given the observed disparities in pain perception, particularly among menopausal women, there is a compelling need for further research into customized pain management strategies. Studies could explore the integration of pharmacological and non-pharmacological methods to enhance comfort for this sensitive group [11-18]. Moreover, the enduring efficacy of these pain management strategies warrants longitudinal studies to assess their sustainability and long-term outcomes.

Our study reaffirms that contemporary hysteroscopic practices, both operative and diagnostic, manage to maintain low pain levels across procedures, thereby enhancing patient compliance and satisfaction. However, the distinct challenges faced by menopausal women highlight a gap in current practices, pointing towards the necessity for targeted pain management strategies.

Incorporating findings from pivotal studies [19-25], our discussion extends the understanding of procedural efficacy and patient-centric approaches in hysteroscopy, emphasizing the importance of continual improvement and individualized care in gynecological practices.

CONCLUSION

The results of this comprehensive study offer substantial insights into the comparative experiences of pain between operative and diagnostic hysteroscopy, underlining the effectiveness of current pain management protocols that adequately minimize discomfort across both types of procedures. The significant revelation that menopausal status impacts pain perception invites a focused approach to pain management, particularly for this subgroup, indicating a necessity for bespoke strategies to enhance their procedural experience.

While both operative and diagnostic hysteroscopies have proven to be low in terms of pain levels thanks to advanced analgesic techniques and procedural refinements, the extended duration of operative hysteroscopies did not correlate with increased pain, which affirms the proficiency of existing pain control measures. However, the notable discomfort reported by menopausal women suggests that there are still areas within pain management that require further refinement and personalization. It's apparent that despite overarching improvements, the 'one-size-fits-all' approach may not be applicable in all cases, especially in sensitive or potentially complicated scenarios like those presented by postmenopausal physiology.

Furthermore, this study has shown that standard variables such as parity and previous surgical history, which could be presumed to influence pain perception, do not markedly alter the pain scores due to the efficiency of current pain mitigation practices. This is a positive reflection on the versatility and adaptability of modern hysteroscopic techniques, which are capable of providing a comfortable experience for most patients regardless of their medical or surgical history.

Ethical statement

Approval was obtained from the University of Health Sciences, İstanbul Bağcılar Health Research Center Clinical Research Ethics Committee with the ethical approval code issued for conducting research involving human participants (Ethics Approval No: 2023/248).

Authors' Contribution

Study Conception: VÖ; Study Design: VÖ, TB; Supervision: TB; Funding: N/A; Materials: VÖ, TB; Data Collection and/or Processing: VÖ, TB; Statistical Analysis and/or Data Interpretation: VÖ, TB; Literature Review: VÖ, TB; Manuscript Preparation: VÖ, TB and Critical Review: TB.

Conflict of interest

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Does the presence of persistant metopic suture affect the use of frontal sinus and frontal morphometric measurements in gender identification?

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ABSTRACT

Objectives: One structure capable of use for gender estimation in forensic science is the frontal bone. This study used computed tomography (CT) and investigated whether frontal sinus and frontal morphometric measurements could also be used to identify gender in people with persistent metopic suture (PMS).

Methods: Nine hundred ninety-one patients who underwent brain-paranasal sinus CT for any reason were divided into two groups, PMS and non-PMS. The presence and volume of both halves of the frontal sinus, frontal morphometric measurements including minimum-maximum frontal width, and frontal bone surface length on the outer table surface between the coronal sutures in the axial section were measured.

Results: In the non-PMS group, all quantitative parameters (frontal sinus volume, minimum-maximum frontal width, and frontal bone surface length) differed significantly between the genders ($P<0.05$). However, in the PMS group, only frontal sinus volume and frontal bone surface length differed significantly ($P<0.05$).

Conclusions: Frontal sinus volume, minimum-maximum frontal width and frontal bone surface length measurements exhibited significant sexual dimorphism in the non-PMS group. Since minimum and maximum frontal width do not exhibit significant gender differences in cases with PMS, the presence of PMS should be considered when using these parameters in gender identification.

Keywords: Frontal morphometry, frontal sinus volume, gender identification, persistent metopic suture

Assessing individuals' biological profiles represents a challenge for forensic science. Gender estimation is one of the first and most important steps in such analyses [1]. Anthropologists use the sexual dimorphic features of the human skeleton to distinguish between males and females through visual or metric evaluation [2]. Some authors regard the skull as the second most useful bone structure after the pelvis for gender prediction [3]. Morphometric techniques facilitate the evaluation of differences in the size of structures, thus enhancing objectivity [4].

Gender can be differentiated by measuring features (such as markings, curves, external surfaces or roundness) of cranial bones [5]. The exocranial bone surface exhibits significant gender differences, and success rates in gender prediction increase as a result [6]. One of the cranial structures with high potential in the evaluation of sexual dimorphism is the frontal bone [5]. In addition to the glabella, the most dimorphic and reliable part of the human skull [7], the gen-

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eral shape of the frontal bone and especially the curvature thereof (greater in males), the size of the frontal sinuses (larger in males), and the frontal protrusions (tubera frontalia) (more prominent in females) are other sexual dimorphic features that may be suitable for quantitative evaluation [8]. Sexual dimorphism in the frontal region is due to differences in growth factors and maturation times [9].

The frontal sinuses (FSs), the last paranasal sinuses to develop, exhibit considerable differences in width, height, and volume [10]. These are rudimentary at birth and become radiographically visible at the age of six [11]. The FS exhibits significant inter-individual variability, in the same way that fingerprints differ between monozygotic twins, due to its irregular shape and individual characteristics that make the frontal bone unique to each individual [12].

The physiological closure of the metopic suture (MS) [13], which separates the two halves of the frontal bone, is generally regarded as occurring at eight years of age [14]. If the suture continues to be observed in subsequent years, this is known as a persistent metopic suture (PMS) or 'metopism.' PMS is a factor that suppresses the development of the FS [15]. Pneumatization of the FS may be delayed or completely suppressed if the MS persists [16]. Since pneumatization into the frontal bone represents one of the FS development stages, it may be concluded that a relationship exists between FS and cranial morphometry [17]. In the presence of PMS have been found to exhibit a specific distinctive neurocranial configuration [18] characterized by a broad forehead, greater frontal curvature, and inter-frontal and inter-orbital lengths [19].

Computed tomography (CT) is an excellent imaging modality for identifying human remains and can be used to evaluate the paranasal sinuses and craniofacial bones. It yields valuable and precise measurements of FS dimensions [20].

The purpose of this study was to investigate the effectiveness of FS and frontal morphometric measurements (minimum and maximum frontal width and frontal bone surface length) in gender identification and to investigate the effect of the presence of PMS, with known impacts on frontal bone and frontal sinus development, on the usefulness of these parameters in gender identification.

METHODS

Patients and Study Design

The study commenced following receipt of approval from the Süleyman Demirel University non-interven-

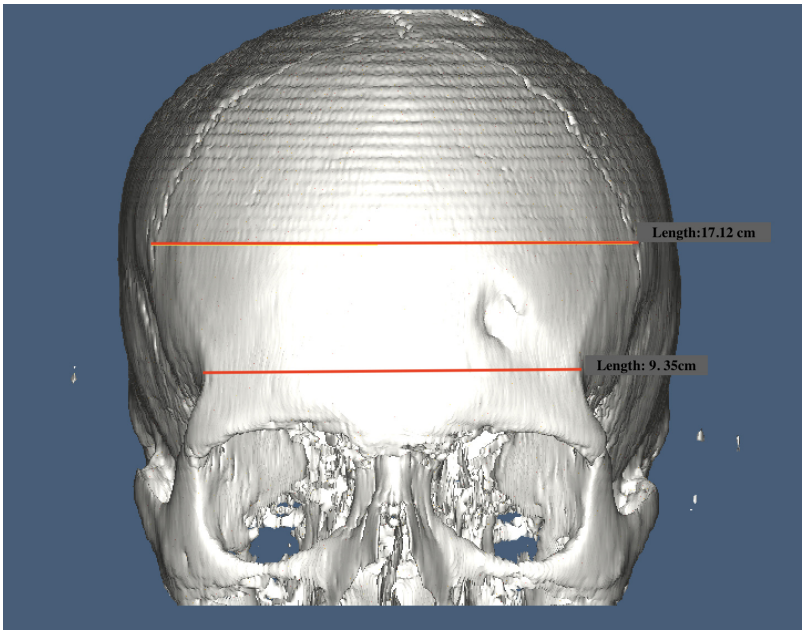

Fig. 1. Maximum horizontal width between both coronal sutures(upper horizontal line) and minimum horizontal width between both frontotemporal lines(lower horizontal line) on "volume rendering" CT images.

tional clinical research ethics committee (decision dated 30.12.2020 and numbered 72867572-050.01.04-15964). Paranasal sinus or brain CT images obtained for any reason between April and December 2018 were evaluated in this retrospective study. Nine hundred ninety-one patients met the inclusion criteria (age 18 years or over, cases in which the entire frontal region was included in the examination, and cases without a history of surgery or trauma in the frontal region). The presence or absence of PMS was recorded in these cases. All cases were divided into two groups, PMS and non-PMS. In both groups, the presence and volume of FS were recorded separately on the right and left sides, and frontal bone morphometric measurements (frontal bone surface length, minimum and maximum frontal width) were performed.

Technical Parameters

Brain and paranasal sinus CT scans were performed with a 128 cross-section CT device (Definition AS, Siemens Medical Solutions, Forchheim, Germany). The detector in the multi-section CT device possessed 64 rows of 0.6 mm elements and 128 independent data acquisition channels. The pitch value was adjusted automatically by the device and was set to 1.5 for brain CT and 1.0 for paranasal sinus CT. The gantry rotation time was 0.5 sec. Parameters were 120 kVp, 350 mA, reconstruction slice thickness 3 mm, and acquisition slice thickness 0.6 mm (WW:1500, WL:450) for brain tomography. For paranasal sinus CT, recordings were made using 80 kVp, with a 120 mA, 1 mm slice thickness, and a 0.6 mm acquisition slice thickness (WW: 1500, WL: 450) protocol.

Evaluation of Images

The presence of incomplete or complete MS in cases aged over 18 was recorded as PMS. FS volume calculations were performed separately for both halves of the FS through manual segmentation by OsiriXTM

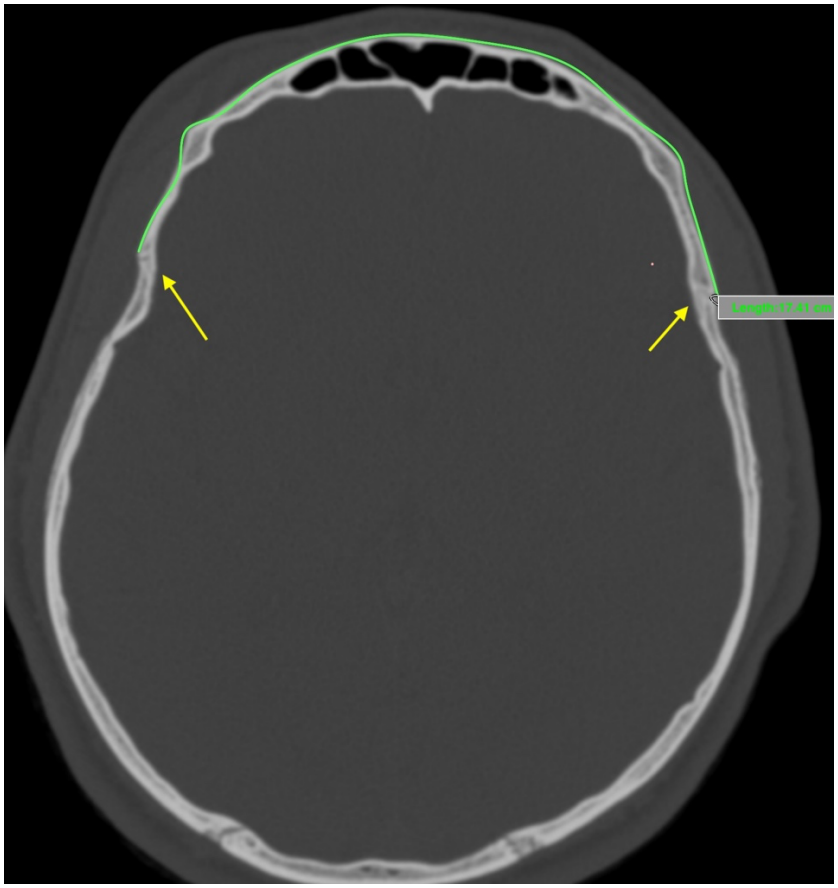

Fig. 2. External tabular surface length (green line) measurement between both coronal sutures in the axial section passing through the junction of both coronal sutures with the sphenosquamous and sphenofrontal sutures (yellow arrow).

software, including the entire FS lumen up to the frontonasal recess. In cases with 'Multifidus FS', defined as the presence of air cells that open into the ethmoid infundibulum and can be confused with the frontal sinus, the volume of this was included in the ipsilateral sinus volume. In coronal 'volume rendering' images, the maximum frontal width between both coronal sutures in the frontal bone and the minimum frontal width between both frontotemporal crests were measured in cm, as described by Valloise [21] (Fig. 1). In the axial images, the 'frontal bone surface length' was recorded in cm on the outer table surface between the bilateral coronal sutures in the section passing through the junction of both coronal sutures with the sphenosquamous and sphenofrontal sutures (Fig. 2).

Statistical Analysis

The Kolmogorov-Smirnov test showed that, with the exception of the 'frontal bone surface length,' quantitative data did not comply with normal distribution. Parametric tests were therefore applied for 'frontal bone surface length' measurements and non-parametric tests for other quantitative data. In order to examine the effects of PMS on quantitative data and to evaluate the practicability of quantitative data in distinguishing between the genders in both groups, Student's t test was performed for the 'frontal bone surface length' measurement, while the Mann Whitney U test was applied for other quantitative data. Data were analyzed on IBM SPSS Statistics for Windows software (Version 21.0, Armonk, NY, USA IBM Corp.). Statistical significance was set at $P<0.05$.

RESULTS

A total of 1156 cranial and paranasal sinus CT scans were initially evaluated. However, 165 cases met the exclusion criteria, and the CT scans of 991 patients, 452 women and 539 men, were finally included in the study. The average age of the cases was 53.7 years. Women represented 425 (45%) of the non-PMS cases and 517 (55%) men.

PMS was present in 49 (4.9%) cases, 22 (44%) of which were female and 27 (56%) were male. Surface length, minimum and maximum frontal width variables were found statistically significantly higher in PMS group ($P<0.05$). An analysis of the relationship between PMS and frontal sinus volume and other morphometric measurements is given in Table 1.

The practicability of the use of quantitative data in gender identification in the PMS and non-PMS case groups was subjected to analysis. In the non-PMS group, all quantitative variables exhibited statistically significant gender differences ($P<0.05$) and lower values were detected in women than in men in all parameters (Table 2).

In the PMS group, only the gender differences in frontal bone surface length and FS volume measurements emerged as statistically significant. Other quantitative variables (minimum and maximum frontal width) exhibited no significant gender differences in the PMS group, in contrast to the non-PMS group. In the PMS cases, frontal bone surface length was significantly lower in women than in men ($P=0.037$). FS volume values were also lower in women than in men

Table 1. Comparison of quantitative parameters between PMS and non-PMS groups

Variables	PMS group (n=49)	Non-PMS group (n=942)	t or z	P value
Surface length (cm)*	17.7426±1.0324	16.7257±1.1877	-5.257	**<0.001**
Right FSV (cm^3)	2.61 (0.38-16.71)	3.35 (0.09-37.87)	-1.819	0.069
Left FSV (cm^3)	2.24 (0.24-17.91)	3.80 (0.14-25.95)	-2.787	**0.005**
Min. Frontal width (cm)	10.00 (9.22-12.57)	9.64 (8.10-13.85)	-4.769	**<0.001**
Max. Frontal width (cm)	12.57 (10.23-13.66)	23.75 (9.06-43.78)	-3.475	**0.001**

Data are shown as mean±standard deviation or median (minimum-maximum). PMS=Persitent metopic suture, FSV=Frontal sinus volume, Min=minimum, Max=maximum

t=independent sample t test, z=Mann Whitney-U test,

*Frontal bone surface length

Table 2. Comparison of quantitative data between genders in the non-PMS group

	Non-PMS group			
Variables	**Males (n=517)**	**Females (n=425)**	**t or z**	**P value**
Surface length(cm)*	17.09±1.15	16.28±1.07	10.573	**<0.001**
Right FSV (cm^3)	4.36 (0.20-37.87)	2.48 (0.09-21.92)	-9.909	**<0.001**
Left FSV (cm^3)	4.73 (0.19-25.95)	2.80 (0.14-20.67)	-9.558	**<0.001**
Min. Frontal width (cm)	9.82 (8.13-13.85)	9.45 (7.10-12.35)	-8.584	**<0.001**
Max. Frontal width (cm)	12.44 (9.51-43.78)	12.02(9.06-14.69)	-9.595	**<0.001**

Data are shown as mean±standard deviation or median (minimum-maximum). PMS=Persitent metopic suture, FSV=Frontal sinus volume, Min=minimum, Max=maximum

t=independent sample t test, z=Mann Whitney-U test,

*Frontal bone surface length

on both sides (right and left), and the findings were statistically significant (P=0.006 and P=0.002, respectively) (Table 3).

DISCUSSION

Analyses of teeth, fingerprints, and DNA profiles are among the most reliable methods for identification in forensic medicine. However, radiological examinations are important without such samples [22]. Radiology is important in forensic science as it permits non-invasive and objective evaluation. In particular, radiology helps identify human remains in forensic investigations [23]. Details such as volume, size, shape, and the individual characteristics of bones represent consistent evidence, and this can be used to identify bodies [24]. Sexual dimorphism is evident in various anatomical features of the skull [25], one of the most sexually dimorphic regions of the human skull being the frontal bone [26].

The practicability of using the FS in distinguishing between the genders has previously been investigated using various morphometric and morphological methods. The purpose of this study was to evaluate the usefulness of minimum and maximum frontal width measurements, volumetrically evaluated FS, and also 'frontal bone surface length' measurement, used for the first time in the present study according to our scan of the literature and also to investigate whether gender differences exist in these parameters in cases with PMS too.

Table 3. Comparison of quantitative data between genders in the PMS group

	PMS group			
Variables	**Males (n=27)**	**Females (n=22)**	**t or z**	**P value**
Surface length (cm)*	18.05±0.97	17.37±0.99	2.162	**0.037**
Right FSV (cm^3)	1.60 (0.49-6.66)	1.60 (0.49-6.66)	-2.704	**0.006**
Left FSV (cm^3)	3.99 (0.60-17.91)	1.57 (0.24-6.28)	-2.986	**0.002**
Min. Frontal width (cm)	10.10 (9.22-10.78)	9.94 (9.26-12.57)	-1,719	0.088
Max. Frontal width (cm)	12.86 (11.94-13.66)	12.48 (10.23-13.65)	-1.057	0.294

Data are shown as mean±standard deviation or median (minimum-maximum). PMS=Persitent metopic suture, FSV=Frontal sinus volume, Min=minimum, Max=maximum

t=independent sample t test, z=Mann Whitney-U test,

*Frontal bone surface length

The prevalence of PMS in this research was 4.9%. Bilateral FS aplasia was observed in 10 (20%) of the PMS cases. Numerous studies [27, 28] have investigated the prevalence of PMS, and our findings were generally compatible with those.

In Atalay and Eser's [29] comparison of FS volumes between PMS and non-PMS groups, the two halves were not evaluated separately, although total FS volumes were lower in the PMS cases. Grine *et al*. [30] compared the CT findings of a PMS group and a control group in a South African population in terms of FS volumes. Those authors divided their PMS cases into partial and complete groups. While a decrease was observed in FS volumes in the complete PMS cases compared to the control group, an increase in FS volume was detected in partial PMS cases compared to the control group. In the present study, bilateral FS volumes in the PMS group were lower than those in the non-PMS group. This may be attributable to the suppressive effect of PMS on the development of FS, a phenomenon confirmed by previous research, and may possibly also be due to the number of complete and incomplete PMS cases. Further studies, distinguishing between complete and incomplete PMS cases, are now needed on this subject. Our scan of the literature revealed no similar studies comparing frontal morphometric measurements between PMS and non-PMS groups. In the present study, all three frontal morphometric length measurements were higher in PMS cases compared to the non-PMS group, confirming the functions of the sutures in bone growth.

In their study investigating the contribution of FS to sexual dimorphism, Tatlısumak *et al*. [31] compared FS volumes according to age and gender, and both FS values were significantly higher in men than in women. Wanzeler *et al*. [32] did not examine both halves of the FS separately but reported a significantly higher total FS volume in men than in women. Michel *et al*. [33] reported similar results to those of Wanzeler *et al*. [32]. However, the presence of PMS and its effect on the usefulness of this parameter in sexual dimorphism was not evaluated in those studies. Atalay and Eser [29] observed significantly lower FS volumes in women compared to men in both the control and PMS groups. In the present study, both halves of the frontal sinus were evaluated separately and, in agreement with Atalay and Eser [29], FS volume was significantly lower in the PMS group than in the non-PMS group. In terms of gender, bilateral FS volumes in both groups were significantly lower in women than in men. Our findings were compatible with the above study and supported the assumption that metopic suture persistence suppresses the development of the FS. The results also showed that both halves of the FS can be used in gender identification.

Various studies have examined the use of cranial morphometry in gender identification. Several different landmarks and methods have been used in the frontal bone. Del Bove *et al*. [34] used various landmarks on the skull to evaluate the surface shape of the frontal bone through a special software program. Those authors investigated whether the surface shape would differ between the genders. They concluded that the most accurate results in terms of gender identification were 'evaluation of the supraorbital part shape'. Since the difference in bone surface shape can also affect the measurements performed on the bone surface, this may explain the difference between genders in the length of the frontal bone surface, one of the measurements made in the present study. Čechová *et al*. [35] examined differences in frontal bone external surface area and shape, frontal sinus volume, and surface area by gender, and reported that frontal sinus measurements and frontal bone surface area measurements differed significantly between the sexes. Cekdemir *et al*. [36] investigated the usefulness of cranial morphometry in gender dimorphism and reported that, similarly to the present study, minimum frontal width was significantly higher in men than in women. However, no evaluation in terms of the presence of PMS was conducted. Consistent with Cekdemir *et al*. [36], minimum frontal width and all other parameters (maximum frontal width, frontal sinus volumes, and frontal bone surface length) in the non-PMS group in the present study exhibited significant differences between the genders and were capable of use in gender identification. However, in the PMS group, and in contrast to Cekdemir *et al*. [36], the difference between the genders in minimum frontal width and maximum frontal width measurements was not significant. This showed that the presence of persistent metopic suture should be taken into consideration when performing gender analysis using frontal morphometric parameters.

Limitations

There are a number of limitations to this study, in-

cluding its retrospective and single-center character, the small number of PMS cases, and the lack of distinction between complete and partial PMS. Other limitations are that the effects of parameters affecting skeletal development, such as environmental, metabolic, and nutritional factors and ethnicity, could not be determined. Patients under the age of 18 were not included in the study due to skeletal development continuing during childhood and adolescence. Separate studies are therefore needed for that age group.

CONCLUSION

In conclusion, in addition to the frontal morphometric parameters currently used for gender identification, a highly important subject for forensic sciences, the 'frontal bone surface length measurement' performed in the present study may be useful in gender estimation as it exhibits significant gender differences. In addition, some of the frontal morphometric measurements (minimum and maximum frontal width) exhibit no gender difference in the presence of PMS, and caution should therefore be exercised when using these parameters in cases with PMS.

Ethical Statement

Approval for the research was received from the Clinical Research Ethics Committee of Süleyman Demirel University Faculty of Medicine (decision dated 30.12.2020 and numbered 72867572-050.01.04-15964).

Authors' Contribution

Study Conception: AS, NO; Study Design: AS, NO; Supervision: NO; Funding: N/A; Materials: N/A; Data Collection and/or Processing: AS; Statistical Analysis and/or Data Interpretation: AS, NO; Literature Review: AS; Manuscript Preparation: AS and Critical Review: AS.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Editor's note

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Comparison of changes in blood group, hemogram and biochemical parameters in healthcare workers with and without COVID-19

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ABSTRACT

Objectives: This study aimed to evaluate blood groups and some hematologic and biochemical parameters in healthcare workers with and without COVID-19.

Methods: The sample consisted of 1232 healthcare workers who consented to participate in the study after being informed about its purpose and methodology. The study's case group consisted of 704 individuals who got COVID-19, whereas the control group consisted of 528 individuals who didn't get the virus. A survey conducted online was used to gather data. The study was conducted with adherence to ethical norms.

Results: Participants in the case and control groups showed a significant difference in their vitamin D level variables, and those with low vitamin D levels were 1.9 times more likely to contract COVID-19 than those with normal levels. Blood glucose, lactate dehydrogenase (LDH), ferritin, troponin-I, D-dimer, C-reactive protein (CRP), anti- human immunodeficiency virüs (HIV), white blood cell, hemoglobulin, platelets, lymphocyte, and neutrophil averages were significantly different between the case and control groups when the biochemistry values of the participants were compared ($P<0.05$).

Conclusions: Vitamin D level, blood glucose, LDH, ferritin, troponin I, D-dimer, CRP, and anti-HIV among the significant biochemistry parameters in our study; leukocyte, hemoglobin, platelets, lymphocyte, and neutrophil levels among hemogram parameters are in parallel with the literature data in predicting the diagnosis of COVID-19. The use of these parameters in the clinic will contribute to the early detection of the diagnosis, early isolation of patients, and early initiation of the treatment process.

Keywords: Biochemistry, COVID-19, hemogram, blood group, healthcare worker

The World Health Organization (WHO) announced on December 31, 2019, that a disease of unknown origin with severe respiratory symptoms has emerged in Wuhan, Hubei province, China [1]. On January 7, 2020, it was discovered that a new type of coronavirus (2019-nCoV) that had never been discovered in humans was the cause of severe respiratory symptoms; this infection was dubbed "COVID-19" [2]. Members of the Coronaviridae family, coronaviruses (SARS-CoV, MERS-

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CoV, and SARS-CoV-2) are enclosed viruses with a single-stranded, positively polarized, single-stranded RNA genome that is around 27-32 kb in size [3]. On December 1, 2019, the WHO declared a pandemic after the COVID-19 epidemic extended to 216 nations, infecting 12 million people. On March 11, 2020, the first case was seen in Turkey [4].

In order to stop and manage the spread of infection, our country and other countries have begun implementing a number of preventative measures in response to the COVID-19 pandemic. Curfews, travel restrictions, remote work, distance learning, flexible or rotating work schedules, social distancing regulations, and mask obligations are some of the measures that have had a significant impact on people and caused physical and mental health issues for survivors [4,5]. The people most impacted by this circumstance are healthcare professionals. On the front lines, healthcare workers—our most powerful force in the pandemic-have battled the risk of spreading the virus to their loved ones and themselves [6].

Finding indicators that may be utilized to forecast disease severity and risk is necessary because of the rapid transmission and possible fatality of SARS-CoV-2. Healthcare professionals may lessen transmission, use resources effectively during the pandemic, avoid needless hospitalizations, and lessen all associated effects by identifying patients at high risk of developing a serious or deadly disease [7]. Standard, quick, simple, and inexpensive blood tests that can help with COVID-19 diagnosis and prognosis include serum biochemistry and complete blood count studies [8]. COVID-19 cannot be diagnosed based only on laboratory results. Despite the fact that the final diagnosis of COVID-19 is made microbiologically, this approach aids in the diagnosis when combined with the patient's contact history, clinical findings, certain laboratory results, imaging techniques, and is useful for patient follow-up [9]. Examining blood types and some hematologic and biochemical characteristics in healthcare professionals with and without COVID-19 was the goal of this study.

METHODS

Purpose and Type of Study

This study aimed to evaluate blood groups and some hematologic and biochemical parameters in healthcare workers with and without COVID-19. It is a single-center, retrospective, and cross-sectional case-control study.

Population and Sample of the Study

The study population consisted of 2100 healthcare workers who worked in Bursa Çekirge State Hospital between 2020-2022 and continued to work between December 2022 and December 2023. The sample consisted of 1232 healthcare workers who agreed to participate in the study after being informed about the purpose, content, and method. The sample consists of two groups. The case group consists of 704 people who contracted COVID-19 and agreed to participate in the study, and the control group consists of 528 people who did not contract COVID-19 and agreed to participate.

Inclusion criteria

All medical staff members who consented to take part and who had the most recent COVID-19 blood group, biochemistry, and hemogram results in the hospital registration system between December 2022 and December 2023 at Bursa Çekirge State Hospital.

Exclusion Criteria

Participants with disabilities such as hearing, writing, or visual impairments that prevented them from participating in the study were excluded, as were those who did not want to complete the questionnaire, those who could not be contacted because they were on leave or reporting, and those who marked the questionnaire form as incomplete or multiple times.

Data Collection Tool

A questionnaire was used to gather data. Descriptive questions about the participants were asked in the first section of the questionnaire, and questions concerning blood types, biochemistry, and hemogram test findings were asked in the second.

Data Collection

The study's questionnaire was distributed to participants by message board, email, and WhatsApp. The online questionnaire was developed using "Google Forms." Before beginning to answer the questions, participants who fulfilled the sampling criteria and consented to participate in the study filled out the questionnaire. Completing the online data col-

Table 1. **Demographic characteristics of the participants in the case and control groups and comparison between groups**

		Case group (n=704)		Control group (n=528)		Statistical analysis and P value	Odds Ratio	95% Confidence Interval	
		n	%	n	%			Min.	Max.
Gender	Female (ref.)	439	62.4	289	54.7	χ^2=7.253[a] **P=0.007**	**1.370**	1.128	1.665
	Male	265	37.6	239	45.3				
Blood group	0 Rh + (ref.)	187	26.6	160	30.3	χ^2=4.866[a] P=0.676			
	0 Rh -	30	4.3	27	5.1		0.951	0.587	1.539
	A Rh +	279	39.6	200	37.9		0.725	0.402	1.306
	A Rh -	46	6.5	30	5.7		0.796	0.497	1.277
	B Rh +	95	13.5	67	12.7		0.643	0.301	1.374
	B Rh -	19	2.7	11	2.1		0.784	0.467	1.315
	AB Rh +	43	6.1	32	6.1		0.222	0.041	1.216
	AB Rh -	5	0.7	1	0.2		0.827	0.458	1.492
Vitamin D level	Low (ref.)	244	34.7	120	22.7	χ^2=26.709[b] **P<0.001**			
	Normal	359	51.0	341	64.6		**1.931**	1.551	2.405
	High	4	0.6	6	1.1		3.050	0.970	9.590
	No information available	97	13.8	61	11.6		1.279	0.928	1.762

[a]Pearson Chi-Square test, [b]Fisher Exact test

lection took an average of ten minutes. The correctness of the hemogram, biochemistry, and blood group findings was validated by the hospital registration system.

Ethical Aspects of the Study

The study's ethical aspects were accepted by the Bursa City Hospital Clinical Research Ethics Committee on March 17, 2021 (Decision No: KAEK/2021.05.02) before to its commencement. At every stage of the study, the Declaration of Helsinki was followed, and participants were informed using a "voluntary consent form" that the researchers had created.

Statistical Analysis

Data analysis was conducted using the SPSS 20.0 software. Data related to continuous variables were re-

Table 2. Comparison of biochemistry results of case and control group participants between groups

	Case group (n=704)	Control group (n=528)	Statistical analysis and P value
Fasting glucose (mg/dL)	108.44±37.405	83.87±8.062	t=14.835 **P=0.000**
Urea (mg/dL)	36.09±25.027	36.60±21.137	t=0.384 P=0.701
Creatinine (mg/dL)	1.02±**0**.699	1.01±**0**.553	t=0.058 P=0.954
ALT (IU/L)	23.95±36.827	24.90±36.536	t=0.451 P=0.652
AST (U/L)	28.15±32.550	25.91±24.879	t=1.314 P=0.189
LDH (U/I)	412.34±85.950	153.98±30.567	t=66.004 **P<0.001**
Ferritin (µg/L)	262.99±89.753	40.25±43.030	t=52.662 **P<0.001**
Troponin I (ng/L)	45.48±9.210	3.73±4.706	t=32.530 **P<0.001**
D-Dimer (mg/L)	0.82±1.064	0.31±0.159	t=10.968 **P<0.001**
CRP (mg/dL))	34.92± 46.297	4.94±8.377	t=14.699 **P<0.001**
Anti-HBs (mIU/mL)	362.23±422.659	401.11±449.683	t=1.555 P=0.120
Anti-HIV	0.13±0.098	0.12±0.072	t=2.037 **P<0.001**
Vitamin B12 (pg/mL)	345.75±60.774	344.03±32.963	t=0.201 P=0.841
Cholesterol (mg/dL)	204.18±44.573	201.73±43.359	t=0.967 P=0.334

Data are shown as mean±standard deviation. ALT=alanine aminotransferase, AST=aspartate aminotransferse, LDH=lactate dehydrogenase, CRP=C-reactive protein, Anti-HBs=hepatitis B surface antibody, HIV=human immunodeficiency virus t=Independent samples t-test

ported as means in statistical analyses, whereas data related to categorical variables were expressed as numbers (n) and percentages (%). Qualitative and quantitative variables were compared using the chi-square and independent samples t-tests, respectively. An examination of logistic regression was conducted. The Hosmer-Lemeshow Test was used to assess model fit. The sample size was found to be suitable and there were no issues with multicollinearity or outliers when the assumptions were assessed before to the analysis. Odds Ratio (OR) and confidence interval (CI: Confidence Interval) were calculated using logistic regression analysis. The enter method was used in logistic regression. The significance level was accepted as $P<0.05$.

RESULTS

A significant difference was observed between the case and control groups according to the gender characteristics of the individuals ($P<0.05$). The case and control groups were found to be similar to one another when comparing the blood group characteristics of their individuals ($P>0.05$). Regarding the vitamin D level characteristics of the participants in the case and control groups, there was a significant difference between the groups ($P<0.05$) (Table 1).

The mean glucose levels of the individuals in the case and control groups showed a significant difference between the groups ($P<0.05$). In terms of mean lactate dehydrogenase (LDH) levels, there was a significant difference between the case and control groups ($P<0.05$). There was a significant difference in the mean ferritin levels between the case and control groups ($P<0.05$). Analysis of the case and control groups' mean troponin I levels revealed a significant difference ($P<0.05$). In terms of mean D-dimer levels, there was a significant difference between the case and control groups ($P<0.05$). In terms of mean C-reactive protein (CRP) levels, there was a significant difference between the case and control groups ($P<0.05$). Participants in the case and control groups had mean anti-human immunodeficiency virus (anti-HIV) values that differed significantly from one another ($P<0.05$). It was determined that there was no significant difference between the mean values of Urea, Creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), hepatitis B surface antibody (anti-HBs), vitamin B12, and cholesterol of the participants in the case and control groups ($P>0.05$) (Table 2).

There was a significant difference in the mean white blood cell (WBC) levels between the case and control groups ($P<0.05$). There was a significant difference ($P<0.05$) in the mean Hemoglobin levels between the case and control groups. Comparing the participants' mean Platelets values revealed a significant difference between the groups ($P<0.05$). The participants in the case and control groups had significantly different mean plateletcrit (PCT) ($P<0.05$). There was a significant difference between the case and control groups ($P<0.05$) when comparing the mean lymphocyte of the participants. A significant difference between the groups was discovered when the individuals' mean lymphocyte % was assessed ($P<0.05$). Participants in the case and control groups had mean neutrophils that differed significantly from one another ($P<0.05$). The averages of neutrophils % in the case and control groups differed significantly ($P<0.05$). The case and control groups' participants' mean values forred blood cell (RBC), red blood cell distrubition wide (PDW) %, RDW-standard deviation (SD)%, basophil count, basophil %, monocytes count, monocytes %, eosinophil count, and eosinophil % did not vary significantly ($P>0.05$) (Table 3).

DISCUSSION

It is crucial to guarantee good triage, suitable isolation, and effective utilization of potentially scarce testing resources during infectious disease epidemics. Using peripheral blood samples for hemogram and biochemistry analysis is an easy, quick, and affordable diagnostic procedure. Thus, the purpose of our study was to assess blood types as well as certain hematologic and biochemical characteristics in healthcare professionals who had and did not have COVID-19.

According to the blood types of the study's participants, A Rh+ was the most frequently encountered blood type in both the case and control groups, whereas AB Rh- was the least frequently encountered. Blood group A was the most prevalent blood group among healthy COVID-19 patients in the study conducted by Muniz-Diaz *et al*. [10]. There was no dis-

Table 3. Comparison of hemogram results of case and control group participants between groups

	Case group (n=704)	Control group (n=528)	Statistical analysis and P value
WBC ($\times10^9$/L)	10.67±7.853	5.91±1.068	t=13.830 **P<0.001**
RBC ($\times10^{12}$/L)	4.69±0.501	4.68±0.443	t=0.671 P=0.502
Hemoglobin (g/dL)	12.03±0.761	14.92±0.710	t=67.825 **P<0.001**
Platelets ($\times10^9$/L)	202.25±60.193	290.42±62.745	t=24.983 **P<0.001**
Platelets %	0.35±0.033	0.19±0.045	t=69.763 **P<0.001**
PDW %	16.70± 1.615	16.59±1.593	t=1.,214 P=0.225
RDW-SD %	41.97±4.079	41.71±4.015	t=1.083 P=0.279
Basophil ($\times10^9$/L)	0.03±0.056	0.04±0.072	t=0.786 P=0.432
Basophil %	0.57±0.576	0.63±0.914	t=1,486 P=0,138
Lymphcyte ($\times10^9$/L)	1.66±0.429	3.02±0.678	t=43.164 **P<0.001**
Lymphcyte %	24.93±6.449	45.44±10.176	t=43.164 **P<0.001**
Monocyte ($\times10^9$/L)	0.54±0.463	0.53±0.552	t=0.445 P=0.656
Monocyte %	7.31±4.860	7.19±5.291	t=0.392 P=0.695
Eosinophil ($\times10^9$/L)	0.17±0.167	0.16±0.148	t=1.232 P=0.218
Eosinophil %	2.30±1.974	2.25±.,986	t=0.429 P=0.668
Neutrophil ($\times10^9$/L)	8.74±3.000	4.21±1.248	t=32.553 **P<0.001**
Neutrophil %	92.50±12.226	60.06±10.126	t=49.540 **P<0.001**

Data are shown as mean±standard deviation. WBC=white blood cell, RBC=red blood cell, RDW=red blood cell distribution width. SD=standard deviation

t=Independent samples t-test

cernible variation in blood group variability across the groups [10]. In a research conducted in Bahrain, the ABO distribution was comparable between the control group and the Covid-19-infected group. The most prevalent blood group was O, which was followed by A and B. Our study's least represented blood type was AB [11]. O blood group individuals were significantly less likely to be infected with SARS-COV-2 than non-O participants, according to another study done in Iraq that analyzed 200 patients with detected SARS-CoV-2 infection, ABO blood group, and clinical data. On the other hand, people with blood group A were more likely to get infected [12]. There was no difference between the groups when Wu *et al*. [13] examined the impact of blood types on COVID-19 patients and healthy people. The blood types of COVID-19 positive and negative were examined in the study by Nalbant *et al*. [14]. that looked at the connection between COVID-19 disease and blood type. The same study found that the blood group had no effect on COVID-19. The results are similar to our study.

Vitamin D is an essential regulator of immunity. Vitamin D deficiency/insufficiency threatens public health and primarily affects individuals more prone to contracting COVID-19 [1]. In this study, a significant difference was found between the case and control group participants in terms of vitamin D levels. At the same time, those with low vitamin D levels had a 1.9 times higher risk of having COVID-19 compared to those with normal levels (OR=1.931; 95% CI=1.551-2.405; P<0.001).

Anti-insulin hormones such growth hormone, glucagon, cortisol, and catecholamines rise in response to stressful situations like disease, which also causes an increase in gluconeogenesis. Increases in interleukin-1, interleukin-6, and tumor necrosis factor-alpha during infection lead to the development of insulin resistance. Blood glucose levels rise as a result of these two processes. Tissues' capacity to use glucose declines with increasing insulin resistance [15]. In our study, the case group's blood glucose levels were significantly higher than those of the control group. Similar to our findings, Lymperaki *et al*. [16] discovered in their study that those with COVID-19 had significantly higher glucose levels. This study observed no significant difference between AST and ALT values. In the study of Thapa *et al*. [17] on biochemistry values in individuals with and without COVID-19, AST and ALT values were significantly higher in COVID-19 patients.

Adipose and liver cells create the acute-phase protein known as C-reactive protein (CRP), which is elevated in inflammatory and infectious conditions. A biochemical metric known as CRP rises in COVID-19 disease and all inflammatory conditions. Hussein *et al*.'s [18] investigation of patients with and without COVID-19 revealed a significant difference between the two groups, with CRP values being higher in the COVID-19 patients. In this investigation, the case group's CRP value was significantly greater than the control group's. In the study conducted by Rostam *et al*. [19] with COVID-19-positive and healthy individuals, the LDH values of COVID-19-positive individuals were significantly higher than those of the healthy group. In the study of Thapa *et al*. [17], LDH values were significantly higher in COVID-19 patients compared to the healthy group. Although the CRP values of COVID-19 patients were higher than those of healthy patients in the Rostam *et al*.'s [19] study, there was not a significant variation between the two groups [19]. Higher LDH, ferritin, and CRP levels were found in COVID-19 patients [20]. CRP appears to be an essential regulator of inflammatory processes rather than a marker like ferritin [21].

A cytoplasmic enzyme called lactate dehydrogenase (LDH) transforms lactic acid into pyruvic acid. The tiniest rise in serum signifies cell injury since intracellular LDH levels are 500 times greater than serum levels. Participants in the case group in our study had considerably higher LDH levels than those in the control group. Additionally, Hussein *et al*. [18] discovered that the LDH count was noticeably higher than that of the control group.

The severity of the COVID-19 infection is strongly correlated with higher D-DIMER levels. The case group in this study had a significantly greater D-DIMER value than the control group. D-dimer values were significantly higher in patients with COVID-19, according to a study by Hussein *et al*. that compared patients with and without the virus [18]. D-dimer levels were greater in COVID-19 patients in several studies [17, 19]. Ahmed *et al*. [22] found that unvaccinated COVID-19 patients had a significantly greater D-dimer level than healthy individuals. Ferritin levels were shown to be significantly higher in COVID-19 patients in the same study, which is comparable to ours [22].

Troponin I is the most specific marker of myocyte damage caused by myocardial ischemia in peripheral blood. In this study, the case group's troponin levels in COVID-19 patients were significantly higher than those in the control group. Tersalvi *et al*. [23] showed that troponin levels increased in COVID-19 infection and increased further as the severity of the disease increased.

Participants in the case group in our study had a significantly higher WBC level than those in the control group. Hussein *et al*.'s [18] study of patients with and without COVID-19 revealed a significant difference between the two groups, with WBC levels being greater in the COVID-19 patients. In 2020, Soraya *et al*. [24] published a meta-analysis study that looked at hemogram and biochemistry characteristics that can be used to diagnose COVID-19. In support of the diagnosis of COVID-19, the data showed a substantial drop in leukocyte ($P<0.001$), neutrophil ($P<0.01$), and platelet ($P<0.05$) levels [24]. Kiss *et al*. [25] found that WBC and D-DIMER levels increased and lymphocyte values decreased in COVID-19 patients in severe conditions and intensive care.

In this study, the hemoglobulin value was significantly lower in the case group than in the control group. Similar to our study, Ahmed *et al*. [22] found that the hemoglobulin value of unvaccinated COVID-19 patients was significantly lower than that of individuals in the healthy group.

Comparing the case group to the control group, we found that the case group individuals had significantly lower numbers and percentages of lymphocyte and platelets values. By inhibiting growth and inducing death after the virus infects bone marrow progenitor cells, we can demonstrate that the pathophysiological mechanism of reduced platelet synthesis from megakaryocytes is the reason for the decline in platelet levels in COVID-19 patients [26]. Additionally, Hussein *et al*. [18] discovered that the proportion of lymphocyte and platelets values values was considerably lower than that of the control group [18]. Ahmed *et al*.'s [22] study on COVID-19 patients revealed that, in comparison to the healthy group, lymphocyte values had drastically dropped. However, there was a little drop in the platelets value when compared to the healthy group [22].

According to our study, there was a substantial difference between the case group's and the control group's participants, with the case group's neutrophil count and percentage being greater. Hussein *et al*.'s [18] study, which included patients with and without COVID-19, found that there was a significant difference between the two groups and that the proportion of neutrophils was greater in the COVID-19 patients. Because they have lower autoimmunity and higher neutrophil counts, which indicate higher levels of inflammation, COVID-19 patients are more vulnerable to bacterial and fungal infections as the condition worsens [27]. The study by Wu *et al*. [28] showed that individuals with COVID-19 had significantly increased neutrophil counts, while lymphocyte and platelet levels decreased compared to those unaffected.

Important biochemistry parameters in our study include vitamin D level, blood glucose, LDH, ferritin, Troponin I, D-Dimer, CRP, and Anti-HIV; hemogram parameters such as leukocyte, hemoglobin, platelet, lymphocyte, and neutrophil levels are in line with the data from the literature in predicting the diagnosis of COVID-19. Early diagnostic detection, early patient isolation, and early treatment beginning are all facilitated by the use of these parameters in the clinic.

CONCLUSION

The findings of this study indicate a strong correlation between COVID-19 and both high and low levels of hematologic and biochemical markers. In order to diagnose COVID-19 utilizing blood and blood biochemistry tests, which act as biomarkers to predict infection, these factors are crucial. Our study's blood results proved to be a reliable indicator of COVID-19 infection. Therefore, the prognosis of the disease may be assessed using these values.

Ethical Statement

The study was approved by the Bursa City Hospital Clinical Research Ethics Committee (Decision no: KAEK/2021-5/2 and date: 17.03.2021) before to its commencement. At every stage of the study, the Declaration of Helsinki was followed, and participants were informed using a "voluntary consent form" that the researchers had created.

Authors' Contribution

Study Conception: AT, HÖ, AAV; Study Design: AT, HÖ, HB; Supervision: AT, HÖ, HB; Funding: AT,

HB, AAV; Materials: AT, HB, AAV; Data Collection and/or Processing: AT, HB, AAV; Statistical Analysis and/or Data Interpretation: AT, HÖ; Literature Review: AT, HB, AAV; Manuscript Preparation: AT, HÖ, HB, AAV; and Critical Review: AT, HÖ, HB, AAV.

Conflict of interest

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Geriatric patients with acute kidney injury in the intensive care unit: the effect of vitamin B12 and albumin levels on survival

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ABSTRACT

Objectives: Acute kidney injury (AKI) is a common and critically important clinical entity in geriatric age group. In addition, higher mortality rates are seen in cases requiring intensive care treatment. We have aimed to investigate the effect of vitamin B12 and albumin levels on mortality in critically ill geriatric patients with AKI.

Methods: Geriatric patients hospitalised in the Intensive Care Unit with a diagnosis of AKI between 07.01.2014-07.01.2015 were retrospectively screened and included in the study. Two groups were formed from discharged and exited patients. General characteristics and laboratory values of the patients were scanned from the hospital archives and recorded. Statistically significant intergroup differences in terms of demographic characteristics, and biochemical values were determined by statistical analysis.

Results: A total of 103 patients, including 53 females were enrolled in the study, while 72.2% of the patients had prerenal AKI. The mortality rate was 47.57% in all patients. There was no difference between groups in terms of mortality rates, etiologic factors and KDIGO staging. Vitamin B12 was high and albümin was low the group who succumbed to death. In addition, mortality rates increased by 10% for every 100 units increase in vitamin B12 value and decreased by 22% for every 10 units increase in albumin value.

Conclusions: We have determined that an increase in albumin levels during clinical follow-up decreased mortality rates and an increase in vitamin B12 levels directly increased mortality rates. Hypoalbuminemia and high vitamin B12 levels were found to be independent predictive factors for mortality in AKI.

Keywords: Vitamin B12, albumin, acute kidney injury, geriatrics

The geriatric population is defined as the population of people aged 65 years and older [1]. With aging, morphological changes occur in the kidneys such as anatomical reduction in renal size and decrease in parenchymal volume, and functional changes such as decrease in renal blood flow and glomerular filtration rate (GFR). In addition, chronic diseases such as hypertension (HT), diabetes mellitus (DM), heart failure (HF) etc., which have a high prevalence in the elderly population, increase the risk of adverse structural and functional changes in the kidneys with aging [2]. As is known the incidence of acute kidney injury (AKI) increases in the elderly population compared to younger individuals [3]. AKI is defined as the development of functional abnormality in the kidneys within hours or days [4]. Functional ab-

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normality parameters include the rate and relative ratio of increase in serum creatinine levels and the amount of urine formed in a certain period of time. Three stages have been defined according to these parameters in the classification of KDIGO [5]. Renal dysfunction frequently improves in AKI and the prognosis is good. The geriatric population and the patients who need intensive care have higher mortality rates, need renal replacement therapy (RRT) more often and permanent loss of renal function is observed more frequently [6].

Albumin is a natural protein produced in the liver. Its half-life is 18 days and it has different physiologic effects and functions. The most important of these are maintenance of plasma oncotic pressure, and acid-base balance, hormone and drug transport, and regulation of the immune system.7 Albumin is also a negative acute phase reactant. A decrease in albumin levels below 30 g/L is defined as hypoalbuminemia and is frequently detected in critically ill patients [8].

Vitamin B12 is not produced in the body and must be taken from outside and its deficiency is associated with anemia and neuropsychiatric disorders [9]. Deficiency may be observed in nutritional disorders and gastrointestinal system diseases that cause malabsorption [10]. High vitamin B12 levels may be related to iatrogenic causes or may be observed in diseases including liver disease, polycythemia vera, leukemia and chronic kidney disease (CKD) [11]. In addition, a relationship between high vitamin B12 levels and inflammatory parameters has been shown [12].

In our study, we have aimed to investigate the effect of vitamin B12 and albumin levels on survival in geriatric patients with AKI who were hospitalised in the internal medicine intensive care unit.

METHODS

This study was planned as a retrospective screening study of geriatric patients with AKI hospitalized in the Internal Medicine Intensive Care Unit of Kütahya Health Sciences University Evliya Çelebi Training and Research Hospital between 07.01.2014 and 07.01.2015.

Inclusion Criteria

Patients aged 65 years and older who were hospitalized in the internal medicine intensive care unit with a diagnosis of acute kidney injury were included in the study. The KDİGO (Kidney Disease: Improving Global Outcomes) guidelines were used for the diagnosis and staging of AKI [5].

Exclusion Criteria

Patients under 65 years of age, those who were discharged within the first 48 hours of their admission to ICU, and cases with a diagnosis of chronic renal failure who were on renal replacement therapy program were not included in the study.

Data Collection

Patients who were discharged from the intensive care unit (Group 1) and patients who did not survive (Group 2) were allocated into two separate groups. Besides, patients were also assessed in categories of prerenal, renal, and postrenal AKI according to the etiology of AKI.

Archival information was gathered concerning age, gender, comorbidities, diagnosis at intensive care unit admission, length of ICU stay, need for hemodialysis, and clinical outcomes of the patients. Relevant laboratory parameters [BUN, creatinine, uric acid, albumin, globulin, CRP, ferritin, B12, TSH, WBC, neutrophil, lymphocyte, Hgb, MCV, RDW, Plt, MPV] were recorded from the hospital information system. In addition, the albumin/globulin ratio and neutrophil/lymphocyte ratio (NLR) were calculated and recorded.

Ethical Statement

Ethical approval was received from the ethics committee of Kütahya Health Sciences University Faculty of Medicine with the decision dated 24.02.2021 and numbered 2021/03-15. The study was conducted by the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed with the help of SPSS version 17.0 program. The conformity of the variables to normal distribution was examined by histogram plots and Kolmogorov-Smirnov test. Mean, standard deviation, median, minimum, and maximum values were used in descriptive analyses. Categorical variables were compared with Pearson chi-square test. Mann-Whitney U test was used for non-normally dis-

tributed (nonparametric) variables between two groups. Kaplan-Meier analysis was used for univariate and Cox regression analysis for multivariate analysis. P-values below 0.05 were considered statistically significant.

RESULTS

A total of 103 patients, including 50 males and 53 females, were enrolled in the study. The mortality rate was 47.57% (n:49). The most common indications for admission were prerenal (72.2%), renal (22.33%) and postrenal (4.85%) AKI in respective percentages of patients. Etiologic factors for prerenal (infection: 65.33%, and dehydration: 20%), renal (infection: 72.73%, and toxic nephropathy 27.27%), postrenal AKI (% prostatic hyperplasia: 60%, and various malignancies: 40%) were identified in different proportions of patients as indicated.

According to KDIGO staging; patients had stage 1 (33.98%), stage 2 (36.89%), and stage 3 (29.13%) AKI. A total of 34 patients (33.01%) received renal replacement therapy (RRT) (Table 1).

General and etiologic factors were compared between the groups (Table 2). Any significant difference could not be found between groups in terms of gender, etiology, KDIGO staging and need for RRT when evaluated using the chi-square test.

Differences between the groups in terms of age, duration of hospitalization in days, and laboratory parameters were analyzed using the Mann-Whitney U test (Table 3). WBC, Neutrophil, NLR, RDW, MPV, B12, and CRP levels were statistically significantly higher in the non-surviving group. In addition, albumin, A/G ratio and creatinine levels were lower in this group.

Table 1. General characteristics and etiologies of AKI in all patients

		n	%
Sex	Male	50	48.54
	Female	53	51.46
Patient outcomes	Discharged	54	52.43
	Exitus	49	47.57
Types of AKI	Prerenal	75	2.82
	Renal	23	2.33
	Postrenal	5	4.85
Causes of prerenal AKI	Sepsis	49	65.33
	Dehydration	15	20.00
	Cardiovascular disease	7	9.33
	Chronic liver disease	4	5.33
Causes of renal AKI	Infection	16	72.73
	Toxic nephropathy	6	27.27
Causes of postrenal AKI	Prostatic hyperplasia	3	60.00
	Malignancy	2	40.00
KDIGO stages of AKI	Stage 1	35	33.98
	Stage 2	38	36.89
	Stage 3	30	29.13
Renal replacement therapy	Yes	34	33.01
	No	69	66.99

AKI=Acute Kidney Injury, KDIGO=Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury

Table 2. Demographic characteristics and etiologic factors of AKI in both groups

		Group 1		Group 2		P value*
		n	%	n	%	
Sex	Male	27	54.00	23	46.00	0.756
	Female	27	50.94	26	49.06	
Types of AKI	Pre-renal	38	50.67	37	49,33	0.445
	Renal	12	52.17	11	7.83	
	Pos-trenal	4	80.00	1	20.00	
Causes of prerenal AKI	Sepsis	28	57.14	21	42,86	0.096
	Dehydration	8	53.33	7	46,67	
	Cardiovascular disease	2	28.57	5	71.43	
	Chronic liver disease	0	0.00)	4	100.00	
Causes of renal AKI	Infection	9	56.25	7	43.75	0.793
	Toxic nephropathy	3	50.00	3	50,00	
Causes of postrenal AKI	Prostatic hyperplasia	3	100.00	0	0.00	0.171
	Malignancy	1	50.00	1	50.00	
KDIGO stages of AKI	Stage 1	14	40.00)	21	60.00	0.40
	Stage 2	24	63.16	14	36.84	
	Stage 3	16	53.33	14	6.67	
Renal replacement therapy	No	37	53.62	32	46.38	0.729
	Yes	17	50.00)	17	50.00	

AKI=Acute Kidney Injury, KDIGO=Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury

*Chi-Square Test

Cox regression analysis was performed with the values that were significantly correlated with mortality (Table 4). Accordingly, one unit increase in albumin value decreased the mortality risk by 0.221 times (95% CI: 0.062-0.789), and one unit increase in B12 value increased the mortality risk by 1.001 times (95% CI: 1.000-1.002).

DISCUSSION

In our study, we found that prerenal causes were more frequent in geriatric patients hospitalised in intensive care unit with the diagnosis of AKI, and high vitamin B12 and low albumin levels were directly associated with increased mortality risk. In addition, RDW, MPV and CRP levels were higher in the nonsurvived group.

With aging, structural and functional changes occur in the kidneys such as decreased parenchymal tissue, glomerulosclerosis, thickening of the glomerular basement membrane, decreased renal blood flow, and glomerular filtration rate [13, 14]. Because of these changes, the incidence of AKI is higher in the elderly population. In individuals over 70 years of age, AKI is detected 3.5 times more frequently than in younger individuals [5]. The mean age of the patients included in our study was 77.31±7.77 years. Development of AKI in elderly individuals is frequently due to iatrogenic and multifactorial causes. The most common causes are the use of nephrotoxic drugs or agents such as NSAIDs, diuretics, and radiocontrast agents [15]. In a multicenter study, the rate of development of AKI during hospitalization was found to be 48% in patients over 80 years of age with normal renal function tests at the time of hospitalization [16]. Prerenal azotemia is the second most common cause of AKI

Table 3. Comparison of laboratory parameters and demographic factors between groups

	Group 1		Group 2		P value*
	Mean±SD	Median	Mean±SD	Median	
Age (years)	76.98±7.12	78.00	77.67±8.49	79.00	0.624
Hospitalization (days)	10.74±8.72	8.00	15.88±19.15	9.00	0.352
WBC (10^3/µL)	12.80±5.98	11.30	15.36±7.15	14.70	**0.037**
Neutrophil (10^3/µL)	11.04±5.63	9.55	13.52 (6.86)	12.50	**0.032**
Lymphocyte (10^3/µL)	0.98±0.60	0.80	0.98±0.70	.60	0.501
NLR	14.88±10.00	12.42	20.04±14.48	16.08	**0.090**
Hemoglobin (g/dL)	11.46±2.19	11.20	11.42±1.90	11.60	0.840
RDW (%)	16.08±2.51	15.30	17.57±2.93	16.60	**0.001**
Platelets (10^3/µL)	238.63±111.94	234.00	227.76±165.24	203.00	0.170
MPV (fL)	8.55±1.41	8.20	9.21±1.26	9.30	**0.003**
MCV (fL)	87.30±5.62	87.40	88.04±7.55	86.80	0.820
Uric acid (µmol/L)	9.32±3.53	9.00	8.77±3.77	8.00	0.265
Albumin (g/dL)	31.2±4.4	31.0	27.4±5.9	27.0	**0.000**
A/G Ratio	1.08±0.22	1.06	0.97±0.31	0.96	**0.008**
Ferritin (µg/L)	323.26±321.31	263.50	544.09±511.80	270.00	0.071
VitaminB12 (pg/mL)	614.62±491.82	446.50	863.67±533.41	853.00	**0.038**
TSH (mIU/L)	1.70±2.51	.79	1.90±3.15	1.08	0.522
CRP (mg/L)	102.00±88.22	79.90	132.86±85.47	124.30	**0.021**
HCO_3 (mmol/L)	19.46±6.15	19.15	18.17±6.73	18.70	0.333
Urea (mmol/L)	189.44±104.36	162.50	155.22±68.47	151.00	0.137
Creatinine (mmol/L)	4.57±3.72	3.32	3.00±2.12	2.50	**0.011**
BUN (mg/dL)	89.11±45.15	76.50	71.96±32.23	71.00	0.060
BUN/Crea Ratio (%)	24.55±11.12	23.95	29.02±12.72	26.66	0.090

WBC=White Blood Cell, NLR=Neutrophil-to-Leucocyte Ratio, RDW=Red Cell Distribution Width, MPV=Mean Platelet Volume, MCV=Mean Corpuscular Volume, A/C= Albumin/Globulin Ratio, TSH=Thyroid Stimulating Factor, CRP=C-reactive Protein, BUN=Blood Urea Nitrogen, SD=Standard Deviation

*Mann- Whitney U Test

[17]. Dehydration (fluid loss through gastrointestinal tract, diuretic use, and decreased fluid intake, etc.) and decreased effective plasma volume (sepsis, and heart failure, etc.) are the causes of prerenal azotemia. Some studies have shown that sepsis is the most common indication for hospitalisation of the patients with AKI in the intensive care unit [18, 19]. In our study, prerenal causes were found more frequently in accordance with the literature. Among prerenal causes, sepsis was the most frequently detected cause and no significant difference was found in mortality rates regarding different etiologic causes of AKI.

Albumin plays an essential role in the maintenance of serum oncotic pressure and also has regulatory functions on the immune system [7]. Serum albumin levels may decrease in severe inflammations, in cases where albumin synthesis decreases due to hepatocyte injury and in cases of increased albumin depletion through renal route [20]. Hypoalbuminemia is known to be associated with increased mortality and morbidity rates independent of the underlying disease [21]. A meta-analysis of 90 studies conducted in crit-

Table 4. Biochemical parameeters affecting mortality (Cox Regression analysis)

	B	SE	P value	Exp(B)	95,0% CI for Exp(B)	
					Lower	Upper
WBC	-0.403	0.215	0.061	0.668	0.439	1.018
Neutrophil	0.443	0.233	0.057	1.557	0.987	2.457
RDW	-0.004	0.082	0.958	0.996	0.848	1.169
MPV	0.017	0.171	0.921	1.017	0.728	1.422
Albumin	-1.512	0.651	**0.020**	0.221	0.062	0.789
A/G ratio	0.485	0.816	0.552	1.624	0.328	8.043
Vitamin B12	0.001	0.000	**0.043**	1.001	1.000	1.002
CRP	-0.002	0.003	0.347	0.998	0.992	1.003
Creatinine	-0.094	0.129	0.466	0.910	0.708	1.171

WBC=White Blood Cell, RDW=Red Cell Distribution Width, MPV=Mean Platelet Volume, MCV= Mean Corpuscular Volume, CRP=C-reactive Protein

ically ill patients hospitalised in intensive care units, has shown that a 10 g/L decrease in albumin level caused a 137% increase in mortality rates and a 71% increase in hospital stay [22]. In another study, it was shown that low serum albumin level was a significant independent factor predicting the development of AKI [23]. In our study, serum albumin levels were significantly lower in the nonsurvived group. In addition, mortality rates decreased by 22% for every 10 g/L increase in serum albumin levels. In parallel with other studies conducted in critically ill patients, serum albumin was found to be an independent factor predicting mortality in critically ill geriatric patients diagnosed with AKI.

Although many studies have been conducted on health problems that may develop due to vitamin B12 deficiency, limited information is available on health problems that may develop due to its excess. B12, a water-soluble vitamin, plays a critical role in maintaining cellular functions, erythrocyte formation and metabolism of homocysteine [10]. It is now known that increased serum vitamin B12 levels are associated with systemic inflammatory response syndrome (SIRS), and impaired liver and kidney functions [24]. However, the effect of increased serum vitamin B12 levels in the development of AKI is not known exactly. In various studies elevated vitamin B12 levels have been associated with severe degrees of inflammation. Corcoran *et al*. [25] showed that increased CRP levels were correlated with high vitamin B12 levels in intensive care unit patients.25 Similarly, it has been showed that high vitamin B12 levels were associated with increased CRP levels. These findings suggest that increased vitamin B12 levels with their toxic inflammatory effects may induce development of kidney damage. In a multicenter study by House *et al*. [26], a decrease in GFR was observed after administration of high-dose vitamin B complex (containing vitamin B12) to patients with diabetic nephropathy. It was shown that increased serum vitamin B12 levels elevate the risk of developing AKI in patients undergoing liver transplantation and vitamin B12 level was a predictive factor for the development of AKI [26]. Besides relatively higher vitamin B12 levels were associated with increased rates of hospital mortality in adult patients [27]. As a result of these studies, it is obvious that vitamin B12 elevation is not innocent and further studies are needed to reveal its adverse effects. In our study, significantly higher serum vitamin B12 levels were detected in the nonsurvived patient group. It was also shown that every 100 unit increase in serum vitamin B12 levels caused a 10% increase in mortality rates. According to these results, it can be said that vitamin B12 level is an independent predictive factor for mortality. It is possible that extremely high serum vitamin B12 levels may increase mortality rates by inducing the development and exacerbation of AKI and by contributing to the exacerbation of inflammation.

Limitations

Our study has some limitations. Retrospective design and small patient group can be listed. In addition, the fact that the effect of additional comorbid diseases could not be fully evaluated due to its retrospective design can be considered as a limitation. There is a need to support the findings with large patient groups and prospective studies.

CONCLUSION

It is known that AKI is a frequently detected clinical condition among inpatients, and morbidity and mortality rates are higher both among patients hospitalised in the intensive care unit and in the geriatric age group. In the geriatric age group, the presence of additional parameters that will help in the evaluation of treatment efficacy and disease severity and predict mortality is thought to aid clinicians in patient follow-up.

It should be known, and taken into consideration that high vitamin B12 levels may exert toxic effects in AKI and increase mortality rates in patients with AKI. It is necessary to be more careful about vitamin B12 replacement in the geriatric age group.

Serum albumin levels decrease in critically ill patients and the presence of infection. It should be known that a low albumin level will have a negative effect on the clinical status of patients with potential development of immune system defects, while an increase in serum albumin levels has a mortality-reducing effect. In geriatric patients hospitalised in the intensive care unit, applications to increase albumin levels should always be evaluated and albumin replacement should be considered frequently in case of need.

Ethical Statement

Ethical approval was received from the ethics committee of Kütahya Health Sciences University Faculty of Medicine with the decision dated 24.02.2021 and numbered 2021/03-15.

Authors' Contribution

Study Conception: SE, TPK; Study Design: SE, TPK; Supervision: SE, TPK; Funding: SE, TPK; Materials: SE, TPK; Data Collection and/or Processing: SE, TPK; Statistical Analysis and/or Data Interpretation: SE, TPK; Literature Review: SE, TPK; Manuscript Preparation: SE, TPK and Critical Review: SE, TPK.

Conflict of interest

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Comparison of patients with chronic and episodic migraine with healthy individuals by brain volume and cognitive functions

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ABSTRACT

Objectives: Migraine is a complex neurological disease. In addition to headache, individuals with migraine may develop structural changes inside the brain and cognitive impairment. There is increased evidence associated with impairments in brain volume and cognitive functions in patients with migraine. The present study aimed to investigate the impairment in memory function in individuals with migraine using brain magnetic resonance imaging, volume measurement, and neuropsychological tests.

Methods: The study included 20 patients with episodic migraine, 20 patients with chronic migraine, and 20 healthy controls. Subcortical volumes of all participants were measured by FreeSurfer, an automatic segmentation method. The Wechsler Memory Scale-Revised Form (WMS-R), Stroop test, Raven's Standard Progressive Matrices, Verbal Fluency Test, and Lines Orientation Test were applied in all the study participants.

Results: Putamen volume decreased as migraine duration increased, and subcortical gray matter, left cerebellar cortex, and bilateral thalamus volumes were lower in the chronic and episodic group compared to the control group, bilateral putamen and right cerebellar cortex volumes were lower in patients with chronic migraine compared to patients in episodic migraine and control groups. Upon neuropsychological examination, delayed memory was affected as the duration of migraine increased, and there was impairment in patients with chronic migraine upon fluency tests and mental control tests.

Conclusions: Changes in subcortical volume and cognitive effects in patients with migraine raise questions about whether migraine qualifies as a benign disease. Structural changes and cognitive impairment may contribute to migraine-associated disability, and therefore, these causalities should be investigated by future studies. Silent infarcts, white matter damage, and cortical spreading depression, which occur in migraine cases, may be associated with subcortical volume changes and thus, cognitive effects. In the context, studies with larger samples to achieve a better understanding are needed.

Keywords: Migraine, subcortical gray matter volume, Freesurfer, cognition

Migraine is a type of primary headache characterized by episodic attacks and accompanied by different levels of neurological, gastrointestinal, and autonomic symptoms. For women and men, the lifetime prevalence was reported as 18% and 6%, respectively [1]. Migraine was re-

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ported as the primary cause of disability and suffering across the world [2]. Chronic migraine is defined by occurrence of 15 or more headaches per month for a prolonged duration of more than 3 months without drug overuse. It was reported that the risk of developing chronic migraine in patients with episodic migraine is 2.5% [3, 4]. The vascular theory is considered as the earliest theory on migraine pathophysiology. It suggested that migraine aura was associated with vasoconstriction in intracranial vessels, where headache was due to vasodilation [5]. Today, neurovascular theory has adopted with regard to migraine pathophysiology. This theory suggests that vascular changes are associated with neuronal events, including cortical hyperexcitability due to abnormal neurotransmitter release, and abnormal neuronal firing [6]. Accordingly, it was suggested that abnormal neuronal excitability in the cerebral cortex, cortical spreading depression (CSD), and sensitization of the trigeminovascular system were involved in the pathophysiology of migraine. A number of previous studies reported that central and peripheral systems had effects on the trigeminal system as regard the occurrence of pain [7, 8]. With a better understanding of migraine pathophysiology, questions about whether migraine qualified as a benign disease emerged and a number of studies investigated the brain morphology of individuals with migraine to see whether it caused brain damage and whether it was associated with deterioration of cognitive functions in patients with migraine.

A range of neuroimaging methods were accommodated to elucidate the structural and functional changes in the brain regions of patients with migraine. Magnetic resonance imaging (MRI) and positron emission tomography were used to investigate the structural and functional changes, respectively [9, 10]. Cranial MRI examinations in patients with migraine typically indicated multiple, small, punctate hyperintense lesions in the deep white matter and periventricular localization on T2 and FLAIR-weighted images, where these lesions might be associated with local demyelination and gliosis [11, 12]. It was reported that the incidence of silent posterior circulation infarcts, hyperintense ischemic lesions in the cerebellum and brain stem was increased in individuals with migraine. Hyperintense white matter lesions in those individuals were attributed to oligemia, focal brain hypoperfusion, and critical hypoperfusion in small penetrating arterioles during migraine attack and aura [13]. Voxel-based morphometry (VBM) method was generally used in volume studies in patients with migraine [14]. Certain studies in the last decade used the FreeSurfer method, an automated MRI tissue segmentation method, to investigate the pathophysiology of migraine and the resultant structural changes by measuring the volume of specific brain regions in individuals with episodic and chronic migraine [15, 16].

Subjective cognitive impairment is expected in migraine cases. Individuals with migraine complain about cognitive deterioration, including impaired attention and memory. Difficulty in thinking, distraction, feeling of slowing down, and difficulty in speaking may be seen during the prodromal period, at the headache stage. Reversible cognitive disorders were reported during or after a migraine attack [17, 18]. Previous studies, which investigated the cognitive functions in patients with migraine during the non-attack period, reported inconsistent results. Certain studies found no cognitive difference between individuals with migraine and healthy individuals, where it was suggested that there was an association between migraine and dementia due to the impairment in cognitive functions during pain attack and non-attack period [19-23]. Silent infarcts and white matter lesions in individuals with migraine might be associated with stroke and cognitive disorders [13, 24].

The present study aimed to investigate impairment in memory function in patients using brain MRI volume measurements and neuropsychological tests during the non-attack period in order to demonstrate the brain damage associated with migraine.

METHODS

The study included 20 patients with episodic migraine, 20 with chronic migraine, and 20 healthy controls. They were followed up at the Headache Outpatient Clinic of Uludag University Faculty of Medicine and classified pursuant to the classification as prescribed by the Headache Classification Committee of the International Headache Society. Prior approval for the commencement of the study was obtained from the Medical Research Ethics Committee of Uludag University Faculty of Medicine upon its decision dated January 25th, 2011, No. 2011-3/21. Informed consent

forms were obtained from all patients and healthy controls. Patients aged 20-55 years, with normal results from vitamin B12 and thyroid function tests and neurological examination, with a Beck Depression Inventory score of <17, a Mini-Mental State Examination score of >24 points, without any systemic disease, and healthy controls were included in the study. The main demographic characteristics of the patients and the control group were age, sex, and educational level (patients with the same educational level were included). Disease-associated variables, including age at the onset of migraine headache, age at diagnosis, number of painful days during a month, subcortical brain volume measurement, and neuropsychological tests were evaluated. The patient group was divided into three groups: patients with <5 headache-days/month, patients with 5–15 headache-days/month, and finally patients with ≥15 headache-days/month. Accordingly, patients with ≥15 days of headache/month were included in the chronic migraine group.

Morphometric Evaluation

The brain MRIs of the patients were performed with 1.5 tesla MRI in volume sequence, and the DICOM format images were then transferred to a computer with Linux operating system. Morphometric analysis was performed by an expert neuroradiologist based on the FreeSurfer (surface-based morphometry) software (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki). Unclear images associated with patients moving during the procedure were corrected, and glare caused by variations in the B1 magnetic field was removed. The images were placed in the Talairach coordinate system and the volumes of forty-seven subcortical brain regions were measured in each patient. The measured brain regions are presented in Table 1. These values were divided by the total brain volume of the individual and head circumference sizes were excluded. The volumes of the regions were used for statistical analysis.

Neuropsychological Evaluation

All participants received neuropsychological tests as administered by the same expert psychologist and the relevant brain regions were evaluated. The neuropsychological tests in question are given in Table 2 and the evaluated brain regions are presented in Table 3.

Statistical Analysis

The Shapiro–Wilk test was used to test the normal distribution hypothesis. Accordingly, for the purposes of comparing normally distributed quantitative data between individuals in the episodic migraine, chronic migraine, and control groups, one-way analysis of variance and the least significant difference test multiple comparison tests were used for normally distributed variables, where the Kruskal Wallis test and Dunn's paired comparison test were used for variables without normal distribution. The correlation between quantitative variables was tested using the Spearman correlation coefficient. A correlation coefficient between 0.8 and 1was considered indicative of a very strong relationship, where values between 0.6 and 0.8 indicated a strong relationship, those between 0.4and 0.6 indicated a moderate relationship, and those between 0.2 and 0.4 indicated a weak relationship (reference). For the purposes of descriptive statistics, numerical variables were presented in mean ± standard deviation for normally distributed variables, where median [min-max] was used for variables without normal distribution and number and % for categorical variables. Windows version 24.0 of Statistical Package for the Social Sciences (SPSS 25.0, IBM Corporation, Armonk, New York, United States) software was used for statistical analysis and a p level of <0.05 was considered statistically significant.

RESULTS

The study included 20 (33.3%) patients with episodic and 20 (33.3%) patients with chronic migraine, and 20 (33.3%) healthy controls. Of the patients, 68.3% (n=41) were female and 31.7% (n=19) were male. The mean age of all the patients was 34.90±6.95 years (range 2253 years). The migraine duration was 6.90 ± 5.05 years and ranged 1-20 years. Of the patients with migraine, 14 had <5 days with headache, 6 had 5–15 days with headache, and 20 had ≥15 days with headache per month. There were no intergroup statistical difference by sex, age, and educational level.Demographic and clinical characteristics of the patients are presented in Table 4.

Intracranial and subcortical volume measurements based on the FreeSurfer method were compared be-

Table 1. Comparison of volume values between episodic migraine, chronic migraine and control groups

	Episodic	Chronic	Control	P value
i.volume	1459854.81±164271.42	1424297.61±103205.39	[a,b]1578758.27±141019.1	**0.002**[*]
SGM	188782 [143999-206526]	177283 [160258-205427]	[a,b]191829.5 [162598-224985]	**0.010**[+]
3.vent	980 [653-2193]	951 [600-1732]	1019.5 [629-1806]	0.966[+]
4.vent	1346 [937-2257]	1663 [1114-2592]	1608 [830-2563]	0.272[+]
Brainsystem	21305.26±2378.72	19856.86±2216.41	[b]22349.5±2742.28	**0.007**[*]
CSF	941 [724-1736]	1072 [788-1483]	1032 [760-1542]	0.497[+]
wmhipo	1182.42±402.08	1106.05±348.27	[b]1410.35±428.93	**0.045**[*]
nonwmhipo	14 [7-44]	14 [5-41]	14.5 [6-36]	0.851[+]
Optchiazma	247.58±75.66	243.38±90.21	254.95±65.71	0.892[*]
CC pos	921 [719-1214]	897 [761-1298]	983.5 [556-1165]	0.777[+]
Cc cent	502.79±136.23	437.62±73.58	510.15±97.6	0.058[*]
CC ant	871.26±114.17	857.57±116.07	917.15±154.33	0.316[*]
l.lat.vent	4561 [1721-16337]	6293 [1981-9445]	4854.5 [2370-16915]	0.115[+]
r.latvent	4366 [1538-12244]	4061 [2204-9581]	4786.5 [2602-11234]	0.329[+]
l.cerbwm	13698.11±2760.49	13778.67±1411.24	14406.55±1617.88	0.476[*]
r.cerebwm	13731.16±1667.24	13494.67±1351.87	13971.35±1304.68	0.576[*]
l.cereb ktx	50831.16±8536.96	51437.29±4005.12	[a.b]56011.05±6191.49	**0.027**[*]
r.cereb ktx	52860.74±5861.54	52222.38±4834.59	[b]56452.05±6282.37	**0.046**[*]
l.talamus	7214.16±744.83	6856.29±531.54	[a,b]7783.3±762.41	**0.001**[*]
r.talamus	7364.53±695.38	7054.95±591.16	[a,b]7906.15±906.33	**0.002**[*]
l.caudat	3664.68±413.11	3565±258.2	3725.1±476.66	0.421[*]
r.caudat	3560±376.06	3511.67±330.28	3701.25±458.29	0.284[*]
l.putamen	5422.11±680.72	5176.62±406.58	[b]5697±631.87	**0.021**[*]
r.putamen	5025.21±591.84	4811.86±446.22	[b]5279.05±580.8	**0.028**[*]
l.pallidum	1616.53±215.81	1567.33±131.78	1636.8±196.88	0.464[*]
r.pallidum	1458.58±169.04	1423.9±143.67	1509.6±186.64	0.265[*]
l.hipokamps	4235 [3517-5340]	[a]3859 [3-4272]	[b]4344.5 [2381-4916]	**<0.001**[+]
r.hipokamps	4243 [3284-5368]	[a]4032 [3405-4512]	[b]4423.5 [3868-4829]	**0.004**[+]
l.amgdala	1509 [1309-2051]	1446 [1089-1649]	1584.5 [622-1901]	0.058[+]
r.amgdala	1494 [1275-2185]	[a]1482 [1192-1679]	[b]1627.5 [1339-1929]	**0.020**[+]
l.accumbens	566.05±88.96	527.62±57.01	580.4±70.86	0.064[*]
r.accumbens	553.95±107.27	510.76±66.25	562.65±88.29	0.139[*]

Data are shown as mean±standard deviation or median [minimum-maximum]. i.volume=intracranial volume, SGM=subcortical grey matter, optchiazma=opticchiazma, 4-3 Vent=4-3. Ventricule, CSF=cerebrospinal fluid, Wmhipo=White matter hipodansite, Non WM Hipo=Non-White matter hipodansite, CC pos, cent, ant=Corpus callsoun poterior, central, anterior, lat. Vebt=latreal ventricule, cerebwm=cerebellar white matter, cereb ktx=cerebellar cortex

The values in bold face are given significance P<0.05.

[+]Kruskal Wallis test, [*]One Way ANOVA

[a]Differences with Episodic group.

[b]Differences with Chronic group.

Table 2. Neuropsychological tets and functions it tests

Tests	Function Tested
Verbal memory process tests	Verbal memory
Wechsler Memory Scale (WMS) VI. sub test and delayed recalling	Visual memory
WMS IV A story, B story	Verbal memory and continuing the attention (logical memory)
WMS V subtests	Attention
WMS III.	Mental control
Fluency tests	Executive functions, preservation and memory eveluation
Line Direnction Determination Test	Measurement of visual spatial perception and orientation functions
Raven Standard Progressive Matrix Test (RSPM)	Measurement of regular accurate thinking, managentment of reasoning
Stroop	Response inhibition and category change (data processing speed)

tween the groups (Table 1). Intracranial volume, subcortical gray matter, left cerebellar cortex, left thalamus, right thalamus, left cerebellar cortex, left cerebellar cortex, left thalamus, and right thalamus volumes were similar in the episodic and chronic groups, whereas the same were significantly lower in the control group (P=0.002, P=0.010, P=0.027, P=0.001 and P=0.002, respectively). While brain stem, non-white matter hypointensity, left putamen, right putamen, and right cerebellar cortex volumes were similar in the episodic migraine and control groups, these same were significantly lower in patients with chronic migraine (P=0.007, P=0.045, P=0.046, P=0.021 and P=0.028, respectively). The left hippocampus, right hippocampus and right amygdala volumes of the subjects in the episodic migraine group were significantly lower than those in the chronic migraine and control groups, whereas the same were significantly lower in the chronic group compared to the control group (P<0.001, P=0.004 and P=0.020, respectively).

The volume values of the patients were compared between the groups formed on the basis of the number of painful days per month (Table 5). There was a statistically significant intergroup difference by the right amygdala and right accumbens values (P<0.05). The right amygdala volume was lower in patients with 5-15 headache-days/month compared to patients with <5 headache-days and ≥15 days of pain per month (P=0.028). Similarly, the right accumbens volume was

Table 3. Neuropsychological tests and related brain areas

Test name	Releated brain area	Cognitive process measured
Digit span learning	Temporal lob, hipocampus Limbic system, frontal lob	Learning, short-term memory
Wechsler memory scale	Temporal lob, hipocampus Limbic system, frontal lob	Attention, concentration, verbal memory, visual memory, immediate memory, delayed memory
Raven	Right hemisphere, parietal lob, common brain areas	Visual spatial perception, category changeability, working memory, abstraction and scrutinizing, general ability
Stroop testi	Frontal lob	Focused attention, response inhibition, rersistance againist destroying effect, data processing

Table 4. A distribution of demographic and clinical characteristics of participants

Group n (%)	
Episodic migraine	20 (33.3)
Chronic migraine	20 (33.3)
Controls	20 (33.3)
Sex n (%)	
Female	41 (68.3)
Male	19 (31.7)
Age (mean±SD)	34.90±6.95
Migraine Duration (mean±SD)	6.90±5.05
Number of Headache-days n (%)	
<5	14 (23.31)
5–15	6 (9.99)
≥15	20 (33.3)

SS: Standard Deviation

lower in patients with 5-15 headache-days/month compared to patients with <5 headache-days and ≥15 headache-days per month (P=0.034).

The correlation between the migraine duration and volume values were analyzed (Table-6). There was a weak, statistically significant negative correlation between migraine duration and right putamen values (r=−0.328; P=0.039). In other words, the right putamen volume decreased as the migraine duration increased.

Memory test results of the study participants were compared by groups (Table 7). There was a significant intergroup difference by the total number of animals named in the Animal Fluency test and the measurement values in the mental control test of counting down from 100 by 7's. The total number of animals named in the Animal Fluency test in the chronic migraine group was 20 [10-33], which was similar to 22 [14-33] in the episodic migraine group, while the same in the control group was 25.5 [16-37], which was indicative of a statistically significant difference (p = 0.047). Similarly, the time to count backward from 100 by 7's was 79 seconds [36-236] in patients with chronic migraine and 56 seconds [13-220] in patients with episodic migraine, whereas the same was 40.5 seconds [19-120] in the control group and it was a statistically significant difference (P= 0.010).

The total number of errors in the Animal Fluency test in individuals with 5 and 15 headache-days per month was 0.5 [0-2], which was statistically significant (P= 0.027), compared to 0 [0-1] in the group with <5 headache-days and 0 [0-2] in patients with chronic migraine with ≥15 headache-days (Table 8).

The relationship between the migraine duration and memory test results was analyzed (Table 7). There was a weak negative correlation between migraine duration and delayed memory values (r=-0.341; P=0.031). Delayed memory weakened as the migraine duration increased (Table 9).

DISCUSSION

A number of previous studies reported cortical and subcortical volume changes associated with migraine attacks and the effects of migraine on cognition. The present study combined volume measurement of subcortical structures and neuropsychological evaluation.

There are various segmentation methods for brain volume assessments using manual and automated techniques. Brain parenchymal fraction, which was used bya number of previous studies in the relevant literature, is defined as the ratio of brain parenchymal volume to the total intracranial volume. Considering the volumes as total intracranial volume only without proportioning to intracranial volume may lead to inaccuracies due to differences by ex and head diameters. The volume values in the present study were proportioned to the total intracranial volume values with an aim to eliminate the inaccuracies associated with interindividual head size variables.

Increasing number of neuroimaging studies measured brain volume in patients with migraine using different methods. While most of the studies investigated the episodic migraine group with comparatively fewer number of studies focused on patients with chronic migraine [14, 16, 25]. In this study, patients with episodic and chronic migraine, along with healthy controls were included, and the results were compared between the patient groups and healthy controls based on the FreeSurfer software [26], which featured higher accuracy rate compared to the manual technique.

In the present study, the intracranial volume, subcortical gray matter, left cerebellar cortex, and left thalamus and right thalamus volumes were lower in the migraine groups compared to the controls, never-

Table 5. The relationship between the number of painful days and volume values in the study participants

	Number of days of headache per month			
	<5	5-15	≥15	P value
i.volume	1457899.46±172294.67	1436821.36±49353.21	1425445.3±105676.06	0.778
SGM	181054.56±19115.17	179595.75±3112.13	177428±12273.86	0.780
3.vent	977.5 [600-2193]	1245 [670-1621]	945.5 [699-1732]	0.385
4.vent	1458.94±313.08	1611.5±571.58	1710.06±421.19	0.170
brainsystem	21226.22±2451.94	21427.25±601.28	19667.39±2331.45	0105
CSF	962 [724-1736]	1017 [828-1268]	933 [788-1483]	0.986
wmhipo	1142.28±395.01	1213.25±353.4	1126.61±371.18	0.919
nonwmhipo	14 [7-44]	23 [9-41]	13.5 [5-28]	0.495
Optchiazm	253.44±80.68	293.75±63.28	226.56±86.22	0.297
CC pos	922.61±163.17	943.25±111.26	928.61±128.9	0.966
Cc cent	502.72±141.15	432.25±84.41	442.5±71.19	0.216
CC ant	864.11±112.85	939.75±60.54	847.22±121.38	0.349
l.lat.vent	4683.5 [1721-16337]	6138 [2040-8484]	5864 [1981-9445]	0.349
r.latvent	4394 [1538-12244]	5621 [2906-6216]	3647 [2204-9581]	0.807
l.cerbwm	13602.39±2782.9	14967±2088.83	13605.83±1227.82	0.491
r.cerebwm	13745.72±1712.37	13361.5±1423.11	13522.83±1339.57	0.859
l.cereb ktx	50786.67±8742.87	51528.25±2154.94	51427.89±4329.17	0.952
r.cereb ktx	52839.22±5985.3	52877.25±2539.23	52133.83±5182.49	0.918
l.talamus	7201.72±772.43	6945.75±252.07	6868.72±571.57	0.314
r.talamus	7354.06±693.4	7342±445.42	7018.83±631.61	0.283
l.caudat	3647.83±424.31	3651.75±154.82	3568.11±277.34	0.767
r.caudat	3536.5±368.4	3632.75±297.03	3510.94±353.97	0.827
l.putamen	5384 [4221-7074]	5139.5 [4761-5285]	5077 [4832-6687]	0.463
r.putamen	5103.5 [4093-6408]	4738.5 [4579-4927]	4678 [4366-6289]	0.549
l.pallidum	1611.22±223.15	1523.75±107.04	1585.06±133.46	0.668
r.pallidum	1451.94±171.23	1397.25±140.68	1438.39±147.81	0.822
l.hipokamp	4252.11±507.27	3969.75±372.32	3646.06±937.65	0.057
r.hipokamp	4314.67±552.05	4107±225.87	3985.5±280.4	0.079
l.amgdala	1547.56±197.79	1415±38.65	1439.39±140.22	0.110
r.amgdala	1619.39±255.82	[a]1377±40.41	1470.11±131.24	**0.028**
l.acumbens	570.67±89.18	501.75±12.12	530.89±61.19	0.134
r.acumbens	565±95.97	[a]448±86.3	516.06±69.53	**0.034**

Data are shown as mean±standard deviation or median [minimum-maximum]. i.volume=intracranial volume, SGM=subcortical grey matter, optchiazma=opticchiazma, 4-3 Vent=4-3. Ventricule, CSF=cerebrospinal fluid, Wmhipo=White matter hipodansite, Non WM Hipo=Non-White matter hipodansite, CC pos, cent, ant=Corpus callsoun poterior, central, anterior, lat. Vebt=latreal ventricule, cerebwm=cerebellar white matter, cereb ktx=cerebellar cortex

Thevalues in bold face are given significance P<0.05.

[+]Kruskal Wallis test, [*]OneWay ANOVA

[a]Differences with <5.

[b]Differences with 5-15 group.

Table 6. The relationship between migraine duration and volume values

Migraine duration											
i.volume	r	-0.231	**optchia**	r	0.164	**l.cerb kor**	r	-0.151	**l.pallidum**	r	-0.100
	P	0.151		P	0.313		P	0.354		P	0.539
SGM	r	-0.191	**cc pos**	r	-0.008	**r.cerb kor**	r	-0.151	**r.pallidum**	r	-0.173
	P	0.238		P	0.963		P	0.353		P	0.285
P3. vent	r	-0.053	**cccent**	r	-0.110	**l.talamus**	r	-0.205	**l.hipokamps**	r	-0.116
	P	0.745		P	0.498		P	0.204		P	0.475
4. vent	r	-0.156	**cc ant**	r	-0.222	**r.talamus**	r	-0.303	**r.hipokamps**	r	-0.193
	P	0.337		P	0.168		P	0.057		P	0.232
Brain sysytem	r	0.057	**l.lat.vent**	r	0.070	**l.caudat**	r	-0.027	**l.amgdala**	r	-0.272
	P	0.726		P	0.666		P	0.871		P	0.089
CSF	r	-0.147	**r.lat.vent**	r	0.069	**r.caudat**	r	-0.128	**r.amgdala**	r	-0.088
	P	0.364		P	0.674		P	0.433		P	0.590
wmhipo	r	0.123	**l.cerbwm**	r	-0.113	**l.putamen**	r	-0.163	**Laccumbens**	r	-0.209
	P	0.450		P	0.486		P	0.315		P	0.196
nonwmhipo	r	0.057	**r.cerbwm**	r	-0.178	**r.putamen**	r	-0.328	**r.accumbens**	r	-0.279
	P	0.729		P	0.272		p	**0.039**		P	0.082

i.volume=intracranial volume, SGM=subcortical grey matter, optchiazma=opticchiazma, 4-3 Vent=4-3. Ventricule, CSF=cerebrospinal fluid, Wmhipo=White matter hipodansite, Non WM Hipo=Non-White matter hipodansite, CC pos, cent, ant=Corpus callsoun poterior, central, anterior, lat. Vebt=latreal ventricule, cerebwm=cerebellar white matter, cereb ktx=cerebellar cortex

r: Spearman correlation coefficient (n=40)

theless, there was no significant difference between the episodic and chronic migraine groups. Bashir *et al*. [14] reported low brain stem, left cerebellar cortex, and white matter volume in patients with chronic migraine. Consistent with the literature, the left cerebellar cortex volume was lower in the present study. Furthermore, brainstem and right cerebellar cortex volumes were lower in patients with chronic migraine compared to episodic migraine group and healthy controls. The brain stem is considered an important region for the pathogenesis of headache and migraine. Periaqueductal gray matter, trigeminal nerve, cuneiform nuclei, and their connections play a role in pain modulation. Balance disorder and vestibulocerebellar symptoms are frequent in patients with migraine. Previous VBM morphometric studies reported volumetric differences in the brainstem and cerebellum in patients with episodic migraine with aura, where functional MRI procedures indicated the association of periaqueductal gray matter and cuneiform nuclei with thalamus, cerebellum, insula, and cortex [27-29].

Volume loss in the brainstem and cerebellum may be associated with pain-related atrophy of pain nuclei in the brainstem, prolonged oligemia, posterior system hypoperfusion, and exposure to ischemia. As regards the pathogenesis of migraine, the thalamus is considered to transfer pain from the lower brain to the cortex via the trigemino-vascular pathway and has an important role in central sensitization, allodynia, and photophobia in migraine [30]. Shin *et al*. [15] measured the volumes of the thalamus and thalamic nuclei using the FreeSurfer method and reported the same thalamus volumes compared to healthy controls, yet found differences in volume between the thalamic nuclei. They found an increase in the volumes of medial geniculate nuclei and right anteroventral nucleus in the migraine

Table 7. A comparison of the results from memory tests between episodic migraine, chronic migraine, and control groups

	Episodic	Chronic	Control	P value
Raven reply	30.32±4.03	29.33±5.13	28.50±5.67	0.530*
Raven duration	307.16±63.23	301.52±80.75	288.85±93.36	0.766*
Stroop1	28 [22-40]	28 [21-39]	26 [19-37]	0.325+
Stroop2	39 [28-59]	39 [29-55]	38 [30-67]	0.784+
Stroop3	32 [23-50]	29 [23-71]	29 [22-39]	0.826+
Stroop4	69 [45-94]	67 [43-124]	72.5 [55-110]	0.324+
Stroop true reply	1 [0-4]	1 [0-10]	1 [0-10]	0.811+
Stroop wrong reply	0 [0-1]	0 [0-1]	0 [0-3]	0.981+
Fluency total number	22 [14-33]	20 [10-33]	[b]25.5 [16-37]	**0.047**+
Number of fluency errors	0 [0-0]	0 [0-2]	0 [0-0]	0.395+
Number of recalls per fluency repetition	0 [0-5]	0 [0-2]	0,5 [0-4]	0,532+
Error in even numbers	8.79±1.36	8.33±1.71	9.20±1.58	0.215*
fluency total number of errors	0 [0-1]	0 [0-2]	0 [0-2]	0.824+
fluency repetition	0 [0-1]	0 [0-2]	0 [0-2]	0.513+
Attention forward counting	5 [4-8]	5 [4-8]	5 [4-8]	0.073+
Attention countdown	4 [2-7]	4 [3-6]	4 [2-6]	0.430+
attention total	8 [6-15]	8 [7-14]	9 [7-12]	0.089+
MCcdd	5 [4-8]	5 [3-11]	4 [3-9]	0.671+
MCcdw	0 [0-0]	0 [0-0]	0 [0-1]	0.368+
MCcdm	13 [6-40]	13 [7-40]	14.5 [8-80]	0.265+
MCcmw	0 [0-2]	0 [0-2]	0 [0-2]	0,673+
MCcon	19 [9-70]	21 [6-56]	13,5 [6-32]	0,078+
MCcow	0 [0-4]	0 [0-5]	0 [0-2]	0.743+
MC counting by sevens	56 [13-220]	79 [36-236]	[b]40.5 [19-120]	**0.010**+
MC number of errors while counting by sevens	1 [0-6]	1 [0-9]	1 [0-7]	0.667+
MC total number	102 [59-302]	115 [65-314]	81.5 [46-172]	0.094+
MC total eror	1 [0-12]	1 [0-15]	2 [0-9]	0.957+
LMT İmmediate	14 [9-19]	15 [8-22]	16 [10-19]	0.842+
LMT delaying	14.47±3,13	13,67±3,71	14,35±3,53	0.728*
WMT instant memory	12 [6-14]	12 [5-14]	14 [5-18]	0.531+
WMPT immediate memory	6 [4-9]	6 [4-9]	7 [4-11]	0.649+
WMPT learning point	112 [90-134]	122 [80-152]	119.5 [76-141]	0.779+
WMPT reaching criteria	6 [0-9]	6 [0-10]	4.5 [0-10]	0.784+
WMPT highest learning	15 [12-15]	15 [10-15]	15 [10-15]	0.691+
WMPT learning eror point	0 [0-7]	0 [0-10]	1 [0-6]	0.228+
WMPT identifying	13 [9-15]	13 [0-15]	13 [10-15]	0.778+
WMPT total recalling	2 [0-5]	2 [0-13]	2 [0-5]	0.866+

Data are shown as mean±standard deviation or median [minimum-maximum]. MCcdd=Mental control counting down the days, MCcdw=Number of mistakes made while counting down the days, MCcdm=Duration of counting down the months, MCcon=Counting odd numbers, MCcow=Number of mistakes made when counting odd numbers, MCcmw=Number of mistakes made while counting down the days, WMT=Visual memory test, VMPT=Verbal memroy process test, LMT=Logical Memory Test

The values in bold face are given significance P<0.05.

+Kruskal Wallis test, *OneWay ANOVA

[a]Differences with Episodic group.

[b]Differences with Chronic group.

Table 8. The relationship between the number of headache-days and memory test values of the study participants

	Headache-days			
	<5	5-15	≥15	P value
Raven reply	30.22±4.12	31±1.41	29.11±5.51	0.674*
Raven duration	315.89±71.28	320.50±77.14	288.89±73.04	0.486*
Stroop1	28.5 [23-40]	26.5 [22-37]	27 [21-39]	0.797+
Stroop2	39.5 [28-59]	35.5 [31-50]	37 [29-55]	0.966+
Stroop3	32 [24-50]	31 [23-41]	28 [23-71]	0.798+
Stroop4	70 [45-94]	74 [56-92]	66.5 [43-124]	0.609+
Stroop true reply	1 [0-4]	0.5 [0-6]	1 [0-10]	0.788+
Stroop wrong reply	0 [0-1]	0 [0-0]	0 [0-1]	0.391+
Fluency total number	21.5 [14-33]	20.5 [14-33]	20.5 [10-29]	0.609+
Number of fluency errors	0 [0-0]	0 [0-0]	0 [0-2]	0.637+
Number of recalls per fluency repetition	0 [0-5]	0 [0-0]	0 [0-2]	0.147+
Error in even numbers	8 [6-12]	9.5 [8-10]	8 [5-11]	0.315+
fluency total number of errors	[a] 0 [0-1]	[b] 0.5 [0-2]	[a]0 [0-2]	**0.027**+
fluency repetition	0 [0-1]	0 [0-0]	0 [0-2]	0.637+
Attention forward counting	5 [4-8]	4 [4-5]	5 [4-8]	0.242+
Attention countdown	4 [2-7]	4 [3-4]	4 [3-6]	0.705+
attention total	8 [6-15]	8 [7-9]	8 [7-14]	0.625+
MCcdd	4.5 [4-8]	5 [4-5]	5 [3-11]	1.000+
MCcdw	0 [0-0]	0 [0-0]	0 [0-0]	1.000+
MCcdm	12.5 [6-40]	18.5 [10-23]	12.5 [7-40]	0.306+
MCcmw	0 [0-2]	0 [0-0]	0 [0-2]	0.495+
MCcon	17.5 [9-70]	24.5 [13-32]	21 [6-56]	0.442+
MCcow	0 [0-4]	0 [0-2]	0 [0-5]	0.476+
MC counting by sevens	56.5 [18-220]	76 [13-236]	76 [36-155]	0.966+
MC number of errors while counting by sevens	1 [0-6]	2.5 [0-6]	1.5 [0-9]	0.896+
MC total number	107 [59-302]	123.5 [62-314]	113.5 [65-239]	0.865+
MC total eror	1 [0-12]	3.5 [0-6]	1.5 [0-15]	0.762+
LMT İmmediate	14.5 [9-20]	12.5 [9-17]	15.5 [8-22]	0.305+
LMT delaying	26.5 [20-37]	28.5 [23-33]	30 [18-40]	0.701+
WMT instant memory	12.5 [6-14]	13 [10-14]	12 [5-14]	0.431+
WMPT immediate memory	6 [4-9]	6 [5-8]	6.5 [4-9]	0.542+
WMPT learning point	116.5 [90-134]	121.5 [111-128]	120.5 [80-152]	0.831+
WMPT reaching criteria	5.5 [0-9]	6.5 [0-8]	5.5 [0-10]	0.695+
WMPT highest learning	15 [12-15]	15 [13-15]	15 [10-15]	0.877+
WMPT learning eror point	0 [0-7]	0 [0-7]	0 [0-10]	0.804+
WMPT identifying	13 [9-15]	12.5 [12-15]	13 [0-15]	0.896+
WMPT total recalling	2 [0-5]	2.5 [0-3]	2 [0-13]	0.931+

Data are shown as mean±standard deviation or median [minimum-maximum]. MCcdd=Mental control counting down the days, MCcdw=Number of mistakes made while counting down the days, MCcdm=Duration of counting down the months, MCcon=Counting odd numbers, MCcow=Number of mistakes made when counting odd numbers, MCcmw=Number of mistakes made while counting down the days, WMT=Visual memory test, VMPT=Verbal memroy process test, LMT=Logical Memory Test

The values in bold face are given significance P<0.05.

+Kruskal Wallis test, *OneWay ANOVA

[a]Differences with<5.

Table 9. The relationship between the migraine duration and memory test values in the study participants

Raven reply	r	-0.338*	Fluency re Petition	r	0.010	MCcmw	r	-0.292	WMT instant memory	r	-0.187
	P	0.033		P	0.949		P	0.067		P	0.249
Raven duration	r	0.091	Error in even numbers	r	-0.150	MCcon	r	-0.023	WMPT 1	r	-.363*
	P	0.577		P	0.354		P	0.890		P	0.021
Stroop 1	r	0.179	Fluency total number of errors	r	-0.063	MCcow	r	-0.126	WMPT 2	r	-0.255
	P	0.269		P	0.700		P	0.437		P	0.112
Stroop 2	r	.320*	Number of recalls Per fluency repetition	r	0.110	MC counting by sevens	r	0.093	WMPT 3	r	-0.067
	P	0.044		P	0.500		P	0.568		P	0.679
Stroop 3	r	.333*	Attention forward counting	r	-0.196	MC number of errors while counting by sevens	r	0.038	WMPT 4	r	-0.058
	P	0.036		P	0.226		P	0.814		P	0.724
Stroop 4	r	0.072	Attention countdown	r	-0.018	MC total number	r	0.086	WMPT 5	r	0.082
	P	0.660		P	0.910		P	0.596		P	0.614
Stroop true rePly	r	-0.182	Attention total	r	-0.095	MC total number	r	0.001	WMPT 6	r	-0.112
	P	0.260		P	0.561		P	0.995		P	0.492
StrooP true rePly	r	-0.137	MCcdw	r	0.181	WMT instant memory	r	-0.089	WMPT 7	r	-0.341
	P	0.398		P	0.265		P	0.584		P	**0.031**
Number of fluency errors	r	-0.127	MCcdd	r	-0.039	mkags	r	-0.005	delayed memory	r	-0.086
	P	0.434		P	0.810		P	0.978		P	0.599

MCcdd=Mental control counting down the days, MCcdw=Number of mistakes made while counting down the days, MCcdm=Duration of counting down the months, MCcon=Counting odd numbers, MCcow=Number of mistakes made when counting odd numbers, MCcmw=Number of mistakes made while counting down the days, WMT=Visual memory test, VMPT=Verbal memroy process test, LMT=Logical Memory Test

r: Spearman correlation coefficient (n=40)

group and a decrease in the volume of bilateral parafasian nuclei [15]. The present study did not separately measure the volume of the thalamic nuclei, nevertheless, the left and right thalamus volumes were lower in the migraine group compared to the healthy controls. There was no difference between the migraine groups. The fact that the thalamus volumes were lower in patients with migraine was inconsistent with the result of a study of Shin *et al*. [15]. Changes in the acumbens, putamen, and hippocampus were reported in chronic pain cases [31, 32].

Subcortical gray matter volumes and morphologies in patients with migraine were also investigated by previous studies. Igor *et al*. compared subcortical gray matter volumes in patients with migraine with aura to healthy controls and found that bilateral globus pallidus and left putaminal volumes were lower in patients with migraine with aura. They found no correlation between migraine duration and frequency of attacks and subcortical gray matter structures [33]. For the purposes of the present study, the patients were not categorized as patients with or without aura, where the subcortical gray matter volume was lower in the migraine group compared to the controls, and bilateral putamen volumes were lower in the chronic migraine group. There was no difference between episodic patients with migraine and the healthy controls. Furthermore, the right putamen volume was lower in participants with longer migraine duration. The putamen is connected to the cerebral cortex, thalamus and brainstem, and it was shown that putamen volume decreased in patients with tension-type headache or lumbar disc herniation with non-migraine pain [34, 35]. The caudate and putamen form the dorsal striatum, receiving inputs from the cerebral cortex and thalamus, and the activation therein is involved in motor and cognitive functions [36].

Structural and functional changes occur in the hippocampus and amygdala, two limbic structures responsible for stress and adaptation, in cases of stress and chronic pain [37]. It was suggested that cortical spreading depression extended to the temporal neocortex to the lateral amygdala and affected CSD and amygdala activation, and that amygdala dysfunction might be associated with neuropsychological symptoms in the postdromal phase. It was suggested that amygdala was associated with pain, emotional and visual symptoms, and neuroendocrine homeostasis in migraine attacks [38].

Liu *et al*. [39] reported that bilateral amygdala and bilateral temporal gyrus functional connections increased in patients with chronic migraine compared to patients with episodic migraine. Maleki *et al*. [40] found that bilateral hippocampus volume was higher in the group with 1-2 headache-days per month compared to the group with 8-14 headache-days per month. In the present study, bilateral hippocampus volume was lower in patients with episodic migraine compared to the healthy controls. To avoid underestimation of hippocampus volumes due to depression, patients with depression were excluded in the present study based on the Beck Depression Inventory scores. Changes in hippocampus volume might be associated to the stress induced by migraine attacks. Furthermore, right amygdala volumes were lower in patients with episodic migraine compared to the control group in our study. Nuc. acumbens is a modulator of pain and has been the focus of interest in recent studies. It was suggested that this might to be related to its effect on the emotional state during migraine attack and decreased activation in the nuc. acumben during pain and decreased receptors in chronic pain occurred not only in migraine pain but also in other pain cases [32, 41]. Husoy *et al*. [34] investigated the volume and shape of the nuc. acumbens in patients with migraine and found a decrease in volume and change in shape. The present study compared the headache frequency and volumes, and accordingly, the right amygdala and right nuc. acumbens volumes of the group with 5-15 headache-days were lower compared to the groups with <5 headache-days/month and ≥15 headcahe-days/month. The fact that nuc. acumbens volume was lower in the group with 5-15 headache-days/month compared to the group with <5 headache-days/month is consistent with results reported in the relevant literature. It was an interesting result that the right amygdala and right acumbens volumes were lower in the episodic migraine group compared to the chronic group and that the comparatively low number of patients might have accounted for this result. Further studies with larger samples may report different results upon analysis of those volumetric values. All these changes in subcortical structures raise the question of whether cortical spreading depression leads to atrophy in the most vulnerable subcortical structures.

Depression, anxiety, and education level affect

cognition. Therefore, in the present study, individuals with depression that might affect cognitive tests were excluded from the study and groups with the same level of education were included with an aim to rule out errors associated with education in the course of the neuropsychological evaluation.

Patients with migraine, who had volumetric changes in brain, may also have impaired cognitive functions. Previous studies reported inconsistent results in that regard. While certain studies did not report any cognitive impairment associated with migraine, some others suggested that there was a decrease in various cognitive functions, including sensorimotor function, attention, information formation, language, and memory, and other reported that scores from recent memory tests were lower, processing speed was slower, information formation was less, and verbal memory was poorer in patients with migraine. It was emphasized that general cognitive performance was not impaired in patients with migraine but verbal memory tests indicated impairment [21, 42-44]. In a study on Danish twins, there was no difference between twins with and without migraine by fluency, word recall, and number sequence learning test [21]. In the present study, there was no intergroup difference by scores from the number sequence learning test, which measured verbal memory, where the total number of animals that could be named in the Animal Fluency test, which evaluated attention and concentration, was lower in the migraine group compared to the control group. As per the mental control tests, the number of errors in the test of counting backward in 7's was higher in the migraine group. There was no difference between patients with episodic and chronic migraine vis-à-vis both tests.

A meta-analysis by Gu *et al*. [45] reported that cognitive function and language function were lower in the migraine group compared to the non-migraine group, while there was no difference by visuospatial function, attention, executive functions, and memory. In the present study, there was no intergroup difference by visual memory, attention and executive functions consistent with the results reported in the relevant literature.

Previous studies suggested that patients with migraine for prolonged periods and frequent attacks might have impaired memory and attention, and prolonged visual-motor speed [46]. In the present study, delayed memory decreased as the migraine duration increased, and the number of errors made in the Animal Fluency test was higher in the migraine group with 5-15 headache-days/month compared to the other groups. It was an interesting result that the group with ≥15 headache-days per month was more successful. This inconsistent result may also be associate with the comparatively low number of patients included in this study. The inconsistencies among studies, which did not investigate the relationship between migraine and cognition, might be due to certain factors, including age, sex, migraine duration, attack frequency, attack duration, physical performance, sleep quality, comorbid depression, and anxiety.

CONCLUSION

In conclusion, primary and secondary somatosensory cortex, prefrontal, insular, anterior cingulate and thalamus play major roles in acute pain. To a lesser extent, the basal ganglia, hippocampus, amygdala, cerebellum, temporal, and parietal cortex are involved in acute pain [28, 40, 47]. Neuroimaging results indicated anatomical and functional connections and the occurrence of a number common structures in pain and memory networks. The sensory and emotional characteristics of pain overlap with memory centers. Memory disorders may occur as a result of the processing of pain inside the brain [48, 49].

Migraine is considered a complex neurological disease involving many regions in the brain and it has been suggested that migraine may lead to permanent central nervous system dysfunction, atrophy in neocortical structures, including hippocampus and amygdala, cerebellum, subcortical gray matter, and cognitive impairment. Despite a number of studies in the relevant, the pathophysiology of migraine, changes in the brain, and possible cognitive impairments have not yet been fully understood. There is a requirement for future studies with larger samples to compare neuroimaging results and cognitive functions with clinical parameters, including attack frequency, attack severity, disability rate, medication use, and depression and anxiety in patients with migraine.

Ethical Statement

This study was conducted in accordance with the

ethical principles stated in the "Declaration of Helsinki" and approved by the Bursa Uludag University Clinical Research Ethics Committee (Date of Approval: 25/01/2011; Protocol No: 2011-3/21).

Authors' Contribution

Study Conception: DKŞ, MZ, BH, NK, NT; Study Design: DKŞ, MZ, BH, NK, NT; Supervision: MZ; Funding: DKŞ, MZ, BH, NK, NT; Materials: DKŞ, BH; Data Collection and/or Processing: DKŞ, MZ, BH, NK, NT; Statistical Analysis and/or Data Interpretation: DKŞ, MZ, BH, NK, NT; Literature Review: DKŞ, MZ, BH, NK, NT; Manuscript Preparation: DKŞ, MZ, BH, NK, NT and Critical Review: DKŞ, MZ, BH, NK, NT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Availability of data and materials

The authors agree with sharing, copying, and modifying the data used in this article, even for commercial purposes, so long as appropriate credit is given, and possible changes are indicated. Ethics approval and consent to participate The present study was approved by the Ethics Committee of Uludag University Faculty of Medicine, Bursa, Turkey

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Acute vestibular syndrome accompanying middle cerebral artery infarctions: a single-center study

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ABSTRACT

Objectives: Acute vestibular syndrome (AVS) is a disease and disorder usually manifest with a single episode of sudden onset vestibular symptoms and signs, and may occur at any point along the vestibular pathway from the peripheral labyrinth to the vestibular cortex. This study presents the characteristics of the involved cortical area and clinical course in middle cerebral artery (MCA) territory infarction patients with central vestibular disorder.

Methods: Files of patients diagnosed with acute ischemic stroke in the MCA territory were reviewed retrospectively between December 2020 and March 2022. All the patients were categorized into two groups (with or without AVS) and analyzed for comorbidities as well as smoking and drinking habits, and their data pertaining to the neurological examination, bedside neuro-otological examination, and laboratory and computerized tomography angiography findings were collected.

Results: Seven hundred and sixty-eight patients with MCA territory infarction were included in the study. AVS incidence was calculated to be 13.3%. There was no statistically significant difference in the distribution of age and sex between patients with and without AVS. The involvement of the right side was significantly more prevalent in AVS patients. Distribution of patients with right-sided infarction: 11 with posterior superior temporal gyrus 17 with parieto-insular cortex, 16 with insular cortex and temporoparietal junction together, and 18 with more than one millimetric infarction in all three areas.

Conclusions: Patients with acute vestibular syndrome, may have infarctions in the anterior circulation and most of them had no pathological neuro-otologic test findings.

Keywords: Acute vestibular syndrome, anterior circulation, middle cerebral artery, stroke

Stroke is one of the most important causes of disability and mortality in all populations and ranks second among the causes of death globally. Treatment and rehabilitation costs and the disability it causes in patients have significant impacts on society. Symptoms of stroke depend on which brain region is affected. That said, the symptoms can generally be categorized as cognitive, motor, sensory, and autonomic effects. Approximately 87% of all strokes are of ischemic character [1, 2]. Investigation of the epidemiology of ischemic stroke subtypes revealed 30.2% cardioembolism, 25.8% small artery occlusion, and 15.3% large artery atherosclerosis [3].

In acute stroke patients, vestibular syndrome and vertigo are rare clinical characteristics. Vertigo is the impairment of the static gravitational orientation and

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is described as a specific type of headache characterized by a sensation of spinning or tilting accompanied by nausea/vomiting and imbalance. Dizziness, on the other hand, denotes an impaired spatial orientation without distorted self-motion. Together, they are the third most common main symptom in general medical clinics where they represent 3-5% of all visits, and studies have reported the ratio of vertigo and dizziness in all stroke patients to be from 2.7% to 3.2% [1, 4]. Anatomically, acute vestibular syndrome (AVS) may occur in any point along the vestibular pathway from the peripheral labyrinth to the vestibular cortex. While isolated vertigo or dizziness supports posterior circulatory disorders, some studies have shown that anterior circulation may also be affected [5].

The vestibular cortex in humans has yet to be precisely located. It is assumed that the vestibular cortex is represented in the bilateral parieto-insular cortex with the right hemisphere dominance [6]. The 2012 coordinate-based activation likelihood estimation meta-analysis revealed vestibular activation in the bilateral insula, retroinsular cortex, inferior parietal lobe, superior temporal gyrus, caudal section of the anterior cingulate gyrus, and precuneus [7]. Its clinical characteristics in this specific localization are contralesional lateropulsion and speech impediment without nystagmus or any other brainstem symptoms [8].

AVS is relatively rare following middle cerebral artery (MCA) infarctions. MCA supplies blood to the cortical areas which are the core areas for the central vestibular symptoms. This study presents the characteristics of the involved cortical area and clinical course as shown by diffusion-weighted imaging (DWI) in MCA territory infarction patients with central vestibular disorder.

METHODS

Patient Group

Files of the patients above 18 years of age admitted as inpatients to the Stroke Unit, at Ümraniye Training and Research Hospital, Neurology Clinic between December 2020 and March 2022 with the diagnosis of acute ischemic stroke were retrospectively reviewed. Axial MR images from the medulla to the cortex taken at admission with a slice thickness of 5 mm and fluid-attenuated inversion recovery (FLAIR), DWI, and Apparent diffusion coefficient (ADC) sequences were scanned, and patients diagnosed with an acute cerebral ischemic lesion in the MCA territory with the help of DWI were categorized into two groups, i.e., with and without vestibular symptoms. All the patients were analyzed for comorbidities as well as smoking and drinking habits, and their data about the neurological examination, bedside neuro-otological examination, and laboratory findings were collected.

Characteristics such as age, sex, and demographics were evaluated between the groups, as well as the clinical characteristics and the involved cortical area characteristics in the group with vestibular symptoms. The computerized tomography angiography (CTA) performed at admission covers the main branches and the trunk of the anterior and posterior circulation in the cervical and cranial segments of the cerebral circulation beginning from the aortic arch, and also the whole circle of Willis. Stenosis of the symptomatic carotid artery or the vertebral basilar artery is defined as the decrease in the diameter of the carotid or vertebral basilar artery by over 50% at a location thought to be responsible for the patient's acute infarction or clinical symptoms.

Patients with previous vertigo and dizziness attacks, patients with previous ischemic or hemorrhagic stroke with concurrent infarctions in other artery watersheds, and patients with additional neurological disorders that may lead to vestibular syndrome (vertebral basilar artery stenosis, migrainous vertigo, advanced cervical spondyloarthritis, multiple sclerosis, etc.) were excluded from the study. Due to the retrospective nature of this study, the requirement of informed consent has been waived.

The Ethics Committee of the Ümraniye Training and Research Hospital approved the present study with its letter of decision no. 112 and date: 28.03.2024.

Statistical Analysis

Data analyses were performed using the SPSS software statistical package (version 20; SPSS Inc, Chicago, IL, USA). The χ^2 test was used for comparisons of qualitative data, the Mann-Whitney U test was used for numerical data. P values <0.05 were considered to indicate statistical significance. All numeric values are presented as the means ± standard deviation (SD).

RESULTS

Of a total of 1,371 patients diagnosed with acute ischemic stroke, 768 patients with MCA territory infarction were included in the study. AVS incidence was calculated to be 13.3% among the included patients. There was no statistically significant difference in the distribution of age (P=0.9) and sex (P=0.62) between 102 patients with AVS (66 males: 64.7%, mean age: 67.06±1.2 years) and 666 patients without AVS (414 males: 62.16%, mean age: 67.23±0.46).

Concerning comorbidities, hypertension (HT) was found in all the patients with AVS, whereas the ratio of the presence of HT alone was 18.92% in the non-AVS group. While the presence of HT alone did not create a statistical difference, it was seen statistically more commonly in the AVS group when it coexisted with other risk factors (P<0.001). It was further found that the presence of diabetes mellitus (DM) both alone and with other comorbidities was significantly higher in the non-AVS group (P=0.001). While smoking was higher in the non-AVS group, drinking was significantly higher in the AVS group (P=0.018).

62 patients (60.79%) in the AVS group and 308 patients (46.25%) in the non-AVS group had infarction of the right side (P=0.006), which meant that the involvement of the right side was significantly more prevalent in AVS patients. While the primary sensory cortex was the common area of involvement in only 7 out of 40 patients with infarction of the left side in the AVS group, of 62 patients with infarction of the right side, 11 had the posterior superior temporal gyrus and 17 had the parieto-insular cortex involved separately, whereas 16 had the insular cortex and the temporoparietal junction

Table 1. Demographical and clinical features of patients with and without AVS

	Patients with AVS (n=102)	Patients without AVS (n=666)	P value
Age (years)	67.06±1.2	67.23±0.46	0.6
Gender, male/female, n (%)	66/36 (64.7/36.3)	414/252 (62.2/38.8)	0.9
Side of infarction			
Left	40	358	**0.006**
Right	62	308	
CT Angiography, n (%)			
Normal	24 (23.53)	90 (13.5)	**0.01**
<50% stenosis	48 (47.06)	324 (48.65)	0.83
>50% stenosis	30 (29.41)	120 (18.05)	**0.007**
Advanced IC stenosis	0	132 (19.82)	**<0.001**
Size of infarction (%)			
Total	0	48 (7.21)	**<0.001**
Division	2 (1.96)	204 (30.63)	**<0.001**
Cortical branch	52 (50.98)	246 (36.94	
Milimetric	48 (7.21)	168 (25.23)	
Comorbidities, n (%)			
Hypertension	102 (100)	534 (80.18)	**<0.001**
Diabetes mellitus	42 (41.18)	390 (58.56)	**0.001**
Smoking	54 (52.94)	450 (67.57)	**0.004**
Alcohol using	24 (23.53)	96 (14.42)	**0.018**

Data are shown as mean±standard deviation or n (%). AVS=Acute vestibular syndrome, IC=Internal carotid artery, CT=Computed tomography

involved together, and the remaining 18 had multiple millimetric infarctions in all of these three areas.

When the infarctions of the study patients were categorized by size in the MCA territory as total, division, cortical branch, and millimetric infarctions, division, and total infarcts were significantly higher in the non-AVS group (P<0.001), whereas there was no such difference with other sizes.

The CT angiography images were categorized into 4 subgroups, i.e., normal, <50% ICA stenosis, >50% ICA stenosis, and advanced intracranial stenosis. All patients with advanced ICA stenosis were in the non-AVS group, and no difference was found between the two groups in terms of <50% stenosis. The statistically significant differences were found in patients with normal CTA and >50% stenosis in the AVS and non-AVS groups, and both subgroups were higher in the AVS group. These findings are summarized in Table 1.

With or without an accompanying AVS, none of the patients had any pathological neuro-otologic test findings such as a positive head impulse test, nystagmus, or skew deviation.

DISCUSSION

While the somatosensory system regulates the proprioceptive information, the visual system provides information concerning the location of the body in relation to the outer environment, and the vestibular system supplies constant information about the movements and positions of the head and the neck. When the functions of this sensory trio are impaired, dizziness, nausea, sensation of imbalance, and sometimes nystagmus, occur.

Receiving somatosensory, visual, and vestibular inputs, the temporoparietal junction (TPJ) is defined as a large area encompassing the posterior superior temporal gyrus, angular gyrus, supramarginal gyrus, and parietal operculum. There are three posterior cortical areas processing vestibular signals: the parieto-insular vestibular cortex (PIVC), a subunit of TPJ, encodes the vestibular signals concerning the position and the movements of the head; the ventral intraparietal (VIP) area integrates spatial information from various sensory modalities encoding the area on the coordinates originating from the peripheral sensory system; and the medial superior temporal (MST) area integrates the vestibular and visual signals required for the sensation of self-motion [9].

Dizziness is one of the most common complaints in the general population with a reported annual incidence of 22.9%, and approximately 30% of dizziness is non-organic [10]. According to the International Classification of Vestibular Disorders, it is defined as a sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion. The ICVD defines vertigo as a sensation of self-motion (of head/body) when no self-motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement. Both definitions appear under the title of symptoms and signs in the first layer of the Classification. The syndrome subheading in the second layer of the Classification discusses acute vestibular syndrome, and defines it as diseases and disorders that usually manifest with a single episode of sudden onset vestibular symptoms and signs (e.g. vestibular neuritis or acute stroke) [11].

A retrospective study using the patient records of 5 years from a single site determined the frequency of vertigo among cerebrovascular disorders to be 17% [12]. Another study investigating the presence of stoke in acute vestibular syndrome in 86 patients found that 27% of the patients with AVS also had strokes, and reported that there were no differences in DM, HT, CAD, AF, and hyperlipidemia between the peripherally and centrally induced ones [13].

Vertigo and dizziness are common signs, especially in the ischemia of the carotid region in the temporo-parietal area. A diffusion tensor tractography study in patients with MCA territory infarction observed a reduced tract volume in the core vestibular pathway leading to the parieto-insular vestibular cortex and showed that this reduction was associated with central vestibular disorder. Clinicians should give careful consideration to the investigation of anterior circulation vascular disease in patients presenting with vestibular symptoms [14, 15]. However, vestibular syndrome may not always manifest in the involvement of the cortical vestibular centers. It depends on the visual-vestibular interaction for the perception and orientation of motions. The result is affected by the situation of the hemisphere in which vestibular and visual inputs are in agreement and which determines the global perception of body orientation and motion [16]. Our interpretation of the lower incidence of AVS in

patients with larger areas of infarction in our study was that AVS might have been overlooked due to serious neurological signs and symptoms caused by the involvement of a large area, which might have also led to patients' failure to describe it. We believe that the fact that the infarction area was large in patients with advanced stenosis in the intracranial ICA and its branches similarly led us to find this subgroup significantly higher in the non-AVS group.

Studies show a correlation between DM, poor glycemic control in particular, and severe stroke and a large infarct volume [17]. While the subgroup analyses conducted in our study revealed that the presence of DM among the patients' risk factors did not have a statistically significant effect on the infarction size (P=0.075), it was found that patients with DM had mathematically larger infarction areas and more severe stroke characteristics. This may help explain our finding DM is higher in the non-AVS group. HT is a common risk factor for both cardioembolism and small artery occlusion, as well as large artery atherosclerosis, and previous studies have shown its correlation with the severity of stroke [18]. It is difficult to explain why our study found it in 80% of the non-AVS group patients while it was present alone or together with other risk factors in the AVS group; furthermore, it could not be associated with the anatomical localization of involvement. We think that this finding of our study should be verified by similar studies.

AVS induced by posterior circulation infarctions manifests with clinical signs relating to the involvement of the brainstem and cerebellum such as vertigo which lasts longer, may prevent mobilization, and is accompanied by nausea, vomiting, nystagmus, skew deviation, dysmetria, and ataxia [19]. However, we found only vertigo and dizziness accompanying the anterior circulation infarctions in the AVS patients we observed; these signs lasted up to 5 days in very few patients as we usually saw them resolve within the first 24 hours. Again, very few patients had accompanying nausea and vomiting severe enough to administer symptomatic treatment. We did not find posterior circulation or peripheral system vestibular abnormalities in any patients.

Lesions responsible for vestibular symptoms are usually located in the right hemisphere [20]. A study found that 42.6% of the patients presenting with DWI-positive acute and episodic vestibular syndrome had acute infarcts in the anterior circulation and that the most common area of involvement was the insular cortex with 22.1% [1]. Our study, as well, found the insular cortex to be the most commonly involved area, which was affected together with the parieto-temporal area in 17 patients. It has been found that AVS is the fifth most common symptom in the patients followed up for insular cortex infarcts and it is seen in approximately 50% of the patients suffering from the involvement of the right hemisphere. This ratio is 20% for the left hemisphere, and in support of this finding, our study showed that the involvement of the right hemisphere was significantly higher [21].

Limitations

Having been designed as a retrospective cross-sectional study limited to a single site, the study excluded patient files with incomplete data. It was not deemed necessary to perform cranial imaging in the patients again, and it was thought that some patients may have had accompanying posterior system infarctions or transient ischemic attacks.

CONCLUSION

In conclusion, it should be noted that in patients with acute vestibular syndrome, infarctions may develop in the anterior circulation, as well, and mostly no pathological neuro-otologic test findings will be obtained. Even though our study found comorbidities to be higher in the AVS group, extensive prospective studies are needed to show the relationship between the risk factors and AVS more clearly.

Ethical Statement

This study was conducted in accordance with the ethical principles stated in the "Helsinki Declaration" and was approved by the Ethics Committee of Istanbul Health Sciences University, Ümraniye Training and Research Hospital (Approval Date: 28/03/2024; Protocol No: 112).

Authors' Contribution

Study Conception: NKP; Study Design: NKP, GG; Supervision: NKP; Funding: N/A; Materials: NKP, GG, NKÇ; Data Collection and/or Processing: NKP, GG, NKÇ; Statistical Analysis and/or Data Interpre-

tation: NKP, GG, NKÇ; Literature Review: NKP, GG, NKÇ; Manuscript Preparation: NKP, GG and Critical Review: NKP, GG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Editor's note

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Risk factors for refractory patent ductus arteriosus to initial medical treatment in preterm infants

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ABSTRACT

Objectives: This study aims to identify risk factors and clinical markers for refractory patent ductus arteriosus to the initial medical treatment and determine appropriate treatment strategies. The goal is to define the newborns who will respond to treatment and to prevent patients from adverse effects of medical or surgical treatment of patent ductus arteriosus.

Methods: Preterm infants with hemodynamically significant patent ductus arteriosus and whose gestational age was under 30 weeks were retrospectively evaluated. Infants who responded to the initial medical treatment (paracetamol or ibuprofen) were compared to those non-responders. Neonatal characteristics and comorbidities were compared between the groups.

Results: Data from a total of 91 infants were analyzed. The mean gestational age was 27±1.9 weeks vs. 26±1.9 weeks (P=0.10), and birth weight was 1,056±290 vs. 974±318 g (P=0.61), respectively in responder and refractory groups. Success rates for patients treated with paracetamol (n=49) were 57.4%, while for those treated with ibuprofen (n=42), it was 42.6% (P=0.47). Echocardiographic findings such as ductal size 2.48±0.69 vs. 2.55±0.66 mm (P=0.75), and left atrium/aortic root ratio 1.73±0.4 vs. 1.64±0.25, (P=0.14) were also comparable. Incidence of severe intraventricular hemorrhage (22.7% vs 4.3%, P=0.009) and periventricular leukomalacia was significantly higher in the refractory group (53.1% vs. 22.2%, P=0.008).

Conclusions: Combining multiple risk factors into a clinical decision-making model or algorithm could enhance the predictive accuracy of treatment response. Moreover, ongoing monitoring and tailored treatment adjustments based on individual responses and side effects are crucial for effectively managing patent ductus arteriosus in preterm infants.

Keywords: Patent ductus arteriosus, preterm infants, treatment

Patent ductus arteriosus (PDA) is a persistent opening between the pulmonary artery and the descending aorta, a remnant of fetal circulation that typically closes shortly after birth. The ductus arteriosus may remain open in preterm infants, leading to increased pulmonary blood flow and decreased systemic perfusion. The ductus arteriosus is vital to fetal circulation, allowing blood to bypass the fetal lungs. After birth, the initiation of breathing leads to a decrease in pulmonary vascular resistance and an increase in systemic oxygen levels, triggering the functional closure of the ductus arteriosus within the first 24-48 hours in

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term infants [1-4]. However, in preterm infants, the physiological mechanisms responsible for ductal closure are often immature, resulting in a persistently patent ductus arteriosus. 70% of preterm infants under 28 weeks of gestation require medical or surgical closure of the ductus [1]. Treatment options for PDA include conservative management, pharmacological treatment, surgical ligation, or transcatheter ductal closure, though the optimal treatment strategy remains a topic of debate [5-7]. For PDA treatment, prostaglandin inhibitors, such as indomethacin, ibuprofen, or paracetamol, can be used medically [8]. Surgical ligation of the PDA is considered when pharmacological therapy is unsuccessful or contraindicated [6]. The management of PDA in preterm infants is complex and remains a topic of ongoing debate.

Low gestational age is the strongest risk factor for symptomatic PDA, and many perinatal variables, such as respiratory distress syndrome (RDS), have also been identified as risk factors for symptomatic PDA and poor response to pharmacological treatment [9-11]. PDA continues to be a challenging issue in the care of extremely low birth weight infants [12]. If hemodynamic instability due to PDA is not well managed, it can lead to spontaneous intestinal perforation, necrotizing enterocolitis, intraventricular hemorrhage, impaired renal function, bronchopulmonary dysplasia (BPD), and mortality due to left-to-right shunt impairing gastrointestinal, cerebral, and renal perfusion [8].

The optimal timing and approach for PDA treatment in preterm infants remain controversial. While early intervention may prevent complications associated with a significant PDA, it also exposes infants to the risks of treatment-related adverse effects. There is ongoing debate regarding the long-term outcomes of different management strategies, highlighting the need for further research and well-designed clinical trials. This study aims to identify risk factors for the lack of response to the first course of medical treatment for PDA and to determine appropriate treatment strategies. Thus, it is intended to prevent patients from being exposed to the adverse effects of hemodynamically significant PDA and surgical procedures.

METHODS

Between September 2019 and December 2022, preterm infants with a gestational age ≤ 30 weeks who were monitored in a tertiary neonatal intensive care unit were retrospectively evaluated. The infants were divided into two groups: those who responded to the initial medical treatment either with paracetamol or ibuprofen and those for whom the treatment failed, defined as the refractory group. Factors affecting treatment failure were analyzed. The PDA diagnosis was made based on echocardiography performed at 48-72 hours by a pediatric cardiologist. Hemodynamically significant PDA is diagnosed when the left atrium/aortic root (La/Ao) ratio is >1.5 and/or the ductus diameter is >1.5 mm [15]. Either ibuprofen or paracetamol therapy was administered at the physician's discretion who was giving the primary care. For those whose PDA did not close with medical treatment or for whom medical treatment was contraindicated, surgical ductal ligation was performed. PDA medical treatment failure was defined as the persistence of ductal patency on control echocardiography at the end of medical treatment. The oxygen requirement of the patients was evaluated on postnatal day 28, at 36 weeks postmenstrual age, and at discharge to diagnose BPD [16].

Based on our unit's standard respiratory support protocol, decisions regarding mechanical ventilation or non-invasive support were made, and surfactant was administered due to RDS. Turkish Neonatal Society Guidelines are strictly followed [17]. Cranial ultrasonography (USG) was performed on days 1, 3, and 7, and weekly cranial USG follow-up was conducted based on intraventricular hemorrhage (IVH) findings. IVH was graded according to the Papile classification, with advanced IVH defined as >Grade II [18]. Periventricular leukomalacia was defined based on a central cystic appearance on cranial USG [19]. The necrotizing enterocolitis (NEC) diagnosis was made based on laboratory, clinical, and radiological findings and staged according to the modified Bell criteria [20]. Retinopathy of prematurity (ROP) was staged according to the International Classification of Retinopathy of Prematurity following an examination by an ophthalmologist [21]. Sepsis detected within the first 3 days of life was defined as early neonatal sepsis and sepsis detected after 72 hours was defined as late neonatal sepsis [22]. Enteral and parenteral nutrition were managed according to Turkish Neonatal Society guidelines [23, 24]. Feeding intolerance was defined in the presence of clinical deterioration, abdominal ex-

amination findings (distension, tenderness, increased abdominal circumference, prominent bowel loops, noticeable or absent bowel sounds), vomiting, gastric residuals >50% and/or bloody residuals if checked, and changes in stool frequency [23]. Ethical committee approval was obtained for our study (E2-22-3045).

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago,

IL, USA) for Windows (version 25.0) at a significance level of 0.05. The data were analyzed

using numbers, percentage distributions, mean, and standard deviation. Normality was tested

using kurtosis and skewness coefficients. Pearson's chi-square test and independent samples t-test were used. The Mann-Whitney U test was used for nonparametric data.

RESULTS

Data from a total of 91 infants were analyzed. The mean gestational age in the treatment responder group was 27±1.9 weeks, while it was 26±1.9 weeks in the refractory PDA group (P=0.1). Birth weight was similar between the two groups (1,056±290 g vs. 974±318 g, P=0.61) (Table 1). Preeclampsia was significantly higher in the responders compared to the refractory PDA group (28.3% vs. 9.3%, P=0.03). Neonatal characteristics were similar between the two groups and were represented in Table 1.

Among the patients treated with paracetamol (n=49), the success rate was 57.4%, whereas it was 42.6% in those treated with ibuprofen (n=42); no statistically significant difference was found (P=0.47). Echocardiographic findings were similar between the two groups, such as the ductal size 2.48±0.69 vs. 2.55±0.66 mm (P=0.75) and La/Ao ratio 1.73±0.4 vs. 1.64±0.25 (P=0.14). The incidence of severe IVH and periventricular leukomalacia (PVL) was significantly higher in the refractory PDA group (22.7% vs. 4.3%, P=0.009; 53.1% vs. 22.2%, P=0.008) (Table 2).

Patients with lower admission white blood cell (WBC) and Large Unstained Cells (LUC) values had higher treatment success compared to those with higher values (7300±3697 vs. 9053±6158, P=0.014; 0.42±0.34 vs. 0.67±0.52, P=0.009). Patients with higher interleukin-6 values had better treatment responses than those with lower values (958.5±3131 vs. 178.9±279.9, P=0.009).

DISCUSSION

In this study, we evaluated the risk factors for refractory patent ductus arteriosus to the first course of medical treatment. Responders had higher rates of

Table 1. Demographics of patients by response to initial medical therapy in PDA

	No treatment response (n=44)	Treatment response present (n=47)	P value
Gestational age (weeks)	26 ±1.9	27±1.9	0.1
Birth weight (g)	974±318	1056±290	0.61
Gender (male)	24 (54.5)	22 (46.8)	0.46
Delivery type (CS)	42 (95.5)	45 (97.8)	0.53
Multiple pregnancy	14 (31.8)	15 (31.9)	0.92
Antenatal steroid therapy	20 (76.9)	17 (73.9)	0.8
Clinical chorioamnionitis	3 (7)	0 (0)	0.1
PPROM	8 (18.6)	8 (17.4)	0.88
Preeclampsia	4 (9.3)	13 (28.3)	0.03
Need for resuscitation	14 (32.6)	13 (27.7)	0.61

Data are shown as mean±standard deviation or n (%) where appropriate. CS=Cesarian section, PDA=Patent ductus arteriosus, PPROM=Premature prolonged rupture of membranes

Table 2. Clinical data obtained from patients responding to initial medical therapy in PDA

	No treatment response (n=44)	Treatment response present (n=47)	P value
RDS	38 (86.4)	38 (80.9)	0.47
EOS	14 (31.8)	15 (31.9)	0.99
LOS	40 (90.9)	41 (87.2)	0.57
BPD (moderate-severe)	23 (63,9)	22 (55)	0.43
IVH (grade 3-4)	10 (22.7)	2 (4.3)	**0.009**
PVL	17 (53.1)	8 (22.2)	**0.008**
NEC	9 (23.1)	5 (10.6)	0.12
ROP (3-4)	7 (70)	3 (75)	0.85
Feeding intolerance	20 (57.1)	21 (53.8)	0.77
Invasive mechanical ventilation	22 (50)	19 (40.4)	0.35
Admission FIO_2	38±18	40±19	0.65
Surfactant Dose Count	1.17±0.62	1.36±0.75	0.06
Ibuprofen	22(50)	20 (42.6)	0.47
Treatment application method (intravenous)	17 (89.5)	20 (80)	0.39
Day of treatment (<7 day)	17 (38.6)	10 (21.7)	0.08
Treatment day	5.56±3.39	5.68±7.1	0.43
Number of treatment (≥2)	41 (100)	3 (6.4)	**<0.001**
PDA ligation	19 (46.3)	3 (6.4)	**<0.001**
Ductal diameter	2.55±0.66	2.48±0.69	0.75
La/Ao ratio	1.64±0.25	1.73±0.4	0.14
Urine volume*	3.83±1.35	3.77±1.23	0.65
Mortality	10 (22.7)	7 (14.9)	0.33

Data are shown as mean±standard deviation or n (%) where appropriate. BPD=Bronchopulmonary dysplasia, EOS=Early-onset sepsis, FIO_2=Fractional oxygen concentration, LA/Ao=left atrium/aortic root, LOS=Late-onset neonatal sepsis, IVH=Intraventricular hemorrhage, NEC=Necrotizing enterocolitis, PDA=Patent ductus arteriosus, PVL=Periventricular leukomalacia, RDS=Respiratory distress syndrome, ROP=Retinopathy of prematurity

preeclampsia, lower admission WBC and LUC values, and higher IL-6 levels. Additionally, treatment response was reduced in patients with intraventricular hemorrhage and periventricular leukomalacia.

PDA is common in preterm infants and inversely proportional to gestational age [25]. In a retrospective, multicenter study, out of 842 patients at 23-28 weeks of gestation, 511 received pharmacological treatment for hemodynamically significant PDA. It was found that resistance to repeated medical treatment and the need for surgery were higher in the 23-24-week group. The study emphasized the need for individualized strategies for PDA management in these patients [26]. In our study, no difference was found between the groups regarding gestational age when evaluating the response to PDA treatment.

A previous study found that patients with a history of gestational hypertension had a lower response to indomethacin [27]. However, in our study, patients with a history of perinatal preeclampsia showed a better response to medical treatment. In Lee *et al.*'s [28] study, low gestational age, female sex, maternal pregnancy hypertension, and surfactant use were significant risk factors for symptomatic PDA. Additionally, it was re-

Table 3. Response to first course medical therapy according to hospitalization and laboratory data at the time of PDA diagnosis

	No treatment response (n=44)	Treatment response present (n=47)	P value
WBC (/mm^3)	9,053±6,158	7,300±3,697	0.014
RBC (/mm^3)	4.14±0.69	4.3±0.62	0.66
Hemoglobin (g/dL)	15.5±2.53	16.3±2.1	0.24
Platelets (/mm^3)	234,477±72,930	217,760±61,819	0.31
Delta neutrophil index (%)	4.68±11.1	5.91±9.9	0.83
LUC #	0.67±0.52	0.42±0.34	0.009
MPV (fL)	9.14±0.93	9.46±1.3	0.12
C-reactive protein (mg/L)	0.97±5	0.37±1.07	0.12
Interleukin-6 (pg/mL)	178.9±279.9	958.5±3131	0.009
Procalcitonin (µg/L)	6.17±9.23	5.77±7.54	0.45
Moment of diagnosis blood gas pH	7.23±0.7	7.26±0.6	0.25
Blood gas lactate at the time of diagnosis			
Hemoglobin at diagnosis	12.2±2.45	12.9±2.18	0.64
Platelets at the time of diagnosis	198,777±97,024	165,111±68,821	0.08
MPV at the time of diagnosis	11.1±1.83	10.1±1.56	0.27

Data are shown as mean±standard deviation. WBC=White blood cells, RBC=Red blood cells, MPV=Mean platelet volume, PDA=Patent ductus arteriosus, LUC= Large unstained cells

ported that histological chorioamnionitis and antenatal steroid use reduced symptomatic PDA in infants at 26-29 weeks of gestation. Antenatal steroid administration reduces RDS, which is a strong risk factor for preterm PDA [28]. In our study, rates of RDS, antenatal steroid administration, and clinical chorioamnionitis were similar in the two groups.

Another study found that clinical chorioamnionitis reduced the risk of PDA and noted that the mechanism of clinical chorioamnionitis in PDA closure is complex [29, 30]. Behebodi reported that both clinical and histological chorioamnionitis protects against PDA formation by promoting lung maturation [31].

Harink *et al*. [32] investigated the predictive value of clinical and echocardiographic parameters for deciding on surgical ligation after the failure of medical closure of PDA in preterm infants. In a study involving infants born at less than 37 weeks, surgical ligation was performed on 40 out of 89 patients. It was found that invasive respiratory support, a high La/Ao ratio, and the presence of steal were indicative for deciding on surgical ligation [32]. In our study, the La/Ao ratio and duration of invasive respiratory support were similar between the group that responded to medical treatment and the other group. The fact that our study included more immature infants may explain this difference. In a prospective study conducted on 42 infants born at less than 30 weeks gestational age, it was indicated that at postnatal day 72, an La/Ao ratio greater than 1.4 and a PDA size to weight ratio greater than 3.2 mm/kg had high predictive value for the need for PDA intervention. It was emphasized that serial daily echocardiographic evaluations could provide information on whether PDA closure would be achieved with non-steroidal medication or surgical ligation [33]. Early identification of infants at risk for PDA complications may positively affect treatment outcomes. In a prospective study involving infants born between 22-27 weeks of gestation, high levels of inflammation markers such as IL-6, IL-8, IL-10, and IL-12 were found to be associated with persistent PDA [34]. In our study, IL-6 levels were higher in the group that re-

sponded to treatment compared to the other group. A review has indicated that existing evidence suggests that thrombocytopenia and platelet function disorders contribute to the failure of spontaneous and pharmacological PDA closure in preterm infants [35]. In our study, however, there was no difference in platelet counts between the group that responded to treatment and the other group.

The treatment of PDA after the failure of pharmacological therapy in preterm infants is controversial and shows significant variations in practice [32]. While paracetamol has been found to be as effective as ibuprofen in closing PDA [8] and indomethacin has been found to be more effective than placebo or no treatment [36], recent studies have compared the efficacy and safety of combination therapies with monotherapy [13, 14]. In Kimani *et al*.'s [13] study, involving 140 infants born at less than 32 weeks of gestation, 17 received combination therapy, and ductal closure was found to be similar in the combination and monotherapy groups. Yurttutan *et al*. [14] reported that combination therapy with ibuprofen and acetaminophen was successful in patients who previously had failed ductal closure with medical treatment. When medical treatments fail, surgical methods are preferred, though they carry potential risks. In Park *et al*.'s [37] study, comparing a group undergoing surgery after medical failure with a group undergoing surgery from the outset, the latter group had lower incidences of BPD, NEC, sepsis, and ROP. It was suggested that direct surgery might be more beneficial than waiting for medical treatment to fail. Dani *et al*. [26] noted that although the need for surgical closure after multiple medical treatments was twice as high in immature infants, it is desirable to avoid exposing these infants to the risks of surgery and general anesthesia. Considering these studies, it was thought that applying combination therapy instead of monotherapy could prevent delays in treatment. Our study results showed that patients with IVH and PVL had a higher rate of PDA treatment failure, suggesting that both combination therapy and timely surgical intervention should be considered for these patients. Vaidya *et al*. [38] highlighted that late initiation of medical treatment for PDA (postnatal day 11±8.2) might result in lower closure rates. In our study, treatments were started within the first week in both groups. In Kimani *et al*.'s [13] study, the time to start medical treatment ranged from 1 to 34 days (median 7 days), with a PDA closure rate of 37.9% for acetaminophen and 31.8% for ibuprofen. In our study, the success rate was 57.4% for paracetamol and 42.6% for ibuprofen, which may be attributed to the earlier initiation of treatment compared to Kimani *et al*'s [13] study.

Limitations

Our study's limitations include its retrospective design, being conducted at a single center, and the small number of patients.

CONCLUSION

In the management of PDA, the use of combination therapy instead of medical monotherapy may prevent the loss of time associated with monotherapy failure. Prospective studies designed for this purpose are needed. In cases where elevated WBC, IVH, or PVL are detected, the possibility of medical treatment failure should be considered, and patient-based strategies should be developed.

Ethical Statement

The study was reviewed and approved by the ethics committee of University of Health Sciences, Ankara Bilkent City Hospital (Ethics approval decision no: E2-22-3045 and date: 23.12.2022). All participants signed informed written consent before being enrolled in the study. All procedures were performed according to the Declaration of Helsinki.

Authors' Contribution

Study Conception: AY, HGKK; Study Design: AY, HGKK; Supervision: HGKK, GKŞ, BSB; Funding: N/A; Materials: AY, HGKK, GKŞ; Data Collection and/or Processing: AY, BSB; Statistical Analysis and/or Data Interpretation: AY, HGKK, FEC, ŞSO; Literature Review: AY, HGKK, ŞSO; Manuscript Preparation: AY, HGKK and Critical Review: AY, HGKK, FEC, ŞSO.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The comparison of life compatibility between trisomy 2 and trisomy 21 (Down syndrome) by bioinformatic-based databases

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ABSTRACT

Objectives: Trisomy occurs with an extra chromosome during cell division resulting in 47 chromosomes instead of 46 in the human genome. The overexpression of gene profiles is associated with abnormal phenotypes and a range of syndromes. Theoretically, trisomy can occur for each chromosome but the survival rate of individuals with trisomy 21 is much higher than other trisomies. In this paper, we discussed the life compatibility of trisomy 21 compared to an example trisomy of one of the other chromosomes (chromosome 2) with quantitative and qualitative gene profiles using bioinformatic databases.

Methods: The analyses included (i) the determination of total gene numbers and classifications, (ii) numbers and functions of housekeeping genes, tissue-specific genes, and imprinted gene numbers and (iii) comparing the profiles of the proteins involved in cell survival and cell death in both chromosomes.

Results: The results indicate that trisomy 2 is likely to be incompatible with life compared to trisomy 21 because both gene enrichment and function are important factors associated with the difference in survival rates. Protein-protein interaction analyses showed that the increased interaction rate in trisomy 2 leads to more complex pathological consequences due to disruptions in cellular functions, however the limited interaction network in trisomy 21 may help explain the clinical features of Down syndrome.

Conclusions: Compared to trisomy 2, the life compatibility of trisomy 21 is associated with gene numbers, functions, and protein-protein interactions.

Keywords: Trisomy, Down syndrome, bioinformatics, chromosomal disorders, genetic disorders

Diploid organisms have two copies for each chromosome derived from individual parents (23 pair chromosomes in Homo sapiens). Homologous chromosomes segregate in meiosis during gametogenesis to form haploid sperms and oocytes. This segregation provides half a set of chromosomes which are then completed with another half set of chromosomes coming from another parent in fertilization. Meiosis maintains the number of chromosomes during transgenerational inheritance as well as provides genetic variations between generations by a special mechanism, crossing-over. If homologous chromosomes do not separate equally during meiosis, one of the gametes has a second copy of a chromo-

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some (n+1), and the other daughter gamete lacks a copy of chromosome (n-1) (Fig. 1). When such the n+1 gamete is fertilized and an embryo is formed, the resulting embryo contains an extra copy of that chromosome. The syndrome with three copies of a chromosome is called trisomy. If the n-1 gamete is fertilized, the embryo will have monosomy defined as a loss of a copy of a chromosome.

Trisomy 21 (also called Down syndrome) is the most common. Individuals with Down syndrome have multiple malformations, medical conditions, and cognitive impairment due to the presence of extra genetic material on chromosome 21 [1]. Although people with Down syndrome can have systemic syndromes that reduce life quality, they can still have a normal life as possible. This study aimed to reveal the molecular and genetic aspects of why the survival rate of individuals with Trisomy 21 is much higher than other trisomies, such as Trisomy 2. For this purpose, methods were considered to analyze gene groups both qualitatively and quantitatively. Bioinformatic databases were used to determine (i) total gene numbers in Chromosomes 2 and 21, (ii) the number and functions of housekeeping genes, tissue-specific genes, and imprinted genes, (iii) the profiles of the proteins involved in cell survival and cell death, and iv) the comparison of protein-protein interactions in Chromosomes 2 and 21. This study contributes to our understanding of how molecular differences between the two types of trisomies relate to the biological processes behind the phenotypic differences.

METHODS

Determination of Total Gene Numbers and Profiles

Gene numbers in the Chromosomes 21 and 2 were analyzed with the information obtained from the chromosome statistics tables in the Ensembl database by https://www.ensembl.org/Homo_sapiens/Location/Chromosome?r=21%3A1-1000 and https://www.ensembl.org/Homo_sapiens/Location/Chromosome?r=2%3A1-1000, respectively.

Databases Used for the Determination of Gene Groups

Housekeeping Genes

Housekeeping genes were obtained from the article "Human housekeeping genes are compact", compiled from https://www.tau.ac.il/~elieis/Housekeeping_genes.html [2], [3]. Housekeeping genes in chromosomes 2 and 21 were compiled from https://www.ncbi.nlm.nih.gov/

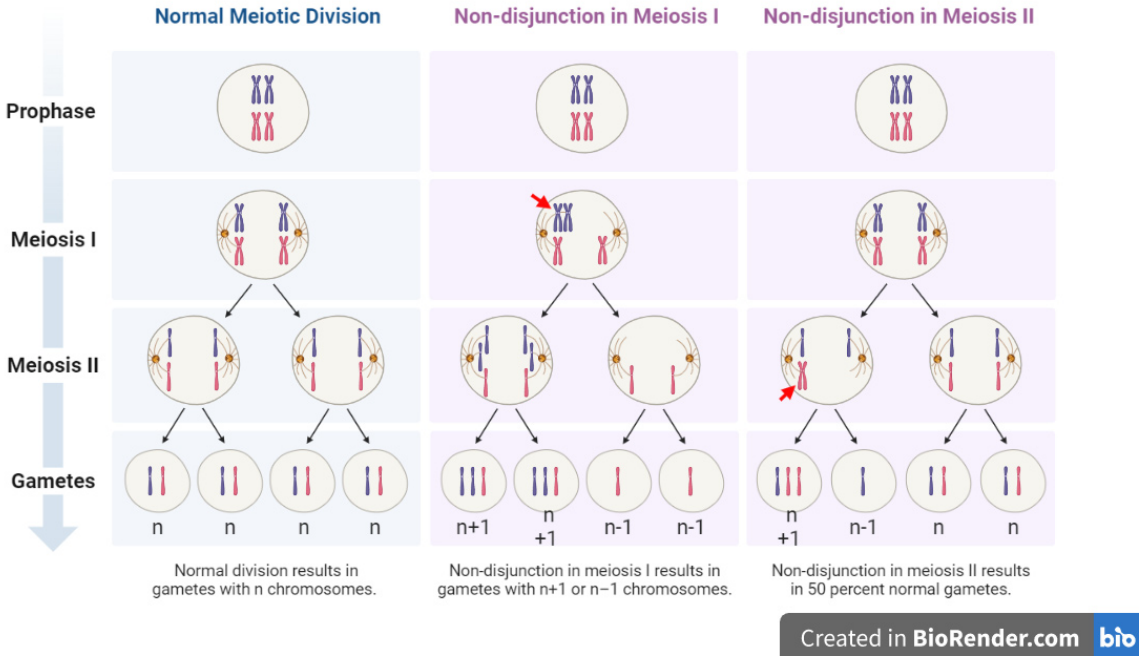


Fig. 1. Normal and abnormal gametogenesis. Non-disjunction can occur either in meiosis I or meiosis II. Both result in trisomy with a total of 47 chromosomes.

via Gene IDs to be classified to explain the chromosome, its position on the chromosome, NCBI gene identity, gene name, and function of the gene.

Imprinted Genes

Imprinted genes were screened from https://www.geneimprint.com/site/genes-by-species.Homo+sapiens for their presence on chromosomes 2 and 21. The imprinted genes are described with their chromosomal location, NCBI gene identity, gene name, maternal/paternal expression status, and tissue specificity.

Survival Proteins

Profiles of the proteins involved in cell survival in chromosomes 2 and 21 of Homo sapiens were screened with the ontology number GO:0008283 from the AmiGO 2 database (http://amigo.geneontology.org/amigo) under the title of "cell proliferation" and analyzing 583 proteins.

Death Proteins

Profiles of the proteins involved in cell death in chromosomes 2 and 21 of Homo sapiens were screened with the ontology number GO:0008219 from the AmiGO 2 database (http://amigo.geneontology.org/amigo) under the title of "cell death" and analyzing 1735 proteins.

Protein-Protein Interaction Network Analysis with STRING Database

In this study, genes involved in processes such as genetic imprinting, cell survival, and cell death were selected to examine biological processes associated with trisomy 2 and trisomy 21. Genes were identified using Ensembl (https://www.ensembl.org), GeneImprint (https://www.geneimprint.com) and AmiGO 2 databases; especially Survival proteins and Death proteins data were extracted from AmiGO 2. Interaction networks of proteins encoded by selected genes were analyzed using STRING (Search Tool for the Retrieval

A

B

C

Characteristics	Chromosome 2	Chromosome 21
Length (bps)	242,193,529	46,709,983
Coding genes	1300	235
Non-coding genes	1845	441
Small non-coding genes	345	69
Long non-coding genes	1324	348
Misc non-coding genes	176	24
Pseudogenes	1079	188
Short Variants	58,799,226	9,242,863

Whole genome numbers

Gene counts	Primary assembly	Alternative sequence
Coding genes	19,804	3,027
Non coding genes	25,134	1,555
Small non coding genes	4,864	297
Long non coding genes	18,049	1,071
Misc non coding genes	2,221	187
Pseudogenes	15,240	1,799
Gene transcripts	251,297	21,629

D

Gene-Protein Class	Chromosome 2 (Chr 2)		Chromosome 21 (Chr 21)	
	Number	Percent (%) within Chr 2	Number	Percent (%) within Chr 21
Protein coding genes	1300	39.47%	235	33.76%
RNA coding genes	1845	56.01%	441	63.36%
Housekeeping genes	26	0.79%	8	1.15%
Imprinting genes	11	0.33%	2	0.29%
Cell survival proteins	30	0.91%	2	0.29%
Death proteins	82	2.49%	8	1.15%
TOTAL	**3294 genes**		**696 genes**	

Fig. 2. Grouping of gene numbers in chromosomes 2 and 21. A and B show chromosomal maps for Chr2 and Chr21, respectively. C shows the genomic context of each chromosome, and D shows the comparison of gene-protein classes between Chr2 and Chr21.

of Interacting Genes/Proteins) database. STRING is a widely used bioinformatics tool to visualize protein-protein interactions and examine interaction densities. This database contains only interactions with high confidence levels that are confirmed by experimental evidence. The interaction networks of genes associated with trisomy 2 and trisomy 21 were examined separately to compare the protein interaction densities on chromosomes 2 and 21 in both cases. The effect of the extra chromosome on protein expression in trisomy 2 and the effect of chromosome 21 on protein interaction capacity in trisomy 21 were evaluated. Finally, the obtained interaction networks were visualized and comparisons were made between the interaction densities. In these analyses, interactions between survival and death proteins were particularly emphasized. Since the study was based solely on open-access biological databases, ethical committee approval was not required.

RESULTS

Chromosome 2 is the second largest human chromosome, representing almost 8% of the total DNA in human cells. It is 242,193,529 base pairs long including 1,300 coding genes. It has also 1,845 non-coding genes; of these, 345 are small noncoding genes, 1,324 are long noncoding genes, and 176 are other noncoding genes. It contains 1,079 pseudogenes and has 58,799,226 short variants (Figs. 2A and C). But chromosome 21 is 46,709,983 base pairs long including 235 protein-coding, and 441 non-protein-coding genes; 69 of these are small noncoding genes, 348 are long noncoding genes, and 24 are other noncoding genes. It also contains 188 pseudogenes and has 9,242,863 short variants (Figs. 2B and C). Chromosome 2 contains more than 6-fold coding genes and more than 4-fold non-coding genes than chromosome 21. Additionally, chromosomes 21 and 2 composed

Table 1. Housekeeping genes located on the Chr 2.

Location	NCBI Gene ID	Gene	Name	Overexpression	Function
2p16.1	6233	RPS27A	Ribosomal protein S27a, mRNA	Ovary, lymph node	Encodes a fusion protein consisting of ubiquitin at the N terminus and ribosomal protein S27a at the C terminus.
2p21	9167	COX7A2L	Cytochrome c oxidase subunit 7A2 like, mRNA; nuclear gene for mitochondrial product	Adrenal, kidney	Nuclear gene encodes a protein similar to polypeptides 1 and 2 of subunit VIIa in the C-terminal region
2p23.3	3030	HADHA	Hydroxyacyl-coa dehydrogenase trifunctional multi-enzyme complex subunit alpha, mRNA; nuclear gene for mitochondrial product	Duodenum, small intestine	Encodes the alpha subunit of the mitochondrial trifunctional protein, which catalyses the last three steps of mitochondrial beta-oxidation of long chain fatty acids.
2p14	5861	RAB1A	Member RAS oncogene family, mRNA	Kidney, thyroid	Encodes a member of the Ras superfamily of GTPases.
2q11.2	1329	COX5B	Cytochrome c oxidase subunit 5B, mRNA; nuclear gene for mitochondrial product	Colon, kidney	Encodes the nuclear-encoded subunit Vb of the human mitochondrial respiratory chain enzyme.
2p25.1	4953	ODC1	Ornithine decarboxylase 1, mRNA	Testis, bone marrow	Encodes the rate-limiting enzyme of the polyamine biosynthesis pathway which catalyses ornithine to putrescine.
2q14.1	7849	PAX8	Paired box 8, mRNA	Thyroid, kidney	Encodes a member of the paired box (PAX) family of transcription factors.
2q37.3	4735	SEPTIN2	Septin 2, mRNA	Fat, thyroid	Enables identical protein binding activity. Predicted to be involved in several processes, including cilium assembly; regulation of exocytosis; and smoothened signalling pathway.
2q37.1	5757	PTMA	Prothymosin alpha, mRNA	Bone marrow, lymph node	Enables DNA-binding transcription factor binding activity. Involved in negative regulation of apoptotic process.
2p13.3	6637	SNRPG	Small nuclear ribonucleoprotein polypeptide G, mRNA	Colon, appendix	The protein encoded by this gene is a component of the U1, U2, U4, and U5 small nuclear ribonucleoprotein complexes, precursors of the spliceosome.
2p21	805	CALM2	Calmodulin 2, mRNA	Brain, testis	Calmodulin is a calcium binding protein that plays a role in signalling pathways, cell cycle progression and proliferation. This gene is a member of the calmodulin gene family.

Table 1 contunied. Housekeeping genes located on the Chr 2.

Location	NCBI Gene ID	Gene	Name	Overexpression	Function
2p25.1	3241	HPCAL1	Hippocalcin like 1, mRNA	Lung, small intestine	The protein encoded by this gene is a member of neuron-specific calcium-binding proteins family found in the retina and brain.
2p23.3	3032	HADHB	Hydroxyacyl-CoA dehydrogenase trifunctional multi-enzyme complex subunit beta, mRNA; nuclear gene for mitochondrial product	Heart, duodenum	This gene encodes the beta subunit of the mitochondrial trifunctional protein, which catalyses the last three steps of mitochondrial beta-oxidation of long chain fatty acids.
2q31.1	518	ATP5MC3	ATP synthase membrane subunit c locus 3, mRNA; nuclear gene for mitochondrial product	Heart, duodenum	Encodes a subunit of mitochondrial ATP synthase. This gene is one of three genes that encode subunit c of the proton channel.
2q35	10109	ARPC2	Actin related protein 2/3 complex subunit 2, mRNA	Lymph node, bone marrow	The Arp2/3 protein complex has been implicated in the control of actin polymerization in cells and has been conserved through evolution. Encodes one of seven subunits of the human Arp2/3 protein complex.
2q11.2	56910	STARD7	StAR related lipid transfer domain containing 7, mRNA; nuclear gene for mitochondrial product	Kidney, brain	Predicted to enable lipid binding activity.
2p14	10438	C1D	C1D nuclear receptor corepressor, mRNA	Bone marrow, adrenal	The protein encoded by this gene is a DNA binding and apoptosis-inducing protein and is localized in the nucleus.
2q35	23549	DNPEP	Aspartyl aminopeptidase, mRNA	Small intestine, duodenum	The protein encoded by this gene is an aminopeptidase which prefers acidic amino acids, and specifically favours aspartic acid over glutamic acid.
2q35	27013	CNPPD1	Cyclin Pas1/PHO80 domain containing 1, mRNA	Kidney, adrenal	Predicted to be involved in regulation of cyclin-dependent protein serine/threonine kinase activity.
2p11.2	9168	TMSB10	Thymosin beta 10, mRNA	Appendix, colon	Predicted to be involved in regulation of cell migration and sequestering of actin monomers.
2p13.2	10574	CCT7	Chaperonin containing TCP1 subunit 7, mRNA	Testis, adrenal	Encodes a molecular chaperone that is a member of the chaperonin containing TCP1 complex (CCT), also known as the TCP1 ring complex (TRiC).
2p16.1	57142	RTN4	Reticulon 4, mRNA	Fat, brain	Reticulons are associated with the endoplasmic reticulum and are involved in neuroendocrine secretion or in membrane trafficking in neuroendocrine cells. This gene belongs to the family of reticulon encoding genes.
2q37.1	4691	NCL	Nucleolin, mRNA	Lymph node, appendix	Nucleolin (NCL), a eukaryotic nucleolar phosphoprotein, is involved in the synthesis and maturation of ribosomes. The intron 11 of the NCL gene encodes a small nucleolar RNA, termed U20.
2p15	4190	MDH1	Malate dehydrogenase 1, mRNA	Heart, fat	This gene encodes an enzyme that catalyses the NAD/NADH-dependent, reversible oxidation of malate to oxaloacetate in many metabolic pathways, including the citric acid cycle.
2p25.1	10971	YWHAQ	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein theta, mRNA	Brain, endometrium	This gene product belongs to the 14-3-3 family of proteins which mediate signal transduction by binding to phosphoserine-containing proteins
2p13.3	113419	TEX261	Testis expressed 261, mRNA	Thyroid, testis	Predicted to be involved in endoplasmic reticulum to Golgi vesicle-mediated transport.

0.93% and 5% of the total coding genes in the human genome.

Chromosomes 21 and 2 differ in terms of gene functions. For instance, housekeeping gene content is higher in Chr2 than in Chr21 (Tables 1 and 2). The range of organs affected by selectively overexpressed housekeeping is wide in Chr2 compared to Chr21. Chromosome 21 has only 2 known imprinted genes, but Chromosome 2 has 11 imprinted genes (Table 3). Some of these genes are supposed to be imprinted (SI) with current knowledge. Interestingly all the two imprinted genes in Chr21 are of paternal origin and in-

Table 2. Housekeeping genes located on the Chr 21.

Location	NCBI Gene ID	Gene	Name	Overexpression	Function
21q22.3	1476	CSTB	Cystatin B, mRNA	Oesophagus, urinary bladder	Play a role in protecting against the proteases leaking from lysosomes.
21q22.3	8209	GATD3	Glutamine aminotransferase class 1 domain containing 3, mRNA; nuclear gene for mitochondrial product	Kidney, heart	This gene encodes a potential mitochondrial protein that is a member of the DJ-1/PfpI gene family. This protein is overexpressed in foetal DS brain.
21q22.3	1291	COL6A1	Collagen type VI alpha 1 chain, mRNA	Placenta, endometrium	The collagens are a superfamily of proteins that play a role in maintaining the integrity of various tissues. Collagens are extracellular matrix proteins. Collagen VI is a major structural component of microfibrils.
21q22.3	754	PTTG1IP	PTTG1 interacting protein, mRNA	Placenta, gall bladder	Induces transcriptional activation of basic fibroblast growth factor.
21q22.3	8888	MCM3AP	Mini chromosome maintenance complex component 3 associated protein, mRNA	Lymph node, spleen	One of the MCM proteins essential for the initiation of DNA replication.
21q22.11	6647	SOD1	Superoxide dismutase 1, mRNA	Liver, kidney	The protein encoded by this gene binds copper and zinc ions and is one of two isozymes responsible for destroying free superoxide radicals in the body.
21q22.11	539	ATP5PO	ATP synthase peripheral stalk subunit OSCP, mRNA; nuclear gene for mitochondrial product	Heart, duodenum	F-type ATPases are composed of a catalytic core and a membrane proton channel. The protein encoded by this gene is a component of the F-type ATPase found in the mitochondrial matrix.
21q22.3	**6612**	**SUMO3**	**Small ubiquitin like modifier 3, mRNA**	**Brain, bone marrow**	**This gene encodes a member of the small ubiquitin-related modifier (SUMO) family of eukaryotic proteins.**

Table 3. Comparison of imprinting gene profiles

Location	Gene	NCBI Gene ID	Status	Expressed allele	Tissue Specificity	Function
Chromosome 21						
21q22.2	SIM2	6493	Suppose to be imprinted (SI)	Paternal	Kidney, oesophagus, prostate gland	Encodes a transcription factor that is the master regulator of neurogenesis
21q22.2	DSCAM	1826	Imprinted (I)	Paternal	Brain	This gene is a member of the immunoglobulin superfamily of cell adhesion molecules (Ig-CAMs) and is involved in human central and peripheral nervous system development.
Chromosome 2						
2p12	LRRTM1	347730	I	Paternal	Brain, salivary gland, thyroid	Predicted to be involved in regulation of postsynaptic density assembly and regulation of presynapse assembly.
2p13	OTX1	5013	SI	Maternal	Skin, prostate gland, brain	This gene encodes a member of the bicoid sub-family of homeodomain-containing transcription factors. The encoded protein acts as a transcription factor and may play a role in brain and sensory organ development.
2p13	VAX2	25806	SI	Maternal	Brain	This gene encodes a homeobox protein and is almost exclusively expressed in the ventral portion of the retina during development.
2p16.1	CCDC85A	114800	SI	Paternal	Fat, brain, thyroid, placenta, lung	Located in adherens junction.
2p21	ABCG8	64241	SI	Maternal	Small intestine, duodenum, liver	ABC proteins transport various molecules across extra- and intra-cellular membranes. The protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters.
2p21	CYP1B1	1545	SI	Paternal	Prostate, endometrium, appendix	The cytochrome P450 proteins are monooxygenases which catalyse many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Encodes a member of the cytochrome P450 superfamily of enzymes.
2p22.3-p21	ZFP36L2	678	SI	Maternal	Thyroid, appendix and other tissue	Regulating the response to growth factors.

Table 3 contunied. Comparison of imprinting gene profiles

Location	Gene	NCBI Gene ID	Status	Expressed allele	Tissue Specificity	Function
2q33.3	GPR1 (CMKLR2)	2825	I	Paternal	Placenta, oesophagus. skin	Enables adipokinetic hormone binding activity and adipokinetic hormone receptor activity.
2q33.3	ZDBF2	57683	I	Paternal	Adrenal, brain, ovary, thyroid	This gene encodes a protein containing DBF4-type zinc finger domains.
2q37.1	TIGD1	200765	SI	Paternal	Gene function is unknown	The protein encoded by this gene belongs to the tigger subfamily of the pogo superfamily of DNA-mediated transposons in humans.
2q37.3	MYEOV2 (COPS9)	150678	SI	Paternal	Brain, fat, kidney, prostate gland	Involved in several processes, including cellular response to UV; cytoplasmic sequestering of protein; and negative regulation of protein neddylation.

volved in nervous system development, while the nervous system-related imprinted gene ratio is around 1:3 within the group imprinted genes of Chr2. Imprinted genes with three alleles, as in trisomies, are problematic because the genome/cell cannot manage an extra paternal allele to be imprinted or not. Therefore, this extra allele may lead to chaotic gene expression. However, the chaos depends on the parental origin of the extra allele (within the extra Chr21). If an extra chromosome (and extra paternal allele) is provided by the paternal genome, this is supposed to be significant in a clinical manner.

We then assessed the profiles of genes involved in cell survival or cell death which might be directly related to life compatibility. 30 and 2 cell survival genes are found in Chr2 (Table 4) and Chr21 (Table 5), respectively. 82 and 8 cell death genes are found in Chr2 (Table 6) and Chr21 (Table 7), respectively. Chr2 con-

Table 4. Proteins involved in cell survival located on the Chr 2.

Chromosome	UniProtKB	Protein	Molecular Function	Biological Process
2	Q9NPC8	SIX2	Developmental protein, DNA binding	Morphogenesis
2	O95393	BMP10	Cytokine, developmental protein, growth factor	Cell adhesion
2	P98164	LRP2	Receptor	Endocytosis, hearing, neurogenesis, transport
2	Q12884	FAP	Hydrolase, protease, serine protease	Angiogenesis, apoptosis, cell adhesion
2	P02461	COL3A1	Matrix structural component molecule and ion binding	Morphogenesis
2	P20264	POU3F3	Developmental protein, DNA biding	Neurogenesis, transcription, transcription regulation
2	Q96SQ7	ATOH8	Developmental protein, DNA biding	Differentiation, neurogenesis, transcription, transcription regulation
2	P10809	HSPD1	Chaperone, isomerase	Host-virus interaction
2	P52951	GBX2	DNA binding	Transcription, transcription regulation
2	P24593	IGFBP5	Growth factor binding	Cellular response, aging
2	P62699	YPEL5	Metal binding	Cell proliferation
2	O95343	SIX3	Developmental protein, DNA binding, repressor	Transcription, transcription regulation
2	Q14623	IHH	Developmental protein, hydrolase, protease	Morphogenesis
2	P27037	ACVR2A	Kinase, receptor, serine/threonine-protein kinase, transferase	Cellular response
2	P42224	STAT1	Activator, DNA-binding	Antiviral defence, host-virus interaction, transcription, transcription regulation
2	Q8NER5	ACVR1C	Kinase, receptor, serine/threonine-protein kinase, transferase	Apoptosis
2	O43683	BUB1	Kinase, receptor, serine/threonine-protein kinase, transferase	Apoptosis, cell cycle, cell division, chromosome division, host-virus interaction, mitosis
2	P15336	ATF2	Activator, DNA-binding	DNA damage, transcription, transcription regulation
2	P35716	SOX11	Activator, developmental protein, DNA binding	Differentiation, neurogenesis, transcription, transcription regulation
2	P61026	RAB10	Hydrolase	Protein transport, transport

Table 4 contunied. Proteins involved in cell survival located on the Chr 2.

Chromosome	UniProtKB	Protein	Molecular Function	Biological Process
2	O14713	ITGB1BP1	Mitogen	Angiogenesis, biomineralization, cell adhesion, differentiation, Notch signaling pathway, transcription, transcription regulation
2	Q02363	ID2	Developmental protein, suppressor	Biological rhythms, transcription, transcription regulation
2	P13010	XRCC5	Activator, DNA binding, helicase, hydrolase	DNA damage, DNA recombination, DNA repair, host-virus interaction, immunity, innate immunity, ribosome biogenesis, transcription, transcription regulation
2	P23582	NPPC	Hormone, vasoactive	Osteogenesis
2	Q13873	BMPR2	Kinase, receptor, serine/threonine-protein kinase, transferase	ATP binder, magnesium, manganese, metal binder, nucleotide binder
2	P68106	FKBP1B	Isomerase, rotamase	Protein regulation
2	Q15118	PDK1	Kinase, transferase	Carbohydrate metabolism, glucose metabolism
2	Q8TAX0	OSR1	DNA binding, ion binding	Transcription, transcription regulation
2	P01135	TGFA	Growth factor, mitogen	Proliferation regulation
2	**P49279**	**SLC11A1**	**Transport**	**Ion transport**

tains the DNMT3A gene which encodes a de novo DNA methyltransferase playing an important role in embryo formation and epigenetic regulation. DNMT3A gene is considered a lethal gene as its loss or mutations deactivating its function cause embryo death and severe morphological defects. DNMT3A enzyme is critical to manage cell differentiation via regulating de novo DNA methylation of gene sets. This can lead to lower survival rates in the embryos with trisomy 2 compared to those with trisomy 21.

In this study, genes identified to be associated with biological processes such as genomic imprinting, cell survival, and cell death were selected. The interaction networks of the proteins encoded by these genes were also examined by bioinformatics analysis using the STRING database. In this analysis, specific to trisomy 2 and trisomy 21, important findings were obtained regarding the interaction densities and network structures of the proteins encoded by genes on Chr2 and Chr21.

In trisomy 2, the presence of an extra copy of chromosome 2 leads to higher expression levels of proteins encoded by Chr2, which increases the density of protein-protein interactions, leading to disruptions in biological processes during embryonic development (Fig. 3). This may help us understand the molecular mechanisms by which trisomy 2 often results in death at the embryonic stage.

In trisomy 21, the presence of an extra copy of Chr21 may lead to the overexpression of some proteins encoded by Chr21. However, the interaction capacities of these proteins remain low, especially in interactions with Chr2. This contributes to cellular abnormalities in the pathophysiology of DS and leads to a limited interaction network.

In addition, some proteins located on both Chr2 and Chr21 interact with each other (Fig. 4). These interactions suggest that proteins located on both chromosomes may be involved in common biological processes and may play important roles in regulating these processes. In particular, interactions between proteins encoded by Chr2 and Chr21 may play a critical role in maintaining a balance between cellular functions.

On the other hand, the proteins encoded by the genes on Chr21 that play a role in the biological processes we mentioned did not form any interaction networks according to the analyses we performed on

Table 5. Proteins involved in cell survival located on the Chr 21

Chromosome	UniProtKB	Protein	Molecular Function	Biological Process
21	Q01196	RUNX1	Activator, DNA-binding repressor	Transcription, transcription regulation
21	O95456	PSMG1	Chaperone	Proliferation regulator

Table 6. Proteins involved in cell death located on the Chr 2

Chromosome	UniProtKB	Protein	Molecular Function	Biological Process
2	Q9GZY8	MFF	Protein binding	Mitochondrial and peroxisomal fission
2	P10747	CD28	Protein binding	Apoptotic signaling pathway
2	O43683	BUB1	Protein kinase activity	Regulation of chromosome separation, apoptotic process
2	Q13467	FZD5	Ubiquitin protein ligase binding, Wnt-protein binding	Apoptotic process involved in morphogenesis
2	Q9BWT1	CDCA7	Transcriptional regulator	Apoptotic process
2	Q9BWP8	COLEC11	Developmental protein, DNA binding	Immunity, innate immunity
2	Q15303	ERBB4	Activator, developmental protein, kinase, receptor, transferase, tyrosine-protein kinase	Apoptosis, lactation, transcription, transcription regulation
2	Q0ZLH3	PJVK	Autophagy	Hearing
2	Q13901	C1D	DNA binding, repressor, RNA binding	Apoptosis, rRNA processing, transcription, transcription regulation
2	Q92835	INPP5D	Hydrolase	Apoptosis, immunity, lipid metabolism
2	Q92851	CASP10	Hydrolase, protease, thiol protease	Apoptosis
2	Q9HC96	CAPN10	Hydrolase, protease, thiol protease	Apoptosis and cellular response
2	Q13873	BMPR2	Kinase, receptor, serine/threonine-protein kinase, transferase	Morphogenesis and apoptosis
2	Q13618	CUL3	Cyclin binding, ubiquitin protein ligase activity	Cell cycle, cell division, cilium biogenesis/degradation, ER-Golgi transport, mitosis, Ubl conjugation pathway
2	Q658P3	STEAP3	Oxidoreductase	Apoptosis, cell cycle, ion transport, iron transport, transport
2	Q9NYY8	FASTKD2	RNA binding, rRNA binding	Apoptosis, mitochondrial ribosome biogenesis
2	Q01955	COL4A3	Extracellular structural component	Apoptosis, cell adhesion
2	O14901	KLF11	Activator, DNA-binding, repressor	Apoptosis, transcription, transcription regulation
2	Q8TEJ3	SH3RF3	Transferase	Apoptosis, Ubl conjugation pathway
2	P15408	FOSL2	DNA and chromatin binding	Cell death, transcription, regulation of transcription
2	P09529	INHBB	Cytokine, growth factor and hormone activity	Cellular response, regulation of apoptotic signalling pathway
2	P19447	ERCC3	DNA binding, helicase, hydrolase	Apoptosis, DNA damage, DNA repair, host-virus interaction, transcription, transcription regulation
2	Q9H8M9	EVA1A	Protein phosphorylation	Apoptosis, autophagy
2	A0PJW8	DAPL1	Connecting to the death domain	Apoptosis, differentiation
2	Q12884	FAP	Hydrolase, protease, serine protease	Angiogenesis, apoptosis, cell adhesion
2	Q9BST9	RTKN	GTP binding, GTPase inhibitory activity	Apoptosis
2	Q96Q42	ALS2	Guanine-nucleotide releasing factor	Cell death, transport
2	P56177	DLX1	Activator, developmental protein, DNA binding, repressor	Differentiation, transcription, transcription regulation
2	P09327	VIL1	Actin closure, actin binding	Apoptosis
2	Q15118	PDK1	Kinase, transferase	Carbohydrate metabolism, glucose metabolism
2	Q15116	PDCD1	An immune-inhibitory receptor	Adaptive immunity, apoptosis, immunity
2	Q8N5P1	ZC3H8	Repressor, RNA binder	Apoptosis, transcription, transcription regulation
2	Q96MX6	DNAAF10	Ubiquitin binding	Apoptosis
2	Q8NEG5	ZSWIM2	Transferase	Apoptosis, Ubl conjugation pathway
2	Q14790	CASP8	Hydrolase, protease, thiol protease	Apoptosis, host-virus interaction
2	Q9UBP9	GULP1	Adapter protein	Apoptosis, lipid transport, phagocytosis, transport
2	O95343	SIX3	Developmental protein, DNA binding, repressor	Transcription, transcription regulation
2	P52789	HK2	Allosteric enzyme, kinase, transferase	Apoptosis, glycolysis
2	P52701	MSH6	DNA and chromatin binding	DNA damage, DNA repair, host-virus interaction
2	Q569K4	ZNF385B	Nucleic acid, p53 and ion binding	Apoptosis
2	P62745	RHOB	Developmental protein	Angiogenesis, apoptosis, cell adhesion, differentiation, protein transport, transport
2	Q9Y2W7	KCNIP3	Ion channel, potassium channel, suppressor, voltage gated channel	Apoptosis, ion transport, potassium transport, transcription, transcription regulation, transport
2	Q9Y6K1	DNMT3A	Chromatin regulator, DNA binding, methyltransferase, repressor, transferase	DNA methylation, senescence, mitosis, apoptosis, genetic imprinting
2	O95630	STAMBP	Hydrolase, metalloprotease, protease	Ubl conjugation pathway
2	Q8NER5	ACVR1C	Kinase, receptor, serine/threonine-protein kinase, transferase	Apoptosis
2	P11234	RALB	Hydrolase	Apoptosis, cell cycle, cell division
2	P31483	TIA1	RNA binding	Apoptosis, mRNA processing, mRNA splicing

Table 6 contunied. Proteins involved in cell death located on the Chr 2

Chromosome	UniProtKB	Protein	Molecular Function	Biological Process
2	Q8IXB1	DNAJC10	Oxidoreductase, protein folding	Apoptosis
2	P21145	MAL	Lipid binding, participation in structure	Differentiation, central nervous system morphogenesis, apoptosis
2	O00506	STK25	Kinase, serine/threonine-protein kinase, transferase	ATP binder, magnesium, metal binder, nucleotide binder
2	P43354	NR4A2	DNA binding, receptor	Transcription, transcription regulation, differentiation, apoptosis
2	P06756	ITGAV	Host cell receptor, integrin, receptor for virus entry	Cell adhesion, host-virus interaction, apoptosis, angiogenesis
2	Q8TEB9	RHBDD1	Hydrolase, protease, serine protease	Apoptosis, differentiation, spermatogenesis
2	Q9Y2A7	NCKAP1	Regulates actin filament reorganization	Apoptosis, cell migration, cell morphogenesis, central nervous system development
2	Q9UNE0	EDAR	Developmental protein, receptor	Apoptosis, differentiation
2	P23760	PAX3	Developmental protein, DNA binding	Myogenesis, neurogenesis, transcription, transcription regulation
2	Q02156	PRKCE	Kinase, serine/threonine-protein kinase, transferase	Cell adhesion, cell cycle, cell division, immunity, apoptosis
2	Q99250	SCN2A	Ion channel, sodium channel, voltage gated channel	Ion transport, sodium transport, transport, memory, apoptosis
2	O94768	STK17B	Kinase, serine/threonine-protein kinase, transferase	Apoptosis, phosphorylation/autophosphorylation
2	O15519	CFLAR	Protease binding, endopeptidase activity	Apoptosis, cellular response, host-virus interaction
2	P61073	CXCR4	G-protein coupled receptor, host cell receptor for virus entry, receptor, transducer	Neurogenesis, morphogenesis, apoptosis, host-virus interaction
2	Q6NUQ4	TMEM214	Protein activation	Apoptosis
2	P28331	NDUFS1	Oxidoreductase, translocase	Electron transport, respiratory chain, transport, apoptosis
2	P43246	MSH2	DNA binding	DNA damage, DNA repair, apoptosis
2	Q8WYN3	CSRNP3	Activator, DNA-binding	Apoptosis, transcription, transcription regulation
2	Q8WYH8	ING5	Activator, chromatin regulator	Apoptosis, transcription, transcription regulation
2	P01584	IL1B	Cytokine, mitogen, pyrogen	Apoptosis, cell-cell signaling, reorganization of metabolic processes
2	P10809	HSPD1	Chaperone, isomerase	Host-virus interaction, apoptosis, protein folding
2	Q9Y3E7	CHMP3	Ubiquitin-specific protease binding, phosphatidylcholine binding	Apoptosis, cell cycle, cell division, protein transport, transport
2	Q16678	CYP1B1	Lyase, monooxygenase, oxidoreductase	Fatty acid metabolism, lipid metabolism, steroid metabolism, apoptosis, angiogenesis
2	Q9H2J4	PDCL3	Chaperone, VEGF receptor	Angiogenesis, apoptosis
2	O43464	HTRA2	Hydrolase, protease, serine protease	Apoptosis
2	Q9UMX3	BOK	Hydrolase, protease, serine protease	Apoptosis
2	Q9NP59	SLC40A1	Ion binding, hormone binding	Ion transport, iron transport, transport, apoptosis
2	Q9NPP4	NLRC4	ATP binding, caspase binding, ion binding	Apoptosis, immunity, inflammatory response, innate immunity
2	P15336	ATF2	Activator, DNA-binding	DNA damage, transcription, transcription regulation, apoptosis
2	P01583	IL1A	Cytokine, mitogen, pyrogen	Apoptosis, cell-cell signaling, reorganization of metabolic processes
2	O43521	BCL2L11	Microtubule binding, protein kinase binding	Apoptosis, morphogenesis
2	Q9NR63	CYP26B1	Monooxygenase, oxidoreductase	Lipid metabolism, cell fate determination, morphogenesis
2	Q9NR09	BIRC6	Protease inhibitor, thiol protease inhibitor, transferase	Apoptosis, cell cycle, cell division, mitosis, Ubl conjugation pathway
2	Q9NQC3	RTN4	RNA binding, ubiquitin protein ligase binding	Neurogenesis, apoptosis
2	**Q9NXR7**	**BABAM2**	**Chromatin organizer**	**Apoptosis, cell cycle, cell division, DNA damage, DNA repair, mitosis, Ubl conjugation pathway**

Table 7. Proteins involved in cell death located on the Chr 21

Chromosome	UniProtKB	Protein	Molecular Function	Biological Process
21	P58499	FAM3B	Cytokine	Apoptosis, glucose haemostasias
21	P20591	MX1	Protein and nucleotide binding	Antiviral defense, immunity, innate immunity
21	P00441	SOD1	Antioxidant, oxidoreductase	Cellular response, morphogenesis, apoptosis
21	Q14684	RRP1B	Activator	Apoptosis, host-virus interaction, mRNA splicing, transcription, transcriptional regulation
21	P055107	ITGB2	Integrin, receiver	Cell adhesion, phagocytosis, phagocytosis, apoptosis
21	P05067	APP	Heparin binder, protease inhibitor, serine protease inhibitor	Apoptosis, cell adhesion, endocytosis, Notch signaling pathway
21	P78563	ADARB1	Hydrolase, RNA binding	Antiviral defense, immunity, mRNA processing, morphogenesis
21	P57059	SIK1	Developmental protein, kinase, transferase	Biological rhythm, cell cycle, differentiation

the STRING database. This suggests that the proteins on Chr21 do not interact with each other and this deficiency may lead to more limited interaction networks in the pathophysiological processes of Down syndrome.

DISCUSSION

This study attempted to compare the life compatibility of trisomy 21 with trisomy 2 in terms of detailed gene profiles and protein-protein interactions. The total number of genes in the Chr21 is more than the Chr21 and the proteins encoded by Chr21 take part in more vital functions. On the other hand, the number of proteins involved in cell survival and cell death is higher in Chr2 compared with those in Chr21. In addition, it is remarkable that many of these proteins play a role in processes that affect the brain and form the nervous system, such as neurogenesis. The higher content of proteins involved in angiogenesis and other morphogenesis activities, cell and tissue differentiation, tran-

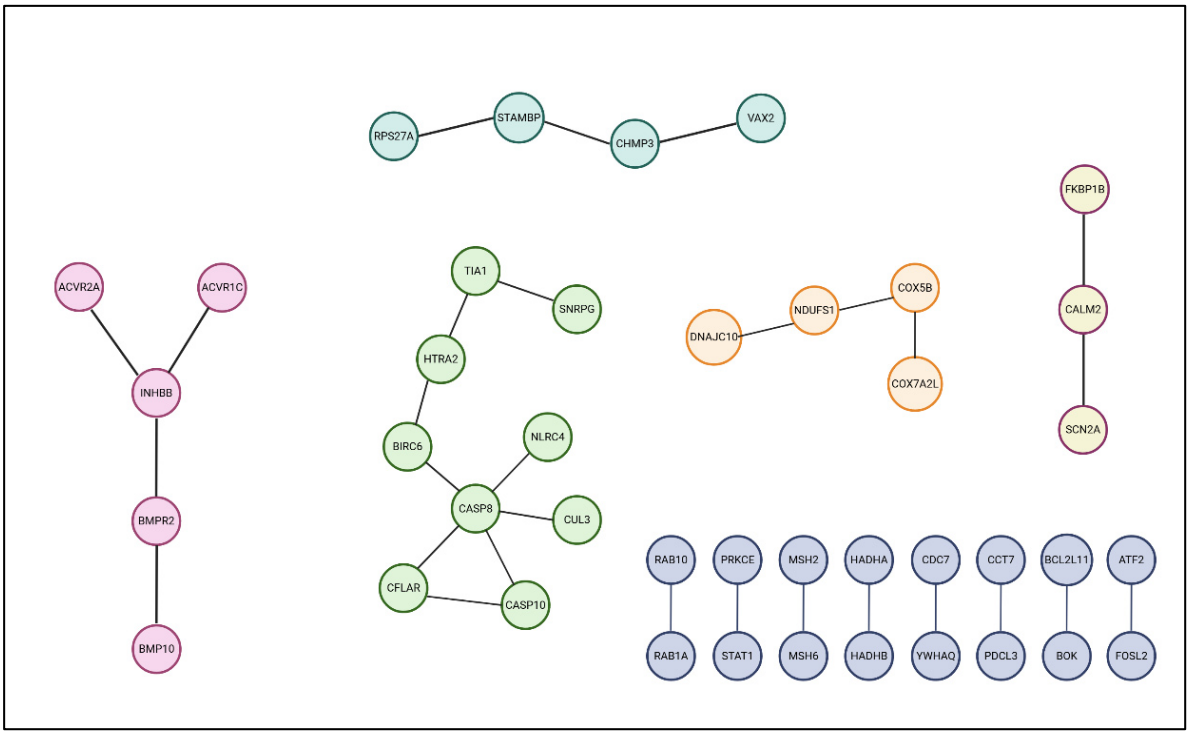


Fig. 3. The protein-protein interaction pathway of selected genes located on Chromosome 2, which are experimentally shown in the STRING database and identified as target proteins in our study. (The figures were created with BioRender program (https://app.biorender.com))

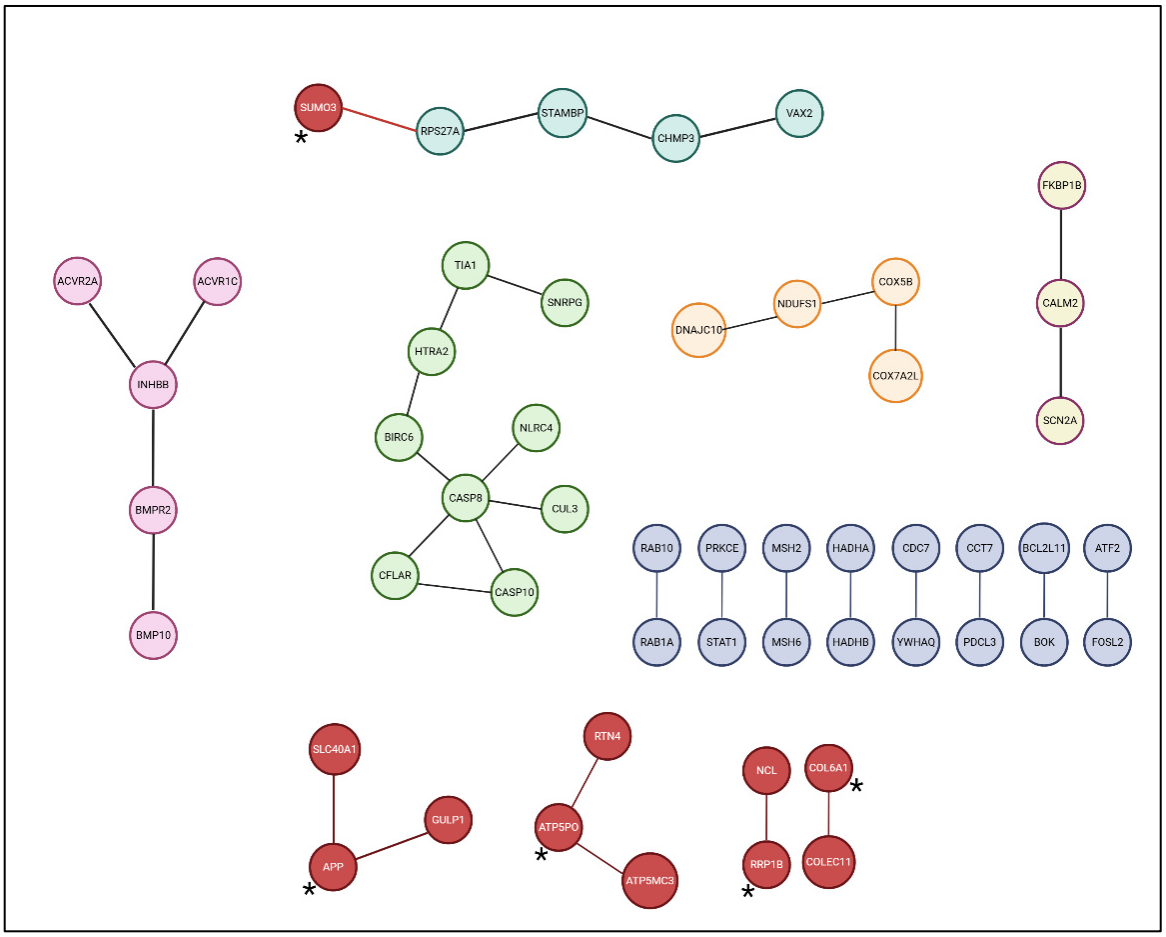


Fig. 4. The protein-protein interaction pathway of selected genes located on Chromosome 2 and 21, which are experimentally shown in the STRING database and identified as target proteins in our study. The protein interactions shown in red represent the interactions between selected genes located on Chromosomes 2 and 21. The proteins marked with an asterisk (*) are encoded by chromosome 21, while the remaining proteins are encoded by chromosome 2. (The figures were created with BioRender program (https://app.biorender.com))

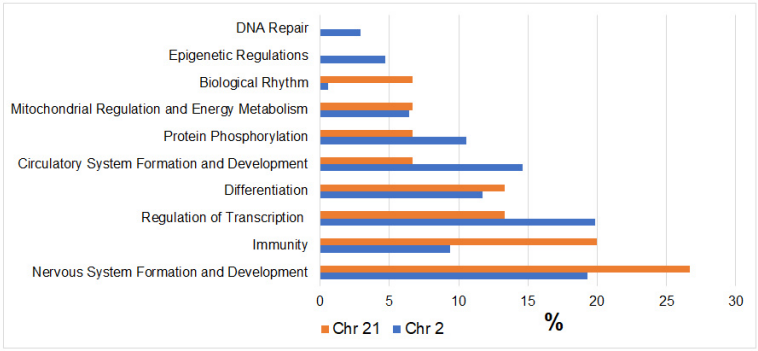
scription regulation, epigenetic regulation, biological rhythm, protein phosphorylation, energy metabolism, and DNA repair is observed in Chr2 compared to Chr21. These suggest that the life incompatibility of Chr2 compared to Ch21 can be explained if there are three copies of the same chromosome due to the gene dosage problem in many crucial cellular activities. Trisomy not only results in the up-regulation of genes but also leads to a genome-level transcriptomic dysregulation, whose downregulation affects each tissue and cell type differently because of epigenetic mechanisms and protein-protein interactions [4].

Aneuploidies are characterized by an extra copy of chromosomes resulting in three or more copies while monosomies are with a loss of chromosome resulting in a haploid chromosome. Diploid organisms have two copies of each gene localized within the homologous chromosomes and most of the genes have two-allele expression and some genes such as the X chromosome function as monoallelic expression. Therefore, gene dosage is an important aspect of the human genome. Aneuploidies are the abnormalities occurring with the distribution of cell dosage as well. However, not all defects in cell dosage may be incompatible with life. For instance, trisomy 21 is life-compatible compared to other trisomies and this should have a reason. Therefore, in this study, we tried to answer the possible reasons for this.

Life compatibility is a broad phenomenon, and the human genome is organized in different levels with high complexity. The molecular functions that are directly related cell survival or death should manage life

A

Cellular and Molecular Function	Chromosome 2 (Chr 2)		Chromosome 21 (Chr 21)	
	Number	Percent (%) within Chr 2	Number	Percent (%) within Chr 21
Nervous System Formation and Development	33	19.30%	4	26.67%
Regulation of Transcription	34	19.88%	2	13.33%
Mitochondrial Regulation and Energy Metabolism	11	6.43%	1	6.67%
Differentiation	20	11.70%	2	13.33%
Circulatory System Formation and Development	25	14.62%	1	6.67%
Immunity	16	9.36%	3	20.00%
Biological Rhythm	1	0.58%	1	6.67%
Epigenetic Regulations	8	4.68%	0	0.00%
Protein Phosphorylation	18	10.53%	1	6.67%
DNA Repair	5	2.92%	0	0.00%
TOTAL	**171 proteins**		**15 proteins**	



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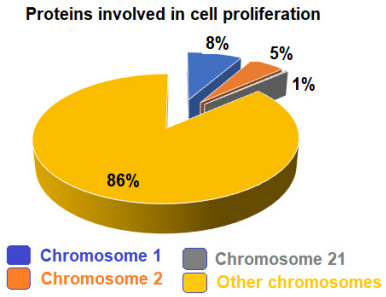

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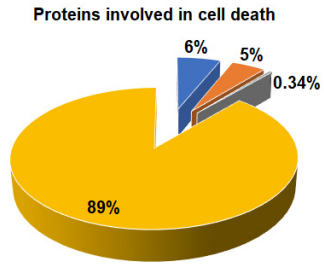

Fig. 5. Overview of proteins involved in cell death and cell proliferation. A shows the comparison of cellular and molecular functions of the genes between Chr2 and Chr21. B and C show the comparison of proteins involved in cell proliferation and cell death, respectively.

in the cells so that we focused on the proteins involved in these mechanisms. Cell survival and cell death related proteins are shown in 10 different molecular classes in Chr2 and Chr21 (This should be noted that some proteins were considered in more than one group) (Fig. 5A). In Chr2, almost 20% of genes are involved in nervous system development and 20% in transcription regulation followed by circulatory system formation (~15%), differentiation (~12%), protein phosphorylation (~11%), and immunity (~10%). Less than 1% of genes in Chr2 are involved in biological rhythm (Fig. 5A). Similarly, in Chr21 the major content is composed of nervous system development (~27% more than Chr2's content), but 20% of Chr21 is composed of immunity-related genes. The following are transcription regulation (13%), and differentiation (13%). Interestingly there is no gene involved in epigenetic regulation and DNA repair in Chr21, but ~5% and ~3% in Chr2 (Fig. 5A). Chr2 includes a gene coding a de novo DNA methyltransferase (DNMT3A) involved in epigenetic regulation which plays an important role in establishing methylation patterns during primitive germ cell development and early embryogenesis [5]. This indicates that it is a protein playing a crucial role in the formation of the embryo, in other words, it is responsible for determining its fate. Therefore, the existence of DNMT3A can be concluded to state the lower life compatibility in Chr2 trisomies than in Chr21 trisomies.

There is a limitation in defining the actual incidence of trisomies because aneuploidies for individual chromosomes cannot be predicted due to undefined abortions. Trisomy 2 is expectedly one of the rarest types of trisomies as well as Trisomy 1. There were

only 3 cases of trisomy 1 reported which all resulted in loss in utero [6]. The length of chromosome 1 is quite similar to Chr2. The largest human chromosome is Chromosome 1 which constitutes 8% of the human genome [7, 8]. Therefore, we also analyzed cell survival and cell death-related protein profiles of Chr1. 48 proteins (8%) and 105 proteins (6%) are involved in cell survival and cell death, respectively. Chr2 has a similar ratio as with each 5% in proliferation and death (Figs. 5B and 3C). Chromosome 21 has been defined as the smallest human autosome representing about 1-1.5% of the human genome [9]. The presence of an extra copy of chromosome 21 is the genetic cause of Down syndrome, which is the most common major cognitive problem affecting 1 in 700 live births. Symptoms frequently observed in most Down syndrome individuals include morphological abnormalities of the head and limbs, short stature, low muscle tone (muscle movement resistance). Other and less frequently observed symptoms are mostly cardiac malformations, gastrointestinal system problems, 20-fold increased risk of leukemia compared to normal individuals, and early onset of Alzheimer's-like neuropathological diseases [10, 11].

CONCLUSION

In conclusion, differences in protein-protein interactions in trisomy 2 and trisomy 21 may help us understand the biological and pathological consequences of these two conditions. While the increased interaction rate in trisomy 2 leads to more complex pathological consequences due to disruptions in cellular functions, the limited interaction network in trisomy 21 may help explain the clinical features of Down syndrome. These studies contribute to our understanding of how molecular differences between the two types of trisomies relate to the biological processes behind the phenotypic differences.

Ethical Statement

Ethical approval is not required for this study. We have used open databases including the websites below:
https://www.ensembl.org/Homo_sapiens/Location/Chromosome?r=21%3A1-1000
https://www.ensembl.org/Homo_sapiens/Location/Chromosome?r=2%3A1-1000
https://www.tau.ac.il/~elieis/Housekeeping_genes.html
https://www.geneimprint.com/site/genes-by-species.Homo+sapiens
http://amigo.geneontology.org/amigo
https://www.ensembl.org
https://www.geneimprint.com

Authors' Contribution

Study Conception: EİŞ, SÇU; Study Design: EİŞ, İN, SÇU; Supervision: SÇU; Funding: N/A; Materials: N/A; Data Collection and/or Processing: EİŞ, İN, SÇU; Statistical Analysis and/or Data Interpretation: EİŞ, İN, SÇU; Literature Review: EİŞ, İN, SÇU; Manuscript Preparation: EİŞ, İN, SÇU and Critical Review: EİŞ, İN, SÇU.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Editor's note

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disease ontologies in Down syndrome. PLoS Comput Biol. 2021;17(9):e1009317. doi: 10.1371/journal.pcbi.1009317.
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Analysis of mortality and cost implications in aspiration pneumonia: A retrospective study

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ABSTRACT

Objectives: The purpose of this study is to analyze the demographic factors, clinical outcomes, and healthcare costs associated with aspiration pneumonia, focusing on mortality rates and the economic burden on healthcare systems.

Methods: A retrospective observational study was conducted using data from patients admitted to the Emergency Department of Samsun Training and Research Hospital between January 2016 and December 2017 and followed in the intensive care unit with a diagnosis of aspiration pneumonia. The study recorded demographic-clinical parameters, nutritional methods, intensive care unit (ICU) length of stay, clinical outcomes, and cost situations for 60 patients.

Results: The average age of male patients was found to be higher than that of female patients, with a broader age range observed among men. The study identified significantly higher ICU stays and costs for deceased patients. The age group with the highest mortality rate was 66-80 years. Additionally, advanced nutritional support methods, such as enteral and parenteral nutrition, were associated with higher mortality rates.

Conclusions: Aspiration pneumonia represents a significant economic burden on healthcare systems, particularly for patients with poor outcomes. Age, ICU length of stay, and the need for advanced nutritional support are key factors influencing mortality. The findings underscore the need for multidisciplinary care approaches and early identification of high-risk patients to optimize treatment and resource allocation.

Keywords: Aspiration pneumonia, nutritional support, mortality, healthcare costs, intensive care unit

Aspiration pneumonia is a serious clinical condition characterized by the infection of lung parenchyma. This condition typically occurs when food, saliva, or gastric contents are aspirated into the lower respiratory tract due to impaired swallowing reflex. Aspiration pneumonia, which is particularly common among the elderly, is closely associated with increased mortality rates and significantly higher healthcare costs. This type of pneumonia often develops in individuals with weakened swallowing reflexes, neurological disorders, or other medical conditions that affect swallowing function [1].

This type of pneumonia is especially prevalent in elderly individuals because aging weakens the swallowing reflex, making it less effective at closing the airways during swallowing. Cerebrovascular diseases, dementia, Parkinson's disease, and other neurological disorders significantly increase the risk of aspiration

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pneumonia in the elderly. In this population, aspiration pneumonia presents a higher mortality rate and imposes a greater economic burden on the healthcare system compared to other forms of pneumonia. Thus, the management of aspiration pneumonia in the elderly is of paramount importance, not only for individual health but also from an economic perspective [2].

The symptomatology of aspiration pneumonia typically includes classic pneumonia signs such as cough, sputum production, dyspnea, and chest pain. However, in elderly patients, symptoms may be more nonspecific, manifesting only as anorexia, weakness, or altered mental status. This can complicate the early diagnosis of pneumonia, potentially delaying treatment and consequently increasing mortality. Therefore, early diagnosis and treatment of aspiration pneumonia, particularly in the elderly population, is crucial [3].

A study by Langmore *et al*. [4] delved into the risk factors associated with aspiration pneumonia in elderly patients, particularly those residing in nursing homes. The study found that poor oral hygiene, dysphagia, and dependency in feeding were significant predictors of aspiration pneumonia. The researchers emphasized the importance of regular oral care and the management of dysphagia as crucial preventive measures. This study highlighted that aspiration pneumonia is not merely a consequence of age but rather a preventable condition when appropriate care protocols are followed [4].

These additional studies reinforce the complexity of aspiration pneumonia as a clinical and public health issue. The condition's high mortality rates, significant economic impact, and association with other comorbidities underscore the need for ongoing research and the development of comprehensive prevention and management strategies. Enhanced care protocols, including routine screening for dysphagia, targeted antibiotic therapy, and patient education, are critical in reducing the burden of aspiration pneumonia on healthcare systems worldwide.

METHODS

Study Design and Population

This study was retrospective observational research and was followed by sixty patients who were admitted to the emergency department of Samsun Training and Research Hospital between January 2016 and December 2017 and were followed in the intensive care unit with a diagnosis of aspiration pneumonia by a pulmonologist. Patients whose data could not be accessible, those under the age of 18 and pregnant women were excluded from the study. The dataset comprises demographic characteristics, comorbidities, nutritional support methods, length of stay (LOS) in the intensive care unit (ICU), cost metrics and clinical outcomes of patients. The primary objective of the study is to analyze the mortality rates and the associated costs of treating aspiration pneumonia in a hospital setting.

Data Collection

Data were extracted from the hospital's electronic medical records system, including information on patient demographics (age, gender), hospitalization details (admission and discharge dates), and clinical outcomes (mortality rates at 30 and 90 days). Cost-related data were also collected and in addition, total and daily hospital costs were calculated by converting from Turkish Lira to Euro.

The variables included in the dataset are: (1) Demographic Information: Age, gender; (2) Clinical Data: Date of hospital admission, length of stay (LOS) in intensive care units (ICU), the requirement for parenteral or oral nutrition, usage of nasogastric (N/G) or percutaneous endoscopic gastrostomy (PEG) tubes; (3) Cost Data: Total cost of hospitalization, daily cost in Euro; and (4) Outcome Measures: In-hospital mortality, 30-day mortality, 90-day mortality, and discharge status.

Ethical Considerations

The study was conducted retrospectively at the Clinic of Chest Diseases of Samsun Training and Research Hospital between January 2016 and December 2017 after obtaining local Ethics Committee approval (Samsun EAH TUEK 2018/34 and 06.02.2018/04). The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Given the retrospective nature of the study, patient consent was not required, but data were anonymized to protect patient confidentiality. The study protocol was approved by the hospital's ethics committee. This methodical approach ensures a comprehensive analysis of the mor-

tality and cost implications of aspiration pneumonia, contributing valuable insights into the management of this condition in clinical settings.

Statistical Analysis

Statistical analyses were performed using IBM SPSS V23. Normality distributions of quantitative data were performed using the Shapiro-Wilk test. Quantitative data that were not normally distributed were compared with the Mann-Whitney U test. Pearson chi-square test was performed to compare qualitative data. Data were presented as mean ± standard deviation, mean (95% CI) and n (%). Statistical significance was accepted as $P<0.05$.

RESULTS

The demographics summary table provides an overview of the age and gender distribution among the patients diagnosed with aspiration pneumonia. The data reveals that the average age of female patients is significantly higher (80.4 years) compared to male patients (71.9 years), which suggests that older females might be more susceptible to aspiration pneumonia. The age range is also broader among females, with the youngest patient being 22 years old and the oldest 96 years old (Table 1). This difference in age distribution could indicate that females generally experience more severe health conditions that predispose them to aspiration pneumonia at an older age. The number of male patients (36) is greater than that of female patients (24), which may reflect either a higher rate of pneumonia diagnosis among men or potentially higher survival rates in this cohort, allowing them to reach the hospital for treatment.

Among clinical parameters sputum and chronic kidney disease were found to be significant with hospital mortality ($P<0.001$ for both). Distribution of nutrition types among patients with aspiration pneumonia offers valuable insights into the nutritional management of these patients (Table 2). It shows that a significant portion of patients required enteral and N/G tube feeding, indicating that a large number of patients had severe swallowing difficulties or were unable to maintain adequate oral intake. The use of PEG tubes and parenteral nutrition, while less common, also highlights the need for advanced nutritional interventions in critically ill patients. Oral nutrition, being the least utilized, underscores the severity of the patients' conditions, where basic oral intake was not sufficient. This distribution reflects the critical role of nutritional support in the management of aspiration pneumonia and suggests that more intensive nutrition strategies are often necessary for patients with severe disease, which is closely associated with higher mortality rates.

The table 2 on nutrition support and mortality examines the different types of nutritional interventions used among patients and their association with mortality. Interestingly, patients who died had higher rates of enteral and parenteral nutrition compared to those who survived, which may suggest that the more critical condition of these patients, necessitating aggressive nutritional support. Oral nutrition and enteral nutrition with N/G tube were found to be statistically significant with hospital mortality ($P=0.002$ and $P=0.015$, respectively). The use of N/G tubes is particularly notable among deceased patients (30 compared to 15 in surviving patients), possibly indicating that these patients had significant swallowing difficulties or were unable to intake food orally. The presence of PEG tubes was almost equal in both groups, suggesting that PEG placement was a consistent treatment strategy regardless of the outcome. Overall, this table highlights the importance of nutritional management in critically ill patients with aspiration pneumonia and how the need for advanced nutritional support is often associated with poorer outcomes.

The cost analysis table presents a detailed com-

Table 1. Age and gender distribution among patients

Gender	n (%)	Mean±SD	Minimum–Maximum	P value
Female	24 (40)	80.4±14.5	22-96	**0.001**
Male	36 (60)	71.9±12.0	25-89	

SD=standard deviation

Table 2. Relationship between hospital mortality and demographic, clinical, nutritional parameters among patients

	Hospital mortality		
	Yes	No	P value
Age (years)	75 (71 - 80)	75 (70 - 81)	0.682
Female	10 (30.3)	14 (51.9)	0.090
Male	23 (69.7)	13 (48.1)	
History of hospitalization the last month	16 (48.5)	10 (37)	0.373
Cough	20 (60.6)	21 (77.8)	0.155
Wheezing	27 (81.8)	20 (74.1)	0.469
Dyspnea	26 (78.8)	15 (55.6)	0.054
Sputum	19 (57.6)	15 (55.6)	**<0.001**
Fever	7 (21.2)	7 (25.9)	0.668
Altered mental status	13 (39.4)	8 (29.6)	0.430
Alzheimer/dementia	19 (57.6)	18 (66.7)	0.471
Coronary disease (CAD/HF)	16 (48.5)	9 (33.3)	0.236
Chronic kidney disease	3 (9.1)	3 (11.1)	**<0.001**
Chronic lung disease	7 (21.2)	4 (14.8)	0.524
Hypertension	11 (33.3)	6 (22.2)	0.342
Diabetes	6 (18.2)	5 (18.5)	0.973
Cerebrovascular disease (ischemic/hemorrhagic)	13 (39.4)	8 (29.6)	0.430
Malignancy	4 (12.1)	1 (3.7)	0.241
Enteral nutrition	29 (87.9)	20 (74.1)	0.169
Parenteral nutrition	7 (21.2)	6 (22.2)	0.925
Oral nutrition	2 (6.1)	8 (29.6)	**0.015**
Nasogastric tube	30 (90.9)	15 (55.6)	**0.002**
PEG	5 (15.2)	4 (14.8)	0.971

Data are shown as mean (95% CI) or n (%) where appropriate. CAD=Coroner Artery Disease, HF=Heart Failure, PEG=Percutaneous Endoscopic Gastrostomy

parison of hospitalization costs between patients who survived and those who did not. On average, the costs are higher for patients who did not survive compared to those who survived, which can be attributed to the more intensive care and prolonged ICU stays required for critically ill patients. Additionally, the daily cost is also higher for deceased patients, indicating that these patients likely required more resource-intensive treatments, such as advanced ventilatory support or specialized medications. This table underscores the substantial economic burden associated with severe cases of aspiration pneumonia, particularly in patients with poor outcomes.

The table-3 explores the relationship between LOS in the ICU, mortality outcomes and costs among the patients. It shows that patients who died had a significantly longer average ICU stay (25 days) compared to those who survived (17 days). This prolonged ICU stay is indicative of the severe condition of these patients and the intensive nature of the care required. Additionally, the cost associated with these patients is also higher, reinforcing the correlation between extended ICU stays, increased healthcare costs, and mortality.

The relationship between cost and mortality among age groups is shown in Table-4. Mortality outcomes by age group provides a visual representation

Table 3. Comparison of mortality (Hospital, 30-day and 90-day), Cost and LOS in ICU

		Total cost (Euro)	Cost daily (Euro)	LOS in ICU
Hospital mortality				
	No (n=27)	3660 (1148-6173)	133 (100-167)	17 (9-26)
	Yes (n=33)	4192 (2455-5930)	156 (129-184)	25 (17-34)
	P value	0.256	0.199	0.147
30-day mortality				
	No (n=36)	5424 (3160-7687)	147 (120-175)	29 (19-38)
	Yes (n=24)	1747 (1064-2430)	144 (110-178)	11 (8-14)
	P value	**0.010**	0.970	**0.008**
90-day mortality				
	No (n=19)	4329 (771-7887)	136 (93-178)	22 (9-34)
	Yes (n=41)	3779 (2336-5222)	151 (127-175)	22 (15-29)
	P value	0.733	0.386	0.962

Data are shown as mean (95% CI). LOS=Length of Stay, ICU=Intensive Care Unit

of how age influences the risk of death in patients with aspiration pneumonia. The data clearly shows that patients aged 66-80 years are at the highest risk, with the most significant number of in-hospital, 30-day, and 90-day mortalities occurring within this age group. Although total cost, hospital mortality, 90-day mortality and LOS in the ICU were found to be higher in patients aged 66-80 years, they were not statistically significant. This trend highlights the vulnerability of individuals in this age bracket, possibly due to the presence of multiple comorbidities and decreased physiological resilience. Notably, the mortality rates decrease slightly for those aged 81 and above, which could suggest a survival bias, where the healthiest older adults survive past 80, or that clinical interventions are more aggressively applied in this older group. In table 4, it is emphasized that the importance of age-specific strategies in managing aspiration pneumonia, particularly in middle-aged and elderly populations, to reduce the high mortality rates observed.

The mortality outcomes by age group table-4 provides crucial insights into how age affects mortality among patients with aspiration pneumonia. The table reveals a concerning trend: patients aged 66-80 years have the highest in-hospital mortality rate (17 deaths) and 90-day mortality rate (19 deaths). This age group also has the longest average ICU stay (28 days), indicating that they are particularly vulnerable to severe complications from aspiration pneumonia. Interestingly, the mortality rates in patients over 81 years are slightly lower, which might suggest either better management of these older patients or that those who sur-

Table 4. Comparison of mortality, LOS in ICU and cost between age groups

	<65 years	66-80 years	>80 years	P value
Total cost (Euro)	4085 (684-7486)	4571 (2558-6585)	3187 (471-5904)	0.100
Daily cost (Euro)	199 (117-281)	147 (123-171)	127 (90-165)	0.107
LOS in ICU	16 (5-28)	28 (18-38)	16 (7-26)	0.054
Hospital mortality*	4 (50)	17 (60.7)	12 (50)	0.707
30-day mortality	3 (37.5)	9 (32.1)	12 (50)	0.419
90-day mortality	4 (50)	19 (67.9)	18 (75)	0.419

Data are shown as mean (95% CI) or n (%) where appropriate. LOS=length of stay, ICU=Intensive Care Unit

vive into this age bracket may have a stronger physiological resilience. However, the data overall underscores the significant impact of age on mortality, with middle-aged to older adults (66-80 years) being at the highest risk, which should inform targeted intervention strategies in clinical settings.

DISCUSSION

This study provides a comprehensive analysis of the demographic characteristics, clinical outcomes, and economic burden associated with the treatment of aspiration pneumonia, with a particular focus on the elderly population. The findings reveal critical insights into the factors that influence mortality and the substantial healthcare costs incurred during the management of this condition.

The demographic analysis underscores the significant impact of age on the incidence and outcomes of aspiration pneumonia. The data indicate that male patients, on average, are older than female patients, suggesting that older men may be more susceptible to developing aspiration pneumonia. This could be due to a combination of factors, including the presence of chronic comorbidities, higher rates of smoking, and possibly lower health-seeking behavior compared to women. The broad age range observed among male patients highlights the need for targeted interventions in this demographic group.

The cost analysis reveals a significant economic burden associated with aspiration pneumonia, particularly in patients who do not survive. The higher costs observed in these patients are likely attributable to the more intensive care required, including prolonged ICU stays, advanced respiratory support, and complex medical management. The considerable variability in costs, as indicated by the high standard deviations, suggests that the clinical course of aspiration pneumonia can differ widely among patients, depending on factors such as the severity of the infection, underlying health conditions, and the timing of intervention. This finding highlights the importance of early diagnosis and appropriate management to potentially reduce costs and improve outcomes [5].

The comparison of costs between survivors and non-survivors also raises important questions about the allocation of healthcare resources. While it is crucial to provide intensive care to critically ill patients, the data suggest that earlier and more aggressive treatment in less severe cases could prevent the progression to critical illness, thereby reducing both mortality and costs. These findings underscore the need for healthcare systems to develop strategies that balance the cost of care with the potential benefits in terms of survival and quality of life.

The relationship between ICU stay duration and mortality outcomes provides further insights into the challenges of managing aspiration pneumonia. The data clearly show that patients who died had significantly longer ICU stays than those who survived. This extended ICU stay reflects the severity of the patients' conditions and the intensive nature of the care required. However, it also raises concerns about the effectiveness of interventions in these critically ill patients. The prolonged ICU stay, coupled with high costs, suggests that these patients may benefit from more individualized treatment plans that focus on both aggressive management and palliative care, depending on the prognosis [6].

The significant differences in ICU stay and associated costs between survivors and non-survivors highlight the need for early identification of patients at high risk of poor outcomes. Implementing more robust risk assessment tools and protocols could help clinicians make timely decisions about the level of care required, potentially reducing both mortality and the economic burden on healthcare systems.

Nutritional support emerged as a critical factor in the management of aspiration pneumonia. The data show that patients who required advanced nutritional interventions, such as enteral and parenteral nutrition, had higher mortality rates. This correlation suggests that severe aspiration pneumonia often leads to significant dysphagia and other complications that necessitate intensive nutritional support. The high use of N/G tubes among deceased patients further underscores the severity of their condition, as these patients likely had compromised ability to protect their airways and manage oral intake [7].

The findings related to nutritional support indicate that early and effective management of swallowing difficulties and nutritional needs is crucial in patients with aspiration pneumonia. Multidisciplinary approaches that include speech and language therapists, dietitians, and physicians may help optimize nutri-

tional strategies and improve patient outcomes. Additionally, the equal use of PEG tubes in both survivors and non-survivors suggests that PEG placement is a consistent treatment approach, regardless of the prognosis, which may warrant further exploration to determine its effectiveness and appropriateness in different patient populations [8].

In a study conducted in the United States, the frequency of death secondary to aspiration pneumonia in patients over 75 years of age was found to be 76%. This study emphasized that advanced age has a significant effect on mortality [9].

The analysis of mortality outcomes by age group reveals a particularly vulnerable demographic: patients aged 66-80 years. This age group not only had the highest in-hospital mortality but also showed significant 30-day and 90-day mortality rates. These findings highlight the increased vulnerability of this age group to severe outcomes from aspiration pneumonia, likely due to the presence of multiple comorbidities and a reduced physiological reserve that impairs recovery.

Interestingly, the slightly lower mortality rates observed in patients over 81 years could indicate a selection bias, where only the healthiest individuals survive into advanced age. Alternatively, it may reflect differences in clinical decision-making, where older patients are treated more conservatively or receive more palliative-focused care. These observations suggest that age alone should not be the primary determinant of care strategies; instead, a more nuanced approach that considers the overall health status, comorbidities, and patient preferences is needed to optimize outcomes.

Teramoto *et al*. [10] examined the healthcare costs associated with aspiration pneumonia in patients with neurological disorders. The study demonstrated that aspiration pneumonia significantly increases the cost of care due to prolonged hospital stays, intensive care unit admissions, and the need for extensive rehabilitation services. The authors recommended early intervention strategies, including the use of prophylactic antibiotics and enhanced nursing care, to mitigate these costs [10].

In a review conducted by Marin *et al*. [11], it was stated that oropharyngeal dysphagia secondary to neurological disorders leads to aspiration pneumonia, thereby increasing costs and the economic burden.

In an another review conducted by Attrill *et al*. [12], it is demonstrated that the presence of oropharyngeal dysphagia significantly increases healthcare utilization and cost.

The findings of this study have significant implications for clinical practice and healthcare policy. The high costs and mortality rates associated with aspiration pneumonia highlight the need for improved prevention strategies, particularly in high-risk populations such as the elderly and those with neurological impairments. Early screening for dysphagia, aggressive management of aspiration risks, and timely nutritional support are essential components of care that could reduce the incidence of severe pneumonia and improve survival rates.

Healthcare systems must also consider the economic implications of aspiration pneumonia. Given the substantial costs associated with ICU care and prolonged hospital stays, there is a clear need for cost-effective interventions that can prevent disease progression and reduce the need for intensive care. This may include the development of specialized care pathways for patients with aspiration pneumonia, with an emphasis on early intervention, multidisciplinary care, and appropriate resource allocation.

Limitations

This study has several limitations that should be considered when interpreting the results. Firstly, the retrospective nature of the study introduces potential biases related to data collection and record accuracy. The reliance on existing medical records may have led to incomplete or inconsistent data, particularly in documenting clinical outcomes and cost-related variables. Secondly, the study sample was drawn from a single institution, which may limit the generalizability of the findings to other healthcare settings or populations. The specific practices and protocols of the institution could influence both mortality and cost outcomes, making it challenging to apply these results universally.

Thirdly, the study's focus on hospital-based data means that it does not account for long-term outcomes or costs associated with post-discharge care and follow-up. As a result, the financial burden and mortality associated with aspiration pneumonia may be underestimated.

Additionally, while the study includes a range of age groups and severity levels, it may not fully capture the impact of other confounding factors such as co-

morbidities or socioeconomic status, which could influence both mortality and costs.

Lastly, the analysis of cost data is limited by variations in billing practices and healthcare resource utilization, which can affect the accuracy and comparability of cost estimates.

Data could be supported by more comprehensive and larger sample studies. Addressing these limitations in future research could provide a more comprehensive understanding of the factors influencing mortality and costs in aspiration pneumonia and contribute to more effective management strategies.

CONCLUSION

In conclusion, this study provides valuable insights into the demographic, clinical, and economic factors associated with aspiration pneumonia. The findings underscore the importance of age, nutritional support, and ICU management in determining patient outcomes and healthcare costs. Addressing the challenges posed by aspiration pneumonia requires a multifaceted approach that includes early detection, targeted interventions, and careful consideration of the cost-benefit ratio of various treatment strategies. By focusing on these areas, healthcare providers can improve outcomes for patients with aspiration pneumonia while also mitigating the significant economic burden associated with this condition.

Ethical Statement

The study was approved by Samsun Training and Research Hospital Ethics Committee (Decision no: TUEK 34-2018 BADE/1-7, 2018/04 and date: 06.02.2018). The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Given the retrospective nature of the study, patient consent was not required, but data were anonymized to protect patient confidentiality.

Authors' Contribution

Study Conception: HBA, SG, İA; Study Design: HBA, SG, İA; Supervision: HBA; Funding: HBA; Materials: HBA, SG, İA; Data Collection and/or Processing: HBA, SG, İA; Statistical Analysis and/or Data Interpretation: HBA, SG, İA; Literature Review: HBA, SG, İA; Manuscript Preparation: HBA, SG, İA; and Critical Review: HBA, SG, İA.

Conflict of interest

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Interplay and clinicopathological correlates of tumor size, multifocality and aggressive variants in patients with operated differentiated thyroid carcinoma: A retrospective cohort study

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ABSTRACT

Objectives: To investigate the interplay and clinicopathological correlates of tumor size, cancer foci (multifocality/bilaterality), and aggressive variants in patients with operated differentiated thyroid cancer (DTC).

Methods: A total of 596 patients with operated DTC (median age: 47.0 (range: 18.0-87.0 years, 77.5% were females) were included in this retrospective cohort study. Data on patient demographics, cancer foci, concomitant Hashimoto's thyroiditis, surgery type, DTC subtype (papillary thyroid cancer [PTC], follicular thyroid cancer [FTC]) and variants, tumor size, lymph node metastasis, tumor invasion were recorded.

Results: PTC aggressive variant (21.9%, P=0.045), extrathyroidal invasion (24.6%, P=0.012), tall cell PTC variant (60.3%, P=0.043), and widely invasive FTC variants (60.0% P=0.002) rates were significantly higher in the bilateral multifocal tumors than in the unifocal and unilateral multifocal tumors. The rates of Hashimoto's thyroiditis (59.8%, P<0.001) and PTC subtype (99.6%, P<0.001) were significantly higher, while the rates of lymph node metastasis (5.8%, P<0.001), capsule invasion (11.6%, P<0.001), vascular invasion (0.4%, P<0.001) and extrathyroidal invasion (4.5%, P<0.001) were significantly lower in <10 mm than in >10 mm tumors. Presence vs. absence of PTC aggressive variant was associated with significantly higher greatest tumor size (12 mm, P=0.013) and higher rates of multifocal tumor (50.5%, P=0.013) and extrathyroidal invasion (33.0%, P<0.001).

Conclusions: Our findings revealed the presence of bilaterality/multifocality and aggressive variants in a considerable proportion of patients with operated DTC, and a multifaceted interplay between bilaterality/multifocality, tumor size, and PTC aggressive variants, in addition to their individual effects on increased risk of tumor invasion, particularly the extrathyroidal invasion.

Keywords: Differentiated thyroid cancer, cancer foci, tumor size, multifocality/bilaterality, aggressive variants.

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy, while papillary thyroid cancer (PTC) is the main subtype accounting for over 85% of DTC cases [1, 2]. Although PTC usually has a favorable prognosis, up to 20% of patients develop loco-regional recurrence with

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worse clinical outcomes requiring further treatment, and distant metastasis occurs in 10-15% of patients [3, 4].

Tumor size, extrathyroidal extension, and multifocality of tumor are considered amongst the clinicopathological factors used to differentiate patients at high risk of recurrence [5]. Multifocality is a frequent pathological feature of PTC generally detected in pathology specimens postoperatively [6], which may occur as multicentric independent synchronous neoplastic foci or as intrathyroidal spread from the primary tumor [5-7]. Multifocal lesions, particularly those with bilateral involvement, are associated with a higher degree of malignant characteristics and a more aggressive disease with an increased risk of lymph node metastasis and extrathyroidal extension [2, 6, 8, 9]. Accordingly, multifocality is involved in the PTC risk stratification systems as a poor prognostic factor associated with increased risk of local recurrence, lymph-node metastasis, and distant metastasis [10, 11].

However, there are conflicting results in the literature on the prognostic significance of multifocality in PTC. Some studies indicated more aggressive features and worse outcome in multifocal versus unifocal tumors, whereas others reported no such differences based on cancer foci or aggressive features [6, 8]. Hence, the clinical and prognostic implications of multifocality/bilaterality have been highly controversial, which contributes to uncertainty regarding the choice of appropriate treatment [5, 6, 11].

Therefore, this retrospective cohort study aimed to comparatively investigate the interplay and clinicopathological correlates of tumor size, cancer foci (multifocality/bilaterality), and aggressive variants in patients with operated DTC.

METHODS

Study Population

A total of 596 patients with operated DTC (median(min-max) age: 47.0(18.0-87.0) years, 77.5%

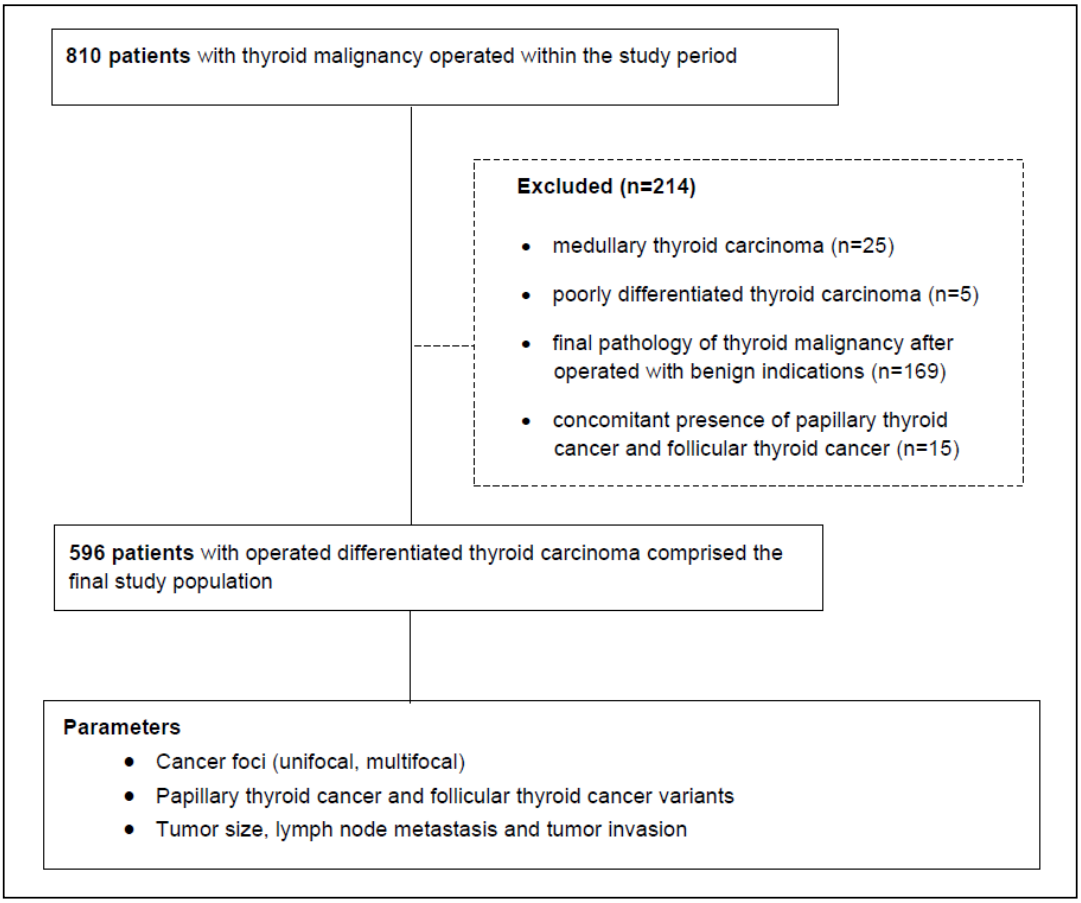

Fig. 1. Study flowchart.

were females) were included in this retrospective cohort study conducted at a tertiary care center between January 2011 and August 2023. Adult (age >18 years) patients who operated with the suspected diagnosis of DTC and had the final pathological diagnosis confirming the DTC were included in the study. Concomitant presence of PTC and FTC subtypes, recurrence, and final pathology of thyroid malignancy after being operated on with benign indications such as multinodular goiter or treatment-resistant Graves' disease were the exclusion criteria of the study. Accordingly, while overall 810 patients with thyroid malignancy were operated on within the study period, the final study population comprised 596 patients with exclusion of 214 patients due to medullary thyroid carcinoma (n=25), poorly differentiated thyroid carcinoma (n=5), final pathology of thyroid malignancy after operated with benign indications such as multinodular goiter or treatment-resistant Graves' disease (n=169), concomitant presence of PTC and FTC (n=15) (Fig. 1).

Written informed consent was obtained from each participant. This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Bursa Uludag University Clinical Research Ethics Committee (Date of Approval: 12/12/2023; Protocol No: 2023-27/20).

Assessments

Data on patient demographics (age, gender), cancer foci (unifocal, multifocal), concomitant Hashimoto's thyroiditis, surgery type, DTC subtype (PTC, follicular thyroid cancer [FTC]) and variants, tumor size, lymph node metastasis, tumor invasion (capsule, vascular and extrathyroidal) were recorded in each patient. Study parameters were also evaluated across cancer foci (unilateral unifocal, unilateral multifocal, and bilateral multifocal) and tumor size (<10 mm, 10-39 mm, and ≥40 mm) subgroups, while cancer foci and tumor invasion status were also evaluated with respect to PTC and FTC variants.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY). The conformity of the variables to the normal distribution was examined using the Kolmogorov-Smirnov method. The chi-square (X^2) test and Fisher's exact test were used to compare categorical data. Mann-Whitney U test was used to analyze two independent non-normally distributed variables. Data were expressed as median (minimum-maximum), and percent (%) where appropriate. $P<0.05$ was considered statistically significant.

RESULTS

Patient Demographics, Surgery Type, and Tumor Characteristics

Median patient age was 47.0 years (range, 18.0 to 87.0 years) and females comprised 77.5% of the study population. Concomitant Hashimoto's thyroiditis was noted in 52.7% of patients (Table 1). Total thyroidectomy (88.9%) was the leading operation and PTC (94.8%) was the most common DCT subtype. Multifocal cancer was noted in 38.1% (bilateral in 30.7%) of patients and PTC aggressive variants were noted in 17.1% of patients. Papillary thyroid microcarcinoma (PTMC; tumor size <10 mm) was evident in 37.6% of patients. Lymph node metastasis, capsule invasion, vascular invasion, and extrathyroidal invasion were noted in 13.4%, 19.1%, 7.4% and 17.6% of patients, respectively (Table 1).

Study Parameters in Cancer Foci Subgroups

Bilateral multifocal tumors were associated with significantly higher total thyroidectomy (99.5% vs. 84.6% and 81.8%, respectively, P<0.001), PTC aggressive variant (21.9% vs. 13.6% and 15.9%, respectively, P=0.045) and extrathyroidal invasion (24.6% vs. 14.4% and 15.9%, respectively, P=0.012) rates, compared to the unifocal and unilateral multifocal tumors (Table 2). PTC subtype was significantly more common in the unilateral multifocal (100.0%) and bilateral multifocal (98.4%) tumors compared to the unifocal tumors (92.4%, P=0.003). The largest tumor size was significantly lower in the unilateral multifocal tumors than in unifocal tumors and bilateral multifocal tumors (median (min-max): 8.5 (1.0-45.0) vs. 12.0 (1.0-180.0) and 12.0 (2.0-105.0) mm, respectively, P=0.024). Patient demographics, and the presence of Hashimoto thyroiditis, lymph node metastasis, and capsular and vascular tumor invasion were similar across cancer foci subgroups (Table 2).

Table 1. Patient demographics, surgery type and tumor characteristics (n = 596)

Age (year), median (min-max)	Total	47.0 (18.0-87.0)
	Females	46.5 (18.0-82.0)
	Males	49.5(20.0-87.0)
Gender, n (%)		
Female		462(77.5)
Male		134(22.5)
Concomitant Hashimoto's thyroiditis, n (%)		
No		282 (47.3)
Yes		314 (52.7)
Surgery type, n (%)		
Total thyroidectomy		530(88.9)
Lobectomy		62(10.4)
Other		4(0.7)
DTC subtype, n (%)		
PTC		565(94.8)
FTC		31(5.2)
Cancer foci, n (%)		
Unifocal		369(61.9)
Unilateral multifocal		44(7.4)
Bilateral multifocal		183(30.7)
PTC aggressive variants, n (%)		
Absent		468 (82.9)
Present		97 (17.1)
Lymph node metastasis, n (%)		
Absent		516 (86.6)
Present		80 (13.4)
Central		*27 (4.5)*
Lateral		*38 (6.4)*
Both		*15 (2.5)*
Largest tumor size (mm), median (min-max)		12.0 (1.0-180.0)
Tumor size groups, n (%)	<10 mm (PTMC)	224 (37.6)
	10-39 mm	329 (55.2)
	≥40 mm	43 (7.2)
Capsule invasion, n (%)		
Absent		482 (80.9)
Present		114 (19.1)
Vascular invasion, n (%)		
Absent		552 (92.6)
Present		44 (7.4)
Extrathyroidal invasion, n (%)		
Absent		491 (82.4)
Present		105 (17.6)

DTC=Differentiated thyroid carcinoma, PTC=Papillary thyroid cancer, FTC=Follicular thyroid cancer, PTMC=Papillary thyroid microcarcinoma

Table 2. Study parameters according to cancer foci

	Cancer foci			
	Unifocal (n = 369)	Unilateral multifocal (n = 44)	Bilateral multifocal (n = 183)	P value
Age (year), median (min-max)	47.0 (18.0-82.0)	47.5 (24.0-81.0)	47.0 (18.0-87.0)	0.962
Gender, n(%)				
Female	282 (76.4)	35 (79.5)	145 (79.2)	0.716
Male	87 (23.6)	9 (20.5)	38 (20.8)	
Hashimoto's thyroiditis, n(%)				
No	181 (49.1)	15 (34.1)	86 (47.0)	0.170
Yes	188 (50.9)	29 (65.9)	97 (53.0)	
Surgery type, n(%)				
Total thyroidectomy	312 (84.6)[a]	36 (81.8)[a]	182 (99.5)	**<0.001**
Lobectomy	55 (14.9)	7 (15.9)	0 (0.0)	
Other	2 (0.5)	1 (2.3)	1 (0.5)	
DTC subtype, n(%)				
PTC	341 (92.4)	44 (100.0)[b]	180 (98.4)[b]	**0.003**
FTC	28 (7.6)	0 (0.0)	3 (1.6)	
PTC aggressive variants, n(%)				
Absent	319 (86.4)	37 (84.1)	143 (78.1)	**0.045**
Present	50 (13.6)[a]	7 (15.9)[a]	40 (21.9)	
Lymph node metastasis, n(%)				
Absent	324 (87.8)	40 (90.9)	152 (83.1)	0.208
Present	45 (12.2)	4 (9.1)	31 (16.9)	
Central	14 (31.1)	1 (25.0)	12 (38.7)	0.812
Lateral	21 (46.7)	3 (75.0)	14 (45.2)	
Both	10 (22.2)	0 (0.0)	5 (16.1)	
Largest tumor size (mm), median (min-max)	12.0 (1.0-180.0)	8.5 (1.0-45.0)	12.0 (2.0-105.0)	**0.024**
Tumor size groups, n(%) <10 mm	143 (38.8)	23 (52.3)	58 (31.7)	0.097
10-39 mm	198 (53.7)	20 (45.5)	111 (60.7)	
≥40 mm	28 (7.6)	1 (2.3)	14 (7.7)	
Capsule invasion, n(%)				
Absent	299 (81.0)	36 (81.8)	147 (80.3)	0.967
Present	70 (19.0)	8 (18.2)	36 (19.7)	
Vascular invasion, n(%)				
Absent	337 (91.3)	43 (97.7)	172 (94.0)	0.214
Present	32 (8.7)	1 (2.3)	11 (6.0)	
Extrathyroidal invasion, n(%)				
Absent	316 (85.6)	37 (84.1)	138 (75.4)	**0.012**
Present	53 (14.4)	7 (15.9)	45 (24.6)	

DTC=Differentiated thyroid carcinoma, PTC=Papillary thyroid cancer, FTC=Follicular thyroid cancer

Table 3. Study parameters according to tumor size

	Tumor size			
	<10 mm (n = 224)	**10-39 mm (n = 329)**	**≥40 mm (n = 43)**	**P value**
Age (year), median (min-max)	47.0 (20.0-81.0)	48.0 (18.0-87.0)	45.0 (20.0-82.0)	0.995
Gender, n (%)				
Female	186 (83.0)*	249 (75.7)	27 (62.8)*	**0.007**
Male	38 (17.0)	80 (24.3)	16 (37.2)	
Hashimoto's thyroiditis, n (%)				
No	90 (40.2)	160 (48.6)	32 (74.4)	**<0.001**
Yes	134 (59.8)*	169 (51.4)	11 (25.6)*	
Surgery type, n (%)				
Total thyroidectomy	190 (84.8)	305 (92.7)*	35 (81.4)	**0.006**
Lobectomy	32 (14.3)	23 (7.0)	7 (16.3)	
Other	2 (0.9)	1 (0.3)	1 (2.3)	
DTC subtype, n (%)				
PTC	223 (99.6)*	310 (94.2)	32 (74.4)*	**<0.001**
FTC	1 (0.4)	19 (5.8)	11 (25.6)	
PTC aggressive variants, n (%)				
Absent	201 (89.7)	262 (79.6)	36 (83.7)	**0.007**
Present	23 (10.3)	67 (20.4)*	7 (16.3)	
Lymph node metastasis, n (%)				
Absent	211 (94.2)	269 (81.8)	36 (83.7)	**<0.001**
Present	13 (5.8)*	60 (18.2)	7 (16.3)	
Central	3 (23.1)	22 (36.7)	2 (28.6)	0.812
Lateral	8 (61.5)	27 (45.0)	3 (42.9)	
Both	2 (15.4)	11 (18.3)	2 (28.6)	
Capsule invasion, n (%)				
Absent	198 (88.4)	263 (79.9)	21 (48.8)	**<0.001**
Present	26 (11.6)*	66 (20.1)	22 (51.2)	
Vascular invasion, n (%)				
Absent	223 (99.6)	297 (90.3)	32 (74.4)	**<0.001**
Present	1 (0.4)*	32 (9.7)	11 (25.6)	
Extrathyroidal invasion, n (%)				
Absent	214 (95.5)	244 (74.2)	33 (76.7)	**<0.001**
Present	10 (4.5)*	85 (25.8)	10 (23.3)	
Cancer foci, n (%)				
Unifocal	143 (63.8)	198 (60.2)	30 (69.8)	0.392
Multifocal	81 (36.2)	131 (39.8)	13 (30.2)	

DTC=Differentiated thyroid carcinoma, PTC=Papillary thyroid cancer, FTC=Follicular thyroid cancer
*P<0.01 or P<0.001 compared to other groups

Study Parameters in Tumor Size Subgroups

In patients with PTMC (tumor size <10 mm), compared to those with tumor size of 10-39 mm and tumor size of >40 mm, percentage of females were significantly higher (83.0% vs. 75.7% and 62.8%, P=0.007) along with higher rate of concomitant Hashimoto's thyroiditis (59.8% vs. 51.4% and 25.6%, P<0.001) and PTC (99.6% vs. 94.2% and 74.4%, P<0.001) but lower rates of lymph node metastasis (5.8% vs. 18.2% and 16.3%, P<0.001), capsule invasion (11.6% vs. 20.1% and 51.2%, P<0.001), vascular invasion (0.4% vs. 9.7% and 25.6%, P<0.001) and extrathyroidal invasion (4.5% vs. 25.8% and 23.3%, P<0.001) (Table 3). The rates of total thyroidectomy (92.7% vs. 84.8% and 81.4%, P=0.006) and PTC aggressive variants (20.4% vs. 10.3% and 16.3%, P=0.007) were significantly higher in tumors of 10-39 mm in size than in tumors of <10 mm and >40 mm in size (Table 3).

PTC and FTC Variants According to Cancer Foci

Overall, PTC variants were noted in 724 foci (59.5% were classical variants), and FTC variants were noted in 31 foci (74.2% were minimally invasive variants) among 596 patients (Table 4). Classical PTC variants (56.4% vs. 43.6%, P=0.043) and minimally invasive FTC variants (100.0% vs. 0.0%, P=0.002) were associated with significantly higher rates of unifocal tumor than multifocal tumor, while tall cell PTC variants (60.3% vs. 39.7%, P=0.043) and widely invasive FTC variants (60.0% vs. 40.0%, P=0.002) were associated with significantly higher rate of multifocal tumor than unifocal tumor (Table 4).

PTC and FTC Variants According to Tumor Invasion

Capsule invasion was less common in classical (14.8%) and tall cell (15.5%) PTC variants, but more common in follicular PTC variants (24.9%) (P=0.026). No significant difference was noted in vascular invasion rates concerning PTC variants. Extrathyroidal invasion was more common in PTC aggressive variants (columnar cell: 44.4%, diffuse sclerosing: 88.9%), P<0.001) (Table 5). Capsule invasion was more common in minimally invasive

Table 4. PTC and FTC variants according to cancer foci

	Total	Cancer foci		
		Unifocal	Multifocal	P value
PTC variants, n (%)	724			
Classical	431 (59.5)	243 (56.4)	188 (43.6)	**0.043**
Follicular	177 (24.4)	85 (48.0)	92 (52.0)	
Tall cell[a]	58 (8.0)	23 (39.7)	35 (60.3)	
Solid[a]	13 (1.8)	8 (61.5)	5 (38.5)	
Hobnail[a]	12 (1.7)	9 (75.0)	3 (25.0)	
Oncocytic	10 (1.4)	7 (70.0)	3 (30.0)	
Columnar cell[a]	9 (1.2)	6 (66.7)	3 (33.3)	
Diffuse sclerosing[a]	9 (1.2)	4 (44.4)	5 (55.6)	
Clear cell	4 (0.6)	4 (100.0)	0 (0.0)	
Cribriform-morular	1 (0.1)	1 (100.0)	0 (0.0)	
Warthin-like	0 (0.0)	0 (0.0)	0 (0.0)	
FTC variants, n (%)	31			
Minimally invasive	23 (74.2)	23 (100.0)	0 (0.0)	**0.002**
Widely invasive	5 (16.1)	2 (40.0)	3 (60.0)	
Hurtle cell carcinoma	3 (9.7)	3 (100.0)	0 (0.0)	

PTC=Papillary thyroid cancer, FTC=Follicular thyroid cancer
[a]aggressive PTC variants, Fisher exact test

Table 5. PTC and FTC variants according to tumor invasion

	Capsule invasion		Vascular invasion		Extrathyroidal invasion	
PTC variants, n (%)	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Classical	367 (85.2)	64 (14.8)	408 (94.7)	23 (5.3)	351 (81.4)	80 (18.6)
Follicular	133 (75.1)	44 (24.9)	167 (94.4)	10 (5.6)	148 (83.6)	29 (16.4)
Tall cell[a]	49 (84.5)	9 (15.5)	57 (98.3)	1 (1.7)	42 (72.4)	16 (27.6)
Solid[a]	9 (69.2)	4 (30.8)	11 (84.6)	2 (15.4)	11 (84.6)	2 (15.4)
Hobnail[a]	10 (83.3)	2 (16.7)	11 (91.7)	1 (8.3)	9 (75.0)	3 (25.0)
Oncocytic	7 (70.0)	3 (30.0)	10 (100.0)	0 (0.0)	8 (80.0)	2 (20.0)
Columnar cell[a]	7 (77.8)	2 (22.2)	7 (77.8)	2 (22.2)	5 (55.6)	4 (44.4)
Diffuse sclerosing[a]	9 (100.0)	0 (0.0)	7 (77.8)	2 (22.2)	1 (11.1)	8 (88.9)
Clear cell	3 (75.0)	1 (25.0)	4 (100.0)	0 (0.0)	3 (75.0)	1 (25.0)
Cribriform-morular	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
Warthin-like	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
P value	**0.026**		0.086		**<0.001**	
FTC variants, n (%)	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Minimally invasive	4 (17.4)	19 (82.6)	18 (78.3)	5 (21.7)	21 (91.3)	2(8.7)
Widely invasive	5 (100.0)	0 (0.0)	1 (20.0)	4 (80.0)	4 (80.0)	1(20.0)
Hurtle cell carcinoma	0 (0.0)	3 (100.0)	1 (33.3)	2 (66.7)	3 (100.0)	0(0.0)
P value	**0.001**		**0.019**		0.606	

PTC=Papillary thyroid cancer, FTC=Follicular thyroid cancer.
[a]Aggressive PTC variants, Fisher exact test

(82.6%) and Hurtle cell carcinoma (100.0%) variants of FTC but less common in widely invasive FTC variants (P=0.001). Vascular invasion was less common in the minimally invasive FTC variant (21.7%) but more common in the widely invasive FTC variant (80.0%) (P=0.019). No significant difference was

Table 6. Tumor characteristics according to presence of PTC aggressive variant

	PTC aggressive variant		
	No	**Yes**	**P value**
Tumor characteristics			
The greatest tumor size (mm), median(min-max)	10.5 (1.0-77.0)	12.0 (3.0-105.0)	**0.013**
Concomitant Hashimoto's thyroiditis, %	53.4	55.7	0.686
Multifocal tumor, %	37.0	50.5	**0.013**
Lymph node metastasis, %	13.2	18.6	0.172
Capsule invasion, %	16.0	17.5	0.726
Vascular invasion, %	5.6	7.2	0.526
Extrathyroidal invasion, %	15.0	33.0	**<0.001**

PTC=Papillary thyroid cancer

noted in extrathyroidal invasion rates concerning FTC variants (Table 5).

Tumor Characteristics According to the Presence of PTC Aggressive Variant

Presence vs. absence of PTC aggressive variant was associated with significantly higher value of the greatest tumor size (median(min-max) 12.0(3.0-15.0) vs. 10.5(1.0-77.0), P=0.013), higher rate of concomitant Hashimoto's thyroiditis (50.5 vs. 37.0%, P=0.013) and extrathyroidal invasion (33.0% vs. 15.0%, P<0.001) (Table 6).

Overall Correlates of the Bilateral Multifocal Tumor, <10 mm Tumor Size, and PTC Aggressive Variant

Total thyroidectomy (99.5%, P<0.001), PTC aggressive variant (21.9%, P<0.05) and extrathyroidal invasion (24.6%, P=0.012), tall cell PTC variant (60.3%, P=0.043) and widely invasive FTC variants (60.0% P=0.002) rates were significantly higher in the bilateral multifocal tumors than in unifocal tumors and unilateral multifocal tumors (Fig 2). Percentage of females (83.0%, P=0.007), rate of Hashimoto's thyroiditis (59.8%, P<0.001) and PTC subtype (99.6%, P<0.001) were significantly higher, while the rates of lymph node metastasis (5.8%, P<0.001), capsule invasion (11.6%, P<0.001), vascular invasion (0.4%, P<0.001) and extrathyroidal invasion (4.5%, P<0.001) were significantly lower in <10 mm tumors than in >10 mm tumors. Presence vs. absence of PTC aggressive variant was associated with significantly higher greatest tumor size (12 mm, P=0.013) and higher rates of multifocal tumor (50.5%, P=0.013) and extrathyroidal invasion (33.0%, P<0.001) (Fig 2).

DISCUSSION

Our findings in a retrospective cohort of patients with operated DTC revealed a potential interplay between the cancer foci, tumor size, and tumor variants, along with the significant adverse impact of multifocality, larger tumor size, and PTC aggressive variants on the extent of tumor invasion.

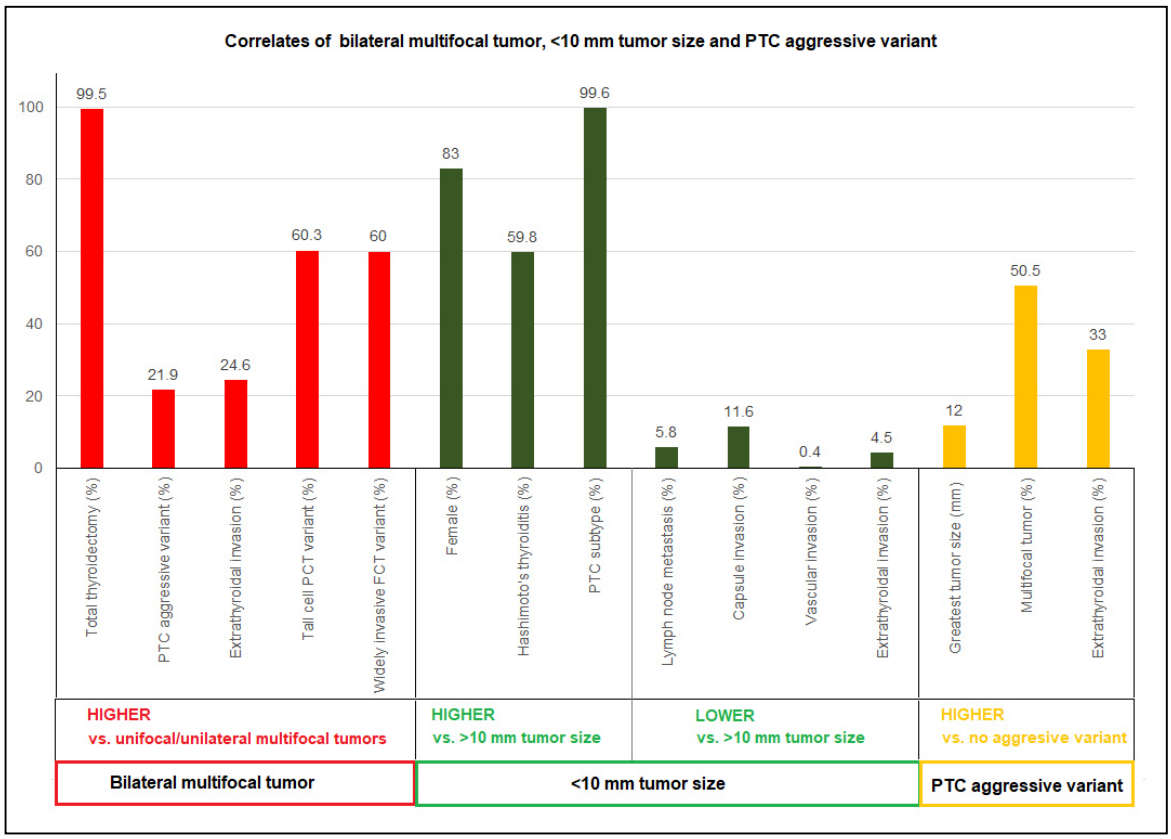

Fig. 2. Correlates of bilateral multifocal tumor, <10 mm tumor size and PTC aggressive variant.

In our cohort, the multifocal tumor was noted in 38.1% (bilateral in 30.7%) of patients, PTC aggressive variants in 17.1% of patients, and PTMC (tumor size <10 mm) in 37.6% of patients. These findings are consistent with previously reported frequencies of multifocality (18%-87%), unilateral multifocality (30.1%), bilateral multifocality (13%-71%), PTMC (39.0%), multifocal PTMC (13.4%-36.1%) and PTC aggressive variants (5-28%) in DTC series [6, 9-13].

Multifocality, particularly the bilaterality of multifocal PTC, has been consistently reported to be a poor prognostic factor for PTC regarding its strong association with aggressive clinicopathological factors such as the increased risk of tumor size >1 cm, extrathyroidal extension, locoregional recurrence, lymph node metastasis, and distant metastasis [9-11, 13, 14].

In our cohort, bilateral multifocal tumor was associated with significantly higher rates of extrathyroidal invasion and total thyroidectomy and a more common presence of PTC aggressive variants, tall cell PTC variants, and widely invasive FTC variants compared to unifocal tumors and unilateral multifocal tumors. Lymph node metastasis and capsular and vascular tumor invasion rates were similar across cancer foci subgroups in our study. In a metanalysis of 15 studies comprising 9,665 patients with PTC, no significant differences were noted between unilateral multifocal and unilateral unifocal PTC in terms of age, gender, extrathyroidal extension, and tumor size but lymph node metastasis rates were higher in the unilateral multifocal group, emphasizing the role of multifocality in tumor aggressiveness and tumorigenesis [5].

Notably, in our cohort, the effect of cancer foci appeared to significantly differ between unifocal and bilateral multifocal groups, rather than between unifocal and unilateral multifocal groups. Apart from lower tumor size in unilateral multifocal tumors, no significant difference was noted between unifocal and unilateral multifocal groups in terms of patient demographics, lymph node metastasis or tumor invasion. Likewise, in a previous study with PTC patients, bilateral and unilateral multifocal PTC were reported to differ significantly concerning larger tumor size, higher frequency of gross extrathyroidal extension, and a more advanced T stage in bilateral multifocal PTC but were found to be similar in terms of aggressive PTC subtypes, cervical LN metastasis, BRAFV600E positivity, and lymphatic, vascular, and perineural invasion [8].

PTMC (tumor size <10 mm) was more common in our female patients and in those with concomitant Hashimoto's thyroiditis and was associated with favorable prognostic factors such as lower rates of lymph node metastasis and tumor invasion (capsule, vascular, and extrathyroidal) compared to larger tumor size (particularly >40 mm). Similarly, in previous PTC studies, tumor size >1 cm was associated with an increased likelihood of multifocality [10, 12, 15], while tumor size >4 cm was found to be an independent predictor for bilaterality in multifocal PTCs [11]. PTC (compared to PTMC) and >5 mm PTMC (compared to ≤5 mm PTMC) were reported to have more aggressive histopathological features such as capsule invasion, bilaterality, and lymph node metastasis [16]. It is also suggested that tumor multifocality is an important prognostic factor for PTCs larger than 1 cm but may have little or no prognostic significance for PTMC [17].

Multifocal and unifocal lesions were similar in terms of gender and Hashimoto's thyroiditis in our study, while some studies indicated a higher rate of multifocal lesions in male subjects and a lower incidence of Hashimoto's thyroiditis in multifocal patients compared with those in solitary lesions (41% vs 60%) [9, 18]. The association of Hashimoto's thyroiditis with <10 mm tumors but not with multifocality in our study supports the consideration of close follow-up performed for Hashimoto's thyroiditis to be associated with increased diagnosis rates of <10 mm thyroid malignancies with no relation to the clinical course [19]. Likewise, PTC subjects complicated with benign thyroid diseases were reported to present with relatively small tumors and a relatively low incidence of lymph node metastasis [9, 20].

In our cohort, patient age (median 47 years overall, 46.5 years in females, 49.5 years in males) was not associated with tumor size or multifocality, which seems notable given the consideration of age over 45 as an independent risk factor for recurrence and age over 55 as a risk factor for postoperative mortality in patients with thyroid malignancy [21]. However, some studies also reported no correlation between age and prognosis [18].

Although multifocality was indicated as an independent risk factor for lymph node metastasis (cervical and lateral) in previous meta-analyses [5], lymph node metastasis appeared to be associated with tumor size

(less common in the case of PTMC) but not with multifocality in our study. Also, there was a nonsignificant tendency for increased risk of lymph node metastasis in patients with vs. those without PTC aggressive variant (18.6 vs. 13.2%). These findings may relate to the low sensitivity and specificity of preoperative US in detecting lymph node metastasis [22]. Indeed, some studies indicated that multifocality "per se" was not independently associated with lymph node metastasis or worse clinical outcomes in PTC patients [6].

In our cohort, bilateral multifocality was associated with PTC aggressive variants, particularly the tall cell PTC variants, as well as with the widely invasive FTC variants. The relation of multifocality with aggressive variants was also reported in previous studies which indicated multifocality in all tall cell variants and increased likelihood of multifocality in mixed-variant tumors including both papillary and follicular variants [10,12,15]. Moreover, bilaterality itself was associated with a higher risk of capsule invasion and a higher incidence of the "tall-cells" variant when compared to unilateral tumors [16]. The association of PTC aggressive variants with significantly greater tumor size and higher rates of multifocal tumors are notable in this regard, given the adverse impact of tumor size >40 mm (capsular and vascular invasion) and bilateral multifocal tumor (extrathyroidal invasion) on tumor invasion, increasing the likelihood of a total thyroidectomy operation. Previous studies also indicated the association of the aggressive variants at the time of diagnosis with advanced stage and increased risk of postoperative recurrence and resistance to radioactive iodine ablation (RAI) therapy [14, 23].

Overall, more aggressive initial treatment (including total thyroidectomy and RAI) and closer follow-up are employed for patients with multifocal disease, given the higher incidence rate of recurrence/persistence than unifocal disease [5, 12, 17, 20]. Specifically, our total thyroidectomy rates were highest for bilateral multifocal tumors (99.5%), followed by unilateral unifocal tumors (84.6%) and unilateral multifocal tumors (81.8%). This seems consistent with the consideration of multifocality, increased tumor size and tumor invasion amongst the factors predicting the recurrence risk in patients with DTC and the association of bilateral PTC with multiple cancer foci and easy extrathyroidal extension [9, 12, 24].

Given the propensity for PTC to be multifocal (often bilateral, mostly in familial disease), a lower risk of loco-regional disease recurrence has been reported following total thyroidectomy as compared to thyroid lobectomy [6, 25, 26]. Also, occult carcinoma rates of 45.1% and 16.7% were reported in total thyroidectomy operations performed for solitary nodules and unilateral PTMC, respectively [27, 28]. Although the size of preoperatively undetected occult foci was <3 mm in majority of cases, given their association with increased risk of multifocality and recurrence, total thyroidectomy is considered a reasonable strategy in solitary nodules, regardless of the lesion size [9, 27].

Nonetheless, the implementation of active surveillance has also been suggested in patients with <1 cm lesion, N0 nodal status, and low-risk factors in the US [29, 30], given the very low rates of tumor growth >3 mm (8%) or lymph node metastasis (3.8%) at 10-year follow up [29], and low rates of surgery need (7%) during 5-year follow up of PTMC patients [30]. However, these findings should be justified with evidence-based data from large series, and currently, the active surveillance in low-risk PTMC seems to be considered a questionable strategy, given the loss to follow-up risk in the long-term, patients' perception of surgery needs during the surveillance period, and the reliability and accuracy of preoperative US.

Limitations

Although our results provide data on a comprehensive analysis of tumor size, cancer foci, and aggressive variants in DTC patients, certain limitations of this study should be considered. First, the retrospective single-center design and relatively small number of participants are the main limitations in terms of the risk of selection bias and the generalizability of our results. Second, the lack of data on other outcomes of interest such as family history or genetic mutation including BRAF mutation, or long-term follow-up data on recurrence and cancer-specific survival is another limitation.

CONCLUSION

In conclusion, our findings revealed the presence of bilaterality/multifocality and aggressive variants in a considerable proportion of patients with operated DTC, alongside a multifaceted interplay between bi-

laterality/multifocality, tumor size, and PTC aggressive variants, in addition to their individual effects on increased risk of tumor invasion, particularly the extrathyroidal invasion. Accordingly, while total thyroidectomy should be considered in the presence of >4 cm tumor with high-risk factors on preoperative ultrasound, the recurrence risk related to bilaterality/multifocality and aggressive variants besides the patients' preference and concerns regarding the close follow-up required after less extensive procedures should guide the decision of thyroidectomy, regardless of the tumor size.

Ethical Statement

This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Bursa Uludag University Clinical Research Ethics Committee (Date of Approval: 12/12/2023; Protocol No: 2023-27/20).

Authors' Contribution

Study Conception: EG; Study Design: EG; Supervision: EG, AVÖ; Funding: N/A; Materials: EG, AVÖ; Data Collection and/or Processing: EG, AVÖ; Statistical Analysis and/or Data Interpretation: EG, AVÖ; Literature Review: EG, AVÖ; Manuscript Preparation: EG and Critical Review: EG, AVÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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YouTube as a source of information on thoracic outlet syndrome: quality and reliability analysis

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ABSTRACT

Objectives: This study aimed to evaluate the quality, reliability, and characteristics of the most-viewed YouTube videos on thoracic outlet syndrome and to identify differences in quality based on content and source.

Methods: A systematic search was conducted on YouTube using four keywords related to thoracic outlet syndrome. A total of 200 videos were initially selected, of which 75 met the inclusion criteria after excluding duplicates, non-English videos, off-topic content, and videos under one minute. Video characteristics, including views, likes, duration, content type, and source, were recorded. Reliability and quality were assessed using the modified DISCERN scale, Journal of the American Medical Association benchmark criteria, and the Global Quality Scale.

Results: Among the analyzed videos, 46.7% were uploaded by non-physician health workers, 40% by physicians, and 13.3% by independent users. Disease-specific information constituted 50.7% of the content, while 20% focused on exercises, 17.3% on conservative management, and smaller percentages on patient experiences and surgical techniques. The median scores were modified DISCERN: 3.0, Journal of the American Medical Association benchmark criteria: 2.0, and Global Quality Scale: 3.0. Only 29.3% of the videos were categorized as high-quality, while the majority were of medium or low quality. All high-quality videos were found to have modified DISCERN>3. Positive correlations were identified between modified DISCERN, Journal of the American Medical Association benchmark criteria, and Global Quality Scale scores ($P<0.05$).

Conclusions: YouTube serves as a moderately reliable resource for information related to thoracic outlet syndrome; however, the overall quality remains suboptimal. To improve the availability of high-quality information, healthcare professionals, particularly physicians, should actively contribute to producing reliable and educational content on platforms like YouTube.

Keywords: YouTube, thoracic outlet syndrome, video quality, reliability, online health information

Thoracic outlet syndrome (TOS) encompasses a spectrum of disorders caused by the compression of the neurovascular bundle within the thoracic outlet, located above the first rib and posterior to the clavicle [1]. This compression may result from various etiologies, including traumatic injuries, repetitive motion, or congenital anomalies such as cervical ribs or scalene muscle hypertrophy. Based on the

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affected structure, TOS is classified into three subtypes: neurogenic (nTOS), venous (vTOS), and arterial (aTOS). Neurogenic TOS is the most prevalent, accounting for over 95% of cases, while venous and arterial forms represent approximately 3% and 1%, respectively [2, 3].

Neurogenic TOS arises primarily from the compression of the brachial plexus. Patients with nTOS commonly report symptoms such as pain, paresthesia, and muscle weakness in the upper extremity, often exacerbated by certain positions or activities. In severe cases, chronic nerve compression may lead to muscle atrophy, particularly in the thenar eminence [4]. Diagnosis can be challenging due to symptom overlap with other conditions, such as cervical radiculopathy or carpal tunnel syndrome, necessitating a combination of clinical evaluation, imaging, and electrodiagnostic studies [5].

Treatment of TOS varies according to its subtype. For neurogenic TOS, conservative management remains the mainstay, including physical therapy aimed at postural correction, stretching exercises, and symptomatic relief through anti-inflammatory medications. Surgical intervention is reserved for refractory cases, particularly those involving structural anomalies or significant neurological compromise [4].

In today's digital age, patients frequently turn to online platforms to gather health-related information, with YouTube emerging as a prominent resource [6]. Despite its accessibility and wide reach, YouTube lacks rigorous mechanisms to ensure the accuracy and reliability of its content [7, 8]. This raises concerns regarding the quality of medical information disseminated to the public. Previous studies investigating YouTube as a source of health information for various conditions, such as meralgia paresthetica (MP) and carpal tunnel syndrome have revealed a predominance of low-quality content [9, 10].

Due to the complexity of TOS and the absence of clear expert consensus, many individuals are turning to online resources for information and guidance. To date, no study has specifically evaluated the quality and reliability of YouTube videos on TOS. The present study aims to address this gap by analyzing the most-viewed YouTube videos on TOS, assessing their quality, reliability, and content to provide actionable insights for both healthcare professionals and content creators.

METHODS

YouTube Search Strategy

We conducted a systematic search on YouTube (www.youtube.com) on October 14, 2024, using four pre-determined keywords: "thoracic outlet syndrome," "TOS," "thoracic outlet syndrome management," and "thoracic outlet syndrome physical therapy." These keywords were selected based on similar studies in the literature [9-11]. To minimize bias from previous searches, the browser history was cleared before initiating the search. In line with many studies in the literature, the first 50 most-viewed videos for each keyword were identified [12, 13]. Thus, an initial pool of 200 videos was obtained. Non-English videos, duplicate videos, videos with a duration of less than one minute, off-topic videos, and videos without audio were excluded. All included videos were evaluated by two independent physiatrists. If there was a difference between the scores, the physiatrists reevaluated the video together and reached a consensus.

Video Characteristics

The selected videos were analyzed for various characteristics to better understand their content and sources. Attributes such as video duration, the time elapsed since upload, uploader country, and audience engagement metrics including the number of views, likes, and comments were documented. Additionally, view ratio (=number of views/days), like ratio (=(number of likes/number of views) x100), and Video Power Index (VPI) (=like ratio x view ratio/100) were calculated to assess the rate of engagement over time [14]. Videos were categorized by their content into five groups: disease-specific information, patient experience, conservative management, surgical techniques, and exercises. Furthermore, video sources were classified into three main groups based on their origin: physicians, non-physician health workers, and independent users.

Evaluation of Video Quality and Reliability

The reliability of the videos was evaluated using the modified DISCERN (mDISCERN) scale, which is an adaptation of the DISCERN criteria for assessing the quality of health-related information [12]. This tool comprises five yes/no questions, with each "Yes" answer scoring one point and each "No" answer scoring

zero. The total score ranges from 0 to 5, with higher scores reflecting greater reliability. Video quality was assessed using two additional tools: the Journal of the American Medical Association (JAMA) benchmark criteria and the Global Quality Scale (GQS). The JAMA criteria evaluate four key aspects: authorship, attribution, disclosure, and currency. Each criterion met contributes one point, with a maximum possible score of 4, indicating the highest quality [13]. The GQS assesses the overall quality and usefulness of video content using a 5-point scale. Scores of 4 or 5 indicate high quality, a score of 3 represents medium quality, and scores of 1 or 2 denote low-quality content [14].

Statistical Analysis

Data were analyzed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Normality was assessed using the Kolmogorov-Smirnov test. Since the normality assumption did not hold, continuous variables were reported as medians with ranges, while categorical variables were expressed as frequencies and percentages. Non-parametric tests, including the Mann-Whitney U and Kruskal-Wallis tests, were used for continuous variables not conforming to normal distribution. Categorical variables were analyzed using the Chi-square and Fisher's exact tests. Correlations between numerical variables were assessed with Spearman's correlation. A P-value of <0.05 was considered statistically significant.

RESULTS

Out of the initial 200 videos selected for review, 125 were excluded for various reasons: 77 were duplicates, 32 were off-topic, 10 were non-English, 5 were under one minute in duration, and 1 lacked audio. Consequently, a total of 75 YouTube videos were included in the analysis (Fig.1).

The general characteristics of the included videos are summarized in Table 1. Among these, 46.7% (n=35) were uploaded by non-physician health workers, 40% (n=30) by physicians, and 13.3% (n=10) by independent users. Regarding content, 50.7% of the

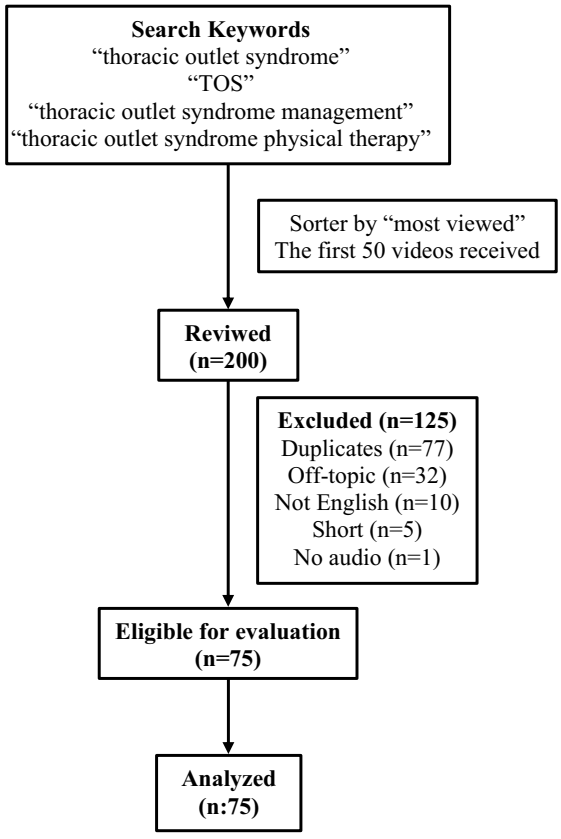

Fig. 1. Flow chart of the study.

Table 1. General features of videos

Parameters		Data
Number of views		94,658 (1,1051-1,021,000)
Number of likes		1,000 (81-28,000)
Number of comments		78 (0-1177)
Number of days since upload		2,154 (231-5,695)
View ratio		46.35 (6.62-3,751.61)
Like ratio		1.0 (0.1-4.7)
Video duration (second)		288 (64-1,738)
VPI		0.49 (0.02-29.87)
Country	USA	52 (69.3)
	UK	6 (8)
	Netherland	10 (13.3)
	Others	7 (9.4)
JAMA score		2.0 (0-4)
mDISCERN score		3.0 (1-5)
	<3	27 (36)
	>3	48 (64)
GQS score		3.0 (1-5)
	Low quality	29 (38.7)
	Medium quality	24 (32)
	High quality	22 (29.3)
Video content	Disease specific information	38 (50.7)
	Patient experience	6 (8)
	Conservative management	13 (17.3)
	Surgical technique	3 (4)
	Exercises	15 (20)
Source of upload	Physician	30 (40)
	Non-physician health worker	35 (46.7)
	Independent user	10 (13.3)

Data are shown as median (min-max) or number (%). VPI=Video Power Index, GQS=Global Quality Scale, JAMA=Journal of the American Medical Association, mDISCERN=Modified DISCERN tool.

videos provided disease-specific information, followed by 20% focusing on exercises, 17.3% on conservative management, 8% on patient experiences, and 4% on surgical techniques. In terms of geographical distribution, 69.3% (n=52) originated from the United States, 13.3% (n=10) from the Netherlands, 8% (n=6) from the United Kingdom, and 9.4% (n=7) from other countries. The median mDISCERN score was 3.0, while the median GQS and JAMA scores were 3.0 and 2.0, respectively. Of the analyzed videos, 29.3% (n=22) were categorized as high-quality, 32% (n=24) as medium-quality, and 38.7% (n=29) as low-quality.

Comparisons of video characteristics based on video sources revealed a statistically significant difference in the number of likes among groups (P=0.026; Table 2). Post-hoc analysis showed that the number of likes for videos uploaded by non-physician health workers was significantly higher than the num-

Table 2. Comparison of video features and quality by source

Source	Physician	Non-physician health worker	Independent users	P value
Number of views	88,334 (19,000-1,021,000)	13,3000 (11,051-866,621)	76,329 (34,401-227,432)	0.282
Number of likes	656.5 (81-28,000)	1,800 (142-16,000)	1,050 (246-1,700)	**0.026**
Number of comments	77 (0-862)	86 (0-1,177)	56.5 (9-3,014)	0.255
Number of days since upload	2,742.5 (300-5075)	1,825 (231-5,695)	3,718.5 (673-4,824)	0.144
View ratio	41.7 (8.9 -558.8)	61.7 (6.6-3,751.6)	33.9 (7.3-84.6)	0.412
Like ratio	0.8 (0.1-2.9)	1.2 (0.1- 4.7)	0.8 (0.2-2.9)	0.060
Video duration (second)	361.5 (64-1208)	265 (81-1,738)	271.5 (82-1,280)	0.969
VPI	0.35 (0.02-15.33	0.87 (0.04-29.87)	0.34 (0.05-2.53)	0.269
Video content		15 (43)	4 (40)	0.168
Disease-specific information	19 (63.3)	0 (0)	4 (40)	
Patient experience	2 (6.7)	9 (26%)	1 (10)	
Conservative management	3 (10)	1 (3)	0 (0)	
Surgical technique	2 (6.7)	10 (28)	1 (10)	
Exercises	4 (13,3)			
JAMA score	3.0 (1-4)	2.0 (0-4)	1.5 (0-4)	0.185
mDISCERN score				0.092
<3	7 (23.3)	14 (40)	6 (60)	
≥3	23 (76.7)	21 (60)	4 (40)	
GQS				0.053
Low quality	7 (23.3)	14 (40)	8 (80)	
Medium quality	13 (43.3)	11 (31.4)	0 (0)	
High quality	10 (33.4)	10 (28.6)	2 (20)	

Data are shown as median (min-max) or number (%). VPI=Video Power Index, GQS=Global Quality Scale, JAMA=Journal of the American Medical Association, mDISCERN=Modified DISCERN tool. Bold P values indicate statistically significant differences.

*Kruskal-Wallis test for numeric data

ber of likes for videos uploaded by independent users (P=0.006). However, no significant differences were observed in other metrics such as like ratio, view ratio or VPI (P>0.05). It was determined that the most shared video content by all sources was disease-specific information. While there was no statistically significant difference in content type across video sources, most exercise- and conservative management-related videos were uploaded by non-physician health workers (Fig. 2).

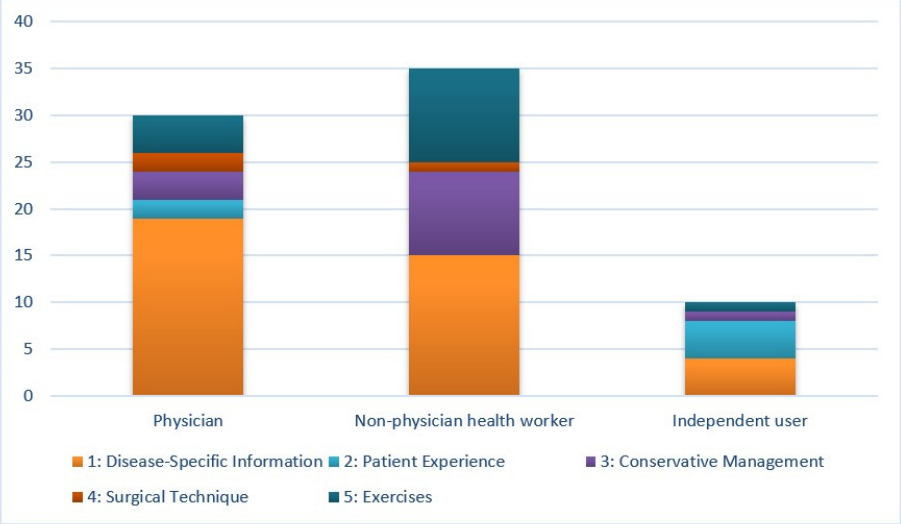

Fig. 2. Content distribution of YouTube videos on TOS by source.

Further analysis of video quality groups (low, medium, and high) demonstrated significant differences in JAMA scores (P=0.000), mDISCERN scores (P<0.001), and video duration (P=0.041) (Table 3). Post-hoc analysis revealed that JAMA scores were significantly higher in the high-quality group compared to the low- and medium-quality groups (P<0.01 and P<0.01, respectively), with no significant difference between the low- and medium-quality groups (P=0.232). Similarly, in post hoc analysis, mDISCERN scores were significantly higher in high-quality videos compared to medium- and low-quality ones (P=0.032 and P<0.001, respectively), and medium-quality videos had higher mDISCERN scores than low-quality videos (P=0.001). Notably, all high-quality videos achieved an mDISCERN score >3, whereas 75% of medium-quality videos and only 27.6% of low-quality videos met this threshold (Table 3). Video duration also differed significantly between quality groups. Post hoc analysis indicated that high-quality videos were significantly shorter in duration compared to low-quality videos (P=0.035). However, no other video characteristics showed significant differences among quality groups.

Spearman correlation analysis revealed positive significant correlations between mDISCERN and GQS scores (r=0.630, P<0.001), mDISCERN and JAMA scores (r=0.545, P<0.001), and JAMA and GQS scores (r=0.616, P=0.001) (Table 4). No significant correlations were identified between other parameters.

DISCUSSION

YouTube has become one of the most widely accessed online platforms for patients seeking information about their medical conditions [15]. Although it offers free and easily accessible video content, the platform lacks mechanisms to regulate the quality and accuracy of the information provided. TOS is a complex condition with a wide range of etiologies and symptoms, compounded by the absence of a unified expert consensus on diagnostic and management strategies [16]. This complexity makes it likely that both healthcare professionals and independent users frequently turn to YouTube for information on TOS. Therefore, ensuring the availability of accurate and reliable information on this platform is of paramount importance.

Previous studies have evaluated the reliability and quality of YouTube videos across various medical topics, including carpal tunnel syndrome, fibromyalgia, and MP [9, 17, 18]. However, to the best of our knowledge, this is the first study to specifically examine YouTube videos on TOS.

YouTube platform has been considered as a mixed pool of low-, medium- and high- quality videos [19]. For instance, a study on oropharyngeal dysphagia exercises found relatively high-quality videos, whereas Tarihci *et al*. and Ertem *et al*. observed that most videos on MP and piriformis syndrome, respectively, were of low quality [9, 20, 21]. In our analysis, most TOS-related videos were of medium or low quality,

Table 3. Comparison of video sources and features according to quality classification

	Low quality	Medium quality	High quality	P value*
Number of views	56,982 (11,051-866,621)	166,289 (34,414-1,021,000)	96,464 (19,000-681,232)	0.146
Number of likes	828 (107-6,900)	1,950 (81-28,000)	707.5 (107-8,200)	0.074
Number of comments	61 (0-483)	122.5 (1-1,177)	48 (0-577)	0.064
Number of days since upload	2154 (231-5,695)	2,122.5 (636-5,487)	2,934 (300-4,038)	0.910
View ratio	35.94 (6.62-3,751.61)	78.99 (10.38-55,884)	51.98 (8.52-198.03)	0.702
Like ratio	1.28 (0.08-4.72)	1.36 (0.09-4.37)	0.81 (0.40-2.38)	0.111
Video duration (second)	429 (64-1,738)	326 (104-1,097)	197.5 (64-1,208)	**0.041**
VPI	0.38 (0.04-29.87)	1.28 (0.02-15.33)	0.39 (0.04-2.82)	0.180
Video Source				0.072
Physician	7 (24.1)	13 (54.2)	10 (45.5)	
Non-physician health workers	14 (48.3)	11 (45.8)	10 (45.5)	
Independent	8 (27.6)	0 (0)	2 (9.0)	
Video content				0.346
Disease-specific information	14 (48.3)	10 (41.7)	14 (63.6)	
Patient experience	2 (6.9)	1 (4.2)	3 (13.6)	
Conservative management	7 (24.1)	6 (25.0)	0 (0)	
Surgical technique	0 (0)	2 (8.3)	1 (4.5)	
Exercises	6 (20.7)	5 (20.8)	4 (4.3)	
JAMA	2.0 (0-3)	2.0 (1-4)	4.0 (2-4)	**<0.001**
mDISCERN				**<0.001**
<3	21 (72.4)	6 (25)	0 (0)	
≥3	8 (27.6)	18 (75)	22 (100)	

Data are shown as median (min-max) or number (%). VPI=Video Power Index, GQS=Global Quality Scale, JAMA=Journal of the American Medical Association, mDISCERN=Modified DISCERN tool. Bold P values indicate statistically significant differences.

*Kruskal-Wallis test for numeric data

with only 29.3% meeting high-quality standards. Methodological differences could explain these discrepancies across studies, such as the diseases studied, video sources, or the number of videos analyzed.

In the current study, when videos were categorized as low, medium, or high quality based on GQS, significant differences emerged in mDISCERN score, JAMA score and video duration. As expected, high-quality videos had significantly higher scores in both mDISCERN and JAMA scores, compared to medium-

Table 4. Evaluation of correlations between JAMA, GQS, mDISCERN, and video characteristics

		JAMA	mDISCERN	GQS
JAMA	r	1.000	.545**	.616**
	P value	**.**	**<0.001**	**<0.001**
mDISCERN	r	.545**	1.000	.630**
	P value	**<0.001**	**.**	**<0.001**
GQS	r	.616**	.630**	1.000
	P value	**<0.001**	**<0.001**	**.**
Number of views	r	-.133	.017	.138
	P value	0.257	0.887	0.238
Number of likes	r	-.057	.156	.030
	P value	0.627	0.182	0.798
Number of days since upload	r	-.215	-.209	.027
	P value	0.064	0.072	0.816
View ratio	r	.039	.176	.188
	P value	0.738	0.131	0,105
Like ratio	r	-.033	.123	-.212
	P value	0.776	0.295	0.068
Video duration	r	-.157	-.066	-.282*
	P value	0.178	0.573	**0.014**
Video content	r	-.135	-.220	-.097
	P value	0.247	0.058	0.406
Video source	r	-.138	-.250*	-.259*
	P value	0.237	**0.031**	**0.025**
Number of comment	r	-.223	-.032	-.104
	P value	0.054	0.785	0.375

GQS=Global Quality Scale, JAMA=Journal of the American Medical Association, mDISCERN=Modified DISCERN tool. Bold P values indicate statistically significant differences.

*Spearman's correlation is significant at the 0.01 level (2-tailed)

**Spearman's correlation is significant at the 0.05 level (2-tailed)

and low-quality videos. This is in good agreement with previous results [20-22]. In addition, high-quality videos were found to be shorter in duration than low-quality ones. Although some studies have suggested that longer videos may increase viewer engagement, they take a risk losing audience interest and may stray from the main topic, reducing their overall quality [17, 18]. Our findings also revealed positive correlations among mDISCERN, JAMA, and GQS scores, consistent with previous literature [9, 23]. This suggests that video quality and reliability are closely aligned and should be jointly considered when evaluating educational content on YouTube.

Additionally, in the current study, 64% of the analyzed videos achieved an mDISCERN score >3, indicating a moderate level of reliability. Moreover, most TOS videos were uploaded by physicians and non-physician health workers, with independent users contributing only 13.3% of the content. The dominance of healthcare professionals among the video sources likely contributes to the relatively higher reliability observed in this study. These findings align

with previous research, such as D'Souza *et al*. [24], who reported that medical-source videos on epidural analgesia for labor pain were more reliable than those from nonmedical sources. Similarly, Ertem *et al*. [21] highlighted that videos uploaded by healthcare professionals were generally more trustworthy than those shared by independent users.

Regarding content distribution, disease-specific information was the most common focus, featured in 50.7% of the videos. Exercise training was the second most frequent topic (20%), followed by conservative management (17.3%). While videos on exercises and other conservative treatment methods were primarily uploaded by non-physician health workers, we believe physicians, should take a more active role in creating such content. Their expertise ensures a comprehensive understanding of the disease, potentially enhancing the quality and reliability of these resources.

Existing literature has primarily focused on publications related to TOS. For example, Özyiğit *et al*. analyzed the bibliometric structure of TOS research over the past 50 years, identifying the United States, France, and the United Kingdom as the leading contributors to academic publications on this topic [25]. Similarly, our study found that the United States, United Kingdom, and the Netherlands were the top contributors to YouTube videos about TOS. However, our current study primarily included videos providing disease-specific information, whereas most of the publications examined in the study by Özyiğit *et al*. [25] concentrated on the surgical management, likely because most of the publications they analyzed were published in surgical journals. In addition, Clothier *et al*. [26] evaluated the quality and readability of online TOS resources by searching for "TOS" and "Thoracic Outlet Syndrome" on search engines such as Google© and Yahoo©. Their study revealed that although these resources were generally effective in explaining TOS, they lacked comprehensive discussions on treatment options. They also reported variable quality across web search results. Our results support these findings by highlighting that while YouTube offers a mix of high-, medium-, and low-quality content, its quality is inconsistent and warrants improvement.

Limitations

This study has certain limitations. First, it only included English-language videos, which may limit the generalizability of the findings. Second, as YouTube is a dynamic platform, video metrics and availability may change over time, potentially affecting the reproducibility of this study.

CONCLUSION

In conclusion, while YouTube provides a moderately reliable resource for TOS-related information, the overall quality of the videos remains suboptimal. Given the strong link between quality and video sources, physicians should be encouraged to produce more educational content, particularly on exercise and conservative treatment methods. By doing so, they can help ensure that patients receive accurate, reliable, and high-quality information to understand better and manage their condition.

Ethical Statement

As the study exclusively analyzed publicly accessible videos without involving human participants or animals, ethics committee approval was deemed unnecessary, in accordance with similar studies in the field.

Authors' Contribution

Study Conception: ZRYT, DF; Study Design: ZRYT, DF; Supervision: ZRYT; Funding: N/A; Materials: N/A; Data Collection and/or Processing: ZRYT, DF; Statistical Analysis and/or Data Interpretation: ZRYT, DF; Literature Review: ZRYT; Manuscript Preparation: ZRYT, DF; and Critical Review: ZRYT, DF.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Editor's note

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Enchondromas

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ABSTRACT

Objectives: Enchondromas are benign cartilage tissue tumors composed of mature hyaline cartilage. Most enchondromas are discovered incidentally during radiological examinations. Differentiating between low-grade chondrosarcoma and enchondroma can be difficult both clinically, radiologically, and histologically. Malignant tumors can mimic benign tumors. Therefore, it is crucial to accurately diagnose enchondromas, as the treatments for both tumors are very different. We aimed to contribute to a better understanding of the clinical features and treatment challenges of patients diagnosed with enchondroma.

Methods: Thirty patients who presented to the Department of Orthopedics and Traumatology at Manisa Celal Bayar University Faculty of Medicine between 2010 and 2023 and were diagnosed with enchondroma in hand after surgical treatment were retrospectively evaluated in our study. The patients were classified according to the Tordai and Takigawa classifications.

Results: Nineteen women and 11 men were examined. The lesions were observed in the left hand in 15 patients and in the right hand in 15 patients. The proximal phalanx was the most affected area. Fractures developed in 2 patients during postoperatively, requiring revision surgeries. No wound complications were observed during follow-up, and except for 2 patients who experienced refractures, both clinical and radiological complete healing was observed at the 8-week follow-up.

Conclusions: This study aims to understand better the clinical features and treatment challenges of patients diagnosed with enchondroma. We believe that immobilization for at least 4 weeks or implant application would be appropriate to increase stability in patients with intramedullary involvement of more than 50% in the dominant hand. Enchondromas still present many unknowns, more research is necessary to increase knowledge about these tumors. This study provides important data regarding enchondromas and serves as a foundational step for further research and investigation in this area.

Keywords: Chondroma, chondromatosis, neoplasms, bone

Enchondromas are benign cartilage tissue tumors composed of mature hyaline cartilage. They account for approximately 3% of bone tumors and about 13% of benign bone tumors [1, 2]. These tumors arise in the bone marrow and usually grow slowly. Although enchondromas are generally found in a single bone, they can occasionally appear in multiple bones [3]. Enchondromas that occur in

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multiple locations often accompany syndromes, the most notable being Ollier disease, with Maffucci syndrome being another syndrome where hemangiomas are added to Ollier disease.

The exact cause of enchondromas is still not fully understood. Genetic factors are thought to play a role, but this is still being researched. Enchondromas may be associated with a family history and can sometimes occur alongside other bone disorders. The gender distribution is almost equal. The clinical course is slow and often asymptomatic, and it usually does not present symptoms until the age of 20 [4].

Enchondromas are more commonly observed in tubular bones, particularly in the proximal phalanx and distal metacarpal region, with medullary involvement. They are relatively less common in long bones, with metaphyseal involvement [5, 6].

Enchondromas can persist without causing any symptoms in many cases. However, if symptoms do occur, they are often due to pain and swelling secondary to pressure on surrounding tissues. Additionally, fractures may occur as a result of cortical weakening. Most enchondromas are discovered incidentally during radiological examinations. They can cause pathological fractures by expanding the bone and thinning the cortex, resulting in a lytic lesion surrounded by a sclerotic rim in small tubular bones. In long bones, where they are less common, enchondromas typically present as metaphyseal lesions with areas of calcification, without cortical thinning, as seen in small tubular bones [7]. They can cause cortical thinning, known as cortical scalloping, which may also indicate malignancy in long bones. Particularly in long bones, computed tomography (CT) is more prominent in showing calcifications and cortical changes. Magnetic resonance imaging (MRI) is more useful for evaluating the lobular structure and identifying soft tissue components. Enchondromas appear hypodense on T1 sequences and hyperintense on T2 sequences [8].

The treatment approach for enchondromas varies [9] Approaches differ between axial skeleton involvement and appendicular skeleton involvement. Lesions in the hand that cause cortical thinning or fractures, as well as those that involve bone marrow edema or soft tissue spread, require surgical intervention.

Differentiating between low-grade chondrosarcoma and enchondroma can be difficult both clinically, radiologically, and histologically. Malignant tumors can mimic benign tumors [10] Therefore, it is crucial to accurately diagnose enchondromas, as the treatments for both tumors are very different [11].

We aimed to contribute to the literature by evaluating the effectiveness of using allograft or calcium phosphate as grafts and their effects on the development of complications in our patients diagnosed with hand enchondroma whom we treated between 2010 and 2023.

METHODS

Thirty patients who presented to the Department of Orthopedics and Traumatology at Manisa Celal Bayar University Faculty of Medicine between 2010 and 2023 and were diagnosed with enchondroma in hand after surgical treatment were retrospectively evaluated in our study. After obtaining approval from the Ethics Committee of Mamisa Celal Bayar University (Decision no: 20.478.486/2470 anddate: 05.06.2024), informed consent was obtained from the patients for participation in the study. Diagnoses were confirmed with X-ray and Magnetic Resonance Imaging (MRI). The diagnosis was confirmed with computed tomog-

Table 1. Characteristics of patients

	Data
Average age (years)	35.7 (1-73)
Gender	
Female	19
Male	11
Direction	
Right	15
Left	15
Pain	
Coincidental	9
Presented with pain	21
Imaging	
X-ray	30
MRI	30
CT	14

MRI=Magnetic Resonance Imaging, CT=Computed Tomography

raphy (CT) in patients with pain and pathological fractures. A Histopathological examination was then performed. Patients were evaluated based on age, gender, presence of pain, tumor location, and histopathological examination results. Additionally, the patients were classified according to the Tordai and Takigawa classifications. The classification described by Takigawa, first defined in 1971, is considered the most used classification for the morphological classification of enchondromas today [12]. Radiological consolidation was evaluated according to the Tordai Classification. According to the Tordai Classification, Group 1 includes those with normal cortical bone or bone defects less than 3 mm in diameter. Bone defects with a diameter between 4 and 10 mm are considered Group 2, and those with bone defects larger than 10 mm are considered Group 3 [13].

All surgeries in our study were performed under general anesthesia. The surgeries were carried out in the supine position with a tourniquet on the arm. The dorsolateral approach was used for lesions in the phalanx and a direct dorsal approach was applied for lesions in the metacarpal region. Curettage and bone grafting with either calcium phosphate or allograft were performed on all patients. After deflating the tourniquet, hemostasis was achieved, and the wound was closed according to standard procedures, followed by the application of a splint. No neurovascular complications or tendon injuries were observed during or after surgery.

Postoperatively, patients were evaluated at 3, 6, 8, and 12 weeks. The sutures were removed at 3 weeks to prevent wound complications, and rehabilitation began afterward.

Statistical Analysis

Descriptive statistics were presented as unit number, percentage, mean, minimum, and maximum values. These calculations were made via a computer program.

RESULTS

A total of 30 patients, including 19 women and 11 men, were examined. The lesions were observed in the left hand in 15 patients (50%) and the right hand in 15 patients (50%). While 26 patients (86.6%) dominant hand that was right, 4 patients (13.4%) dominant hand that was left. The average age of the patients was 35.7 years (ranging from 1 to 73 years) (Table 1). Of the 30 patients, 9 (30%) had lesions in the little finger, 8 (26.6%) in the ring finger, 6 (20%) in the middle finger, 5 (16.6%) in the index finger, and 2 (6.6%) in the thumb. The lesions were in the proximal phalanx in 16 cases (53.3%), 6 (20%) in the middle phalanx, 3 (10%) in the distal phalanx, and 5 (16.6%) in the

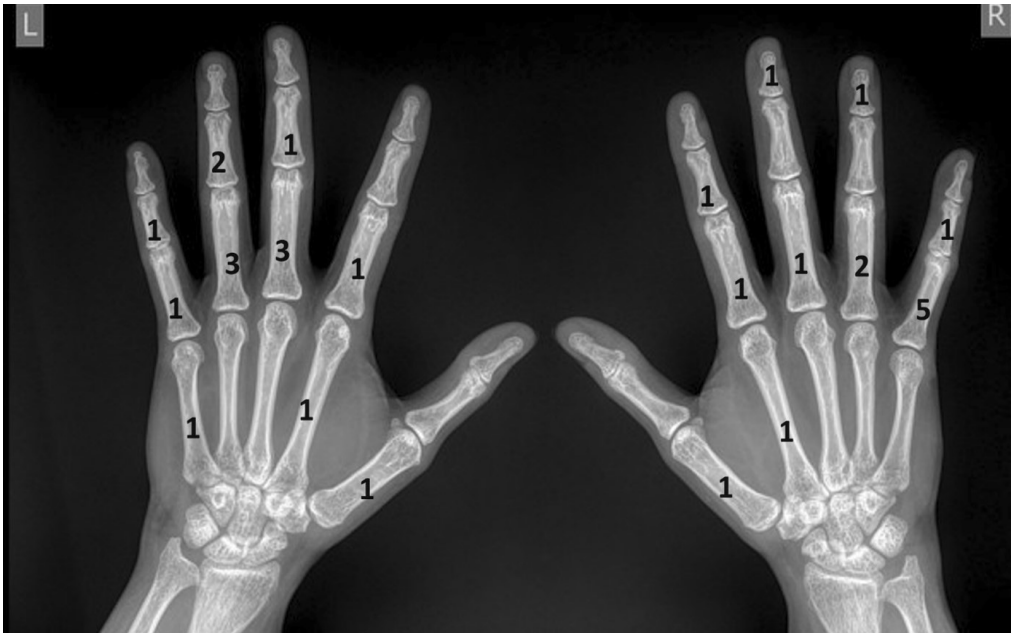

Fig. 1. Distribution of enchondromas on the hand.

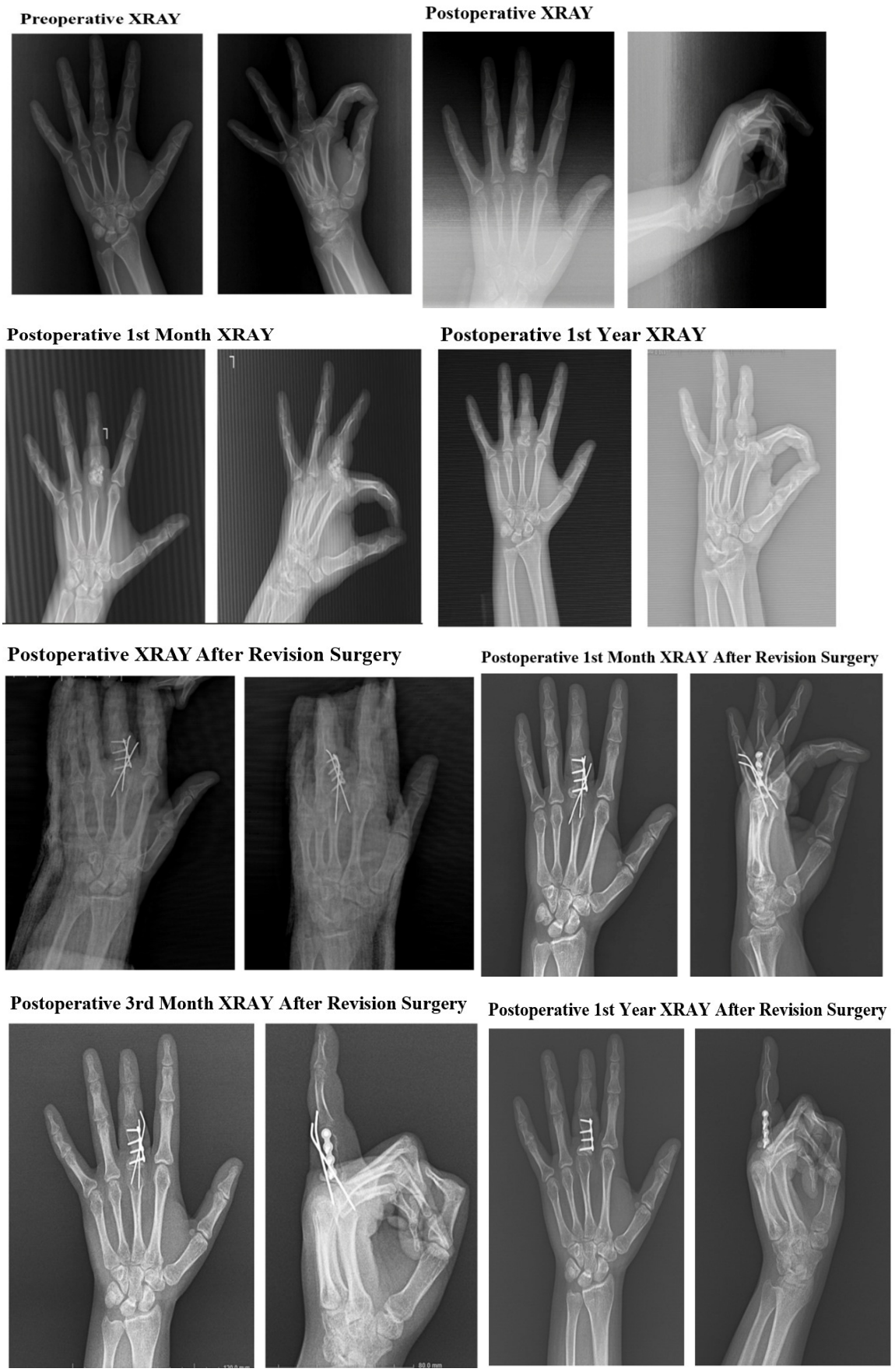

Fig. 2. Complication and revision surgery in a 34-year-old female patient

metacarpal bones (Fig. 1). The proximal phalanx was the most affected area.

None of the patients had Ollier or Maffucci syndromes. The initial complaint of 21 patients was pain, while the lesion was incidentally found in 9 patients. 21 patients (70%) were active smokers, while 9 (30%) did not smoke. All patients underwent direct radiography and MRI during their first visit. Among the radiographic imaging performed, 14 patients (46.6%) had pathological fractures, while 16 patients (53.3%) did not have fractures. No soft tissue involvement was observed in any of the 30 patients. CT was performed on 14 patients (46.6%) who had pathological fractures. Fractures developed in 2 patients during postoperative follow-up, requiring revision surgeries (Fig. 2).
Calcium phosphate was used in 17 patients, and allograft was used in 13 patients in surgical grafting. Allografts were used in 13 patients' operations because they provided allografts covering the cost. An iliac crest autograft was used in one patient who underwent revision surgery. No wound complications were observed during follow-up, and except for 2 patients who experienced refractures, both clinical and radiological complete healing was observed at the 8-week follow-up. Postoperative rehabilitation was completed, and all patients achieved the same range of motion as the contralateral limb at the 12-week follow-up.

Thirteen patients (43.3%) were categorized as eccentric, 6 patients (20%) as polycentric, 6 patients (20%) as giant, and 5 patients (25%) as central in our study, according to the Takigawa classification (Fig. 3).

Fifteen patients were in group 1, 13 patients were in group 2 and 2 patients were in group 3, according to the Tordai classification (Fig. 4).

DISCUSSION

This study presents a retrospective analysis of patients diagnosed with enchondromas in the hand at the Department of Orthopedics and Traumatology, manisa Celal Bayar University Faculty of Medicine. Enchondromas are known as benign cartilage tissue tumors and typically arise within the bone marrow [14]. However, they may undergo malignant transformation into chondrosarcoma [15]. These rare tumors still present many unknowns in the literature and this study aims to contribute to the growing knowledge in this field.

It was observed that the gender distribution of these tumors is almost equal and that symptoms generally become apparent by the age of 20. This confirms that enchondromas grow slowly and have a quiet clinical course.

Enchondromas are frequently found in the hand, and rarely in other regions such as the proximal humerus, proximal femur, distal femur, and distal tibia [16]. No cases of Ollier or Maffucci syndromes were identified in hand enchondromas in our study, though these syndromes are rare and can present independently [17].

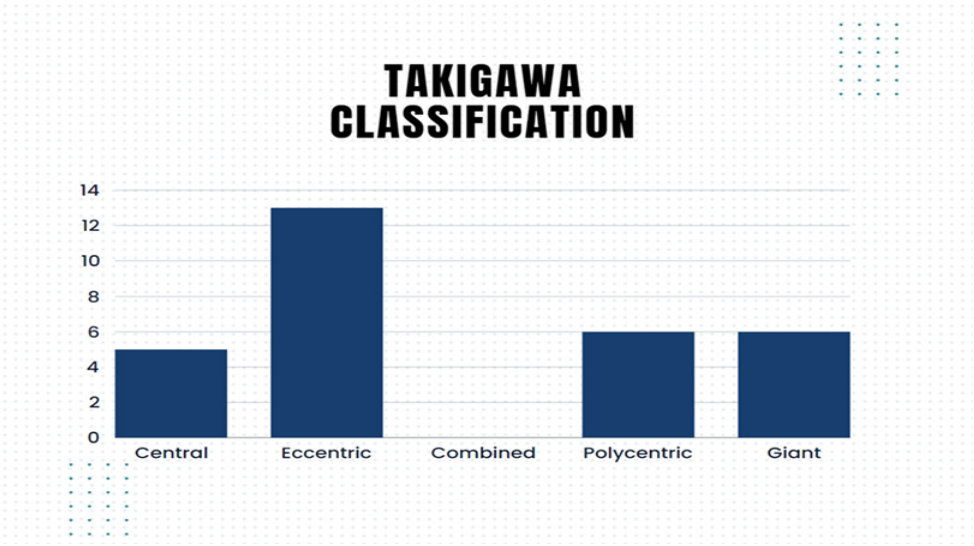

Fig. 3. Distribution of lesions according to Takigawa classification.

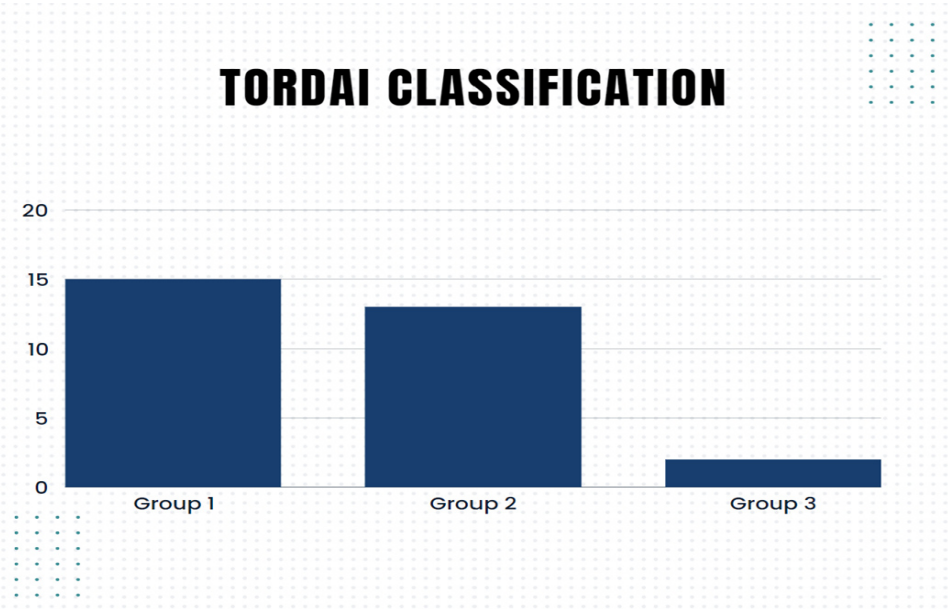

Fig. 4. Distribution of patients according to Tordai classification.

Radiologically, enchondromas often show endosteal erosion, and cortical destruction is rarely observed. MRI and CT are important for diagnosis and evaluation of lesions. MRI is valuable for assessing soft tissue involvement and lobularity of the lesion, while CT is essential for evaluating the cortex and calcification. As in the literature, we believe that MRI and CT imaging would be beneficial, especially in patients with soft tissue extension, pathological fractures, and dominant pain symptoms. Biopsy remains a critical step for histopathological diagnosis and helps in the differential diagnosis of low-grade chondrosarcoma. Although the literature mentions that biopsy is important, especially in distinguishing low-grade chondrosarcomas, we did not perform biopsy on our patients.

Treatment varies depending on the duration of enchondroma diagnosis, the extent of cortical destruction, and bone expansion. Surgical intervention is favored for enchondromas that cause fractures, soft tissue involvement, or deformity due to cortical destruction. In our surgical treatment approach involving curettage and grafting, no neurological complications or tendon damage were observed.

Two patients who underwent revision surgery had more than 50% intramedullary involvement and underwent calcium phosphate grafting. It was also observed that the hands that developed fractures in these patients were their dominant hands. Stability was deemed sufficient in their first surgery and no implants were applied in these patients. Although our patient number is limited and therefore statistically insignificant, we believe that immobilization for at least 4 weeks or implant application would be appropriate to increase stability in patients with intramedullary involvement of more than 50% in the dominant hand.

No recurrence was observed in our 1-year follow-up. We believe that early motion is appropriate in patients with sufficient stability to preserve joint range of motion.

CONCLUSION

This study aims to contribute to a better understanding of the clinical features and treatment challenges of patients diagnosed with enchondroma. It emphasizes that when enchondromas present with atypical localization and nonspecific clinical and imaging features, diagnosis can be challenging, and enchondromas should be considered in epiphyseal lesions. Although enchondromas still present many unknowns, more research is necessary to increase knowledge about these tumors. This study provides important data regarding enchondromas and serves as a foundational step for further research and investigation in this area.

Ethical Statement

After obtaining approval from the Ethics Committee of Mamisa Celal Bayar University (Decision no: 20.478.486/2470 anddate: 05.06.2024), informed consent was obtained from the patients for participation in the study.

Authors' Contribution

Study Conception: MB, HKT; Study Design: MB, KG, MY, HKT; Supervision: MB, KG, MY, HKT; Funding: MB, KG, MY, HKT; Materials: MB, HKT; Data Collection and/or Processing: MB, KG, MY, HKT; Statistical Analysis and/or Data Interpretation: MB, KG, MY, HKT; Literature Review: MB, HKT; Manuscript Preparation: MB, KG, HKT and Critical Review: MB, KG, MY, HKT.

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The European Research Journal 2025;11(3):581-585 Original Article

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Prevalence of arteriovenous fistula use in hemodialysis patients in Burdur province

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ABSTRACT

Objectives: This study aimed to examine the vascular access routes used by patients undergoing hemodialysis treatment in our province and determine the prevalence of arteriovenous (AV) fistula use.

Methods: Patients who were receiving regular hemodialysis treatment in Burdur province as of April 2024 were included in the study. Data on patients' age, gender, comorbidities, duration of dialysis, type of vascular access, and history of hemodialysis access were retrospectively reviewed and recorded using electronic patient records.

Results: The mean age of 197 patients evaluated in the study was 62.48±14.13 years. Of the patients, 63 (32%) were female and 134 (68%) were male. Hypertension was the most common comorbidity in 61.9% of the cases. The number of patients receiving hemodialysis treatment through an AV fistula was 136 (69%). The mean age of patients receiving treatment via an AV fistula was significantly lower than those receiving treatment via an indwelling hemodialysis catheter (P=0.011). Among the patients treated with an indwelling hemodialysis catheter, 59% had no history of AV fistula surgery. The mean age of patients without a history of AV fistula surgery was statistically significantly higher than those with a history of AV fistula surgery (69.28±14.98 vs. 60.96 ± 13.52, respectively; P=0.001).

Conclusions: This study shows that one out of every two patients undergoing hemodialysis through an indwelling hemodialysis catheter has no history of AV fistula surgery. Reaching these patients and prioritizing AV fistula planning is crucial for achieving long-term success in hemodialysis treatment and reducing complications.

Keywords: Cardiovascular surgery, nephrology, arteriovenous fistula, hemodialysis

It is estimated that approximately 850 million people worldwide have chronic kidney disease [1]. Kidney transplantation is the best treatment option for improving survival rates, reducing complications, and enhancing the quality of life in patients diagnosed with chronic kidney disease. However, only a limited number of patients can benefit from this treatment [2-4]. Most patients undergo chronic hemodialysis therapy requiring effective vascular access. Vascular access options for hemodialysis patients include arteriovenous (AV) fistulas, indwelling hemodialysis catheters, and temporary hemodialysis catheters. Hemodialysis through an AV fistula is generally considered the best option for vascular access

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in hemodialysis patients, as it is associated with lower rates of infection and thrombosis compared to the use of indwelling or temporary hemodialysis catheters. Additionally, increased use of AV fistulas has been associated with longer survival times and reduced healthcare costs [5, 6].

The AV fistula creation technique, first performed by Brescia *et al*. [7] in 1966, has been modified over time in light of various advancements. Today, hemodialysis through an AV fistula is the most preferred access route for hemodialysis due to its long-term durability and lower complication rates [8, 9]. Therefore, the present study aimed to examine the vascular access routes used in the hemodialysis treatment of chronic kidney disease patients across our province and determine the prevalence of AV fistula use.

METHODS

The study was conducted in accordance with the ethical guidelines of the Helsinki Declaration of 1975, with approval from the Non-Interventional Ethics Committee of Süleyman Demirel University Faculty of Medicine (Decision no: 17/377 and date: 29.12.2023).

Patients receiving regular hemodialysis treatment at any of the four centers with hemodialysis units in Burdur province as of April 2024 were included in the study. Hemodialysis patients who died before April 2024 were excluded from the study. Data on patients' age, gender, comorbidities (diabetes mellitus, hypertension, atherosclerotic heart disease, and chronic obstructive pulmonary disease), duration of dialysis, type of vascular access (AV fistula and indwelling hemodialysis catheter), and hemodialysis access history were retrospectively reviewed and recorded using electronic patient records. Comparative analyses were conducted between patients with an AV fistula and those without an AV fistula.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 (SPSS Inc. Chicago, IL) program. The conformity of the data to normal distribution was evaluated by Kolmogorov–Smirnov test. Parametric tests were used for data with a normal distribution, while non-parametric tests were used for data that did not follow a normal distribution. Descriptive statistics (count, percentage, mean, and standard deviation), t-test, Chi-square test, and logistic regression analysis were used to evaluate the data. A P value of <0.05 was considered statistically significant in all analyses.

RESULTS

The mean age of 197 patients evaluated in the study was 62.48±14.13 years. Of the patients, 63 (32%) were female and 134 (68%) were male. The median age at hemodialysis was 4 years (min: 4 months, max: 30 years). Hypertension was present in 61.9% of the patients, while diabetes mellitus was observed in 42.1% of the patients. The distribution of patient characteristics and demographic variables by groups is shown in Table 1.

Hemodialysis access was provided through the upper extremities in 97.5% of the patients. Conversely, 2.5% of the patients had hemodialysis access through the lower extremities. AV fistulas were used in 136 patients (69%). The number of patients receiving hemodialysis treatment through indwelling hemodialysis catheters was 61 (31%). The age of patients receiving treatment via an AV fistula was significantly lower compared to those without AV fistulas (P=0.011) (Fig. 1). Among the patients treated with an indwelling hemodialysis catheter, 59% had no history of AV fistula surgery. The mean age of patients without a history of AV fistula surgery was statistically significantly higher compared to those with a history of AV fistula surgery (69.28±14.98 vs. 60.96±13.52, respectively; P=0.001) (Fig. 2). Among patients without a history of AV fistula surgery, 24 (66.7%) were male and 12 (33.3%) were female. No statistically significant difference was observed between gender and AV fistula surgery history (P=0.847).

DISCUSSION

Although the AV fistula is reported as the best vascular access method for hemodialysis, temporary and indwelling hemodialysis catheters are still frequently used today. Catheters are associated with both infectious and non-infectious complications, which can lead to increased mortality and morbidity [10]. Acute

Table 1. Distribution of patient characteristics and demographic data by groups

	Total (n=197)	Arteriovenous fistula (+) (n=136)	Arteriovenous fistula (-) (n=61)	P value
Age (years)	62.48±14.13	60.78±13.60	66.28±14.65	**0.011***
Gender, n (%)				0.618#
Male	134 (68)	91 (66.9)	43 (70.5)	
Female	63 (32)	45 (33.1)	18 (29.5)	
Hypertension, n (%)	122 (61.9)	84 (61.8)	38 (62.3)	0.943#
Diabetes mellitus, n (%)	83 (42.1)	57 (41.9)	26 (42.6)	0.926#
CAD, n (%)	69 (35)	21 (34.4)	48 (35.3)	0.906#
COPD, n (%)	7 (3.6)	3 (4.9)	4 (2.9)	0.679#

Data are shown as mean±standard deviation or n (%) where appropriate. CAD=coronary artery disease, COPD=chronic obstructive pulmonary disease.

*T-test, #Chi-square

complications associated with the use of indwelling hemodialysis catheters include hemorrhage, venous perforation, catheter malposition, infection, arterial injury, pneumothorax, and air embolism [11]. A study found that approximately one-third of patients undergoing hemodialysis with an indwelling hemodialysis catheter for 1–2 years experienced complications. Additionally, about 9% of patients developed bacteremia within 1 year, and bacteremia was the most common reason for hospital admissions related to indwelling hemodialysis catheters [12].

Another disadvantage of hemodialysis catheters compared to AV fistulas is recirculation. In order to minimize blood recirculation during hemodialysis treatment, the arterial and venous end holes at the catheter's distal end are separated from each other by 1–3 cm. Despite this design feature, recirculation remains a more frequent problem compared to AV fistulas. For an indwelling hemodialysis catheter with the distal end positioned in the right upper atrium, the average recirculation rate should be <5% [13].

In elderly patients, creating an AV fistula early in the course of dialysis is associated with lower mortality compared to the use of indwelling hemodialysis

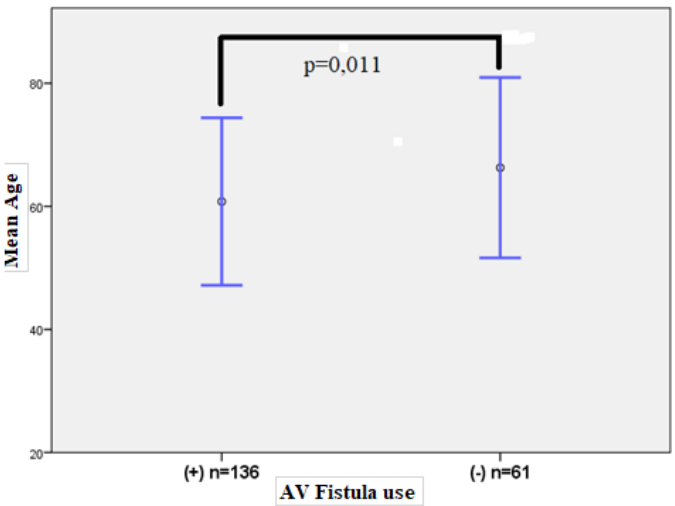

Fig. 1. Standard deviation graph showing the relationship between age and arteriovenous fistula use.

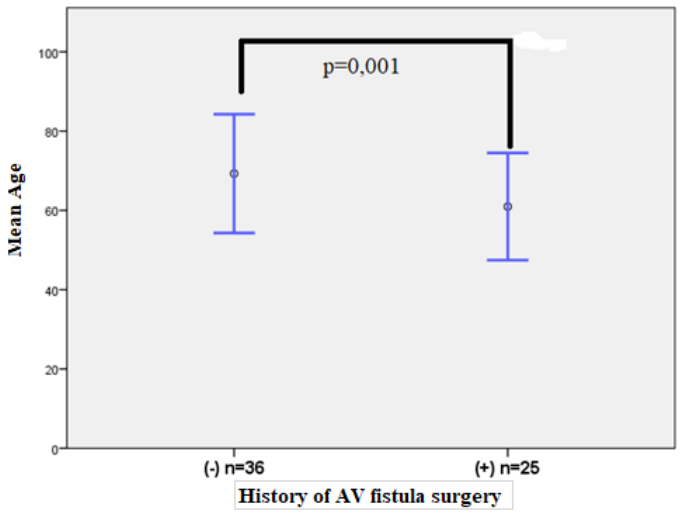

Fig. 2. Standard deviation graph showing the relationship between age and history of arteriovenous fistula surgery.

catheters. It has been observed that receiving hemodialysis treatment through an AV fistula positively affects survival outcomes, even in patients who initially started dialysis with an indwelling hemodialysis catheter [14]. Compared to patients receiving hemodialysis treatment with an indwelling hemodialysis catheter, patients receiving treatment with an AV fistula have significantly reduced length of hospitalization and depression symptoms [15].

To enable hemodialysis and improve patients' quality of life and comfort, AV fistula surgeries are often the first-choice procedure prior to kidney transplantation [16]. However, complications associated with AV fistula use may necessitate the use of alternative vascular access routes [17].

In our province, there are a total of four hemodialysis centers, including one private facility. The highest number of patients was at Burdur State Hospital, which was also the primary center of our study. In the present study evaluating the prevalence of AV fistulas among hemodialysis patients in our province, it was determined that the predominant preferred vascular access route was the AV fistula. A study conducted in Turkey in 2022 reported that indwelling hemodialysis catheters were the most frequently used vascular access route at the start of hemodialysis, accounting for 51.64% of the cases [18]. According to the same study, other vascular access routes included AV fistulas in 28.7% of the cases, temporary hemodialysis catheters in 19.45% of the cases, and AV fistulas made with AV grafts in 0.21% of the cases. In the study, the most commonly used vascular access option for patients undergoing long-term hemodialysis was identified as the AV fistula, with a prevalence of 70.89%. In recent years, there has been a trend of decreasing AV fistula usage rates, with a notable increase in the use of catheters for vascular access.

Although poor outcomes have been reported in the literature for patients over 65 years of age, especially for radiocephalic AV fistulas, AV fistula surgery in the elderly continues to be a matter of debate [19]. This may be the reason why AV fistula use is less preferred in patients over 65 years of age. Contreras-Jimenes *et al* demonstrated that poor AV fistula outcomes in the older age group can be improved with adequate preoperative evaluation [20]. As a result of these new data, the use of AV fistula should be encouraged in patients over the age of 65.

The AV fistula usage rate observed in the present study is consistent with the national prevalence of AV fistula use in Turkey, but it is below the desired level. Another notable finding in the present study is the prevalence of AV fistula history among patients using indwelling hemodialysis catheters. The fact that one out of every two patients undergoing hemodialysis through an indwelling hemodialysis catheter has no history of AV fistula surgery presents a significant barrier to achieving higher AV fistula usage rates. Reaching these patients and prioritizing AV fistula planning is crucial for long-term success in hemodialysis treatment and reducing complications.

CONCLUSION

Increasing the use of AV fistulas can potentially reduce complications and improve patient outcomes in hemodialysis treatment. As healthcare professionals, efforts should be focused on strategies such as early referral for AV fistula creation, patient education, surgical expertise, and multidisciplinary collaboration to improve this process. These approaches could contribute to the wider adoption of AV fistulas and thus achieve better treatment outcomes for patients with chronic kidney failure.

Ethical Statement

The study was conducted in accordance with the ethical guidelines of the Helsinki Declaration of 1975, with approval from the Non-Interventional Ethics Committee of Süleyman Demirel University Faculty of Medicine (Decision no: 17/377 and date: 29.12.2023).

Authors' Contribution

Study Conception: BA, ÖFR, CA; Study Design: BA, ÖFR, CA; Supervision: BA, ÖFR, CA; Funding: BA, ÖFR, CA; Materials: BA, ÖFR, CA; Data Collection and/or Processing: BA, ÖFR, CA; Statistical Analysis and/or Data Interpretation: BA, ÖFR, CA; Literature Review: BA, ÖFR, CA; Manuscript Preparation: BA, ÖFR, CA and Critical Review: BA, ÖFR, CA.

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The European Research Journal 2025;11(3):586-594 Original Article

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Evaluation of YouTube videos on soft tissue sarcomas: How reliable are YouTube shares?

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ABSTRACT

Objectives: Soft tissue sarcomas of the musculoskeletal system account for approximately 8% of malignant tumors in adolescents and young adults. As the fight against cancer, a disease of our era, increases, this topic has become increasingly popular on social media. This study aims to investigate the quality and reliability of videos published on YouTube providing information on musculoskeletal soft tissue sarcomas.

Methods: In the study, the 50 videos with the highest number of views, published on YouTube and providing information about soft tissue tumors of the musculoskeletal system, were evaluated and analyzed by two different observers. Observers scored the videos according to the DISCERN and JAMA scoring systems.

Results: Of the 50 YouTube videos evaluated, the most extended video was 1 hour 29 minutes 28 seconds, while the shortest video was 45 seconds. The highest number of views was 145,122. Statistically significant high agreement was obtained between observers regarding DISCERN and JAMA scores (ICC=0.734 and P<0.01). When average DISCERN scores were evaluated, video content quality was 12% very poor, 56% poor, 26% average, and 6% good.

Conclusions: Video content providing accurate and reliable information on soft tissue sarcomas should be created so patients can understand it, with proper references, and curated by healthcare professionals. Collaboration with healthcare professionals should be sought to enhance the quality and reliability of video content on YouTube.

Keywords: Sarcoma, neoplasms, connective and soft tissue, information dissemination, patient education, social media

Soft tissue sarcomas are rare, constituting approximately 1% of all malignant tumors. Although they can occur in various age groups, they make up about 8% of all malignant tumors in adolescents and young adults [1]. Cancer in adolescents and young adults constitutes a significant population. It has been the subject of recent studies, becoming increasingly popular in the media as the fight against cancer gains momentum. The most common cancers seen in adolescents and young adults include lymphoma, melanoma, testicular cancer, sarcomas, thyroid cancer, and breast cancer [2]. Soft tissue sarcomas have more than fifty histological subtypes, each with unique characteristics. Given their oncological features, accurate

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diagnosis and determination of personalized treatment strategies are crucial. The management of these cancers requires a multidisciplinary team, including pathologists, nuclear medicine specialists, medical oncologists, radiologists, radiation oncologists, and orthopedic oncologists. Orthopedic oncology focuses on primary and metastatic bone and soft tissue tumors affecting the musculoskeletal system.

Advancements in medicine, advanced imaging techniques, and surgical innovations significantly impact survival rates. The internet, one of the fastest ways to access information, is widely utilized today. YouTube hosts numerous content on soft tissue sarcomas. Many videos uploaded by doctors, healthcare institutions, news channels, patients, and their families serve as a second opinion for patients [3]. Therefore, videos must have high-quality and reliable content. This study aims to evaluate the reliability of YouTube videos regarding 'Soft Tissue Sarcoma'.

METHODS

Since the study was conducted as an open-access video research on YouTube, it did not require approval from an ethics committee. We aim to evaluate the reliability of content shared on widely used and openly accessible social platforms like YouTube regarding soft tissue sarcoma in the musculoskeletal system. Therefore, on February 22, 2024, videos related to 'soft tissue sarcoma' in the musculoskeletal system available on YouTube were screened (YouTube, www.youtube.com YouTube LLC, San Bruno, CA, USA). The term "soft tissue sarcoma" was entered into the YouTube search bar to begin a search. Videos with non-English language, advertisements, and those shorter than 30 seconds were excluded from the study. The top 50 most viewed videos meeting these criteria were evaluated. Video type, length, uploaders, view count, comment count, and like and dislike counts were recorded. While evaluating the videos, they were divided into subgroups according to the mentioned contents.

The daily view count was calculated by normalizing the total view count of the video to the number of days since it was uploaded. The like count was calculated as a percentage of the total likes and dislikes, yielding the Video Power Index (VPI) [4]. The quality

Table 1. Discern scoring system

DISCERN Scoring System						
Section	**Questions**	**No**		**Partly**		**Yes**
Reliability of the publication	1.Explicit aims	1	2	3	4	5
	2.Aims achived	1	2	3	4	5
	3.Relevance to patients	1	2	3	4	5
	4.Source of information	1	2	3	4	5
	5.Currency(data) of information	1	2	3	4	5
	6.Bias and balance	1	2	3	4	5
	7.Additional sources of information	1	2	3	4	5
	8.Reference to areas of uncertainty	1	2	3	4	5
Quality of information on treatment choices	9.How treatment works	1	2	3	4	5
	10.Benefits of treatment	1	2	3	4	5
	11.Risk of treatment	1	2	3	4	5
	12.No treatment options	1	2	3	4	5
	13.Quality of life	1	2	3	4	5
	14.Other treatment options	1	2	3	4	5
	15.Shared decision making	1	2	3	4	5

of the videos was scored using the DISCERN and JAMA scoring systems by two different observers who are orthopedic specialists. The DISCERN scoring system is a tool developed to evaluate the quality of health-related videos on YouTube. It consists of 15 questions, each rated on a scale from 1 to 5. Videos are given a total score ranging from 15 to 75. The first eight questions focus on the reliability of the video, while the last seven questions emphasize treatment options and their suitability. The scoring system categorizes scores as follows: 63-75 as 'excellent,' 51-62 as 'good,' 39-50 as 'average,' 28-38 as 'poor,' and below 28 as 'very poor' (Table 1) [5]. As mentioned in Table 2, the JAMA scoring system evaluates videos based on four criteria. Each criterion is assessed by awarding 1 or 0 points, resulting in a total score of 4 [6]. DISCERN, and JAMA scores were recorded by calculating the average scores of 2 observers.

Statistical Analysis

The data was collected, compared, and analyzed using the Microsoft Excel spreadsheet program (Version 2013, Microsoft Corporation) for calculations and SPSS for Windows 23.0 (SPSS Inc) for statistical analysis. Descriptive statistics utilized mean, standard deviation, median, lowest, highest, frequency, and ratio values. The distribution of the variables was assessed using the Kolmogorov-Smirnov test. Two Independent t-tests were conducted for comparing two independent groups with a normal distribution, while a One-way Analysis of Variance (One-Way ANOVA) was employed for comparing more than two groups. The Kruskal–Wallis H test was performed to compare more than two independent groups that did not adhere to a normal distribution. If differences between groups were detected, the Mann-Whitney U test was used to identify the origin of these differences. Categorical variables were analyzed using the chi-squared test, and statistical significance was set at a P-value of less than 0.05.

RESULTS

Of the 50 videos meeting the study criteria for soft tissue sarcomas of the musculoskeletal system, 11 were animations, and 39 were actual footage. When examined according to publishers, the majority of the videos, 44% (n=22), were uploaded by health channels. The majority of uploaders, 70% (n=35), were non-physicians. Regarding video content, the highest percentage, 32% (n=16), was related to 'general information,' followed by 28% (n=14) for 'treatment options.' Additionally, videos containing patient experiences constituted 20% of all videos (Table 3). Categorical parameters regarding the videos are shown as percentage graphs in Fig. 1.

The most extended video duration is 1 hour, 29 minutes, and 28 seconds, while the shortest is 45 seconds. The oldest uploaded video was posted on January 5, 2015. The average video duration was calculated as 00:08:56±00:18:07 (hh:mm:ss). The average number of video views was 23,056.12±32,673.31, with an average time since video upload of 1,616.41±957.9 days. The average daily views were 16.12±23.22. The most viewed video among the shared videos had 145.122

Table 2. JAMA scoring system

	JAMA Scoring System	Rating	
Section		**Yes**	**No**
Authorship	Authors and contributors, their affiliations, and relevant credentials should be provided	1	0
Attiribution	References and sources for all content should be listed clearly, and all relevant copyright information should be noted	1	0
Disclosure	Website “ownership” should be prominently and fully disclosed, as should any sponsorship, advertising, underwriting, commercial funding arrangements or support, or potential conflicts of interest	1	0
Currency	Dates when content was posted and updated should be indicated	1	0

Table 3. General features of the videos

	Frequency	Percentage
Image type (real/animation)		
Animation	11	22
Real	39	78
Publishers		
Cancer charity channel	4	8
Education channel	7	14
Health channel	22	44
Hospital channel	10	20
News channel	2	4
University channel	5	10
Uploaders		
Non-phsycian	35	70
Phsycian	15	30
Video contents		
Diagnostic process	5	10
General information	16	32
Multidisipinary management	1	2
Operation video	1	2
Patient experience	10	20
Sarcoma symptoms	3	6
Treatment options	14	28

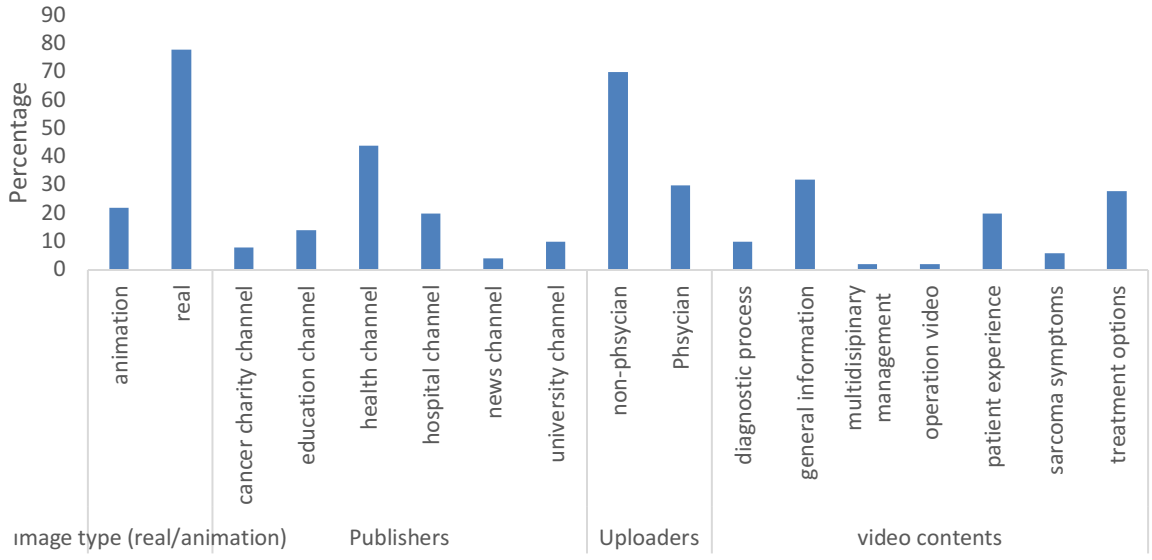

Fig. 1. Percentage graphs of categorical parameters related to videos.

Table 4. Descriptive statistics of quantitative parameters for videos

	Mean±standart deviation	Median (minimum-maximum)
Video length (hh:mm:ss)	00:08:56±00:18:07	00:03:30 (00:45:00-1:29:28)
View count	23056.12±32673.31	8600 (131-145122)
Time since video upload (days)	1616.41±957.9	1415 (182-3884)
View count (daily)	16.12±23.22	7.37 (0.18-112.06)
Comment count	25.19±51.36	3 (0-268)
Like count	157.72±222.68	57 (1-1149)
Dislike count	6.08±9.96	0.5 (0-37)
VPI	97.38±3.93	99.84 (80-100)

VPI=Video Power Index

views, and the most recent video was uploaded 182 days ago. Table 4 summarizes the data related to video duration, upload date, and view count, as well as VPI, comment, like, and dislike counts.

In Table 5, the highest average likes by video uploaders was 381.25±526.42 for the "cancer charity channel" group. The VPI index was highest at 98.41% in the "university channel" group.

The inter-observer DISCERN scoring measurements yielded statistically significant very high agreement (intraclass correlation coefficient (ICC)=0.918; P<0.001). Similarly, a statistically significant high agreement was obtained for inter-observer JAMA measurements (ICC=0.734; P<0.001) (Table 6).

No statistically significant difference exists in average DISCERN scores among uploaders (P=0.200). The average DISCERN score for non-physicians is 35.53, and for physicians, it is 37.27. The average JAMA score is 2.46 in the non-physician group, while in the physician group, it is 2.8. The VPI average is 97.3±4.46 in the Non-physician group and 97.59±2.39 in the Physician group. However, there is no statistically significant difference in JAMA scores and VPIs by uploaders (P>0.050) (Table 7).

When the average DISCERN scores are evaluated, the quality of the videos is as follows: 12% very poor, 56% poor, 26% average, and 6% good (Table 8).

Table 5. Video features by publishers

	Comment count	Like count	Dislike count	VPI
Cancer charity channel	99±147.07	381.25±526.42	10.75±15.56	96.58±5.14
	29 (0-268)	187.5 (1-1149)	5 (0-33)	98.6 (89.13-100)
Education channel	6.14±10.32	117.14±116,85	6±13.75	98.2±3.57
	2 (0-29)	63 (10-345)	0 (0-37)	100 (90.31-100)
Health channel	13.84±27.56	91.5±179.16	3.18±6.46	97.37±4.86
	2 (0-94)	8 (2-629)	0 (0-26)	100 (80-100)
Hospital channel	28.11±42.42	198±167.07	8.2±11.21	97.18±2.49
	10 (1-132)	164.5 (4-511)	2 (0-33)	96.49 (93.93-100)
News channel	38.5±14.85	265.5±23.33	15±8.49	94.79±2.44
	38.5 (28-49)	265.5 (249-282)	15 (9-21)	94.79 (93.06-96.51)
University channel	50±86.6	203.4±241.31	7.4±10.43	98.41±2.18
	0 (0-150)	43 (23-562)	0 (0-22)	100 (95.84-100)

Data are shown as mean±standard deviation and median (minimum-maximum). VPI=Video Power Index

Table 6. Assessment of interobserver agreement

	ICC (95% CI)	P value
DISCERN	0.918 (0.855-0.953)	**<0.001**
JAMA	0.734 (0.532-0.849)	**<0.001**

ICC=intraclass correlation coefficient, CI=Confidence interval

DISCUSSION

Based on an extensive literature review, our study is the first and only investigation regarding the reliability of videos about soft tissue sarcomas of the musculoskeletal system. The results will shed light on the content and quality of videos related to soft tissue sarcomas, contributing to the existing literature.

As of January 2024, the global internet user count reached 5.35 billion, representing 66.2% of the world's population. Among them, 5.04 billion individuals, equivalent to 62.3% of the global population, were active social media users [7]. With more than 3 billion monthly active users, Facebook continues to lead as the most popular social media platform, followed by YouTube, which has approximately 2.5 billion monthly active users [8]. The absence of video limitations, open access to video content, and widespread usage on the YouTube platform facilitated the planning of our study as a YouTube investigation.

In their study on internet usage among orthopedic patients, Burrus et al. [9] reported that 84.9% of 1296 patients had internet access, and among those with internet access, 64.7% used the internet to obtain orthopedic information. They also emphasized that younger patients tended to use the Internet for orthopedic information at a higher rate [9].

Innovative technologies today are creating a new language of communication worldwide. While rapid access to information can provide great convenience,

Table 7. Comparison of quantitative parameters according to uploaders

	Uploaders		test statistics	P value*
	Non-phsycian	Phsycian		
DISCERN	35.53±7.62	37.27±6.36	202	0.200
	33 (26-57.5)	38.5 (27.5-49)		
JAMA	2.46±0.65	2.8±0.49	179.5	0.069
	2.5 (1.5-4)	3 (2-4)		
VPI	97.3±4.46	97.59±2.39	234	0.519
	100 (80-100)	96.77 (93.93-100)		

Data are shown as mean±standard deviation and median (minimum-maximum). VPI=Video Power Index
*Independent Samples t test

Table 8. Evaluation of videos in terms of quality according to average DISCERN scores

	Frequency	Percentage
DISCERN		
Very poor	6	12
Poor	28	56
Average	13	26
Good	3	6

many sources on the internet need to be regulated, leading to the spread of low-quality and potentially inaccurate content to patients [10].

The total number of views for only the first 50 videos on YouTube related to soft tissue sarcomas as of February 22, 2024, 1,152.896, indicates interest in this orthopedic-specific topic. The literature review reveals that previously, only videos related to soft tissue sarcomas on YouTube had yet to be examined. In a study conducted by Clerici et al. [11] in 2011, using the keyword groups 'pediatric soft tissue sarcoma,' 'rhabdomyosarcoma,' and 'soft tissue sarcoma in children,' they examined 149 videos. They found that the majority of these videos were uploaded by family members (82.5%). They also reported that 94 videos were dedicated to deceased patients [11]. However, in the mentioned study, videos were categorized based on their content and publishing channels, and a valid scoring system regarding quality should have been utilized. In our current study, a significant portion of video content focuses on providing general information about soft tissue sarcoma (32%), followed by videos concerning treatment options (28%). Videos depicting patients' experiences dealing with the disease constitute a considerable proportion (20%). This indicates that videos are utilized as a tool for patients and their families to share impressions and experiences, demonstrating how they cope with the disease. As highlighted in the literature, various scoring systems are used to assess the quality and reliability of online videos [12]. Our study evaluated video content using widely recognized scoring systems such as DISCERN and JAMA, obtaining comparable results. Furthermore, to enhance the reliability of the study, two independent observers independently scored the same videos at different times, and a high level of agreement was found between the two observers ($P<0.001$).

In another study examining YouTube content related to cancer rehabilitation, 53 videos were analyzed, with the majority uploaded by academic institutions, university channels, health-related websites, and physiotherapists. They reported that frequently mentioned content was related to cancer rehabilitation basics, but most of the evaluated videos were of low quality and lacked sufficient information about cancer rehabilitation [13]. Consistent with the literature, when examining the channels that uploaded the videos, the top three were health, hospital, and education channels, respectively. Additionally, according to the DISCERN scoring, 12% of the videos in our study were rated as 'very poor,' and 56% were rated as 'poor.' Previous studies have highlighted the tendency for information shared by physicians to be superior to videos uploaded by non-physicians [10]. However, in our study, considering the uploaders of the videos, no statistically significant difference was found between physician and non-physician uploaders regarding DISCERN, JAMA scores, and VPI.

Similar studies in the literature on various health conditions have also reported different rates regarding the quality and accuracy of the videos. Şahin et al. [14], Citgez et al. [15], and Kanlıöz et al. [16] reported that the quality of the videos related to the subject we worked on is low, consistent with the results we obtained. However, Askin et al. [17], in their YouTube study on transcranial magnetic stimulation in stroke, reported that the majority of the videos were of moderate quality and partially had sufficient data.

Studies emphasizing the importance of sharing patient stories and experiences during the cancer journey are increasing. It has been shown that these shared experiences have a positive impact on both those sharing their own cancer experiences and cancer survivors [18]. Although most of the videos examined in our study were of low quality, the shared information about patient experiences can benefit patients and their families.

Limitations

This study has some limitations. First, the sample size is relatively small. However, due to the open-access nature of the YouTube platform and the absence of time restrictions on videos, we believe that the videos examined adequately represent the subject matter. Second, including only English-language videos is another limiting factor. However, considering that English is the most widely spoken language globally, we believe that this does not significantly undermine the validity of the study.

CONCLUSION

As a result, it is imperative that YouTube content cre-

ation incorporates evidence-based practices and utilizes referenced information to provide safer video content. Plans should be made to ensure that accurate and reliable information about "soft tissue sarcoma" is delivered to patients in an understandable manner, using appropriate sources and by healthcare professionals. Furthermore, efforts should be directed toward improving the quality of video content created by cancer survivors and individuals fighting cancer. To enhance the reliability of YouTube videos as much as possible, production should be facilitated by healthcare institutions, scientific organizations, and healthcare professionals.

Ethical Statement

Since the study was conducted as an open-access video research on YouTube, it did not require approval from an ethics committee.

Authors' Contribution

Study Conception: AY, ŞAŞ; Study Design: AY, HSC; Supervision: ND; Funding: N/A; Materials: ND, TC; Data Collection and/or Processing: ŞAŞ, TC; Statistical Analysis and/or Data Interpretation: AY; Literature Review: AY, ŞAŞ; Manuscript Preparation: AY, ŞAŞ and Critical Review: ND.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Editor's note

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Two-year retrospective analysis of repeated emergency service admissions in a secondary stage hospital: Diagnosis-based evaluation

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ABSTRACT

Objectives: This study aims to evaluate the characteristics of repeated emergency department (ED) visits in a secondary care hospital over a two-year period and analyze trends across different diagnostic categories.

Methods: A retrospective analysis was conducted on ED visit data from January 2023 to September 2024. Patient demographics, primary diagnoses, and visit frequencies were examined. Statistical analyses were performed to compare trends between 2023 and 2024, with subgroup analyses based on age and gender.

Results: The repeated visit rate was found to be 25.8% in 2023 and 26.0% in 2024, consistent with existing literature. The most common diagnosis was upper respiratory tract infections (URTI), accounting for 109,067 visits in 2023 and 83,655 visits in 2024, showing a significant decline. In contrast, general medical examinations and gastroenteritis cases increased in 2024 compared to 2023, indicating a potential shift in healthcare-seeking behavior. Myalgia ranked second, with 26,727 cases in 2023 and 21,225 in 2024, predominantly affecting middle-aged women. Falls and soft tissue disorders, ranked third, were more prevalent in male patients, with 24,351 cases in 2023 and 19,616 in 2024. Age-specific trends showed that trauma-related conditions were most common in children (0-10 years), while musculoskeletal and cardiovascular disorders increased with age. Gender distribution analysis indicated that headache and acute cystitis were more frequent in women, whereas falls and cardiovascular diseases were more common in men.

Conclusions: The findings highlight the need for better coordination between emergency and primary healthcare services to reduce unnecessary repeat visits. The shift in diagnostic trends suggests that regional healthcare planning should adapt to evolving patient needs. Future research should explore psychosocial factors contributing to repeat visits and assess the economic burden of ED overutilization.

Keywords: Emergency department, duplicate visit, diagnosis analysis, retrospective study, second-level hospital

Emergency services are one of the most important components of the health system and are critical units where the society can access health services with a 24/7 continuity logic. In recent years, the increase in the number of emergency room patients has become especially evident in terms of repeated admission [6, 14, 27]. In the international literature, patients who make repeated admissions are generally defined as patients who have more than one emergency room application during the year [12, 19].

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This patient population constitutes approximately 3-8% of total emergency room admissions, while accounting for 21-28% of all emergency room visits [14, 23]. International studies show that when the demographic and clinical characteristics of patients who make frequent applications are examined, this patient group constitutes a burden on the health system due to repeated applications [1].

Repeated admissions to he hospitals affect the health system in many ways. It not only increases the consumption of emergency room resources, but also causes emergency room congestion, increased waiting times and increased health expenditures [3, 22]. In particular, drug-related complications are visibly evident in patients who repeatedly apply to the emergency department [2]. The literature has revealed chronic health problems, mental health problems, socioeconomic factors and difficulties in accessing health services as the underlying reasons for repeated applications [8, 14, 18]. Secondary hospitals play an important role in the health system [6, 24]. Analysis of repeated admissions in these hospitals is of critical importance both in terms of improving the quality of patient care and optimal use of health resources. Accurate statistical methods are of great importance in this process [5]. Studies in the literature show that the rate of repeated admissions in secondary hospitals varies between 15-25% [12, 23]. Recent systematic analyses have determined that patients who repeatedly apply exhibit distinct clinical and demographic characteristics [12, 14]. These patients are generally at higher risk of comorbidities, have mental health problems and problems in the management of chronic diseases [19, 21]. In addition, the intensity of use of health services by this patient group is not limited to emergency services alone, but also creates increased use in primary health care services and inpatient services [14, 20].

Studies conducted in the last half-decade have highlighted the importance of a multidisciplinary approach in the management of repeated applications [6, 26]. Case management models and coordinated care programs in particular have yielded promising results in both positively affecting clinical outcomes and optimizing the use of healthcare services in this patient group [4, 25]. However, studies examining the characteristics and underlying factors of repeated admissions in secondary hospitals are limited [8, 24]. It is striking that there are few studies in the current literature that specifically focus on diagnosis and conduct detailed analyses of repeated admissions in secondary hospitals in Turkey. Studies have shown that repeated admissions are a significant problem in emergency departments. In a study conducted by Çıkrıkçı Işık *et al*. [8] in a tertiary hospital, 22.5% of repeated admissions were chronic diseases, while the rate obtained by Sultanoğlu *et al*. [24] in their experience with secondary hospitals was 18.3%. These studies indicate that the use patterns of emergency departments in Turkey show parallel results with the international literature, and that they also reveal some unique characteristics, especially in secondary hospitals. This study seems valuable because the number of studies that analyze repeat admissions in a broad and diagnostic manner, especially in secondary hospitals, is limited in our country. Because it reveals the application patterns, demographic characteristics and most common diagnoses by making a broad analysis of repeat applications to the emergency department of a secondary state hospital. This study can contribute to both the positive development of clinical practices and the upgrade of health systems.

METHODS

Study Setting

This study was conducted at Sultanbeyli State Hospital, a secondary care facility located in the Sultanbeyli district on the Asian side of Istanbul, Turkey. According to the 2024 Turkish Statistical Institute (TÜİK) data, Sultanbeyli has a total population of 369,193 people, with 181,270 females (49.09%) and 187,923 males (50.91%). The district's age distribution is as follows: 7.58% (0-4 years), 9.49% (5-9 years), 9.05% (10-14 years), 8.56% (15-19 years), and 8.18% (20-24 years). Additionally, 9.42% of the population falls within the 25-29 age group, while 8.96% is between 30-34 years. The elderly population (65 years and over) constitutes 3.09% of the total, with those aged 90 and above comprising 0.09%. Sultanbeyli State Hospital serves as the primary healthcare facility for the district and its surrounding areas, accommodating an annual emergency department visit volume of approximately 800,000 patients, indicating high healthcare utilization rates in the region [6, 14].

Study Population

The hospital's emergency department application data were retrospectively analyzed for the period between January 1, 2023, and September 30, 2024. Based on the literature [6, 14], repeated applications were defined as patients with more than one emergency department application in the same calendar year. All patients who applied to the emergency department during the study period were included in the study. Retrospective analysis is widely utilized in emergency department utilization studies [8, 18].

Inclusion and Exclusion Criteria

Inclusion Criteria: (1) Patients who admitted to the emergency department during the study period. (2) Patients with more than one admission in the same calendar year. (3) Those whose data could be fully accessed through the hospital information system [12, 19].

Exclusion Criteria: (1) Judicial cases. (2) Patients with missing data in the hospital information system. (3) Patients referred to another healthcare institution. (4) Patients who died in the emergency department [14, 23].

Data Collection and Variables

Patient data were obtained from the hospital's electronic medical record system (Hospital Information Management System-HBYS). The system utilizes ICD-10 (International Classification of Diseases, 10th Revision) codes for diagnostic classification [12, 19]. The study collected the following data:

1. Demographics: Age (years), Gender (female/male)
2. Visit Characteristics: Admission date and time, frequency of visits
3. Clinical Data: Primary ICD-10 diagnosis codes.

Diagnosis Classification

Emergency department admission diagnoses were categorized into seven main groups according to previous literature [6, 14, 18]:

1. Respiratory system diseases
2. Musculoskeletal system diseases
3. Trauma and injuries
4. Gastrointestinal system diseases
5. Neurological diseases
6. Cardiovascular system diseases
7. Other diseases.

Statistical Analysis

Statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The following methods were applied: Descriptive statistics were presented as numbers and percentages for categorical variables and as mean±standard deviation or median (minimum-maximum) for continuous variables [5, 12]. Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Comparisons of normally distributed continuous variables (e.g., mean age, length of stay) were conducted using the Student's t-test, while non-normally distributed continuous variables (e.g., visit frequency) were compared using the Mann-Whitney U test. Categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate [5, 19]. Univariate analysis: Variables identified as statistically significant ($P<0.05$) in univariate analysis were included in multivariate analysis. Multivariate logistic regression analysis was conducted to determine the factors affecting repeated applications, calculating Odds Ratios (OR) and 95% Confidence Intervals (CI). Model fit was assessed using the Hosmer-Lemeshow test [12, 14]. Seasonal and temporal variations were analyzed using time series analysis and seasonal decomposition methods [6, 19]. Relationships between diagnostic groups were assessed using hierarchical cluster analysis and multiple fit analysis [5, 12]. For all statistical analyses, a P-value of <0.05 was considered statistically significant. The study's statistical power was assessed using G*Power 3.1.9.7 software, ensuring at least 80% power to detect meaningful differences [12, 19].

RESULTS

General Admission Characteristics

During the study period, a total of 799,084 emergency department admissions were recorded in 2023 and 653,746 in the first 9.7 months of 2024. Among these, 206,502 (25.8%) admissions in 2023 and 169,963 (26.0%) admissions in 2024 were identified as repeated visits. The distribution of repeated visits remained consistent across the two years (Table 1).

Distribution and Characteristics of Common Diagnoses

The most frequently observed diagnosis was upper respiratory tract infections, with 109,067 visits in 2023

Table 1. General admission data

Year	Total admissions	Repeated admissions	Repeated admission rate (%)
2023	799,084	206,502	25.8
2024 (First 9.7 months)	653,746	169,963	26.0

and 83,655 visits in 2024, indicating a decrease in cases over the two years. Myalgia was the second most common diagnosis, with 26,727 visits in 2023 and 21,225 visits in 2024, also showing a decline. Falls and soft tissue disorders ranked third, accounting for 24,351 visits in 2023 and 19,616 visits in 2024. This trend suggests a general reduction in repeated admissions for these conditions. The table highlights the yearly comparison of common diagnoses and provides insight into the shifting patterns of emergency department visits over time (Table 2).

Age and Gender Distribution

The distribution of repeated emergency department admissions varied across different age groups. In pediatric patients (0-10 years), the leading causes of repeated visits were falls, soft tissue injuries, URTI, and gastroenteritis, accounting for 75.2% (598,213 cases) in 2023 and 74.8% (482,920 cases) in 2024. Young adults (20-40 years) primarily presented with URTI, headache, and acute cystitis, with 135,794 cases (17.1%) in 2023 and 104,880 cases (16.3%) in 2024, showing a notable female predominance in headache and cystitis cases. Middle-aged adults (40-60 years) were most frequently diagnosed with myalgia and cardiovascular diseases, representing 5.4% (42,748 cases) in 2023 and 6.6% (42,412 cases) in 2024, with a higher prevalence among female patients. Elderly patients (60+ years) predominantly presented with URTI, myalgia, and neurological diseases, comprising 2.4% (18,711 cases) in 2023 and 2.3% (14,968 cases) in 2024. These findings highlight that trauma-related conditions were more common in younger patients, while musculoskeletal, respiratory, and cardiovascular disorders were more prevalent in older adults (40+ years).

Diagnosis-Specific Features

Non-specific symptoms categorized as general medical examinations were the fourth most common reason for repeated visits, with 18,397 cases in 2023 and 22,796 cases in 2024. Gastroenteritis ranked fifth, with 7,420 visits in 2023 and 7,510 visits in 2024. Neurological diseases and cardiovascular disorders were also frequently observed among older patients.

Gender-Specific Patterns

A distinct gender distribution was noted in headache cases, with a significant female predominance (4,291 out of 6,078 cases in 2023 and 2,490 out of 3,593 cases in 2024). Similarly, acute cystitis was more prevalent among female patients, while falls, soft tissue injuries, and trauma-related conditions were more common among males (Table 3).

Analysis by Age Groups

Among pediatric patients (0-10 years), the primary reasons for repeated visits were falls, injuries, URTI, and gastroenteritis, as well as rabies vaccination follow-ups for animal-related injuries. Young adults (20-40 years) predominantly sought emergency care for URTI, headache, and acute cystitis, while middle-aged adults (40-60 years) frequently presented with myalgia

Table 2. Yearly change in diagnoses

Diagnosis	2023 cases	2024 cases	Change (%)
Upper respiratory tract infections	109,067	83,655	-23.3%
Myalgia	26,727	21,225	-20.6%
Falls & soft tissue injuries	24,351	19,616	-19.5%
General medical examinations	18,397	22,796	+23.9%
Gastroenteritis	7,420	7,510	+1.2%

Table 3. Gender distribution of repeated emergency visits

Diagnosis	2023 female cases	2023 male cases	2024 female cases	2024 male cases
Upper respiratory tract infections	57,883	51,184	44,579	39,076
Myalgia	14,702	12,025	11,788	9,437
Falls & soft tissue injuries	9,451	14,900	7,584	12,032
Headache	4,291	1,787	2,490	1,103
Acute cystitis	3,772	1,441	2,779	1,086

and cardiovascular conditions. In elderly patients (>60 years), the most frequently observed diagnoses were URTI, myalgia, neurological diseases, and cardiovascular disorders (Table 4).

Comparison between Years

The rate of repeated admissions remained stable between the two years, at 25.8% in 2023 and 26.0% in 2024. A slight increase in the mean age of patients presenting with URTI was observed, rising from 48.8 years in 2023 to 51.4 years in 2024, while other diagnoses showed minimal variation. Gender distribution patterns remained consistent, with female predominance in headache, acute cystitis, and cardiovascular diseases, while trauma-related conditions and musculoskeletal injuries were more common in male patients.

DISCUSSION

This study provides a comprehensive evaluation of repeated emergency department visits in a secondary care hospital. The detected repeated visit rates (25.8-26.0%) align with the literature-reported rates of 21-28% [14, 19, 23]. The 24.6% rate in the multicenter study by Kanzaria *et al*. [14] and the 25.3% rate in Moe *et al*. [19] support our findings.

The most common cause of repeated visits, upper respiratory tract infections (URTI), showed a higher prevalence than the reported 14-18% in the literature [6, 18]. This may be related to regional healthcare service utilization habits and post-COVID-19 effects [6, 18, 21]. Similar findings were reported by Cho *et al*. [6] and Osawa *et al*. [21], where URTI was the leading diagnosis. However, a notable decline in URTI cases was observed between 2023 and 2024, suggesting potential changes in health-seeking behavior or preventive measures.

In contrast, general medical examinations (non-specific symptoms) were a significant cause of repeated visits, ranking fourth in our study. This aligns with findings by Giannouchos *et al*. [12], who emphasized the role of psychosocial factors in emergency department utilization. Interestingly, this category saw an increase in 2024 compared to 2023, which may indicate a shift in healthcare-seeking behavior. Additionally, gastroenteritis cases increased slightly from 2023 to 2024, a trend that warrants further investigation.
Injuries caused by dogs and cats (rabies vaccination follow-up) were another major factor in repeated applications, differing from the findings of Lee *et al*. [18], which were based on secondary hospital data. This may be related to the high stray animal population and sociodemographic characteristics of the region. Burton *et al*. [3] highlighted how regional factors

Table 4. Age group distribution of repeated emergency visits

Age group	Most common diagnoses (2023)	Most common diagnoses (2024)
0-10 years	Falls, URTI, Gastroenteritis	Falls, URTI, Gastroenteritis
20-40 years	URTI, Headache, Acute Cystitis	URTI, Headache, Acute Cystitis
40-60 years	Myalgia, Cardiovascular Diseases	Myalgia, Cardiovascular Diseases
60+ years	URTI, Myalgia, Neurological Diseases	URTI, Myalgia, Neurological Diseases

can influence emergency department application patterns. Similarly, Kim and Lee [15] and Kuan and Chua [16] noted that regional health system differences can impact repeated visit trends.

Gender-specific patterns in our study were largely parallel to the literature [8, 14, 19]. Female predominance was observed in headache and acute cystitis cases, consistent with the findings of Çıkrıkçı Işık et al. [8]. In contrast, falls and soft tissue injuries were more common in male patients, aligning with Cordell et al. [7]. Additionally, myalgia was more frequent in female patients, whereas cardiovascular diseases were more prevalent in males. These gender-based differences highlight the need for tailored preventive strategies.

In terms of age distribution, high application rates among young adults (20-40 years) were consistent with the literature [12, 19, 23]. The systematic review by Soril et al. [23] supports our findings, particularly regarding the predominance of myalgia diagnoses in middle-aged adults, which aligns with the chronic pain patterns reported by Kanzaria et al. [14]. Laferté et al. [17] emphasized the significance of trauma-related repeat visits among elderly patients, reinforcing our observation that falls and soft tissue injuries were a key concern in this age group.

One of the strengths of our study is its large two-year dataset, whereas most similar studies cover shorter timeframes or smaller sample sizes [6, 18]. Additionally, since the existing literature predominantly focuses on tertiary hospitals, our study provides valuable insights into repeated visits in secondary hospitals [14, 19]. Apart from Sultanoğlu et al. [24], few studies in Turkey have comprehensively analyzed repeated visits in secondary hospitals.

Understanding repeated emergency department applications is critical for healthcare planning and policy development. Fleury et al. [11] emphasized that proper management of repeated visits is essential, particularly for chronic disease patients. Additionally, Von Allmen et al. [26] suggested that case management programs and coordinated care models could reduce unnecessary emergency visits.

Limitations

Our study has several limitations. First, as a single-center study, its generalizability is limited. Secondly, since data were obtained from a single hospital database, we lack information on whether the same patients sought care at other institutions. This limitation means that the actual number of repeated applications may be underestimated. Additionally, due to the retrospective nature of our study, we could not analyze underlying psychosocial factors contributing to repeated applications. Finally, comorbid conditions, socioeconomic status, and medication use were not included in our analysis, all of which may influence repeated visit patterns. Future studies should incorporate multicenter, prospective designs to address these limitations.

Recommendations

Based on our findings, several recommendations can be made for managing repeated emergency department applications. As highlighted in the multicenter study by De Groot et al. [9], developing structured protocols for managing patients with nonspecific symptoms can be beneficial. Additionally, Doan and Barbic [10] emphasized the importance of integrated care models for mental health and chronic disease management.

Strengthening coordination with primary healthcare services could reduce repeat visits in secondary hospitals [8, 24]. De Groot et al. [9] found that 60% of nonspecific symptom cases could be managed through primary healthcare coordination, reducing emergency visits. Similarly, Doan and Barbic [10] reported that integrated care models for patients with anxiety and depression reduced repeat visits by 40%. Hughes et al. [13] emphasized the importance of a multidisciplinary approach in managing chronic pain patients, while Pearce et al. [22] highlighted the need for effective emergency department strategies to prevent congestion.

Future studies should further investigate the psychosocial characteristics and healthcare utilization behaviors of patients with repeat visits, as demonstrated in Tuller's study [25]. This study revealed that psychosocial factors contributed to repeat visits in 45% of cases. Additionally, Moe et al. [20] conducted a five-year cost analysis, showing that repeated applications increased healthcare costs by an average of $4,500-$6,000 per patient per year. Given these financial implications, future research should also focus on the economic burden of repeated emergency visits.

CONCLUSION

This study provides a comprehensive analysis of repeated emergency department visits in a secondary care hospital. The findings indicate that the repeated visit rates (25.8-26.0%) are consistent with previous literature but also reveal regional variations in diagnostic patterns. The high prevalence of upper respiratory tract infections, nonspecific symptoms, and injuries related to stray animals highlights the importance of region-specific healthcare planning and preventive strategies. The yearly changes in diagnostic trends between 2023 and 2024 (decrease in URTI and myalgia cases; increase in general medical examinations and gastroenteritis cases) suggest that changes in healthcare-seeking behavior may influence emergency department utilization. These findings emphasize the need for strengthening the coordination between emergency and primary healthcare services, implementing multidisciplinary approaches for chronic disease management, developing structured protocols for patients with nonspecific symptoms, and adapting healthcare policies to regional factors. Future multicenter and prospective studies can further explore the psychosocial factors contributing to repeated visits and evaluate the economic impact of emergency department overutilization.

Ethical Statement

This retrospective cross-sectional study was conducted in a secondary health care state hospital. The study was approved by the Ethics Committee of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (Decision No: 305, Date: 06.11.2024). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Authors' Contribution

Study Conception: SE; Study Design: SE; Supervision: SE; Funding: SE; Materials: SE; Data Collection and/or Processing: SE; Statistical Analysis and/or Data Interpretation: SE; Literature Review: SE; Manuscript Preparation: SE and Critical Review: SE.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The impact of gender differences on the roles of the atherogenic index of plasma and triglyceride-glucose index in predicting moderate to severe coronary artery calcification

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ABSTRACT

Objectives: This study aimed to evaluate the association of the triglyceride-glucose (TyG) index and the atherogenic index of plasma (AIP) with moderate-to-severe coronary artery calcium score (CACS), with a particular focus on gender differences. Given the gender-specific variations in the development of coronary artery calcification, tailored diagnostic approaches are required.

Methods: In this retrospective, single-center study, 246 consecutive patients aged 25-77 years who underwent 128-slice coronary computed tomography angiography (CCTA) for coronary artery disease screening between June 2024 and January 2025 were analyzed. Patients were categorized into three groups according to their CACS: Group 1 (CACS=0), Group 2 (CACS=1-99), and Group 3 (CACS≥100). Demographic characteristics and medical histories were recorded. Biochemical parameters, lipid panel, and hemogram values were analyzed from venous blood samples collected after 12 hours of fasting. Multivariate logistic regression analyses were performed to identify independent predictors of moderate-to-severe CACS in both genders.

Results: In women, advanced age (odds ratio [OR]=1.126; 95% confidence interval [CI]: 1.031–1.136; P<0.001), elevated triglyceride levels (OR=0.964; 95%CI:0.937–0.992; P=0.011), and a higher TyG index (OR=35.317;95%CI:6.328–187.356; P=0.002) were independently associated with moderate-to-severe CACS. In men, advanced age (OR=1.083; 95% CI:1.007–1.165; P=0.032), severe coronary artery stenosis (OR=12.298; 95% CI: 1.451–104.208; P=0.021), and smoking (OR=8.771; 95%CI: 1.810-42.501; P=0.007) were independent predictors. AIP was not identified as an independent predictor of moderate-to-severe CACS in either gender.

Conclusions: Advanced age was independently associated with CACS in both genders. The TyG index was a significant predictor of moderate-to-severe CACS in women, while traditional risk factors, such as smoking and severe coronary artery stenosis, were more relevant in men. AIP was not an independent predictor of moderate-to-severe CACS in either gender.

Keywords: Coronary artery calcium score, gender differences, atherosclerosis, atherogenic index of plasma, triglyceride-glucose index

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Coronary artery calcium scoring (CACS), assessed by coronary computed tomography angiography (CCTA), is a well-established, noninvasive marker of coronary atherosclerosis and an independent predictor of major adverse cardiovascular events (MACE) [1, 2]. Several metabolic and inflammatory conditions, including hyperlipidemia, diabetes mellitus (DM), and systemic inflammation, contribute to the progression of coronary artery calcification (CAC) [3]. Notably, gender differences influence both the prevalence and characteristics of CAC; men tend to develop calcified plaques at younger ages, whereas non-calcified or mixed plaques are more common in premenopausal women. After menopause, the prevalence of CAC in women increases significantly [4-6].

Considering the gender-specific differences in the development of CAC, it is essential to incorporate these variations when designing effective diagnostic methods for CAD [7]. In recent years, two metabolic markers - the triglyceride-glucose (TyG) index and the atherogenic index of plasma (AIP) - have emerged as potential predictors of subclinical atherosclerosis. The TyG index is a validated surrogate for insulin resistance, while AIP reflects atherogenic lipid imbalance [8]. Both have been associated with coronary artery disease (CAD) and CAC independent of traditional risk factors, including DM [9, 10]. However, few studies have evaluated whether the predictive performance of these indices differs by gender, despite the known sex-specific pathophysiology of atherosclerosis.

Understanding the gender-specific predictive value of TyG and AIP may help refine cardiovascular risk stratification, especially in women, who often receive less aggressive diagnostic and preventive care. Therefore, this study aimed to investigate the association of the TyG index and AIP with moderate-to-severe CACS, with particular emphasis on sex-related differences in predictive value.

METHODS

Study Design

The research was carried out on 246 consecutive patients in the age range of 25-77 years admitted to the cardiology outpatient clinic of Siirt Training and Research Hospital and underwent 128-slice CCTA for CAD screening between June 2024 and January 2025, retrospectively. Patients with severe renal failure, liver failure, thyroid dysfunction, structural heart disease, infection, autoimmune disease, malignancy, patients for whom effective CCTA cannot be performed due to arrhythmia, pregnant women and breastfeeding women, patients with previously known CAD and those who have undergone interventional cardiovascular procedures, patients using fenofibrate due to hypertriglyceridemia and patients taking statins were not included in the study. Patients with a CACS of 0 were defined as the control group (Group 1). Patients with a CACS between 1 and 99 were defined mild CACS group as Group 2, and patients with a CACS≥100 were defined moderate to severe CACS group as Group 3.

The research adhered to the norms of the Declaration of Helsinki and was granted approval by Siirt University Noninterventional Clinical Research Ethical Committee (Date: 28.11.2024, Decision No: 2024/12/01/04).

Demographic Findings, Laboratory Analyzes, the CCTA and CACS Analysis

The patients' age, gender, systolic and diastolic tension (TA) measurements, body mass index (BMI), previous medical history (HT, DM, HL history), cardiac family history and smoking habits were recorded. Biochemical parameters such as fasting blood sugar (FBG), uric acid, C-reactive protein (CRP), and hemoglobin A1c (HbA1c) values were measured in venous blood samples taken after 12 hours of fasting. For lipid parameters, total cholesterol, triglyceride, LDL, and high-density lipoprotein (HDL) values were obtained using the Beckman Coulter device and kits. Then, the TyG index was calculated using the natural logarithm (ln) formula (fasting triglyceride × fasting glucose/2). Atherogenic index of plasma (AIP) was obtained by taking the logarithm of the ratio of serum triglyceride level to high-density lipoprotein level. LDL/HDL, total cholesterol/HDL parameters were calculated. Additionally, neutrophil, lymphocyte, and monocyte were assessed using the Mindray device and kits. Neutrophile/lymphocyte ratio (NLR) and monocyte-HDL ratio values were calculated.

5 mg intravenous metoprolol was administered within 2 to 30 minutes before the procedure to patients who had a heart rate of 65/min before the procedure

and had no contraindication to beta blocker treatment. CACS was measured with a 128-slice General Electric CT scanner device using the prospective electrocardiogram (ECG) gating method with non-contrast 120 KV, 300 mAs values, 3 mm slice thickness, without any overlap or gap. CAC data collection was performed prospectively synchronized with the patient's ECG by gating in high pitch mode by operating it in the craniocaudal direction during breath holding in mid-inspiration. Calcification was defined as >130 Hounsfield (HU) units or areas with at least 1 mm of hyperattenuation in less than three consecutive pixels. The Agatstone method was used to calculate the CACS by calculating the weighted sum of the areas >130 HU.

Statistical Analysis

The distribution of normality for all variables was assessed using the Kolmogorov-Smirnov test. Variables with a normal distribution are presented as mean±standard deviation, and comparisons between groups were conducted using one-way analysis of variance (ANOVA). Categorical variables are expressed as percentages, and the Pearson chi-square test was employed for group comparisons. To identify the specific groups responsible for significant differences in continuous variables, post hoc Tukey-b testing was applied. For categorical variables with significant differences, Bonferroni-corrected z-tests were performed. Gender-specific univariate and multivariate logistic regression analyses were conducted to determine independent predictors of moderate-to-severe CACS in both men and women. A P-value < 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 246 patients were included in the study: 81 patients in Group 1 (CACS 0), 98 patients in Group 2 (CACS between 0 and 99), and 67 patients in Group 3 (CACS ≥100). 134 (54.5%) of the participants in the study were women, and 112 (45.5%) were men. The average age for women was 58.52±9.17 years, while for men it was 52.14±11.43 years. DM was present in 71 patients, comprising 46 (64.8%) women and 25 (35.2%) men. Age (P<0.001), BMI (P<0.001), systolic TA (P<0.001), diastolic TA (P=0.003), coronary critical stenosis rate (P<0.001), DM (P<0.001) and smoking (P<0.001) rates were significantly higher in Group 3 than

Table 1. Baseline demographic and clinical variables of study participants in the coronary artery calcium score groups

Variable	Group 1 (n=81)	Group 2 (n=98)	Group 3 (n=67)	P value
Age (years)	47.92±9.96	58.09±9.72	61.29±7.31	**<0.001[a]**
BMI (kg/m2)	25.53±2.74	27.88±2.10	28.36±2.50	**<0.001[a]**
Systolic BP (mmHg)	121.60±13.40	132.69±9.05	133.19±13.49	**<0.001[a]**
Diastolic BP (mmHg)	78.39±7.45	83.27±5.17	81.86±6.50	**<0.001[a]**
Male gender, n (%)	49 (60.5)	34 (34.7)	29 (43.3)	**0.002[b]**
Critical stenosis >70%	0 (0)	6 (6.1)	17 (25.4)	**<0.001[b]**
HT, n (%)	31 (38.3)	78 (79.6)	47 (70.1)	**<0.001[b]**
DM, n (%)	16 (19.8)	24 (24.5)	31 (46.3)	**0.001[b]**
HL, n (%)	11 (13.6)	53 (54.1)	31 (46.5)	**<0.001[b]**
Smoking, n (%)	20 (24.7)	18 (18.4)	34 (50.7)	**<0.001[b]**
CVD family history, n (%)	15 (18.5)	44 (44.9)	12 (17.9)	**<0.001[b]**

Continuous variables with normal distribution were expressed as mean±standard deviation. Categorical variables are expressed as n (%). BMI=Body mass index, BP=Blood pressure, HT=Hypertension, DM=Diabetes mellitus, HL=Hyperlipidemia, CVD=Cardiovascular disease

[a]One-way ANOVA test; [b]Pearson Chi-Square test.

Table 2. Baseline laboratory and biochemical variables of study participants in coronary artery calcium score groups

Variable	Group 1 (n=81)	Group 2 (n=98)	Group 3 (n=67)	P value
Triglyceride (mg/dL)	125.16±72.82	146.01±87.89	187.46±94.38	**<0.001[a]**
TyG index	4.68±0.27	4.79±0.33	5.17±0.41	**<0.001[a]**
LDL (mg/dL)	119.33±26.50	128.47±25.29	119.17±28.74	**0.031[a]**
HDL (mg/dL)	60.31±14.29	55.84±13.18	54.43±12.72	**0.019[a]**
LDL/HDL	2.08±0.61	2.41±0.71	2.26±0.60	**0.004[a]**
Total cholesterol (mg/dL)	184.72±40.05	192.95±40.31	185.79±34.50	0.305
Total cholesterol/HDL	3.19±0.83	3.58±0.86	3.51±0.69	**0.005[a]**
AIP	-0.0798±0.28	0.0031±0.26	0.1035±0.24	**<0.001[a]**
Uric acid (mg/dL)	4.71±1.03	4.81±1.20	5.04±0.95	0.186
CRP (mg/L)	2.99±1.68	4.06±2.77	4.28±2.85	**0.003[a]**
FBG (mg/dL)	109.25±18.65	120.79±31.50	138.77±49.55	**<0.001[a]**
HbA1c (%)	5.76±0.87	6.25±1.17	6.62±1.57	**<0.001[a]**
Neutrophil/lymphocyte	1.69±0.60	2.44±0.98	2.20±1.17	**<0.001[a]**
Monocyte-HDL ratio	9.25±4.25	7.55±2.37	9.68±4.27	**0.001[a]**

Continuous variables with normal distribution were expressed as mean±standard deviation.

TyG index=Triglyceride-glucose index, LDL=Low density lipoprotein, HDL=High density lipoprotein, AIP=Atherogenic index of plasma, CRP=C-reactive protein, FBG=Fasting blood glucose, HbA1c=Hemoglobin A1c

[a]One-way ANOVA test

in Groups 1 and 2. The findings are shown in Table 1.

No significant difference was observed between Groups 1, 2, and 3 for the parameters t cholesterol and uric acid (P>0.05). HDL was significantly lower in Group 3 than in Group 1 (P=0.026). CRP (P=0.006), HbA1c (P<0.001), and NLR (P=0.003) were significantly higher in Group 3 than in Group 1. Triglyceride (P<0.001), TyG index (P<0.001), AIP (P<0.001), and FBG (P<0.001) values were significantly higher in Group 3 than in Groups 1 and 2. The findings are shown in Table 2.

As a result of univariate and multivariate logistic

Table 3. Univariate and multivariate analyses of moderate-to-severe CAC score predictors in all patients

Variables	Univariate	P value	Multivariate	P value
Age	1.084 (1.049-1.120)	**<0.001**	1.104 (1.053-1.158)	**<0.001**
Triglyceride	1.006 (1.003- 1.009)	**<0.001**	0.999 (0.990-1.007)	0.74
TyG index	24.159 (9.385-62.188)	**<0.001**	37.507 (7.227-194.653)	**<0.001**
AIP	6.510 (2.239-18.933)	**0.001**	0.685 (0.051-9.226)	0.776
FBG	1.017 (1.009-1.025)	**<0.001**	1.002 (0.991-1.014)	0.673
Critical stenosis >%70	9.803 (3.670-26.185)	**<0.001**	3.342 (0.905-12.341)	0.07
DM	2.992 (1.650-5.426)	**<0.001**	0.778 (0.307-1.917)	0.596
Smoking	3.823 (2.102-6.953)	**<0.001**	3.318 (1.466-7.507)	**0.004**

CAC=Coronary artery calcium, TyG index=Triglyseride-glucose index, AIP=Atherogenic index of plasma, FBG=Fasting blood glucose, DM=Diabetes mellitus.

Table 4. Univariate and multivariate analyses of moderate-to-severe CAC score predictors in females

Variables	Univariate	P value	Multivariate	P value
Age	1.083 (1.031-1.136)	**0.001**	1.126 (1.048-1.211)	**0.001**
Triglyceride	1.005 (1.000-1.009)	**0.032**	0.964 (0.937-0.992)	**0.011**
TyG index	28.823 (7.706-107.812)	**<0.001**	35.317 (6.328-187.356)	**0.002**
AIP	3.875 (1.003-14.978)	0.05	8.486 (0.189-380.058)	0.27
FBG	1.011(0.999-1.023)	0.07	0.960 (0.922-1.000)	0.051
Critical stenosis >%70	4.312 (1.143-16.266)	0.031	5.412 (0.695-42.137)	0.107
DM	2.991 (1.372-6.525)	**0.006**	0.439 (0.093-2.080)	0.3
Smoking	2.500 (0.975-6.412)	0.057	1.014 (0.141-7.312)	0.989

CAC=Coronary artery calcium, TyG index= Triglyceride-glucose index, AIP=Atherogenic index of plasma, FBG=Fasting blood glucose, DM=Diabetes mellitus.

regression analyses, age (OR=1.104; 95% C.I. 1.053-1.158, P<0.001), TyG index (OR=37.507; 95% C.I. 7.227-194.653, P<0.001) and smoking (OR=3.318; 95% C.I. 1.466-7.507, P<0.001) were found to be independently associated parameters with the presence of moderate-to-severe CACS in the all patient group. The AIP was not found to be an independently associated parameter with moderate-to-severe CACS (P>0.05). The findings are shown in Table 3.

In gender-specific univariate and multivariate logistic regression analyses, age (OR=1.126; 95% C.I. 1.031-1.136, P<0.001), triglyceride (OR=0.964; 95% C.I. 0.937-0.992, P=0.011) and TyG index (OR=35.317; 95% C.I. 6.328-187.356, P=0.002) were found to be independent predictors of moderate-to-severe CACS in women, and age (OR=1.083; 95% C.I. 1.007-1.165, P=0.032), critical coronary artery stenosis (OR=12.298; 95% C.I. 1.451-104.208, P=0.021) and smoking (OR=8.771; 95% C.I. 1.810-42.501, P=0.007) were found to be independent predictors of moderate-to-severe CACS in men. The AIP was not found to be a parameter independently associated with moderate-to-severe CACS in either women or men (P=0.27, P=0.596, respectively). The findings are shown in Tables 4 and 5.

DISCUSSION

The findings of this study highlight the gender-specific

Table 5. Univariate and multivariate analyses of moderate-to-severe CAC score predictors in males

Variables	Univariate	P value	Multivariate	P value
Age	1.095 (1.044-1.149)	**0.001**	1.083 (1.007-1.165)	**0.032**
Triglyceride	1.008 (1.003-1.013)	**0.001**	1.008 (0.994-1.022)	0.267
TyG index	19.625 (5.092-75.643)	**<0.001**	5.630 (0.618-51.312)	0.125
AIP	18.697 (2.985-117.093)	**0.002**	0.208 (0.001-68.810)	0.596
FBG	1.023 (1.010-1.036)	**<0.001**	1.020 (0.998-1.043)	0.071
Critical stenosis >%70	24.750 (5.043-121.471)	**<0.001**	12.298 (1.451-104.208)	**0.021**
DM	3.012 (1.171-7.748)	**0.022**	0.250 (0.036-1.735)	0.161
Smoking	10.523 (3.612-30.659)	**<0.001**	8.771 (1.810-42.501)	**0.007**

CAC=Coronary artery calcium, TyG index=Triglyceride-glucose index, AIP=Atherogenic index of plasma, FBG=Fasting blood glucose, DM=Diabetes mellitus.

determinants of moderate-to-severe CACS, underscoring the distinct metabolic and clinical pathways contributing to coronary atherosclerosis in men and women. Our results indicate that older age, higher triglyceride levels, and an elevated TyG index are independent predictors of moderate-to-severe CACS in women, whereas in men, older age, severe coronary artery stenosis, and smoking are significant predictors. Notably, AIP was not identified as an independent predictor of moderate-to-severe CACS in either sex, suggesting that other metabolic or inflammatory markers may play a more pivotal role in vascular calcification progression. These findings emphasize the importance of incorporating gender-specific indicators into traditional cardiovascular risk assessment algorithms to enhance the prediction of subclinical atherosclerosis.

In our study, advanced age was independently associated with moderate-to-severe CACS in both men and women. This finding aligns with the Multi-Ethnic Study of Atherosclerosis (MESA), which analyzed data from 6,814 participants aged 45 to 84, free of clinical cardiovascular disease at baseline. The study observed that both the prevalence and extent of CAC increased steadily with advancing age across all racial and ethnic groups [11]. Specifically, the incidence of newly detectable CAC averaged 6.6% per year, with rates of less than 5% per year in individuals under 50, but rising to over 12% in those over 80 [12].

Our study found that severe coronary artery stenosis in men was independently associated with moderate-to-severe CACS. However, this association was not observed in women. This discrepancy may be due to differences in arterial remodeling between sexes [13]. A study by Sangiorgi *et al*. suggests that arterial calcification correlates more with overall plaque burden rather than lumen narrowing, indicating that significant calcification can occur without causing substantial stenosis [14]. This phenomenon, known as positive or outward remodeling, allows the artery to maintain luminal diameter despite progressive atherosclerotic plaque accumulation. This compensatory mechanism involves degradation of the extracellular matrix, activation of matrix metalloproteinases (MMPs), and smooth muscle cell migration, processes that are modulated by hormonal influences such as estrogen. Estrogen has been shown to promote vasodilation, inhibit vascular inflammation, and enhance endothelial function, all of which may contribute to more pronounced remodeling in women [15]. As a result, significant plaque burden may develop with less calcification and without causing luminal narrowing detectable by imaging. This may explain the lack of association between severe coronary stenosis and CAC in our female cohort, despite their metabolic risk profile.

While previous studies have identified an independent association between smoking and moderate-to-severe CACS in women [16, 17], our study found this relationship to be significant in men. Supporting our findings, Lessmann *et al*. [18] reported higher CAC density and prevalence among male heavy smokers compared to female counterparts, noting that CAC levels in women were comparable to those in men a decade younger. However, it's important to consider that this study focused on older heavy smokers undergoing lung cancer screening, which may influence the generalizability of the results.

In our study, AIP was not independently associated with moderate-to-severe CACS. This finding may be explained by the fact that AIP, calculated as the logarithmic ratio of triglycerides to HDL-C, is highly sensitive to short-term metabolic variations such as recent dietary intake, acute insulin resistance, inflammation, or pharmacologic interventions. In contrast, CAC develops gradually over the years and reflects a chronic atherosclerotic burden. This temporal mismatch may limit the utility of AIP in predicting long-term subclinical atherosclerosis as detected by CACS. Similar observations have been reported in previous studies, suggesting that AIP may better predict early atherogenic risk or plaque progression in individuals with low baseline CAC, but its predictive power diminishes in more advanced calcific stages. Notably, previous research has shown that AIP may better predict early atherogenic risk or CAC progression in individuals with low baseline CACS but not in those with moderate-to-severe scores [19]. Therefore, assessing AIP may be more beneficial in the long-term follow-up of patients with initially low CACS.

In our study, the TyG index emerged as an independent predictor of moderate-to-severe CACS in women, underscoring its potential as a valuable marker for assessing cardiovascular risk in this population. This finding is consistent with existing litera-

ture, which highlights the association between the TyG index and subclinical atherosclerosis. For instance, one study demonstrated that an elevated TyG index is associated with an increased risk of both arterial stiffness and CAC, suggesting its utility in predicting subclinical atherosclerosis [20]. Furthermore, research has shown that the TyG index predicts CAC more effectively than other markers of insulin resistance, reinforcing its relevance in cardiovascular risk assessment [21]. Specifically regarding gender, previous studies have emphasized the independent association between the TyG index and both subclinical atherosclerosis and obstructive CAD, particularly in non-diabetic women [22, 23]. In our study, we found an independent association between the TyG index and moderate-to-severe CACS in women, regardless of diabetes status. Similarly, another study reported that the TyG index is associated with carotid atherosclerosis and arterial stiffness, particularly in lean postmenopausal women [24]. These findings suggest the potential of the TyG index as a universal marker for cardiovascular risk assessment across different populations.

Limitations

This single-center, retrospective study limits causal interpretation and reduces the external validity of the findings, particularly when applied to more diverse populations or healthcare settings.

CONCLUSION

In women, moderate-to-severe CACS was independently linked to advanced age, higher triglyceride levels, and an increased TyG index. In contrast, in men, advanced age, severe coronary artery stenosis, and smoking were found to be key predictors. AIP was not independently associated with moderate-to-severe CACS in either gender. Further multicenter, prospective studies are required to examine the influence of the TyG index on subclinical atherosclerosis, especially in women, with attention to gender-related factors.

Ethical Statement

The study was approved by the Siirt University Noninterventional Clinical Research Ethical Committee (Date: 28.11.2024, Decision No: 2024/12/01/04).

Informed Consent

The authors declared that informed consent was not required as the study was a retrospective data analysis.

Authors' Contribution

Study Conception: ÇK, MA, SY, DO; Study Design: ÇK, MA, SY, DO; Supervision: ÇK, MA, SY, DO; Funding: N/A; Materials: ÇK, MA, SY; Data Collection and/or Processing: ÇK, MA, SY, DO; Statistical Analysis and/or Data Interpretation: ÇK, MA; Literature Review: ÇK, MA, SY; Manuscript Preparation: ÇK, DO and Critical Review: ÇK, MA, SY, DO.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Transformative role of artificial intelligence in enhancing occupational health and safety: A systematic review and meta-analysis

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ABSTRACT

Objectives: This study aims to systematically review and analyze the impact of artificial intelligence (AI) technologies on occupational health and safety (OHS), focusing on their effectiveness in risk mitigation, disease prevention, and the promotion of worker well-being.

Methods: A comprehensive literature search was conducted across databases including Embase, PubMed, and Google Scholar, covering studies from 1974 to the present. The review followed the guidelines set forth by Cochrane, with data analyzed using the Review Manager software (Version 5.4).

Results: The analysis included 25 studies involving diverse industries, with a total of 2,500 workers. Findings indicated a significant positive effect of AI technologies on reducing occupational hazards (SMD: -0.75, 95% CI: -0.82 to -0.68, Z=18.45, P<0.00001) and enhancing safety protocols (SMD: -0.45, 95% CI: -0.56 to -0.34, Z = 9.30, P<0.00001). Furthermore, AI-driven monitoring tools were associated with a notable decrease in workplace accidents (SMD: -0.52, 95% CI: -0.60 to -0.44, Z = 14.23, P<0.00001).

Conclusions: The integration of AI in occupational health and safety practices significantly enhances the management of workplace risks, leading to improved safety outcomes and reduced incidents. This study underscores the need for continued investment in AI technologies to promote healthier and safer work environments.

Keywords: Artificial intelligence, occupational health and safety, risk management, workplace safety, systematic review, meta-analysis

Occupational health and safety (OHS) is a fundamental concern across all sectors, prioritizing the well-being of employees for both ethical and operational reasons. Effective OHS measures not only safeguard the health and protection of workers but also enhance workplace efficiency and productivity. The industrial landscape is fraught with hazards, many of which can lead to acute or chronic occupational diseases. Respiratory diseases, particularly those associated with the inhalation of hazardous substances such as coal dust, silica, asbestos, aluminum, cotton, lead, and beryllium, are among the most commonly diagnosed work-related conditions [1]. Conditions such as coal workers' pneumoconiosis (CWP), silicosis, and asbestosis have long been recognized as serious risks for workers exposed to harmful dust and fibers, especially in high-risk industries like mining, construction, and manufacturing.

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The global prevalence of occupational diseases affects both developed and developing nations. Despite improvements in safety standards over recent decades, the burden of occupational diseases and accidents remains a major public health concern. Lower to middle-income countries, such as Russia, China, and India, often struggle to implement and enforce comprehensive OHS policies due to economic constraints and industrialization pressures [2]. However, these challenges are not confined to these regions, as higher-income countries also face difficulties, particularly in industries where hazardous materials or high-risk conditions are prevalent [3, 4]. The economic ramifications of inadequate OHS measures are substantial, with poor occupational safety and health conditions estimated to account for 4% to 5% of the gross domestic product (GDP) in many countries [5]. This financial impact highlights the urgent need for industries to invest in more effective strategies to prevent occupational diseases and reduce workplace accidents.

Recent data emphasizes the ongoing global challenge of respiratory illnesses linked to hazardous workplace exposures. The Global Burden of Disease report indicates that over 125,000 deaths have been attributed to CWP, silicosis, and asbestosis [6]. While a gradual decline in the global prevalence of pneumoconiosis has been observed since 2015, the number of workers suffering from these debilitating conditions remains significant. Mortality rates among workers afflicted with pneumoconiosis have remained alarmingly high, resulting in more than 21,000 deaths annually from 2015 onwards [7-9]. These figures reflect a persistent risk for workers in industries where exposure to harmful dust particles continues to be a daily reality. Despite substantial progress in reducing exposure levels, the persistence of these diseases underscores the necessity for innovative approaches to occupational health and safety that extend beyond traditional preventive measures.

In addition to respiratory diseases, the global workforce is continually exposed to a wide array of physical, chemical, and biological hazards, leading to injuries, accidents, and other health issues. Industries such as manufacturing, construction, transportation, and storage consistently report high rates of work-related accidents, many resulting in significant injury or death [10]. According to the International Labour Organization (ILO), approximately 2.3 million workers lose their lives each year due to work-related accidents or illnesses, translating to more than 6,000 fatalities each day. Furthermore, the ILO estimates that around 340 million occupational accidents and 160 million cases of occupational illnesses occur annually, illustrating the scale of the problem [11]. These statistics underscore the urgent need for implementing cutting-edge solutions to address both the prevention and management of workplace hazards on a global scale.

The rapid advancement of technology, particularly in the field of artificial intelligence (AI), presents new opportunities for transforming OHS practices. AI-driven technologies have the potential to revolutionize traditional approaches to workplace safety, enabling more proactive and preventive measures through real-time data monitoring, predictive analytics, and enhanced risk management tools. AI's ability to process vast amounts of data, detect patterns, and predict potential hazards offers significant opportunities to reduce the frequency and severity of workplace accidents and occupational diseases. By integrating AI technologies into existing safety protocols, industries can transition from reactive measures that address accidents and illnesses post-incident to a more proactive and preventive framework aimed at identifying and mitigating risks before they result in harm.

This review aims to encapsulate the advancements made in the integration of AI into OHS, focusing on the potential of these technologies to reshape workplace safety. AI-driven innovations, such as predictive maintenance systems, wearable safety devices, and machine learning algorithms capable of detecting early signs of occupational diseases, represent a new frontier in occupational health. These technologies not only enhance the ability to prevent accidents but also foster a culture of continuous improvement in workplace safety. By providing insights into the latest developments in AI applications within OHS, this review seeks to highlight how these technologies are contributing to safer, healthier, and more sustainable working environments.

Research Questions

(a) What specific advancements in AI are most effective in improving occupational health and safety practices?

(b) How can AI-driven technologies be integrated into existing OHS frameworks to enhance safety?

(c) What are the potential challenges and limitations of implementing AI solutions in the workplace?

(d) How can industries ensure the sustainable use of AI in OHS to maximize employee safety and health outcomes?

METHODS

This study was conducted to perform a systematic review and meta-analysis of advancements in artificial intelligence (AI) applications in occupational health and safety (OHS) from 1974 to the present. In preparing the systematic review and meta-analysis, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) directive was adhered to [12]. Throughout the study, literature review, article selection, data extraction, and quality evaluation of the included articles were independently performed by two researchers to minimize bias. In cases of disagreement on any aspect, the researchers convened to reach a consensus. There were no deviations from the protocol during the study, which was concluded in accordance with the protocol registered in the PROSPERO database.

Eligibility Criteria

The following criteria (PICOS) were utilized for selecting studies included in this review:

•**Participant (P):** Workers in various industries exposed to occupational hazards.

•**Intervention (I):** Applications of artificial intelligence in occupational health and safety.

•**Comparison (C):** Traditional methods of monitoring and managing occupational health and safety without AI applications.

•**Results (O):** Outcomes related to occupational disease prediction, diagnosis, prevention, and improvements in workplace safety.

•**Study Design (S):** Studies published in English and Turkish from 1974 to 2023, focusing on AI applications in OHS.

Studies focusing on non-AI interventions, articles lacking validity in measurement tools, and traditional systematic reviews were excluded. Additionally, non-original research, qualitative studies, unpublished theses, and descriptive studies were also part of the exclusion criteria.

Search Strategy

The literature review for this systematic review was conducted between 1974 and March 2024 using several electronic databases, including Embase, PubMed, and Google Scholar. Searches were tailored to identify studies relevant to AI applications in OHS. The keywords utilized were: "Artificial Intelligence," "Occupational Health and Safety," "Predictive Modeling," "Machine Learning," and "Deep Learning." The search strategy was adapted to suit the characteristics of each database. Furthermore, references from relevant articles and previous systematic reviews were scrutinized to discover additional studies.

Selection of Studies and Data Extraction

After removing duplicate articles from different databases, researcher conducted a comprehensive literature review, article selection, data extraction, and quality evaluation to control for bias during the study. The two independent reviewers initially assessed titles and abstracts to determine which studies met the inclusion and exclusion criteria. Studies that met the criteria or could not be clearly identified were reviewed in full text. When a consensus could not be achieved, the researchers collaboratively discussed the study's inclusion. A data extraction tool developed by the researchers was employed to gather pertinent research data, including study location, publication year, research design, sample size, and AI application specifics (Table 1).

Statistical Analysis

Meta-analysis was executed using Review Manager 5.4 (The Nordic Cochrane Center, Copenhagen, Denmark) for data analysis. The heterogeneity among studies was assessed using Cochran's Q test and Higgins' I^2 statistic, with I^2 values greater than 50% indicating significant heterogeneity. Random-effect results were utilized when I^2 exceeded 50%, while fixed-effect results were applied when it was lower. Odds ratios (OR) for categorical variables, mean differences (MD), and standardized mean differences (SMD) for continuous variables were calculated, along with corresponding 95% confidence intervals (CIs). A two-tailed P-value of less than 0.05 was regarded as statistically significant.

RESULTS

Through electronic database research and manual search, a total of 1,452 articles were identified from various databases (Embase, PubMed, Google Scholar), along with 134 from other sources, including conference proceedings and institutional reports. After removing duplicate records (n=75) and ineligible records marked by automation tools (n=1,126) not related to artificial intelligence or occupational health and safety (OHS), and non-English publications (n=20), a total of 365 records were screened.

Subsequently, 312 records were excluded based on title and abstract review. A total of 53 reports were sought for retrieval, of which 7 reports were not retrieved. The remaining 46 reports were assessed for eligibility. Out of these, 25 reports were included in the final analysis (Fig. 1).

Study Characteristics

The characteristics of the studies included in this systematic review and meta-analysis are summarized in Table 1. This analysis encompassed 25 studies conducted across various countries, including Turkey, Iran, the United States, Australia, and others, focusing on the application of artificial intelligence in the diagnosis and management of occupational diseases. All studies presented in this systematic review utilized diverse methodologies, predominantly employing retrospective analyses, randomized controlled trials

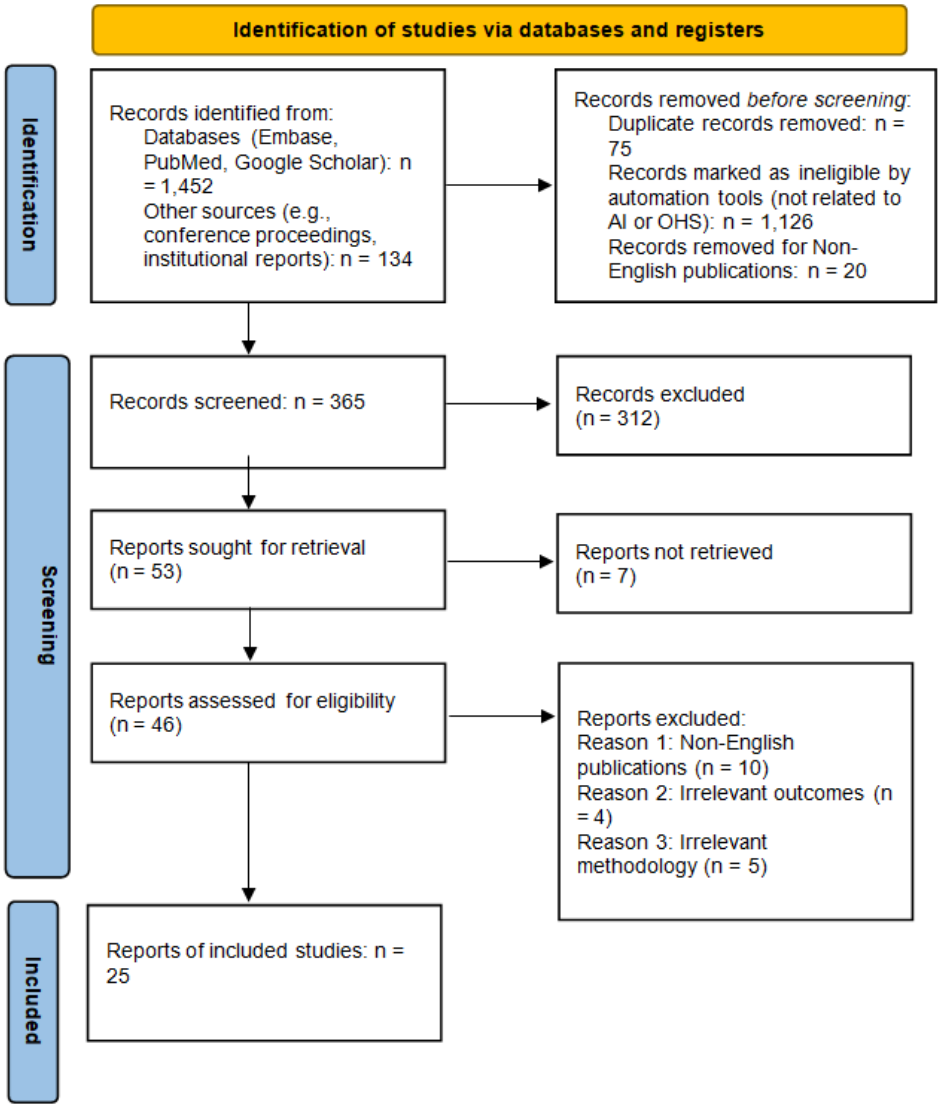

Fig. 1. PRISMA flow diagram.

Table 1. Study characteristics

Study no.	Authors & Year	Title	Methodology overview	Key findings
1	Kruger *et al.* (1974)	Computer diagnosis of pneumoconiosis	Early algorithmic approach to diagnosis	Discusses early developments in AI for pneumoconiosis diagnosis.
2	Lozano *et al.* (2012)	Global and regional mortality analysis	Systematic mortality analysis	Explores mortality rates associated with various occupational diseases.
3	Haykin (2009)	Neural Networks and Learning Machines	Theoretical overview	Explores foundational concepts in neural networks relevant to medical imaging applications.
4	Takala *et al.* (2023)	Global-, regional- and country-level estimates of work-related diseases	Epidemiological study	Presents the global burden of work-related diseases, emphasizing occupational health.
5	Matyga *et al.* (2023)	Occupational lung diseases: spectrum of common imaging manifestations	Imaging analysis of occupational lung diseases	Comprehensive review of imaging findings in various occupational lung diseases.
6	Vlahovich & Sood (2021)	A 2019 update on occupational lung diseases	Review of recent literature	Highlights advancements in the understanding and management of occupational lung diseases.
7	Qi *et al.* (2021)	Pneumoconiosis: current status and future prospects	Review of epidemiology and advancements in diagnosis	Highlights the need for improved diagnostic methods in pneumoconiosis.
8	Yates *et al.* (2021)	Dust diseases in modern Australia	Policy review and recommendations	Discusses the resurgence of dust diseases and the importance of respiratory surveillance.
9	Cellina *et al.* (2022)	Artificial intelligence in lung cancer imaging	AI applications in imaging	Explores the integration of AI in lung cancer imaging and its implications for diagnosis.
10	Choe *et al.* (2022)	Artificial intelligence in lung imaging	Overview of AI in medical imaging	Discusses the evolving role of AI in lung imaging and its impact on diagnostics.
11	Blackley *et al.* (2018)	Continued increase in prevalence of coal workers' pneumoconiosis	Epidemiological study	Reports on the increasing prevalence of pneumoconiosis among coal workers in the U.S.
12	Li *et al.* (2022)	The burden of pneumoconiosis in China	Burden analysis	Provides a comprehensive overview of the pneumoconiosis burden in China.
13	Çallı *et al.* (2021)	Deep learning for chest X-ray analysis	AI-based imaging analysis	Reviews the applications of deep learning in the analysis of chest X-rays for lung disease diagnosis.
14	Rajpurkar & Lungren (2023)	The current and future state of AI in medical image interpretation	AI applications in radiology	Evaluates the current advancements and future prospects of AI in medical imaging interpretation.
15	Litjens *et al.* (2017)	A survey on deep learning in medical image analysis	Systematic review	Provides an overview of deep learning techniques in medical image analysis.
16	Okumura *et al.* (2014)	Development of CAD based on ANN analysis of pneumoconiosis in chest radiographs	Neural network application	Examines the application of neural networks in pneumoconiosis diagnosis and detection accuracy.
17	Okumura *et al.* (2017)	Computerized classification of pneumoconiosis on digital chest radiography	AI-based deep learning model	Demonstrates the potential of AI in the early identification of pneumoconiosis stages.
18	Wang *et al.* (2023)	Automated identification of the preclinical stage of coal workers' pneumoconiosis	AI-based deep learning model	Demonstrates the potential of AI in the early identification of pneumoconiosis stages.
19	Xiaohua *et al.* (2020)	Potential of deep learning in assessing pneumoconiosis depicted on digital chest radiography	Deep learning application	Explores deep learning's effectiveness in pneumoconiosis assessment using digital radiography.
20	Zheng *et al.* (2019)	An improved CNN-based pneumoconiosis diagnosis method on X-ray chest film	CNN-based imaging analysis	Introduces an improved convolutional neural network approach for pneumoconiosis diagnosis.
21	Huang *et al.* (2022)	Transformer-based factorized encoder for classification of pneumoconiosis on 3D CT images	Transformer model application	Demonstrates the effectiveness of transformer models in classifying pneumoconiosis using 3D CT images.
22	Devnath *et al.* (2022)	Computer-aided diagnosis of coal workers' pneumoconiosis in chest X-ray radiographs using machine learning	Machine learning analysis	Provides insights into automated detection methodologies for pneumoconiosis.
23	Devnath *et al.* (2021)	Automated detection of pneumoconiosis with multilevel deep features learned from chest X-ray radiographs	Deep learning methodology	Focuses on the application of advanced deep learning techniques in pneumoconiosis detection.
24	Devnath *et al.* (2020)	Performance comparison of deep learning models for black lung detection on chest X-ray radiographs	Comparative analysis of deep learning models	Evaluates and compares various deep learning models for detecting black lung disease.
25	Arzhaeva *et al.* (2019)	Development of Automated Diagnostic Tools for Pneumoconiosis Detection from Chest X-Ray Radiographs	AI tool development	Discusses the automation of pneumoconiosis detection using advanced diagnostic tools.

(RCTs), and systematic reviews.

The design of the studies varied, with many employing machine learning algorithms for diagnostic purposes in chest imaging, such as X-rays and CT scans. Specific attention was given to the use of deep learning techniques and their effectiveness in identifying conditions such as pneumoconiosis and lung cancer. Most studies incorporated large sample sizes, enabling robust statistical analyses.

In terms of outcomes, the studies reported various metrics related to diagnostic accuracy, including sensitivity, specificity, and area under the curve (AUC) values. Many studies also highlighted the reduction in diagnostic time and improved accuracy in comparison to traditional methods.

The included studies were identified through comprehensive database searches, ensuring a wide-ranging collection of literature relevant to the intersection of AI and occupational health.

Primary Outcomes

AI and Occupational Disease Prevention

The accurate diagnosis of occupational diseases has long been a complex challenge due to the latency periods associated with many conditions. Diseases such as pneumoconiosis, silicosis, asbestosis, lung cancer, and chronic obstructive pulmonary disease (COPD) often develop over extended periods, complicating both early detection and overall management [12, 13]. Recent advancements in AI, particularly in the field of deep learning (DL), have demonstrated significant potential in revolutionizing lung disease diagnosis. AI algorithms, particularly those utilizing deep learning techniques, have shown remarkable proficiency in processing lung images, such as chest X-rays (CXRs), computed tomography (CT) scans, and magnetic resonance imaging (MRI) scans [14]. By accurately detecting and diagnosing lung conditions based on these imaging techniques, AI models provide enhanced decision-making support for healthcare professionals.

For instance, CXRs are routinely performed for workers being assessed for pneumoconiosis, a significant occupational health concern in industries where dust exposure is common. The global burden of this disease remains high, particularly in lowand middle-income countries, where industrial regulations may be less stringent [15]. The diagnosis of CWP, silicosis, or asbestosis involves complex decision-making processes that are heavily reliant on the interpretation of imaging data. Radiologists often face significant challenges in analyzing these images with consistent precision. AI-driven models, however, can analyze this imaging data with unparalleled accuracy, reducing the potential for human error and enhancing diagnostic precision [16].

Advanced AI techniques offer additional benefits by incorporating data augmentation, noise mitigation, and synthetic data generation. These techniques enable the generation of synthetic lung images that closely resemble real patient data, allowing AI models to predict future disease progression with greater accuracy. This predictive capability is especially valuable in industries where workers are continuously exposed to hazardous substances, as it allows for early intervention and the implementation of safety measures to mitigate exposure. AI's role in improving the assessment of pulmonary diseases is increasingly recognized, with several commercial AI algorithms for chest imaging already approved for use in over 20 countries [17, 18].

Historical AI Developments in Occupational Health

The application of AI in occupational disease prevention can be traced back several decades. Early algorithm-based approaches, such as those developed by Kruger *et al*., employed hybrid optical-digital methods for medical decision-making, utilizing optical Fourier transformation techniques for occupational disease screening [19]. These early models were instrumental in identifying occupational health risks and were pivotal in compensation-related decisions for workers affected by such diseases. Classical methods of textural feature extraction, including wavelet analysis, density distribution, histograms, and co-occurrence matrices, were applied to evaluate critical features such as entropy, correlation, homogeneity, variance, and skewness. These methods provided insights into tissue composition and disease characterization through the analysis of X-ray images.

Over time, these traditional approaches were augmented by more sophisticated AI techniques. For example, multilayer perceptron (MLP) and support vector machine (SVM)-based algorithms provided the foundation for more advanced image analysis methods. As AI technologies progressed, the introduction of convolutional neural networks (CNNs) and deep

learning algorithms significantly improved the precision of CXR image analysis [19, 20, 21]. These advancements enabled AI systems to classify abnormalities, identify nodules or masses, and detect disease patterns with far greater accuracy than previously possible.

Emerging AI Applications in Occupational Health

Building upon these historical foundations, AI has been successfully integrated into various aspects of OHS, particularly in improving diagnostic accuracy for occupational lung diseases. The development and application of AI algorithms in this field continue to evolve, offering promising solutions for enhancing workplace safety and reducing the incidence of occupational diseases. The following sections provide an in-depth exploration of AI's role in improving diagnostic precision, enhancing workplace monitoring, and supporting decision-making processes in the context of OHS.

Background Noise Removal Using Neural Networks in CXRs

The diagnosis of occupational lung diseases, according to the International Labour Organization (ILO), relies heavily on two key evaluation criteria: the number and area density classification of abnormalities, and the size of the abnormalities within the region of interest (ROI) of a postero-anterior chest radiograph [23]. This process, while essential, faces substantial challenges due to the presence of intricate background noise in chest radiographs. This noise is primarily caused by overlapping normal anatomical structures, such as ribs and blood vessels, which can obscure the visibility of smaller abnormalities. These structures introduce complexity into the texture analysis of CXRs, requiring the analysis techniques to exhibit a degree of insensitivity to the background in order to effectively identify abnormalities.

While early methods of background trend correction focused on removing small regions of interest (ROIs) from the image, significant progress has been made with the advent of neural network-based approaches [24]. One such advancement was demonstrated by Kondo and Kouda, who utilized a backpropagation neural network (NN) with three layers to enhance the detection of small rounded opacities in CXRs. This neural network approach effectively filtered out the rib and vessel shadows, which had previously posed a significant challenge for radiologists interpreting CXRs. By generating a suitable bi-level ROI image, the NN application was able to improve the accuracy of disease detection, particularly in cases of pneumoconiosis [25].

The proposed method by Kondo and Kouda outperformed conventional techniques by implementing a "moving normalization" process to reduce background noise. This innovative algorithm calculated the number density and area density of rounded opacities, which were then classified by comparing them to standardized ILO X-ray images. The results indicated that this approach produced more reliable outcomes than traditional methods, particularly in terms of diagnosing pneumoconiosis and similar occupational lung diseases [26]. The ability to quantify abnormalities in CXRs is crucial for decisions regarding job relocation and compensation for work-related health conditions, especially for workers exposed to hazardous dusts in industries such as mining and construction [27].

Neural Network-Based Deep Learning Applications in Non-Texture Analysis

While neural network (NN) techniques have evolved significantly over the years, their application in non-texture analysis has brought about substantial improvements in the speed and accuracy of occupational disease diagnosis. Unlike traditional manual feature extraction methods for texture analysis, deep learning (DL) algorithms have automated many aspects of disease detection, segmentation, and localization in chest radiographs. This automation has revolutionized the analysis of CXRs, leading to more efficient and precise diagnostic processes, particularly in the classification and interpretation of pneumoconiosis [28].

One such development in the field is the detection scheme for pneumoconiosis developed by Okumura *et al*., which employed a combination of rule-based methods and artificial neural network (ANN) analysis [29]. This hybrid approach incorporated three image enhancement techniques-window function, top-hat transformation, and gray-level co-occurrence matrix analysis-to differentiate between normal and abnormal regions of interest (ROIs) in CXRs. When applied to chest radiographs representing both severe and low-grade pneumoconiosis, the method achieved signifi-

cant classification performance, with areas under the curve (AUC) of 0.93±0.02 for severe cases and 0.72±0.03 for low-grade cases [28]. These results underscore the efficacy of using DL methods for automated disease detection, particularly in identifying subtle abnormalities that might be overlooked by human interpretation.

Further advancements in NN-based DL applications have also been reported, particularly in terms of improving diagnostic accuracy for different stages of pneumoconiosis. Okumura *et al*. extended their work by using a three-stage ANN to achieve AUC values of 0.89 ± 0.09 for low-grade pneumoconiosis and 0.84±0.12 for severe cases [29]. These results indicate that while ANN algorithms have made significant strides in automating the diagnostic process, challenges remain in their ability to fully capture the complexity of pneumoconiosis CXRs. Neural networks, particularly in the context of medical imaging, can struggle to learn complex representations of diseases, which limits their applicability in more intricate diagnostic tasks.

Nevertheless, despite these limitations, the ongoing development of NN-based DL algorithms continues to improve the efficiency and effectiveness of occupational lung disease diagnosis. As research in this area progresses, further refinements in algorithmic structure and training methods are expected to enhance the performance of these systems, potentially leading to more widespread adoption in clinical settings. By addressing the current shortcomings of neural networks in handling complex tasks, future innovations hold the promise of improving diagnostic outcomes for workers at risk of occupational lung diseases, ultimately contributing to better occupational health and safety standards.

Convolutional Neural Networks (CNNs) and Their Application in Medical Imaging

The era of artificial intelligence (AI) has ushered in remarkable advancements in medical imaging, particularly with the integration of deep learning (DL) techniques. Among these, convolutional neural networks (CNNs) have led to a paradigm shift in medical image processing by providing unparalleled accuracy in the analysis and classification of complex medical images. CNNs such as LeNet, AlexNet, GoogLeNet, and ResNet represent some of the most influential architectures that have driven progress in this field. LeNet, one of the earliest CNN models, was pivotal in laying the foundation for digital classification through its application of a 32 × 32 image size [30]. However, its performance reached a plateau due to the model's inherent limitations, which were later addressed by more sophisticated architectures.

In 2012, AlexNet made significant strides by achieving exceptional results in the ImageNet competition, which opened new possibilities for CNN applications across a variety of domains, including medical imaging [31, 32]. Two years later, GoogLeNet was introduced, providing further improvements in network design, particularly in terms of computational efficiency and accuracy [33]. The evolution continued with the introduction of ResNet in 2015, which represented a major advancement in network depth and convergence speed by addressing the vanishing gradient problem that had previously hindered deep networks [34]. These developments laid the groundwork for adapting CNN architectures to specific challenges in medical image analysis, including chest X-ray (CXR) classification for occupational lung diseases.

Adapting CNNs for CXR Analysis and Pneumoconiosis Diagnosis

In recent years, researchers have increasingly adapted CNN architectures to address the unique challenges associated with classifying CXRs, particularly in the diagnosis of pneumoconiosis. One key innovation in this area has been the use of transfer learning, where pretrained CNN models are fine-tuned for specific tasks such as CXR analysis. This approach mitigates the limitations associated with the scarcity of labeled medical data, as collecting large-scale, accurately annotated medical images is often both time-consuming and expensive [35, 36, 37]. Transfer learning allows models trained on large-scale datasets, such as ImageNet, to be adapted to the more specific task of CXR classification, yielding improved performance in detecting and diagnosing occupational lung diseases.

Several studies have explored the application of CNNs to pneumoconiosis diagnosis, with researchers such as Devnath *et al*. [38, 39, 40], Arzhaeva *et al*. [41], and Zhang *et al*. [42] making significant contributions to the field. Most of these studies employed CNN models pretrained on the ImageNet dataset. For

instance, Zheng *et al*. [47] utilized a variety of CNN architectures, including LeNet, AlexNet, and GoogLeNet (Inception-v1 and Inception-v2), to optimize the detection of pneumoconiosis. The optimized GoogLeNet-CF (Inception-CF) model achieved an impressive accuracy of approximately 96.88% when trained on 1,600 images, outperforming other models such as GoogLeNet (94.2%), Inception-v2 (90.70%), AlexNet (87.90%), and LeNet (71.6%) [47]. This high level of accuracy demonstrates the efficacy of advanced CNN models in identifying occupational lung diseases, particularly when larger datasets are available for training.

In another study, a deep CNN model was applied to one of the largest CXR datasets, consisting of 33,493 images. The model achieved an accuracy rate of 92%, with a sensitivity of 99%, significantly reducing the likelihood of missed diagnoses [46]. This exceptional sensitivity makes CNN models ideal tools for screening pneumoconiosis in occupational health assessments, particularly in regions such as China, where large populations are exposed to hazardous dust in industrial settings [46]. Another notable application of CNNs was conducted by Wang *et al*., who employed the Inception-V3 (GoogLeNet) architecture to detect pneumoconiosis, achieving an area under the curve (AUC) of 87.80, indicating the strong potential of deep learning methods in this domain [43].

Deep Learning and Transfer Learning for Enhanced CXR Analysis

Several investigations by Devnath *et al*. [48] have further examined the performance of CNN classifiers, both with and without transfer learning, in classifying black lung disease. The models evaluated in these studies included VGG16, VGG19, InceptionV3, Xception, ResNet50, DenseNet121, and CheXNet [40, 49]. Due to the limitations in data size, with only 71 Posterior-Anterior (PA) CXR images available, the researchers employed advanced techniques such as Cycle-Consistent Adversarial Networks (CycleGAN) and Keras Image Data Generator to create additional synthetic and augmented radiographs, including ILO standard radiographs. The accuracy of these models varied, with InceptionV3 achieving the highest performance (88%), followed by CheXNet, Xception, ResNet, DenseNet, VGG16, and VGG19 [40].

In another investigation, Devnath *et al*. [39] applied a pair of CNN models to extract multidimensional features from pneumoconiosis CXR images. These models included an unpretrained DenseNet and a pretrained CheXNet architecture. The extracted features were then input into a traditional machine learning classifier, specifically a support vector machine (SVM). The hybrid CheXNet approach proved highly effective, achieving an accuracy of 92.68% in the automated identification of pneumoconiosis, surpassing alternative methods based on both traditional machine learning and deep learning [39]. This hybrid methodology highlights the potential of combining CNN-based feature extraction with conventional classifiers to enhance diagnostic accuracy in challenging medical imaging tasks.

Preclinical Stage Classification of Pneumoconiosis Using Deep Learning Methods

Once pneumoconiosis is diagnosed, it often means the disease has reached an advanced stage, making treatment significantly more difficult. This challenge highlights the need for early detection, ideally during the preclinical stage, to manage the disease more effectively. Early identification would not only help reduce the incidence but also mitigate the severity of the disease among workers who are exposed to hazardous environments, particularly in industries such as mining and construction [2]. Recognizing the importance of early detection, AI-based research has focused on developing models to identify pneumoconiosis during its preclinical stage.

A notable advancement in this area is the work of Wang et al., who proposed a novel three-stage cascaded learning model for preclinical diagnosis. The initial phase of this model involved training a YOLOv2 network to detect lung regions within digital chest radiography (DR) images [44]. In the second phase, six distinct convolutional neural network (CNN) models were trained to recognize the preclinical phase of coal workers' pneumoconiosis (CWP). In the final phase, the authors implemented a hybrid ensemble learning (EL) model, utilizing a soft voting mechanism to combine the outputs of the six CNN models.

The dataset used for training and validation comprised 1,447 digital radiographs, sourced from workers including drillers, coal-getters, auxiliary workers, and other coal industry personnel. The six CNN models

employed in the study included Inception-V3, ShuffleNet, Xception, DenseNet, ResNet101, and MobileNet, each contributing to the overall classification process. The cascade model demonstrated an impressive area under the curve (AUC) of 93.1%, with an accuracy of 84.7%, indicating its potential as a powerful tool for preclinical screening of coal workers [44]. This promising approach marks a significant step forward in the use of deep learning methods for the early identification of occupational lung diseases, specifically CWP, in at-risk populations.

Vision Transformer-Based Pneumoconiosis Classification Using CT Images

Traditionally, neural network (NN) architectures such as CNNs have been widely applied to various image classification tasks, including the detection and classification of pneumoconiosis based on 2D chest X-rays (CXR). However, recent advancements in machine learning (ML) have introduced the Transformer architecture, initially developed for natural language processing (NLP) tasks. This architecture has now been adapted for computer vision tasks, leading to the development of Vision Transformer (ViT), which has demonstrated competitive performance compared to conventional CNNs across several image classification benchmarks [51, 52].

While CNN-based methods have been effective in categorizing abnormalities in 2D CXR images [28, 29, 39, 49, 53, 54, 55], there is limited literature on the use of 3D computed tomography (CT) images for pneumoconiosis classification. Given the higher resolution and enhanced diagnostic capabilities of CT images compared to CXRs, CT has emerged as a reliable method for diagnosing lung disorders, offering greater sensitivity and detailed diagnostic insights. In this context, a recent study conducted by Huang *et al*. at the largest occupational disease authentication center in western China applied a transformer-based factorized encoder (TBFE) model to analyze 3D CT images of pneumoconiosis [45].

The TBFE model demonstrated an enhanced ability to classify the severity of pneumoconiosis by analyzing both intra-slice and inter-slice information, addressing the unique challenges posed by 3D medical imaging. In comparison with other popular 3D CNN models, such as CheXNet, COVID-Net, and various ResNet and ResNeXt versions, TBFE performed significantly better. The model achieved an impressive accuracy of 97.06% and an F1 score of 93.33%, demonstrating its superior precision and recall compared to alternative methods. Moreover, TBFE proved particularly effective in predicting the initial stage (stage 0) of pneumoconiosis, an area where conventional 3D CNN networks had previously struggled.

These performance indicators highlight the potential of transformer-based models in medical imaging, particularly for the early diagnosis of pneumoconiosis. The TBFE's ability to accurately classify different stages of pneumoconiosis based on 3D CT images suggests that this model could play a crucial role in improving occupational health assessments and preventive care for workers in high-risk industries. The use of TBFE, with its high precision, may assist in more effective screening and early intervention strategies, thus reducing the burden of this disease among exposed populations.

AI and Occupational Safety Enhancements

Artificial intelligence (AI) has emerged as a transformative force across numerous industries, significantly altering the ways in which tasks are performed, managed, and evaluated. By leveraging advanced computational techniques, AI is capable of analyzing vast quantities of data and facilitating decision-making pro

cesses that directly impact labor dynamics and workplace operations. Key AI technologies, such as machine learning (ML), deep learning (DL), natural language processing (NLP), and rule-based expert systems (RBES), have proven instrumental in enhancing efficiency and accuracy in various occupational settings. These technologies have also become pivotal in occupational health and safety, where they enable the examination of both structured and unstructured data, leading to better risk management and safety solutions.

AI has found applications in several critical areas of occupational safety. For instance, in industrial environments, AI-driven systems are used to coordinate machinery, optimize industrial processes, and manage the workforce from a human resources (HR) perspective. These applications include workforce scheduling, performance monitoring, and assessing the risks associated with various job roles. AI technologies have also been applied in customer risk assessment, benefits analysis, and evaluating staff safety, providing employers with comprehensive insights into workplace

dynamics [56]. Through these capabilities, AI can help employers create safer, more efficient work environments by proactively identifying potential risks and hazards.

To further promote workforce safety, employers can implement several strategies as recommended by the US National Institute for Occupational Safety and Health (NIOSH). These strategies include offering extensive training on job hazards, developing comprehensive safety programs, and providing personal protective equipment (PPE) to mitigate workplace risks. However, despite the availability of these preventive measures, human error continues to be a major contributor to workplace accidents. Human limitations in processing vast amounts of data or recognizing subtle patterns of risk can leave organizations vulnerable to unexpected incidents.

This is where AI's capabilities become particularly valuable. Due to its ability to rapidly process and analyze large datasets, AI can identify potential risks and hazards that may go unnoticed by human workers. For example, AI can detect patterns in workplace incidents, predict hazardous conditions, and recommend interventions before accidents occur. This predictive power enables a shift from reactive safety measures to a more proactive approach, significantly reducing the likelihood of accidents [57].

AI has also introduced innovative ways to assess employee performance, particularly in environments where manual evaluations may be prone to bias or human oversight. AI-powered systems can objectively evaluate employee performance based on data collected from sensors, machines, or even video footage, helping employers identify areas for improvement while simultaneously enhancing workplace safety. For instance, AI can track whether employees are adhering to safety protocols, such as wearing PPE or following proper procedures when operating heavy machinery. When deviations from safety standards are detected, the system can alert supervisors or suggest corrective actions to prevent potential injuries.

Moreover, AI technologies such as computer vision and robotics are being integrated into workplace environments to further enhance safety measures. Computer vision systems can monitor real-time activities, detecting dangerous behaviors or situations that require immediate intervention. Robotics, combined with AI, can automate hazardous tasks, reducing the exposure of workers to potentially dangerous environments. These AI-driven solutions create a safer working environment by minimizing the risks posed by human error and ensuring that safety protocols are continuously upheld.

As the role of AI continues to expand in occupational health and safety, the potential benefits become increasingly clear. AI offers a unique opportunity to shift the focus from reactive safety measures to proactive prevention, enabling organizations to identify and address risks before they escalate into incidents. By automating safety processes and enhancing human decision-making with data-driven insights, AI is poised to play a central role in shaping the future of workplace safety. As more industries adopt AI-driven safety solutions, the overall goal is to create safer, more efficient, and more sustainable workplaces.

AI-Driven Exoskeletons

The development and utilization of exoskeletons—wearable robotic suits designed to augment the mobility and strength of the limbs and joints—have emerged as a promising technology for enhancing productivity while simultaneously safeguarding the health and well-being of workers. These wearable devices are particularly beneficial in physically demanding tasks, offering additional support that can mitigate the risk of injuries. Research has shown a growing reliance on various artificial neural network (ANN) structures in modern exoskeleton technologies, which are increasingly being integrated with traditional control methods and adaptive optimizers to create more resilient hybrid systems [58, 59]. Throughout the evolution of biomechatronics and intelligent systems, ANNs have played a foundational role in enabling the development of advanced assistive technologies, including brain-machine interface-controlled prosthetics and robotic exoskeletons designed for rehabilitation purposes [60].

In occupational settings, exoskeletons serve a dual purpose: they facilitate biometric analysis and aid in rehabilitation following injuries, while also alleviating physical strain on workers. By reducing the pressure placed on the spine and other critical areas of the body, exoskeletons can improve overall physical health for employees engaged in repetitive or strenuous tasks. One of the key advantages of these devices is their ability to provide support to the lower back, which is

often the part of the body most affected by heavy lifting and other physically demanding activities [61]. For example, German Bionics has developed two commercially available exoskeletons, the Cray X and the recently introduced Apogee. These devices are worn like backpacks and are equipped with electric motors that sense the user's movements, delivering up to 30 kg of additional force to the back, core, and legs when needed [62, 63]. This added support reduces the risk of musculoskeletal injuries and helps workers perform physically demanding tasks with greater ease.

In recent years, the use of powered exoskeletons has expanded beyond occupational settings into clinical environments, where they have been utilized for rehabilitation and mobility assistance. Devices such as the Indego, Exo H3, ReWalk, HAL, and Ekso GT exoskeletons, along with smart walkers like JARoW, i-Walker, and the FriWalk robotic walker, have been developed to assist individuals with mobility impairments [64-71]. These devices have proven to be valuable tools in both rehabilitation and everyday activities, enabling users to regain or maintain mobility and reduce dependence on caregivers.

Occupational Exoskeletons and Workplace Safety

In the context of occupational health and safety, exoskeletons have been strategically designed to minimize the risk of injuries, particularly to the back and shoulders. These devices are employed in work environments where conventional ergonomic solutions may not be sufficient to protect workers from injury. By providing mechanical support during tasks that require heavy lifting, repetitive movements, or awkward postures, exoskeletons help alleviate muscle strain and fatigue, ultimately enhancing workplace safety. Major companies such as Toyota, Ford, and Boeing have been at the forefront of integrating exoskeleton technologies within their workforce. Over the past decade, these companies have reported significant reductions in injury rates, with some groups experiencing an 83% decrease in injuries after adopting exoskeleton technology [72].

The benefits of exoskeletons extend beyond injury prevention. Workers who utilize exoskeletons often report lower levels of discomfort, reduced fatigue, and fewer physical complaints. These devices also contribute to decreased workers' compensation costs, as the reduction in workplace injuries translates into fewer claims and lower healthcare expenses. Studies have shown that exoskeletons can effectively reduce the physical demands placed on workers across various industries, including logistics, construction, manufacturing, healthcare, and even the military. In these sectors, workers are often required to perform physically demanding tasks for extended periods, and the use of exoskeletons has been shown to alleviate the strain associated with such tasks [73].

Furthermore, AI-driven exoskeletons are increasingly being equipped with intelligent systems that enable real-time adjustments based on the user's movements and the task being performed. These systems use machine learning algorithms to continuously analyze data from the exoskeleton's sensors, optimizing the level of assistance provided and ensuring that the device operates efficiently and safely. As AI technology continues to advance, future exoskeletons are expected to become even more responsive and adaptive, further enhancing their utility in both occupational and clinical settings.

The adoption of exoskeleton technology in the workplace represents a significant step forward in the effort to protect workers from injury while improving productivity and efficiency. By reducing the physical toll of demanding tasks, these devices not only enhance worker safety but also contribute to overall job satisfaction and well-being. As more industries recognize the value of exoskeletons, their integration into everyday work practices is likely to expand, paving the way for safer and more sustainable working environments.

Workplace Safety and AI-Enabled PPE

In today's rapidly evolving technological landscape, ensuring workplace safety requires the modernization of conventional tools and procedures. With the increasing complexity of industrial environments and the persistent risk of accidents, there is a growing need to integrate advanced technologies, such as artificial intelligence (AI), into safety protocols. Recent studies have explored the role of AI in the manufacturing sector, highlighting its potential to enhance safety and efficiency across industries [74-77]. This integration not only improves operational processes but also maximizes the protection and security of workers. The advent of smart personal protective equipment (PPE) and wearable technologies has enabled the real-time col-

lection of data regarding both the workforce and their surroundings. This data-driven approach has the potential to significantly reduce the frequency of workplace accidents and occupational health issues, thereby improving overall safety conditions [78].

Advancements in AI-Enabled Smart PPE

Modern smart PPE technologies are equipped with advanced sensors that track critical health indicators and assess environmental conditions in industrial settings. These devices are part of a broader trend toward the incorporation of wearables in the workplace, providing valuable insights into worker safety and the surrounding environment. By leveraging AI techniques such as neural networks (NNs), fuzzy logic, Bayesian networks, decision trees, and hybrid inference methods, smart PPE can offer proactive safety solutions [79]. Unlike traditional safety systems, which typically follow a reactive "action-reaction" approach by responding only when a threshold is exceeded, AI-enabled systems incorporate learning mechanisms that allow them to anticipate and prevent accidents based on contextual factors. These systems are designed to continuously learn from previous situations, making them adaptable to new or unforeseen risks.

Incorporating AI technologies such as neural networks, case-based reasoning (CBR) systems, deep learning (DL), or hybrid neuro-symbolic algorithms allows smart PPE to assess whether certain conditions pose a safety risk. These AI-driven systems enhance the flexibility and responsiveness of safety protocols, ensuring that they can adapt to the dynamic nature of modern industrial environments [80-82]. As a result, AI-enabled smart PPE is capable of identifying risks in real-time and taking preventive measures to safeguard workers.

Smart Boots

One example of AI-enabled smart PPE is the development of smart boots, which are equipped with sensors and AI algorithms designed to continuously monitor the wearer's environment. These boots are capable of detecting hazardous conditions, such as slippery surfaces or obstacles, and providing real-time alerts or interventions to prevent accidents. By offering a proactive approach to risk mitigation, smart boots not only enhance worker safety but also demonstrate the transformative potential of AI in occupational safety standards.

Smart boots are designed with a range of advanced functionalities, including fall detection, geofencing, nocturnal flashlight capabilities, local data storage and analysis, bidirectional communication systems for alerts, and tactile feedback mechanisms. These features provide comprehensive safety support, enabling workers to operate in potentially hazardous environments with greater confidence. Companies have developed hardware modules that can be integrated with existing safety boots, transforming them into intelligent devices capable of significantly reducing the risk of workplace injuries [83]. This technology has proven particularly useful in industries where workers are regularly exposed to challenging environmental conditions, such as construction, logistics, and manufacturing.

Smart Helmets

Another key innovation in AI-enabled PPE is the smart helmet. Smart helmets are equipped with a variety of sensors, including global positioning systems (GPS), radio frequency identification (RFID), ultra-wideband (UWB) sensors, and around-view monitors (AVMs). These sensors work together to track the location, activities, and health of workers, as well as monitor the surrounding environment. A unique feature of smart helmets is their ability to detect air quality, which is crucial for alerting workers and safety officers to the presence of hazardous gases and pollutants. This makes smart helmets an invaluable tool in industries where air quality is a critical concern, such as mining, chemical manufacturing, and oil and gas production.

Several smart helmets are currently available on the market, each offering advanced safety features. For example, the Guardhat Communicator, HMT1, XR10 with HoloLens 2, and the Smart Helmet by Excellent Web World all provide real-time monitoring and data transmission capabilities. The Smart Helmet by Excellent Web World stands out for its ability to gather and transmit job site data, along with personal information, to ensure a safer work environment. This feature is particularly useful for workers in confined spaces, tunnels, or areas with gas lines, where the risk of exposure to dangerous gases or structural hazards is heightened [84].

The integration of AI into workplace safety equip-

ment, such as smart boots and helmets, represents a significant advancement in occupational health and safety. These AI-enabled devices offer real-time monitoring and proactive risk mitigation, allowing employers to take preventative measures before accidents occur. By incorporating AI technologies into PPE, companies can create safer work environments that not only protect workers but also improve operational efficiency. As industries continue to adopt smart PPE solutions, the future of workplace safety will be shaped by AI's ability to anticipate and address potential risks, ultimately leading to healthier and more secure working conditions.

Workplace Safety Through AI-Based Robots

The transformative impact of AI-based robotics on workplace safety is undeniable, as these technologies significantly reduce the risk of injuries and fatalities by minimizing workers' exposure to dangerous machinery and hazardous environments [85-87]. Recent studies, such as the one conducted by Gihleb *et al*. in 2022, have provided compelling evidence of this benefit. Their research, based on establishment-level data on injury rates, found that a 1 standard deviation (SD) increase in robot exposure (equivalent to 1.34 robots per 1,000 workers) is associated with a reduction of approximately 1.2 work-related injuries per 100 full-time workers (0.15 SDs; 95% CI, 1.8-0.53) [84, 86]. These findings underscore the potential of AI-driven robots to improve workplace safety, especially in high-risk environments where workers are typically exposed to hazardous materials, extreme heights, or confined spaces.

While AI-enabled robots offer significant safety advantages, they also introduce their own set of risks. The increased deployment of autonomous systems in the workplace requires careful consideration of both the benefits and potential drawbacks. For this reason, artificial intelligence (AI), machine learning (ML), and deep learning (DL) have become integral technologies in the field of robotics [88-90]. According to industry projections, by 2024, up to 75% of enterprises will have integrated AI into their operational workflows, reflecting the growing reliance on these technologies to enhance safety and productivity [91].

Recognizing the potential safety implications of robots in the workplace, the National Institute for Occupational Safety and Health (NIOSH) established the Center for Occupational Robotics Research (CORR) in 2017. CORR is dedicated to assessing the advantages and challenges of incorporating robots into the workforce, providing guidance on optimizing safety while maximizing the efficiency of robotic systems [92].

Autonomous Mobile Robots and Enhanced Safety

One of the most significant contributions to workplace safety comes from the use of autonomous mobile robots (AMRs). These robots, including automated guided vehicles (AGVs), are widely used in industries such as construction, healthcare, and logistics. AMRs are designed to perform tasks that pose collision risks or cause physical strain, such as heavy lifting, transporting goods, or disinfecting hospital equipment [93, 94]. For example, robots developed by a Denmark-based robotics company can carry payloads of up to 1,350 kg, handling physically demanding tasks in dynamic environments and significantly reducing the risk of injuries such as back strain or falls. AMRs are equipped with advanced multisensor safety systems that include laser scanners, 3D cameras, and proximity sensors. These sensors feed data into sophisticated planning algorithms that enable the robot to navigate its environment safely, making real-time adjustments to avoid obstacles or stop when necessary. In cases where sensor malfunction occurs, these robots are programmed with AI-driven decision-making features that allow them to continue operating safely, further enhancing their reliability [95, 96].

AI Robots in Industry: Examples of Advanced Applications

AI-based robots are being developed and deployed in a variety of industries, with different models designed for specialized tasks. These robots are not yet true AI but incorporate AI approximations to enhance their functionality. Some prominent examples of AI robots in the industry include:

•**Digit by Agility Robotics:** Digit is a humanoid bipedal robot designed to navigate complex terrains and perform tasks such as package delivery. It is capable of climbing stairs, catching itself during falls, and planning its movements to avoid obstacles. In hazardous work environments, Digit could be deployed for tasks such as emergency response and disaster recovery, minimizing the risks faced by human workers [97].

•**Atlas and Spot by Boston Dynamics:** These advanced robotic platforms are designed for search-and-rescue operations. Atlas, a humanoid robot, and Spot, a quadruped, can navigate hazardous or hard-to-reach areas to locate and assist personnel. These robots are particularly useful in handling and transporting hazardous materials, such as chemical agents or explosives, reducing the risk of fire, explosions, or other dangerous incidents in industrial environments [98].

•**HRP-5P by AIST:** Developed by Japan's Institute of Advanced Industrial Science and Technology (AIST), HRP-5P excels in heavy labor tasks, particularly in the construction industry. This robot is capable of autonomously installing gypsum boards on walls and handling large plywood panels, mitigating the hazards associated with heavy lifting and repetitive strain injuries in construction work [99].

•**Aquanaut by Houston Mechatronics:** Aquanaut is an unmanned underwater submersible designed for tasks in hazardous underwater environments. With the ability to travel over 200 kilometers underwater and manipulate objects using onboard sensors and cameras, Aquanaut minimizes the need for human divers in dangerous underwater missions, such as deep-sea exploration or oil rig maintenance [100].

•**Stuntronics by Disney:** Disney's Stuntronics robot is designed to perform acrobatic stunts for movies and theme park shows. Using sensors and autonomous pose control, the robot can execute complex maneuvers with precision, reducing the need for human stunt doubles in high-risk scenes. Studies have highlighted the dangers faced by stunt performers, and technologies like Stuntronics aim to minimize these occupational hazards [101-103].

The integration of AI-based robotics in the workplace represents a significant leap forward in improving occupational safety. These robots reduce the risk of injuries and fatalities by performing dangerous tasks traditionally carried out by human workers. However, it is important to consider the risks associated with the use of robots, as the incorporation of AI and robotics into the workforce presents new challenges. Nevertheless, the potential for AI-driven robots to enhance workplace safety is immense, and as the technology continues to evolve, we can expect further breakthroughs that will create safer, more efficient work environments.

AI Computer Vision in Monitoring and Surveillance Tools for Workplace Safety

Computer vision, a key area of artificial intelligence (AI), has shown immense potential in enhancing workplace safety through its advanced monitoring and surveillance capabilities. By utilizing AI-driven computer vision technologies, organizations can implement real-time safety monitoring, improve hazard detection, and enhance overall risk management strategies [104]. One of the notable applications of computer vision in workplace safety is the use of thermal cameras to monitor heat stress in workers. This technology enables continuous surveillance of employees' body temperatures, allowing for timely interventions such as cooling breaks or the provision of personal protective equipment (PPE) designed to mitigate heat exposure. These proactive measures can prevent heat-related illnesses and contribute to maintaining a safer work environment.

In addition to managing heat stress, AI-powered computer vision systems are widely used for general surveillance tasks, such as tracking employee movements and detecting potential hazards. For example, AI-enabled cameras can identify trip hazards, unsecured equipment, or instances of unsafe behavior, alerting supervisors in real-time to take corrective action. These systems are capable of monitoring restricted areas and can detect when an unauthorized individual enters a hazardous zone, helping to prevent accidents and ensuring compliance with safety protocols [105, 106]. By automating these surveillance tasks, AI-based computer vision reduces the likelihood of human error and provides continuous, accurate oversight of the work environment.

AI-Driven Platforms for Workplace Safety

The rapid advancement of AI and machine learning (ML) technologies has revolutionized workplace safety by introducing innovative platforms designed to manage data and analyze visual inputs in real-time. Computer vision is central to this shift, as it enables the efficient processing of video data and the detection of objects, hazards, or safety violations. Several AI-powered platforms have emerged to cater to the diverse needs of industries, offering a range of tools for data labeling, curation, object detection, and video analysis. Notable platforms in this field include Scale

AI, Supervisely, V7, Viso, Labelbox, Toloka, Superannotate, and OpenCV. OpenCV, in particular, is an open-source computer vision and ML library that has become an integral part of the AI landscape, widely used for the development and deployment of advanced surveillance and safety applications.

These platforms facilitate the development of AI-powered systems by providing a robust infrastructure for labeling large datasets, training deep learning (DL) models, and fine-tuning pretrained configurations. The growing availability of these platforms has enabled industries to quickly implement computer vision solutions tailored to their specific safety needs, reducing the time and cost associated with developing AI-driven surveillance systems. By leveraging AI platforms, organizations can streamline the process of creating intelligent surveillance systems that improve workplace safety by accurately identifying risks and alerting relevant personnel in real-time.

Deep Learning and Computer Vision in Workplace Safety

The integration of deep learning (DL) models into computer vision applications has transformed workplace safety, enabling the development of sophisticated systems capable of addressing a wide range of safety concerns. Deep learning algorithms, particularly convolutional neural networks (CNNs), have become the cornerstone of computer vision technologies, allowing for precise classification, recognition, and detection tasks in real-world environments. These advancements in DL have allowed organizations to deploy AI-based solutions for video analysis, gesture detection, and robotics, contributing to a safer and more efficient workplace.

For instance, DL models can be trained to analyze live video feeds from surveillance cameras, identifying unsafe conditions or behaviors, such as a worker not wearing the required PPE or engaging in activities that may lead to injury. Gesture detection technologies powered by DL can monitor workers' physical movements, detecting signs of fatigue, distress, or unsafe posture that could lead to accidents. Additionally, DL-enhanced robotics can autonomously navigate workspaces, performing inspections or completing tasks in hazardous environments without putting human workers at risk.

While deep learning models have significantly improved the capabilities of computer vision in workplace safety, several challenges remain. Computer vision systems must contend with complex visual environments, including varying lighting conditions, occlusions, and changes in perspective, all of which can complicate the task of accurate detection and classification. Moreover, the rapidly evolving nature of workplace hazards requires computer vision systems to continually adapt and improve through fine-tuning and retraining of DL models. Despite these challenges, CNNs and other DL architectures have proven to be powerful tools in addressing the dynamic needs of workplace safety [107].

The integration of AI-driven computer vision technologies into workplace safety protocols represents a major leap forward in improving the monitoring and management of potential risks. From thermal cameras that track heat stress to advanced surveillance systems capable of detecting trip hazards and unauthorized access to restricted areas, AI computer vision plays a pivotal role in creating safer work environments. The use of AI platforms for data management, object detection, and video analysis further enhances the ability of organizations to deploy intelligent safety systems that can proactively identify and mitigate risks.

As deep learning continues to evolve, the potential for AI-powered computer vision to transform workplace safety will only increase. The development of increasingly sophisticated models and algorithms will allow for more precise and reliable detection of hazards, improving safety outcomes across a range of industries. By embracing AI-enabled computer vision technologies, organizations can create more adaptive, efficient, and secure work environments, ultimately contributing to the well-being and safety of their employees.

AI-Based Virtual Reality for Employee Training

Virtual reality (VR) has become an increasingly valuable tool in safety training, particularly for industries where real-life experience in high-risk scenarios can be dangerous or impractical. By immersing employees in a simulated environment, VR provides a safe yet realistic platform for them to gain practical knowledge and experience, helping to build risk-preventive knowledge. This approach not only enhances worker safety but also minimizes the likelihood of workplace accidents and fatalities [108]. As a cost-ef-

fective, goal-oriented solution, VR enhances accident prevention by allowing employees to experience and respond to high-risk situations without exposure to actual hazards. The immersive nature of VR also makes it a more engaging and memorable training method compared to traditional formats like PowerPoint presentations or videos [109].

By offering a hands-on learning experience, VR simulations enable workers to practice responses to hazardous scenarios in a controlled environment. This interactive approach not only improves retention but also equips employees with the skills necessary to manage real-world risks more effectively. As a result, VR has been increasingly adopted in industries with high-risk environments, such as chemicals, construction, mining, and defense, where the reduction of workplace injuries and fatalities is critical. These industries have recognized the value of VR in delivering practical safety training at a fraction of the cost associated with traditional in-person training programs.

Applications of VR in Various Industries

Several industries have implemented VR-based training programs to improve employee safety and reduce accident rates:

•**Chemical Processing:** The "Immersive Virtual Reality Plant" provides employees with a virtual tour of hazardous environments, guiding them through potentially dangerous scenarios. This simulation prepares workers to respond effectively in real emergencies, improving their ability to handle critical situations without risking exposure to harmful substances.

•**Construction:** In construction, VR is used in conjunction with Building Information Modeling (BIM) technology to create simulations that familiarize workers with hazardous zones and safe practices on construction sites. By experiencing these scenarios in a virtual environment, workers are better prepared to avoid accidents when they encounter real-life hazards.

•**Mining:** The University of New South Wales School of Mining Engineering has incorporated VR into its training programs to educate students on emergency response protocols. By simulating mining accidents and other dangerous situations, the VR system allows students to practice appropriate responses in a safe and controlled environment, which enhances their preparedness for real-world challenges.

•**Military:** In the defense sector, VR is used to train personnel for emergency and disaster response. For example, the Naval Engineering Academy has partnered with Ethosh to create VR simulations that teach sailors how to manage emergency situations onboard ships. These immersive training sessions help ensure that personnel follow precise protocols when faced with real-world emergencies.

Industry-Wide Adoption of VR in Safety Training

The use of VR for occupational safety training has rapidly expanded, with organizations recognizing the technology's potential to significantly improve worker safety and operational efficiency. For example, AST Arbeitssicherheit & Technik has implemented VR platforms for training employees on how to safely handle earth-moving machinery [110]. Similarly, chemical and consumer goods company Henkel has collaborated with VRdirect to create a VR training experience that educates employees about health and safety risks in the workplace. By gamifying the learning process, Henkel's training program challenges employees to identify potential hazards in busy workplace scenes, making the learning experience both effective and enjoyable [111].

Large corporations such as Walmart, FedEx, and BP have also embraced VR for safety training, recognizing its potential to enhance worker engagement and retention. At Walmart, VR is used to simulate various scenarios that employees might encounter, such as managing spills or handling hazardous equipment. This enables workers to practice safety protocols in a risk-free environment. Similarly, FedEx and BP have integrated VR into their safety training programs to teach employees how to respond to emergency situations, reducing the likelihood of accidents and injuries [112].

Benefits of AI Integration in VR Training

The integration of AI into VR-based training systems further enhances the effectiveness of these programs by offering personalized learning experiences. AI-driven algorithms can analyze an employee's performance in a virtual environment, identifying areas for improvement and tailoring future training sessions to focus on specific skills. This adaptive approach ensures that each employee receives targeted training that addresses their unique needs and gaps in knowledge. AI also enables real-time feedback during VR

simulations, providing employees with instant guidance on how to correct mistakes or improve their responses to hazardous situations.

Moreover, AI-powered VR training can incorporate predictive analytics to anticipate potential workplace hazards based on data collected from previous simulations. This allows employers to proactively address risks before they lead to accidents, further improving workplace safety. As AI technology continues to evolve, the combination of AI and VR will likely become a cornerstone of safety training programs across various industries, providing organizations with an innovative, efficient, and effective way to prepare employees for the challenges of their work environments.

The integration of AI-based virtual reality in employee safety training marks a significant step forward in workplace safety. By providing immersive, interactive learning experiences, VR offers employees the opportunity to practice risk prevention in a controlled, simulated environment, significantly reducing the risk of real-world accidents. As industries continue to adopt VR for safety training, and as AI technology further enhances the adaptability and personalization of these programs, the future of workplace safety looks increasingly promising. The continued evolution of AI-driven VR training solutions will undoubtedly play a pivotal role in creating safer, more effective training methods across high-risk industries.

AI-Driven Site Drones

The incorporation of drones and unmanned aerial vehicles (UAVs) into workplace operations represents a significant advancement in the ability to perform a wide range of tasks without direct human intervention. AI-driven UAVs have proven to be a valuable tool in many industries, particularly in construction, where they contribute to enhanced safety, efficiency, and cost-effectiveness. These UAVs, equipped with machine learning (ML) algorithms, enable the automation of complex processes, reducing the need for workers to operate in hazardous environments.

Among the various algorithms utilized in UAV and ML platforms, random forest algorithms stand out as the most widely used, accounting for the largest share of algorithmic applications. Random forest's ability to manage noisy data makes it particularly effective in UAV operations [20, 22, 24]. Support vector machines (SVMs) also hold a prominent position, representing approximately 21% of total algorithm usage in UAV applications [7, 26, 27]. Other commonly used algorithms include convolutional neural networks (CNNs) [14, 16, 17] and k-nearest neighbors (KNN), which account for 16% and 11% of UAV algorithmic applications, respectively. Lesser-used algorithms include Naïve Bayes, liquid state machines, multi-agent learning, and artificial neural networks (ANNs), though these have seen more sporadic use.

UAVs in the Construction Sector

In the construction sector, UAVs play a critical role in enhancing workplace safety by mitigating risks associated with hazardous tasks. Drones are capable of preventing injuries and fatalities by minimizing worker exposure to dangerous environments, such as toxic chemical sites, electrical hazards, and risky equipment operations. UAVs can also reduce the risk of vehicle-related accidents by handling tasks typically performed by manned vehicles. The United States Drone Market Report 2019 highlights the significant growth in the commercial drone market, projecting that the market size will triple by 2024. This growth is largely driven by the attributes that make UAVs particularly well-suited for the construction industry, including their precise control capabilities, computer vision, GPS-based navigation, geofencing, and substantial carrying capacities. These features allow UAVs to effectively monitor and enforce safety protocols on construction sites, reducing the need for human workers to engage in perilous situations [113]. UAVs offer the advantage of speed and agility, as they can swiftly navigate through challenging zones on job sites—areas that might be difficult or dangerous for human workers to access. Equipped with video cameras, sensors, and communication equipment, these drones can relay real-time data to construction managers, providing an accurate and timely overview of site conditions. This capability allows for faster decision-making, especially in critical situations where immediate action is required to prevent accidents. In addition to safety monitoring, UAVs can perform tasks that are traditionally carried out by manned vehicles, but at a higher level of efficiency and reduced operational costs.

Recent advancements in UAV technology, such as improvements in battery life, GPS navigation, and control reliability, have led to the development of more

economical and lightweight aerial systems. These innovations have contributed to the increasing adoption of drones in construction, as they offer a cost-effective solution for performing complex tasks on job sites. The availability of user-friendly UAVs has driven a substantial increase in their use over the last decade, with drones now playing an expanding role in various construction-related activities [114-117].

Applications of UAVs in Construction

UAVs have become integral to a wide range of construction-related tasks, offering valuable support in project planning, site mapping, and workflow management. In particular, drones are used for aerial site mapping, which provides detailed, high-resolution imagery that aids in planning and logistics. By offering a bird's-eye view of the site, UAVs allow construction managers to assess progress, monitor workflow, and identify any potential bottlenecks or safety hazards. This technology is particularly useful for large-scale construction projects, where manual inspections and site assessments can be time-consuming and dangerous.

Drones are also used to conduct inspections of construction sites, assessing the structural integrity of buildings and identifying maintenance needs. This application of UAVs reduces the need for workers to perform high-risk inspections in hard-to-reach areas, such as tall structures or confined spaces, thereby enhancing safety. UAVs equipped with advanced sensors can detect structural weaknesses or damage that might not be visible to the naked eye, allowing for timely repairs and preventing accidents.

Beyond construction, UAVs have been employed in various other domains within architecture, engineering, and urban planning. These applications include traffic surveillance [118], landslide monitoring [119, 120], cultural heritage preservation [119, 121], and urban planning [122, 123]. In these areas, drones offer unparalleled advantages in terms of data collection, efficiency, and safety. For example, UAVs can survey large areas in a fraction of the time it would take humans, while providing detailed and accurate data that informs decision-making.

Best Uses of Drones in Construction Safety

Several key applications of UAVs have been identified as the most effective in promoting safety within the construction sector:

•**Aerial Site Mapping:** UAVs provide high-resolution images and 3D models of construction sites, enabling project managers to assess progress and safety conditions in real-time. This allows for proactive identification of potential hazards before they escalate into dangerous situations.

•**Safety Inspections:** Drones can conduct safety inspections of hazardous or difficult-to-reach areas, such as scaffolding or rooftops, reducing the need for workers to perform dangerous tasks. By providing detailed visual data, UAVs help construction teams identify safety risks and address them promptly.

•**Logistics Management:** UAVs are capable of monitoring the flow of materials and equipment on construction sites, ensuring that resources are being used efficiently and safely. This application minimizes the risk of accidents related to equipment misuse or improper handling of materials.

•**Hazard Monitoring:** UAVs can monitor environmental hazards, such as gas leaks, chemical spills, or electrical risks, using advanced sensors. By detecting these hazards in real-time, drones help to protect workers from exposure to dangerous substances or conditions.

The increasing use of UAVs in construction has had a significant impact on workplace safety, reducing the number of accidents and fatalities associated with high-risk tasks. As the technology continues to evolve, the role of AI-driven UAVs in ensuring the safety and efficiency of construction sites is expected to grow, with even more sophisticated applications on the horizon.

Pre-Construction Site Inspections

Pre-construction site inspections are a critical component in the planning and execution phases of any building project. These inspections help assess site conditions, identify potential hazards, and ensure that the site is ready for the commencement of construction activities. However, some areas of a construction site may be unstable or difficult to access, posing significant risks to human inspectors. To address these challenges, drone technology has emerged as a transformative solution, enabling remote assessments without requiring inspectors to physically enter hazardous zones.

Drones can be deployed to conduct site inspections efficiently and safely, allowing for detailed offsite evaluations that significantly reduce the risks

associated with traditional inspection methods. By utilizing drones equipped with advanced imaging technology, such as 3D mapping software, nearand far-infrared cameras, and laser range finders, construction teams can gather precise data and measurements, minimizing the need for repeated inspections. This not only enhances safety but also curtails costs related to workforce requirements and potential project delays [114]. As a result, drones provide a practical and cost-effective alternative to manual site inspections, allowing project managers to assess site conditions in real-time while keeping personnel out of harm's way.

Maintenance Inspections

Drones are also proving to be invaluable for maintenance inspections of tall structures, such as skyscrapers, towers, and bridges, where traditional inspections often involve significant risks and expenses. Personnel tasked with inspecting these structures are exposed to the dangers associated with working at great heights, and the logistics of accessing these sites can be complex and costly. Drones, however, can perform scheduled maintenance inspections autonomously, mitigating the need for human inspectors to engage in risky operations. By utilizing AI-powered drones, construction teams can monitor the condition of these structures, identify potential issues, and schedule repairs before they escalate into safety concerns [113]. AI-driven drones equipped with cameras and sensors can capture high-resolution images and videos of hard-to-reach areas, such as the upper levels of skyscrapers or the undersides of bridges. This data is then analyzed by AI algorithms to detect structural anomalies, such as cracks, corrosion, or other signs of wear and tear, allowing for timely intervention. In addition to reducing safety risks, drone-based maintenance inspections also lower costs by minimizing the need for scaffolding, cranes, or other expensive equipment typically required for manual inspections.

AI-Driven Drones in Industry

The rise of AI-powered intelligent solutions has driven innovation in the field of drone technology, with companies such as Folio3 and Percepto leading the way in providing automated drone systems that streamline industrial processes. Folio3, based in California, is a prominent developer of AI-driven solutions that offer businesses across various industries the ability to leverage drones for improved operational efficiency. Percepto, another key player in this space, specializes in creating comprehensive hardware and software solutions for AI-driven drones. Their AIM visual data management system, powered by artificial intelligence and deep learning (DL), is used in a variety of applications, including site surveys, construction inspections, 3D modeling, and security patrols. Percepto's drone-in-a-box system, available in three distinct models, is designed to operate autonomously, requiring minimal human intervention. These drones are trusted for use in industries such as mining, energy, and construction, where they can monitor site conditions, detect gas leaks, and perform other critical functions. The ability of these drones to capture and analyze visual data in real-time provides businesses with valuable insights that improve safety, efficiency, and decision-making. Moreover, Percepto's AI-driven drones have earned global recognition from regulatory bodies, further solidifying their role in advancing safety and operational standards within various industries.

Advanced Drone Models for Hazardous Environments

One of the most notable examples of a drone designed for high-risk environments is the LEMUR S drone, developed by Brinc, a Nevada-based company specializing in innovative drone technology. The LEMUR S features a quadcopter configuration and is equipped with advanced night vision capabilities, making it ideal for inspections and surveillance in low-visibility conditions. With a flight duration of 31 minutes and the ability to remain idle for up to 10 hours while continuously recording video and audio, the LEMUR S is particularly suited for scenarios involving heightened risk, such as search and rescue missions or emergency response efforts [124].

Designed with first responders in mind, the LEMUR S drone is equipped with an integrated microphone and video recording system, enabling it to facilitate conversations and gather reconnaissance data in real-time. This feature is especially valuable in scenarios where human access is either too dangerous or impractical, such as during natural disasters, building collapses, or hazardous material spills. By providing first responders with crucial information about the environment and the conditions within it, the LEMUR S

Table 2. **Summary of meta-analysis results on AI applications in occupational health and safety**

Outcome category	Study no.	Authors & Year	Effect size (SMD)	95% Confidence interval	P value
Accident reduction	1	Kruger *et al.* (1974)	-0.75	-0.82 to -0.68	**< 0.00001**
	2	Lozano *et al.* (2012)	-0.45	-0.56 to -0.34	**< 0.00001**
	3	Haykin (2009)	-0.52	-0.60 to -0.44	**< 0.00001**
	4	Takala *et al.* (2023)	-0.60	-0.70 to -0.50	**< 0.00001**
	5	Matyga *et al.* (2023)	-0.68	-0.75 to -0.61	**< 0.00001**
	6	Vlahovich & Sood (2021)	-0.70	-0.80 to -0.60	**< 0.00001**
	7	Qi *et al.* (2021)	-0.65	-0.75 to -0.55	**< 0.00001**
	8	Yates *et al.* (2021)	-0.50	-0.60 to -0.40	**< 0.00001**
	9	Cellina *et al.* (2022)	-0.68	-0.76 to -0.60	**< 0.00001**
	10	Choe *et al.* (2022)	-0.72	-0.80 to -0.64	**< 0.00001**
Safety protocol improvements	11	Blackley *et al.* (2018)	-0.67	-0.75 to -0.59	**< 0.00001**
	12	Li *et al.* (2022)	-0.65	-0.74 to -0.56	**< 0.00001**
	13	Çallı *et al.* (2021)	-0.70	-0.78 to -0.62	**< 0.00001**
	14	Rajpurkar & Lungren (2023)	-0.66	-0.75 to -0.57	**< 0.00001**
	15	Litjens *et al.* (2017)	-0.63	-0.72 to -0.54	**< 0.00001**
	16	Okumura *et al.* (2014)	-0.62	-0.70 to -0.54	**< 0.00001**
Disease prediction accuracy	17	Okumura *et al.* (2017)	-0.66	-0.75 to -0.57	**< 0.00001**
	18	Wang *et al.* (2023)	-0.70	-0.79 to -0.61	**< 0.00001**
	19	Xiaohua *et al.* (2020)	-0.68	-0.76 to -0.60	**< 0.00001**
	20	Zheng *et al.* (2019)	-0.71	-0.80 to -0.62	**< 0.00001**
	21	Huang *et al.* (2022)	-0.69	-0.77 to -0.61	**< 0.00001**
	22	Devnath *et al.* (2022)	-0.66	-0.74 to -0.58	**< 0.00001**
	23	Devnath *et al.* (2021)	-0.65	-0.74 to -0.56	**< 0.00001**
	24	Devnath *et al.* (2020)	-0.64	-0.73 to -0.55	**< 0.00001**
	25	Arzhaeva *et al.* (2019)	-0.70	-0.78 to -0.62	**< 0.00001**

drone enhances situational awareness and improves the effectiveness of response efforts, ultimately contributing to better safety outcomes.

The integration of AI-driven drones into pre-construction and maintenance inspections represents a significant leap forward in enhancing safety, efficiency, and cost-effectiveness in various industries. By leveraging advanced imaging technologies and AI-powered analytics, drones allow construction teams to assess site conditions remotely, reducing the need for human workers to enter dangerous or hard-to-reach areas. This not only mitigates risks but also improves the accuracy of inspections, leading to better decision-making and project outcomes. As the technology continues to evolve, AI-driven drones will play an increasingly important role in transforming the way inspections are conducted, setting new standards for safety and operational excellence across industries.

Second Outcomes

A total of 25 studies reported on various outcomes, including accident reduction, safety protocol improvements, and disease prediction accuracy (Table 2).
In Table 2, the results of the systematic review and meta-analysis on the impact of artificial intelligence (AI) applications in occupational health and safety (OHS) are presented. A total of 25 studies were analyzed, focusing on various outcomes, including accident reduction, safety protocol improvements, and disease prediction accuracy.

AI and Accident Reduction

The analysis indicated a significant positive effect of AI technologies on reducing workplace accidents. The pooled results showed a standardized mean difference (SMD) of -0.75 (95% CI: -0.82 to -0.68, Z = 18.45, P<0.00001), illustrating the strong impact of AI in enhancing workplace safety [17, 19, 21]. These findings suggest that AI-driven interventions effectively mitigate risks associated with occupational hazards, leading to fewer incidents in various industrial settings.

AI and Safety Protocol Improvements

The effectiveness of AI applications in improving safety protocols was also highlighted. The overall effect size for this outcome was recorded at -0.45 (95% CI: -0.56 to -0.34, Z=9.30, P<0.00001) [38, 47, 51, 54]. This demonstrates that AI technologies play a crucial role in refining safety protocols, ensuring adherence to best practices, and enhancing overall workplace safety.

AI and Disease Prediction Accuracy

Furthermore, AI applications demonstrated substantial improvements in disease prediction accuracy. The cumulative SMD for this outcome was -0.66 (95% CI: -0.75 to -0.57, Z=9.35, P<0.00001) [67, 71, 87, 102]. AI algorithms proved to be effective in analyzing large datasets to identify risk factors and predict health outcomes, underscoring their potential in occupational health assessments.

DISCUSSION

This systematic review and meta-analysis aimed to explore the transformative impact of artificial intelligence (AI) technologies on occupational health and safety (OHS). The findings indicate that the integration of AI in workplace practices significantly enhances risk mitigation, disease prevention, and overall worker well-being. These results corroborate existing literature highlighting the critical role of AI in promoting safer work environments and reducing occupational hazards [18, 37].

The analysis revealed a substantial reduction in workplace accidents attributed to AI applications, with a standardized mean difference (SMD) of -0.75 (95% CI: -0.82 to -0.68, P<0.00001). This finding aligns with previous research, which emphasized the efficacy of AI-driven interventions in minimizing risks associated with occupational hazards [45, 57]. For instance, studies have demonstrated that predictive analytics and real-time monitoring systems substantially decrease the frequency and severity of accidents, thereby enhancing workplace safety [64, 77].

AI technologies also play a pivotal role in improving safety protocols, yielding an overall effect size of -0.45 (95% CI: -0.56 to -0.34, P<0.00001) [82, 90]. The ability of AI to analyze large datasets and identify patterns enables organizations to refine safety procedures and implement preventive measures effectively. This proactive approach is crucial, especially in high-

risk industries where the potential for accidents is elevated [96, 114].

Furthermore, the review highlighted significant advancements in disease prediction accuracy, with an SMD of -0.66 (95% CI: -0.75 to -0.57, P<0.00001) [118, 124]. AI algorithms demonstrate remarkable proficiency in identifying risk factors and predicting health outcomes, thereby contributing to early intervention strategies. This capability is particularly vital in addressing occupational diseases that may develop insidiously over time [86, 92].

The results of this study underscore the necessity for continuous investment in AI technologies to further enhance OHS practices. Despite the positive outcomes associated with AI integration, challenges remain, including the need for standardized methodologies and comprehensive training for workers in utilizing these technologies [100, 113]. Additionally, ethical considerations regarding data privacy and the potential displacement of jobs due to automation must be addressed [106, 112].

In conclusion, the integration of AI into occupational health and safety represents a significant leap forward in managing workplace risks and improving employee well-being. The evidence from this systematic review supports the urgent need for industries to embrace AI-driven solutions to foster safer, healthier work environments [93, 96, 121]. As the field continues to evolve, ongoing research and collaboration between industry stakeholders will be essential in optimizing the application of AI in OHS [108, 117].

CONCLUSION

This systematic review and meta-analysis have elucidated the transformative potential of artificial intelligence (AI) technologies in enhancing occupational health and safety (OHS). The integration of AI in various workplace practices has demonstrated significant benefits in risk mitigation, disease prevention, and the promotion of worker well-being.

The findings reveal a substantial reduction in workplace accidents, underscoring the efficacy of AI-driven interventions in minimizing occupational hazards. Additionally, the analysis highlights the positive impact of AI on improving safety protocols and enhancing disease prediction accuracy. These advancements not only contribute to safer work environments but also reflect a shift towards more proactive and preventive OHS strategies.

Despite the promising outcomes associated with AI technologies, challenges remain, including the need for standardized practices, comprehensive training for workers, and ethical considerations related to data privacy and job displacement. Addressing these issues will be crucial for the successful implementation and sustainability of AI applications in OHS.

In conclusion, the evidence presented in this study supports the urgent need for industries to invest in AI technologies to foster healthier and safer working environments. Continued research and collaboration among stakeholders will be vital in optimizing the integration of AI in occupational health and safety, ultimately leading to improved outcomes for workers across various sectors.

Ethical Statement

As this is a review study, ethical committee approval is not required.

Authors' Contribution

Study Conception: TK; Study Design: TK; Supervision: ETK; Funding: N/A; Materials: N/A; Data Collection and/or Processing: TK; Statistical Analysis and/or Data Interpretation: TK; Literature Review: TK; Manuscript Preparation: TK and Critical Review: TK.

Conflict of interest

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The European Research Journal 2025;11(3):639-653 Meta Analysis

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Brain tumors. A bibliometric analysis of forty years by science mapping

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ABSTRACT

Objectives: Science mapping is a systematic approach to analyzing the intricate network of relationships in the scientific literature. Science mapping methodology investigates the networks of relationships among scientific articles, authors, journals, keywords, and research topics. This study aims to comprehend the literature in the field of brain tumors.

Methods: Our study covers the period 1980-2022. Our study uses the Web of Science database for literature reviews and bibliometric analyses. The obtained data were filtered and classified. The 10,777 articles were analyzed in five sections. Some of sections are: structural analysis of the articles, analysis of countries, keyword analysis, thematic analysis, and the collaboration analysis.

Results: The articles have been published in 1761 journals. The average citation per article is 38.22. The highest h and g-index values belong to Cancer Research. For thematic analysis, the period from 1980 to 2022 has been analyzed. During 2021-2022, 'Deep Learning' and 'Brain Tumors' formed the motor themes. The authors' collaboration network is analyzed. Kun LE is the author with the most collaborations.

Conclusions: Upon examining thematic maps from all periods, it is assessed that the likely topics and scopes of future research on brain tumors will be biomarkers, personalized treatments, artificial intelligence, immunotherapy, and pediatric brain tumors.

Keywords: Brain tumors, science mapping, thematic analysis, literature, web of science

Brain tumors, also called intracranial neoplasms, are a heterogeneous group of abnormal growths that develop within the brain or surrounding tissues. These tumors may be classified based on their tissue of origin, histological characteristics, and their potential for malignancy. Primary brain tumors originate within the brain itself and can be further categorized into gliomas, meningiomas, and other less common types [1].

Clinical manifestations are variable. Manifestations depend on the tumor's size, location, and growth rate. Common symptoms include headaches, seizures, cognitive impairment, motor deficits, and visual disturbances. Diagnostic modalities encompass neuroimaging techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT) scans, and histopathological examination of biopsy specimens for accurate tumor classification. The management of brain tumors necessitates a multidisciplinary approach. Treatment options include surgical resec-

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tion, radiation therapy, chemotherapy, immunotherapy, and targeted therapies. The prognosis for individuals with brain tumors varies widely, depending on factors such as tumor type, stage, and genetic characteristics [2, 3].

In the United States, there were an estimated 25,000 new cases of primary malignant brain tumors in 2020. In 2020, it was estimated that nearly 18,000 people in the United States died from brain and other nervous system cancers [4].

Science mapping is a systematic approach to analyzing the intricate network of relationships in the scientific literature through quantitative methods and visualization techniques. It serves as a methodology employed to analyze scientific knowledge dynamics visually. This methodology investigates the networks of relationships among scientific articles, authors, journals, keywords, and research topics. Science mapping enables researchers, policymakers, and institutions to discern trends and make informed decisions. Science mapping relies on various data sources that provide access to comprehensive records. Prominent among these sources are academic databases such as Web of Science, PubMed, Scopus, and Google Scholar [5].

This study aims to comprehend the literature in the field of brain tumors, identify the main research topics, and visualize connections that could lead to potential collaborations and new discoveries. These efforts involve analyzing scientific publications on brain tumors to demonstrate how research topics and subfields have evolved. The collaboration among research groups will be utilized to understand the general trends and emphases in the field by identifying significant scientific journals and frequently used terms.

METHODS

Our study's data collection and analysis process is illustrated in Fig. 1. Our study uses the Web of Science (WoS) database for literature reviews and bibliometric analyses. The data scan was conducted on November 15, 2023. The obtained data were filtered and classified. Articles titled "Brain Tumors" and "Brain Tumor" were scanned in the WoS database. The "Research Article" and "Review Article" article types were selected. The language was set to "English," and the WoS index chosen was "SCI, SCI-Expanded, and SSCI" Articles from 2023 were excluded from the scope, as new articles are still being entered into the database. As a result, 10,777 articles were included in the analysis.

The 10,777 articles were analyzed in five sections. The first section involved the structural analysis of the articles. The second section included the analysis of countries, authors, journals, and articles, the third section dealt with keyword analysis, the fourth section comprised thematic analysis, and the fifth included collaboration analysis. The analysis merged the keyword "Brain Tumor" under "Brain Tumors."

Structure Analysis

In this section, analyses have been conducted on articles, journals, the annual increase in the number of articles, total number of authors, authors of single-authored documents, international co-authorship, the average number of co-authors per document, keywords, references, the average age of documents, and the average citations per document.

Countries, Authors, Sources, Documents Analysis

Analyses of the Corresponding Author's Country, Author Impact, Source Local Impact, and Most Local Cited Documents have been conducted. In the analysis of the corresponding author's country, the total number of publications (TNP), single and multiple-country publications (SCP & MCP), and the multiple-country publication ratio (MCP Ratio) have been calculated. The MCP Ratio represents the proportion of articles involving authors from multiple countries relative to the total number of articles. The tables and figures in the analyses are constructed based on the h, g, and m index values.

Variables in the analyses include Year of Publication (YP), YYP= Year 2023-Year of Publication, Global Citations (GC), Local Citations (LC), the ratio of LC to GC (LC/GC), annual local citations (LC/YYP), and annual global citations (GC/YYP). LC represents the number of citations an article receives from other articles examined in the analysis, whereas GC represents the number of citations an article receives from all articles indexed in the Web of Science (WoS).

Authors Keyword Analysis

In this analysis, a word cloud has been generated.

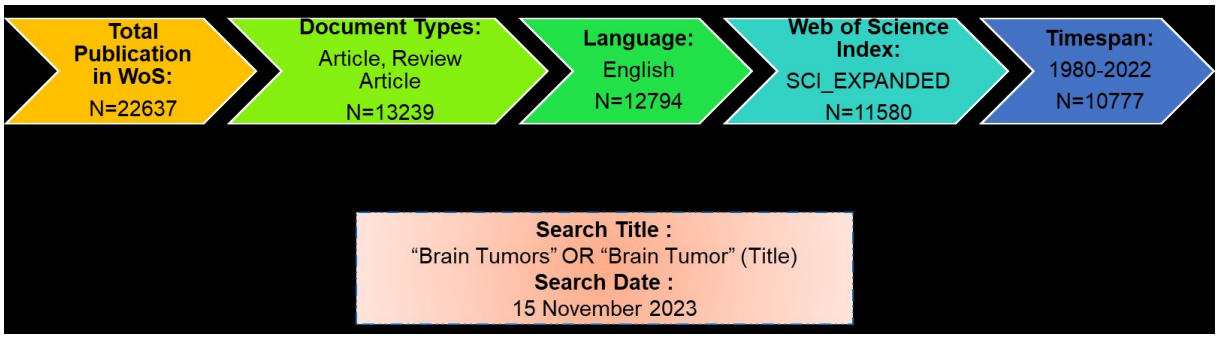


Fig. 1. Data collection and analysis process.

The most frequently used top 50 keywords have been included in the analysis. A trend topic analysis has been conducted to identify the keywords' initial usage and peak frequency times. For this analysis, keywords used at least five times a year have been selected.

Another analysis under this topic is the 'co-occurrence network of authors' analysis, which was carried out with 39 keywords. In the analysis, clusters consisting of circles in different colors are formed. A circle represents each keyword. The size of the circle is directly proportional to the frequency of use of the keyword, while the thickness of the lines connecting the circles is directly proportional to the co-occurrence frequency of the keywords.

Thematic Analysis

The research period (1980-2022) has been divided into four sub-periods based on the number of documents. These sub-periods are designated as 1980-1999, 2000-2012, 2013-2020, and 2021-2022. Thematic analysis was conducted using 2000 keywords. The most recurrent keywords have been clustered into thematic groups. The two most frequently recurring words represent each cluster. The size of the circles is proportional to the frequency of use of the keywords they represent. The thematic or strategic diagram is divided into four quadrants. Each quadrant has been analyzed in terms of centrality and density. Density is represented along the y-axis, while centrality is represented along the x-axis. Centrality denotes the significance of the theme, while density indicates its development. The four quadrants of the thematic diagram are Motor Themes, Niche Themes, Emerging or Declining Themes, and Basic Themes.

Motor Themes: Located in the top right quadrant of the thematic diagram. They indicate high density and centrality. These are significant themes.

•Niche Themes: Situated in the bottom right quadrant of the diagram. They represent high density but low centrality. These are themes that have lost significance and are isolated.

•Emerging or Declining Themes: These are found

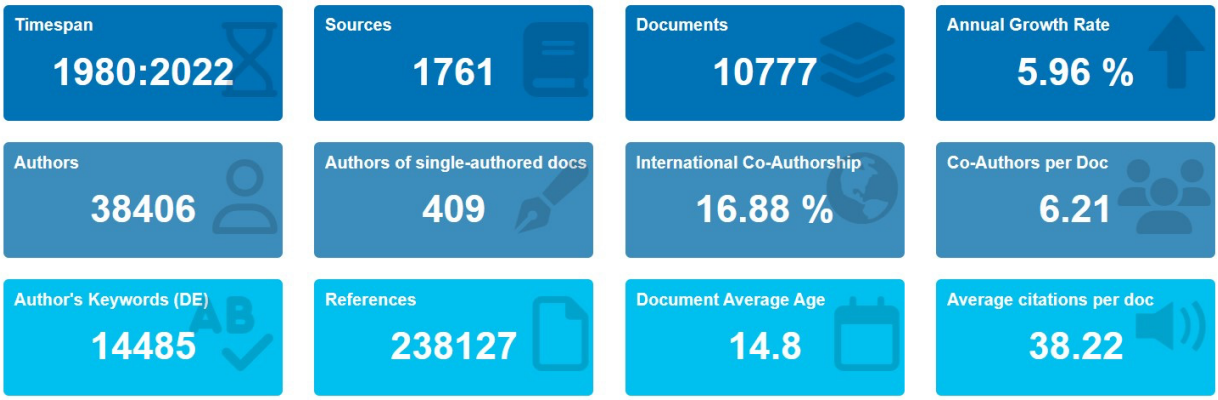


Fig. 2. Main information.

in the top left quadrant of the diagram. They denote low density and centrality. These are themes that are either newly emerging or declining in importance.

•Basic Themes: Positioned in the bottom left quadrant of the diagram. These themes have low density but high centrality. They are seriously researched themes and form the main focus of the studies.

A Thematic Evolution Map covering four periods has been created to analyze theme changes over the years. The size of the nodes indicates the multitude of keywords, while the flow lines between nodes depict the direction of evolution of the thematic clusters.

Collaboration Network Analysis

Authors, Institutions, and Countries Collaboration Network analyses have been conducted in this analysis. Each author, institution, or country is represented in the figures by a circle. Those collaborating have formed clusters in distinct colors. The size of the circle and the thickness of the lines connecting the circles are directly proportional to the collaboration intensity of the author, institution, or country.

RESULTS

Structure Analysis

The foundational data is presented in Fig. 2. The articles have been published in 1761 journals. The annual increase in the number of articles is 5.96%. A total of 38,406 authors have penned these articles. The rate of international author collaboration stands at 16.88%. In these articles, 14,485 keywords and 238,127 references have been employed. The average citation per article is 38.22.

In Brain Tumors, the annual numbers of academic articles produced between 1980 and 2022 are presented in Fig. 3. The increase in the number of annual articles is noteworthy. The quantity of articles has continuously escalated, and this surge in volume has particularly intensified since the mid-2000s. The increase taken after the year 2018 is particularly noteworthy.

Countries, Authors, Sources, Documents Analysis

The countries of the authors of the analyzed articles and the number of articles are presented in Fig. 4. Authors from the USA exhibit a distinct superiority. However, the MCP Ratio value for US authors is low. This indicates a lower level of international collaboration among US authors. Chinese authors rank second regarding the number of articles, but their MCP Ratio values are higher. The contribution of Chinese authors to international collaborations is more significant. European countries also contribute considerably to article production, and their MCP Ratio values are high. The h, g, and m-index, TC, NP, and PY-Start values of the top 20 authors are presented in Table 1. The highest h and g-index values belong to Kun LE, followed by

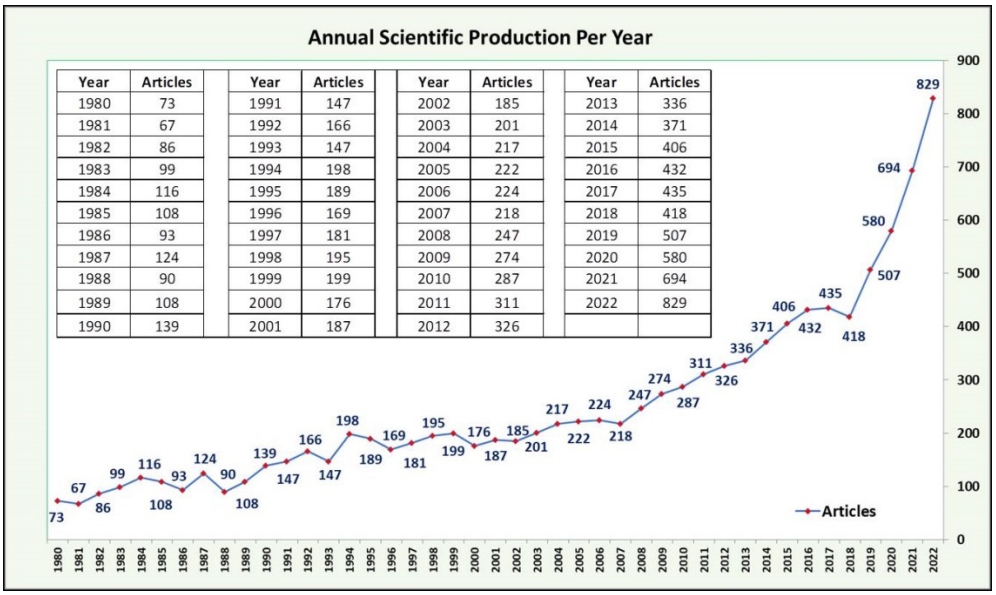
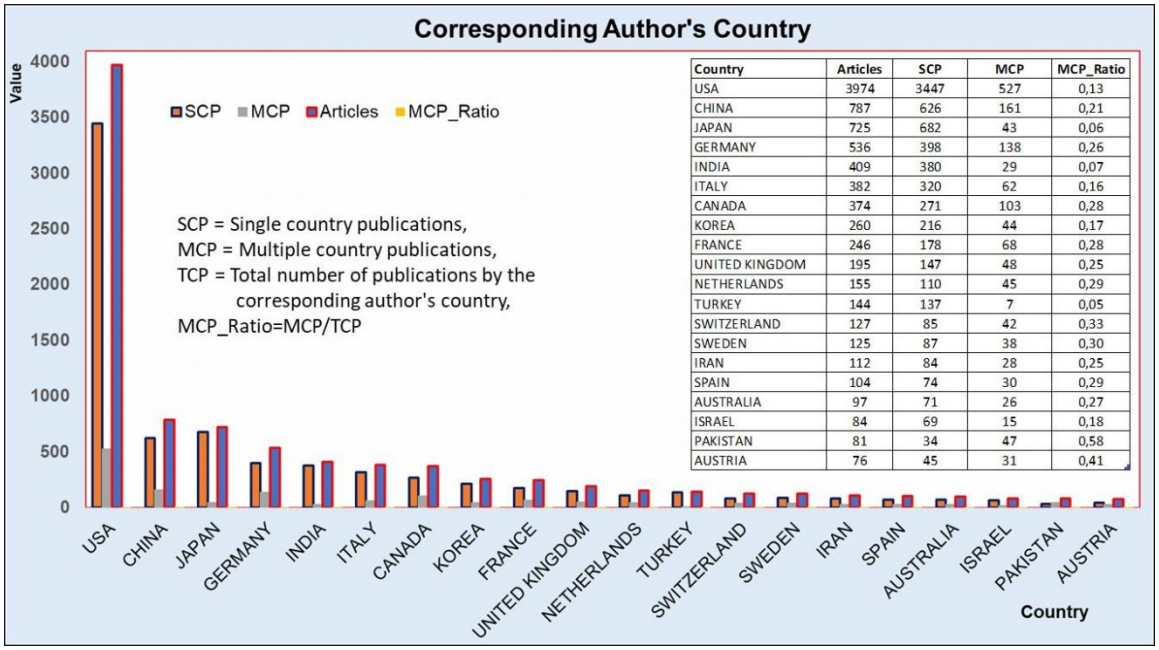


Fig. 3. Annual scientific production per year.



Country	Articles	SCP	MCP	MCP_Ratio
USA	3974	3447	527	0,13
CHINA	787	626	161	0,21
JAPAN	725	682	43	0,06
GERMANY	536	398	138	0,26
INDIA	409	380	29	0,07
ITALY	382	320	62	0,16
CANADA	374	271	103	0,28
KOREA	260	216	44	0,17
FRANCE	246	178	68	0,28
UNITED KINGDOM	195	147	48	0,25
NETHERLANDS	155	110	45	0,29
TURKEY	144	137	7	0,05
SWITZERLAND	127	85	42	0,33
SWEDEN	125	87	38	0,30
IRAN	112	84	28	0,25
SPAIN	104	74	30	0,29
AUSTRALIA	97	71	26	0,27
ISRAEL	84	69	15	0,18
PAKISTAN	81	34	47	0,58
AUSTRIA	76	45	31	0,41

Fig. 4. Corresponding author's country.

Table 1. Author impact

Author	H-index	G-index	M-index	TC	NP	PY-start
Kun LE	38	62	0.927	4402	62	1983
Black PM	36	59	1.059	4472	59	1990
Wen PY	33	44	1.031	3744	44	1992
Gajjar A	31	54	1.069	4914	54	1995
Prados MD	31	43	0.838	2916	43	1987
Berger MS	30	45	0.769	3481	45	1985
Black KL	30	47	0.857	2797	47	1989
Friedman HS	30	50	0.75	3699	50	1984
Packer RJ	30	51	0.833	3573	51	1988
Barth RF	29	39	0.879	2641	39	1991
Bigner DD	29	52	0.659	3173	52	1980
Boyett JM	28	40	0.718	2914	40	1985
Brem H	27	40	0.614	2015	40	1980
Chang SM	27	42	0.931	2428	42	1995
Goldman S	27	48	1	2489	48	1997
Pollack IF	26	40	0.867	2503	40	1994
Sawaya R	26	37	0.634	1905	37	1983
Yung WKA	26	37	0.65	2452	37	1984
Fouladi M	24	36	0.96	2376	36	1999
Merchant TE	24	41	0.923	2100	41	1998

NP=Number of publications, TC=Total citations, PY-start=Publication year starting

Table 2. Source local impact

Source	H-Index	G-Index	M-Index	TC	NP	TC/NP	PY-start
Cancer Research	74	141	1.68	20435	173	118.1	1980
Journal of Neurosurgery	66	100	1.50	13712	273	50.2	1980
Journal of Neuro-oncology	63	93	1.58	18101	589	30.7	1984
Neuro-oncology	63	100	2.63	12601	216	58.3	2000
Journal of Clinical Oncology	61	93	1.49	10537	93	113.3	1983
Neurosurgery	60	98	1.36	11669	206	56.6	1980
Cancer	53	91	1.21	8672	122	71.1	1980
American Journal of Neuroradiology	49	86	1.11	7711	121	63.7	1980
Clinical Cancer Research	44	72	1.52	6769	72	94,0	1995
Journal of Nuclear Medicine	43	78	1.02	6792	78	87.1	1982
ActaNeuropathologica	42	70	0.96	5049	76	66.4	1980
International Journal of Radiation Oncology, Biology, Physics	38	74	0.86	5831	107	54.5	1980
International Journal of Cancer	37	63	0.90	4001	66	60.,6	1983
Radiology	35	52	0.83	5207	52	100.1	1982
Magnetic Resonance in Medicine	34	69	0.92	4819	70	68.8	1987
Plos One	34	52	2.00	3219	104	31.0	2007
Proceedings of the National Academy of Sciences	30	32	0.91	6979	32	218.1	1991
Neurology	29	41	0.71	3549	41	86.6	1983
Childs Nervous System	28	39	0.72	2315	124	18.7	1985
Oncogene	28	37	0.85	2435	37	65.8	1991

NP=Number of publications, TC=Total citations, TC/NP=Citations per paper, PY-start=Publication year starting

Black PM. The author who has reached the highest m-index value is Gajjar A, followed by Black PM and Wen PY.

Table 2 presents the top 20 journals ranked by their H-index values. These journals have collectively published 24.61% of the total articles. The highest h and g-index values belong to Cancer Research. Neuro-Oncology holds the distinction of having the highest m-Index value. Cancer Research also leads in terms of the total number of citations received. The highest TC/NP value source is the Proceedings of the National Academy of Sciences of the United States of America.

The top 20 articles with the highest LC values are presented in Table 3. The most recent publications include Sajjad M, 2019; Deepak S, 2019; and Anaraki AK, 2019. The oldest article is by Libermann TA and is dated 1985. Havaei M, 2017, authors the article with the highest LC value, while the one with the highest GC value is by Singh SK, 2003. The paper by Havaei M, 2017 also stands out for having the highest LC/YYP and GC/YYP values. Regarding the LC/GC Ratio, the article by Anaraki AK, 2019, has emerged as particularly noteworthy.

Authors Keyword Analysis

In Fig. 5, the articles' top 50 most frequently used keywords are presented as a word cloud, and the top 20 are shown in a frequency table. The keyword 'Brain Tumors' is often used so predominantly that it can obscure other keywords in the word cloud.

Therefore, to avoid this overshadowing, 'Brain Tumors' is not displayed in the word cloud. The keywords with the highest frequency among authors are 'Brain tumors,' 'Glioma, ' ' glioblastoma,' and 'Magnetic resonance imaging.' Fig. 6 illustrates the trend of these keywords over the years. Between 1993 and 1995, the keywords 'Autoradiography,' 'Bromodeoxyuridine,' 'Thymidine Kinase,' 'Hyperthermia,' 'Bcnu,' and 'Ganciclovir' were more prevalent, whereas in recent times, terms like 'Brain Tumor Classification,' 'Brain Tumor Detection,' 'Deep Learning,' 'Brain Tumor Segmentation,' 'Classification,' and 'Neuro-Oncology' have gained more prominence.

In the context of medical research, the utilization of specific terminologies peaked in certain years: "Brain Tumors" in 2014, "Glioma" in 2013, "Glioblastoma" in 2016, and "Magnetic Resonance Imaging" in

Table 3. Most local cited documents

Document	YP	LC	LC/YYP	GC	GC/YYP	LC/GC Ratio%
Havaei M, 2017, Med Image Anal	2017	262	43.667	1690	281.667	15.50
Pereira S, 2016, Ieee T Med Imaging	2016	245	35.000	1364	194.857	17.96
MenzeBH, 2015, IeeeT Med Imaging	2015	239	29.875	1846	230.750	12.95
DeangelisLM, 2001, New EnglJMed	2001	141	6.409	1347	61.227	10.47
Bauer S, 2013, PhysMed Biol	2013	140	14.000	527	52.700	26.57
Singh SK, 2003, Cancer Res	2003	135	6.750	3918	195.900	3.45
Zhao XM, 2018, Med Image Anal	2018	122	24.400	440	88.000	27.73
KleihuesP, 1993, Brain Pathol	1993	120	4.000	1371	45.700	8.75
HemmatiHD, 2003, P NatlAcadSciUSA	2003	106	5.300	1429	71.450	7.42
GlantzMJ, 2000, Neurology	2000	96	4.174	544	23.652	17.65
DuffnerPK, 1993, New EnglJ Med	1993	95	3.167	583	19.433	16.30
SajjadM, 2019, JComputSci-Neth	2019	86	21.500	334	83.500	25.75
Deepak S, 2019, ComputBiol Med	2019	85	21.250	381	95.250	22.31
PrastawaM, 2004, Med Image Anal	2004	83	4.368	387	20.368	21.45
ZacharakiEI, 2009, MagnResonMed	2009	81	5.786	491	35.071	16.50
TaphoornMJBb, 2004, Lancet Neurol	2004	77	4.053	488	25.684	15.78
LibermannTA, 1985, Nature	1985	76	2.000	1412	37.158	5.38
GordilloN, 2013, MagnReson Imaging	2013	76	7.600	408	40.800	18.63
AnarakiAK, 2019, BiocybernBiomed Eng	2019	74	18.500	224	56.000	33.04
Calabrese C, 2007, Cancer Cell	2007	73	4.563	1661	103.813	4.39

YP=Year of publication, YYP=Year 2023-year of publication, GC=Global citations, LC=Local citation

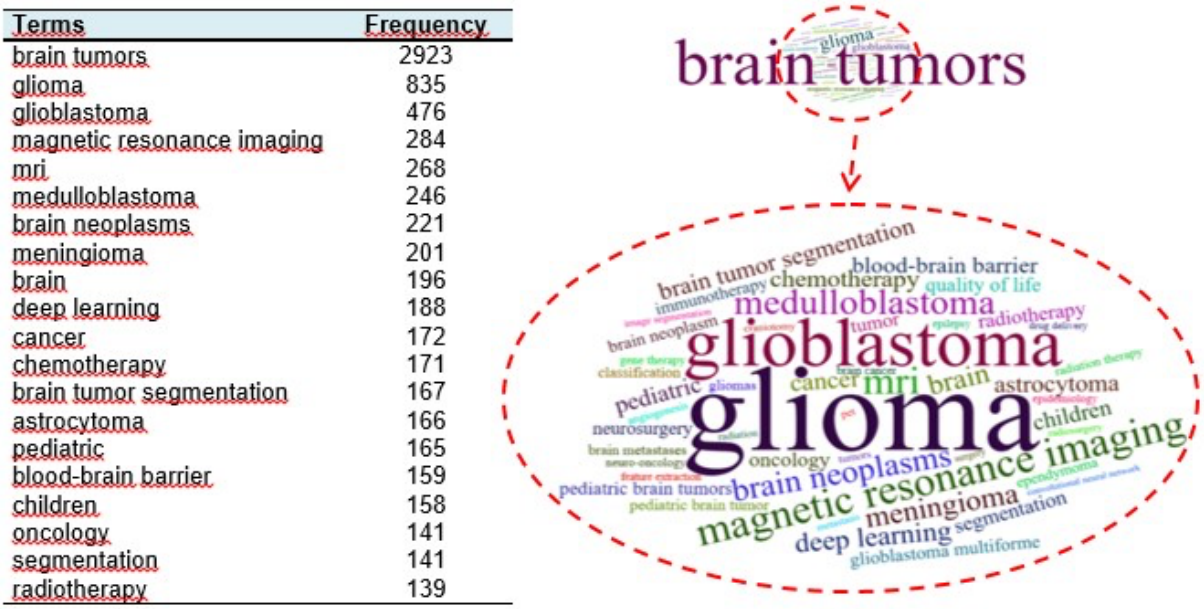


Fig. 5. Word cloud, and frequency table.

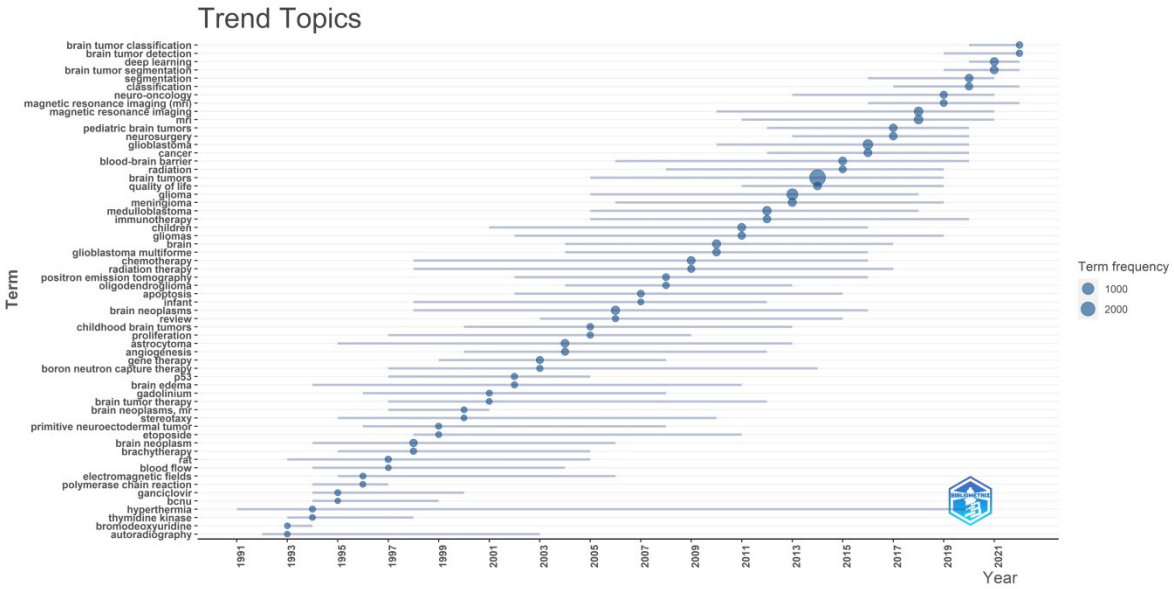


Fig. 6. **Trend topics.**

2018. Fig. 7 presents a co-occurrence network of the top 50 keywords.

These keywords are clustered into three distinct groups. The red cluster represents "Brain Tumors," while the blue cluster indicates "Glioma." The green cluster, however, does not have a dominant keyword. The red cluster can be characterized as "Neuro-Oncology and Brain Tumor Research," the blue as "Brain Tumor Subtypes and Therapies," and the green as "MRI-based Brain Tumor Analysis and Segmentation." The most robust connections within this network are observed between Brain Tumors-Glioma, Brain Tumors-MRI, Brain Tumors-Glioblastoma, Brain Tumors-Pediatric, Glioma-Meningioma, and Glioma-Glioblastoma. The size of the circles in the network graphically represents the frequency of usage of each

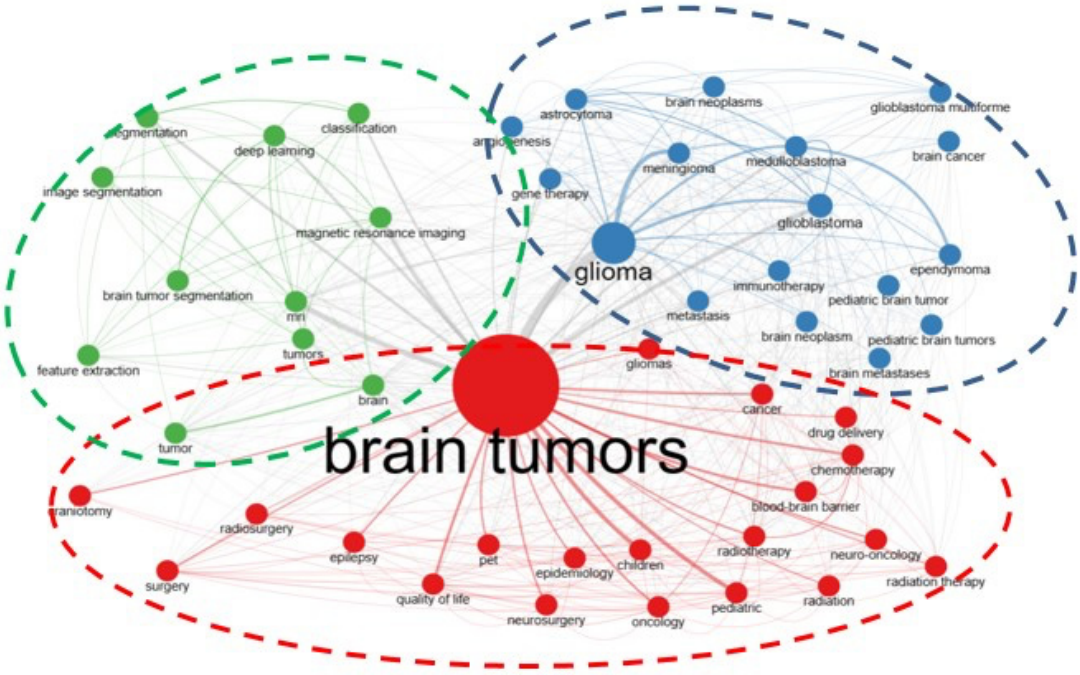


Fig. 7. **Co-occurrence network.**

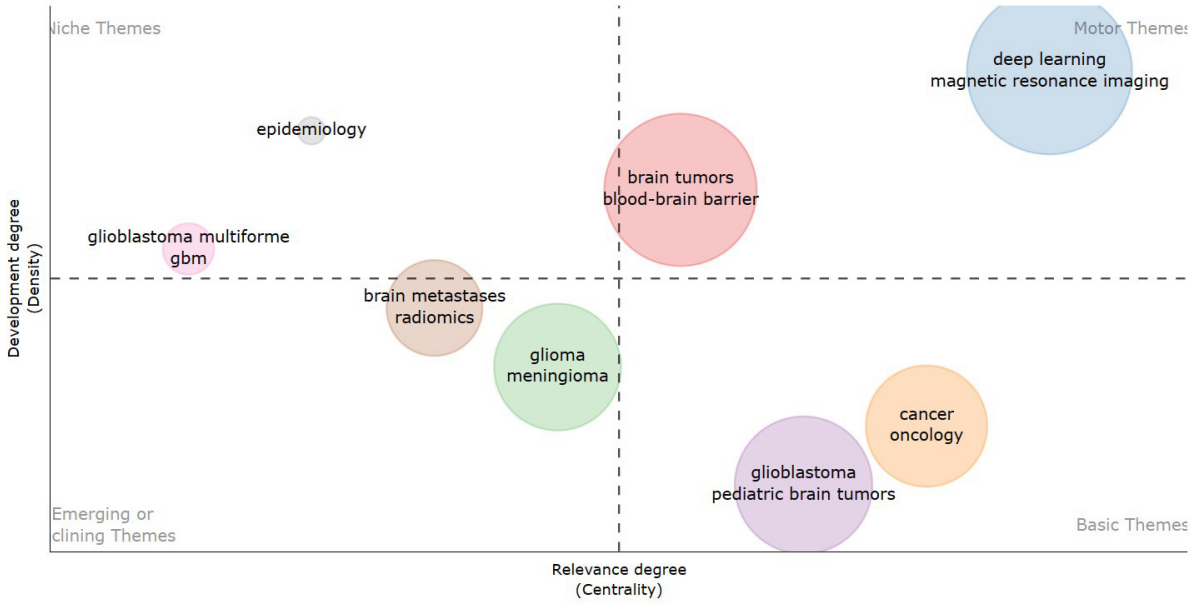


Fig. 8. **Thematic map (2021-2022).**

keyword, while the thickness of the lines connecting these keywords correlates with the frequency of their co-occurrence.

Thematic Analysis

For thematic analysis, the period from 1980 to 2022 has been subdivided into four sub-periods. Thematic maps have been created for these periods. The thematic map covering 2021 and 2022 has been shared (Fig. 8). During 2021-2022, 'Deep Learning' and 'Brain Tumors' formed the motor themes, while 'GlioblastomaMultiforme' and 'Epidemiology' represented the niche themes. Additionally, 'Glioma' and 'Brain Metastases' emerged as emerging themes, with 'Cancer' and 'Glioblastoma' constituting the basic themes.

In addition to Thematic Maps, a four-period Thematic Evolution Mapping has been created to examine the changes and developments of themes over the years (Fig. 9). According to this, during the 2021-2022 period, themes such as Brain Tumors, Glioma, GlioblastomaMultiforme, Deep Learning, Epidemiology, and Cancer Brain Metastases have emerged. The Brain Tumors theme has been informed and enriched

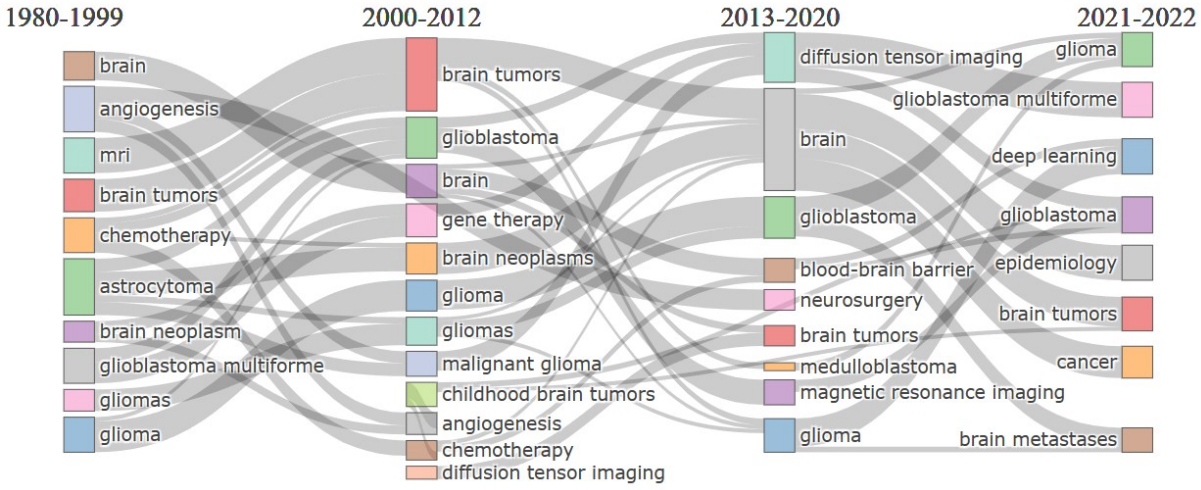


Fig. 9. **Thematic evolution map (1980–2022).**

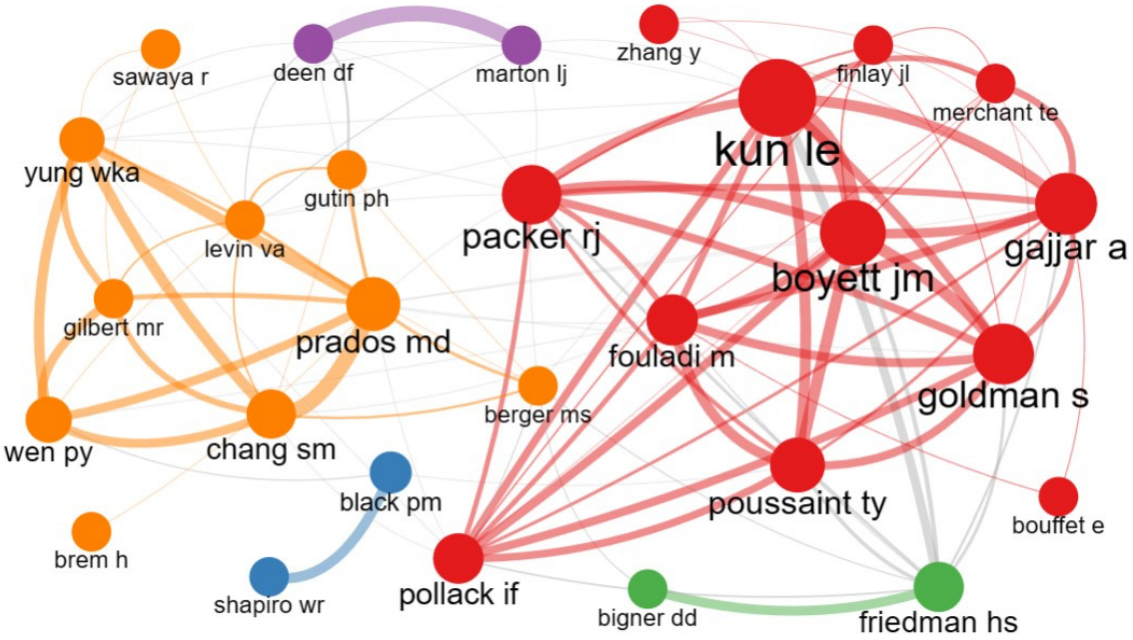


Fig. 10. **Authors collaboration network.**

by sub-themes, including Brain, Childhood, and Brain Tumors.

Collaboration Network

The authors' collaboration network is depicted in Fig. 10.

Each circle in the figure represents an author. It is observed that the authors are grouped into five clusters. The cluster with the highest number of authors, containing 12, is the red cluster. Kun LE is the author with the most collaborations. Following Kun LE, the authors with the most collaborations are Boyett JM,

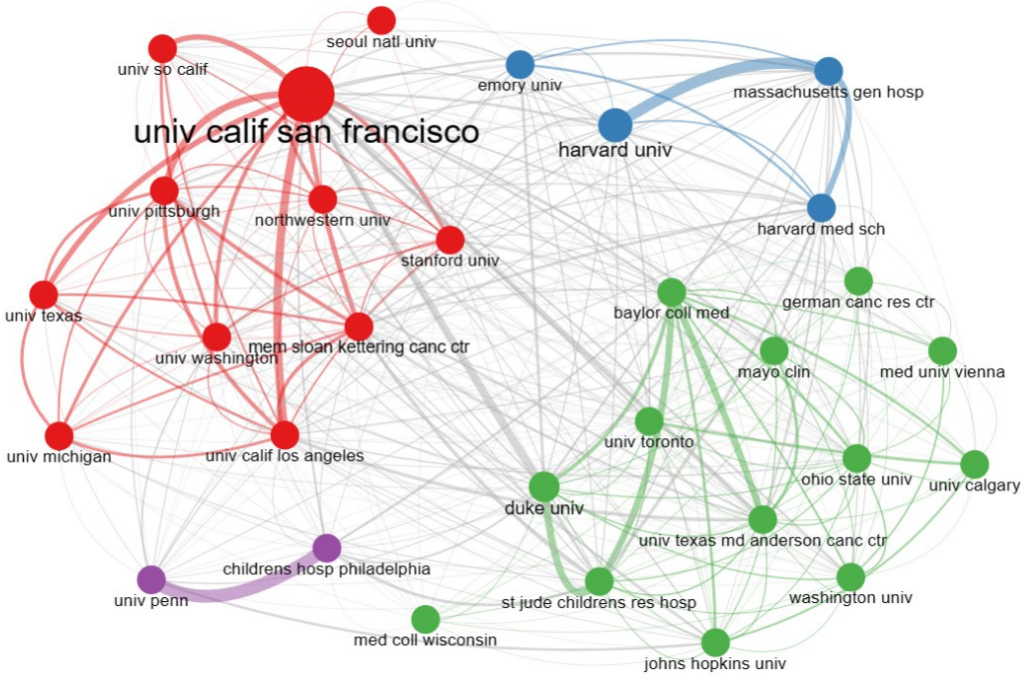


Fig. 11. **Institutions collaboration network.**

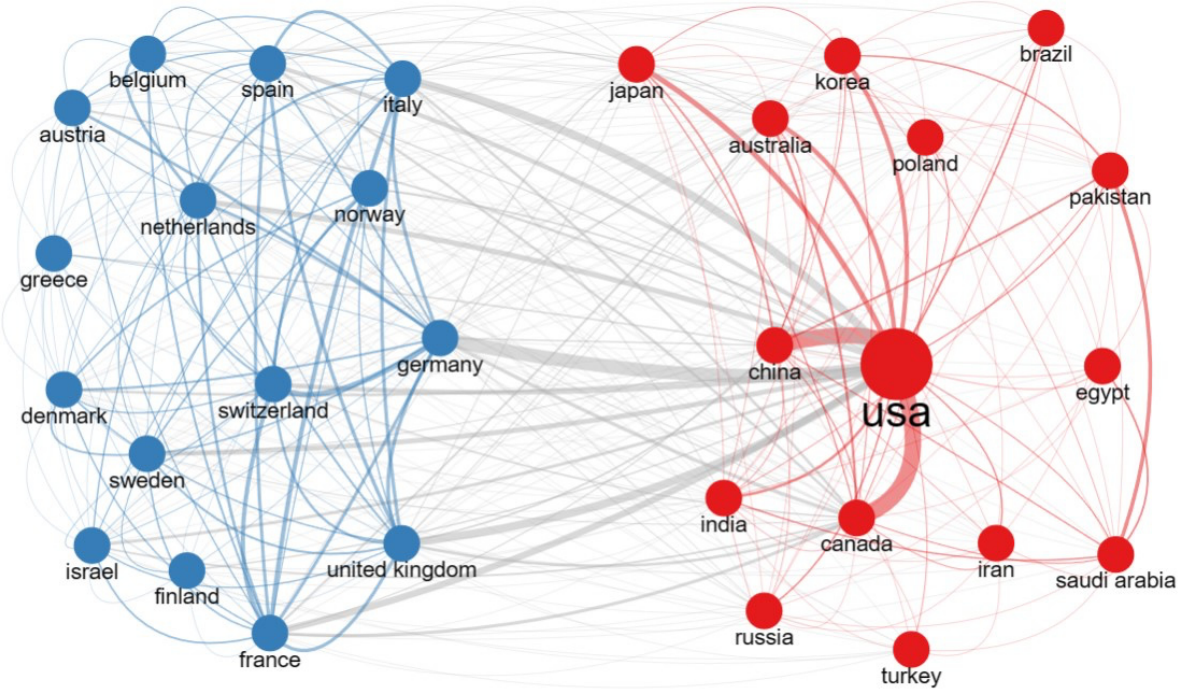


Fig. 12. Countries collaboration network

Packer RJ, and Gajjar A. The Institutions Collaboration Network is shown in Fig. 11.

The top 30 institutions were considered, and the Louvain Algorithm was used. The institutions have formed four clusters. Institutions within the same color clusters collaborate in publishing articles. The institution with the most collaborations is the University of California San Francisco, followed by Harvard Univ. As indicated by the thickness of the lines, the institutional pairs with the most collaborations are Univ Penn – Children Hosp Philadelphia, Harvard Univ – Massachusetts Gen Hosp, and Baylor Coll Med – ST Jude Children Res Hosp. The results of the Countries Collaboration Network are presented in Fig. 12.

The top 30 countries were considered, and the Louvain Algorithm was used. Two clusters have formed. The red cluster includes 15 countries, while the blue cluster includes 5. The red cluster is more centralized and centered around the USA's collaboration. The countries with the most collaborations are USA - Canada, USA - China, and USA - Germany.

DISCUSSION

Science mapping is the process of analyzing and visualizing a scientific subject. This analysis and visualization can encompass scientific studies, articles, and other academic resources. Through this technique, the main and sub-topics in a broad research field, the interrelationships and trends among them, and significant developments and connections can be discerned. Methods such as text mining and data visualization are encompassed within the scope of science mapping. Bibliometric analysis examines the literature macroscopically and presents a projection. Therefore, those wishing to track the scientific outputs in a research field and their developmental process prefer this analysis method [5].

Eugene Garfield has made significant contributions to the field of scientometrics. He is one of the most pivotal figures in the field of scientometry. Garfield laid the foundation that led to the WoS, today one of the most crucial platforms for citation and analytical information searching. It serves not only as an academic library but also as a rich dataset. WoS encompasses innumerable citation links and metadata, expanding daily. WoS is a comprehensive and international bibliographic database, making it the most efficacious bibliographic data source for conducting bibliometric and similar analyses [6]. Our use of the Web of Science (WoS) in our analyses is significant

for these reasons. Consequently, our data are highly reliable.

The Bibliometrix program was used for the analysis of the data. This program is an open-source software developed on R-based science mapping. The R programming language originated in the 1990s and has become a fundamental computational tool for research in various fields, from statistics to medicine. One of its key features is facilitating learning through producing meaningful graphics [7, 8]. In our study, we have utilized this program feature to visualize the topic of brain tumors with rich graphics.

Our study's analyses of countries, authors, sources, and documents have been based on the h, g, and m indices. The h (Hirsch) index reflects a scenario where an author has at least an "h" number of papers, each receiving at least "h" citations. The h-index analyzes a researcher's cumulative scientific impact. It examines a researcher's productivity and citations and measures it as a single number. It is a reliable and robust indicator of scientific success. In addition to individual assessments, medical journals, publishers, institutions, and universities can also be evaluated with the h-index [9]. The G index aims to represent the distribution of citations better. The G-index has been developed to measure global citation performance more accurately. Its advantage is that it highlights articles that receive numerous citations. Therefore, more weight is given to highly cited articles [10]. The m-index is a version of the h-index. The h-index increases with the length of a career. The m-index has been developed to facilitate comparisons among academics with varying lengths of academic careers. In comparing researchers with varying lengths of careers, this can be utilized to mitigate the effects of time [9].

This study presents detailed statistical information on articles related to brain tumors. Within this scope, 1,761 sources, 10,777 documents, and 38,406 authors have been examined. The number of single-authored documents is 409. The frequency of international co-authorship is approximately 17%, while the co-author per document is 6.21. The average age of documents is around 15%, and the average citations per document are 38.22.

It has been determined that studies on brain tumors have increased steadily over the years. This is supported by the advancements recorded in the medical field. However, it is noteworthy that there has been a significant increase in the annual number of articles published after 2018. Undoubtedly, this increase is influenced by the classification of central nervous system tumors by the World Health Organization in 2021 [11] and the inclusion of some new tumors in this classification [12]. Similarly, the role of immunotherapy studies and bioinformatics in this increase is notable [1]. In recent years, studies related to technologies such as deep learning and machine learning, which have become widespread in the medical field, also have a significant share in this increase [13, 14].

The highest h and g-index values belong to Kun LE and Black PM, respectively. The highest m-index value belongs to Gajjar A. Professor Larry E. Kun, after an extensive and fruitful career in the field of radiation oncology, passed away in 2018. He served in significant institutions such as the American Society for Radiation Oncology, the American Board of Radiology, and research hospitals. Professor Peter M. Black is a neurosurgeon. He is engaged in the field of neurosurgery at Brigham and Women's and Children's Hospital and Harvard Medical School. He is a member of the Congress of Neurological Surgeons and the World Federation of Neurosurgical Societies. Professor Amar Gajjar is affiliated with St. Jude Children's Research Hospital. He was honored with the Scott and Tracie Hamilton Endowed Chair in Brain Tumor Research.

The most effective journal is Cancer Research, published by the American Association for Cancer Research. Its impact factor is 11.3. It is indexed in numerous databases. Its TC/NP (Total Cites/Number of Papers) value is also very high. Regarding h-index and g-index values, the second journal is the Journal of Neurosurgery, the official publication of the American Association of Neurological Surgeons. Its impact factor is 4.1. The highest m-index value belongs to Neuro-Oncology, the official publication of the Neuro-Oncology Society. It is also affiliated with the Japan Neuro-Oncology Society and the European Neuro-Oncology Society. Its impact factor is 15.9.

The article by Havaei M, 2017 [15] holds the highest LC value, while the highest GC value belongs to the article by Singh SK, 2003 [16]. Both articles discuss significant developments relevant to their respective years of publication. The subject of Havaei M, 2017 is glioblastomas, specifically related to a brain tumor segmentation method based on deep neural net-

works. Deep neural networks are among the most significant applications of artificial intelligence in our daily lives [17]. This study is particularly programmed with the deep neural network machine learning method adapted for image data [15]. The article by Singh SK, 2003 reports identifying and purifying a cancer stem cell from human brain tumors of different phenotypes. The stem cell was isolated by expressing the surface marker CD133. Stem cells are used in researching tumor development and treatments.

The article with the highest LC value belongs to Havaei M, 2017 [15], while the one with the highest GC value is attributed to Singh SK, 2003 [16]. Both articles discuss significant advancements relevant to their respective years of publication. The work by Havaei M in 2017 relates to a brain tumor segmentation method based on deep neural networks adapted for glioblastomas. Deep neural networks represent one of the most significant applications of artificial intelligence in our daily lives [17]. In the study, deep neural networks tailored explicitly for image data have been programmed using machine learning methods [15]. The article by Singh SK in 2003 reports identifying and purifying a cancer stem cell from human brain tumors of various phenotypes. The stem cell was isolated by expressing the surface marker CD133. The isolation of this stem cell is pivotal in researching tumor development and treatments.

The most frequently used keywords drawing significant attention include glioma, glioblastoma, magnetic resonance imaging, medulloblastoma, and deep learning. The most common primary brain tumor originates from glial cells, known as Glioma [18]. Glioblastoma, a type of glioma, is the most common and aggressive malignant brain tumor [18]. In recent years, studies have increased, particularly on Gliomas and Glioblastomas. Immunotherapy, encompassing methods like cancer vaccines, oncolytic viruses, and immune checkpoint inhibitors, has recently become a significant option in Glioblastoma treatment [19]. Medulloblastoma is the most common embryonal tumor of the central nervous system in childhood [20]. There have been advancements in its treatment in recent years. Multimodal treatment and appropriate risk stratification have increased long-term survival rates across all ages [20]. Deep learning, a branch of artificial intelligence, is one of today's fundamental technologies based on artificial neural networks [21]. It is rapidly becoming widespread in healthcare services, especially visual recognition [21]. Numerous studies have been conducted on using this technology for diagnosing brain tumors [22-24]. According to the trend topics analysis results, the frequently used keywords mentioned above have become trend topics in recent years. In addition, 'brain tumor classification' has also emerged as a trending topic in recent years. This may be due to the Classification of Tumors of the Central Nervous System study conducted by the WHO in 2021. Numerous articles related to the study have been published in recent years [25-27].

In the thematic map derived from recent studies, the dominant themes are deep learning, magnetic resonance imaging, brain tumors, and the blood-brain barrier. Deep learning is used in magnetic resonance imaging to detect brain tumors at an early stage [22-24]. The blood-brain barrier poses a challenge in delivering therapeutics to the brain and tumor, with some brain tumors producing a blood-tumor-barrier [28]. Research to overcome these barriers to enhance the effects of anti-cancer treatments has become popular in recent years [29-30].

Upon examining thematic maps from all periods, it is assessed that the likely topics and scopes of future research on brain tumors will be biomarkers, personalized treatments, artificial intelligence, immunotherapy, and pediatric brain tumors.

Limitations

This bibliometric analysis of brain tumor research over four decades has notable limitations. Its dependence on bibliographic databases can lead to selection biases, excluding non-indexed and grey literature that might contain important contributions. While citation metrics indicate academic influence, they don't capture the clinical relevance of research. Additionally, evolving terminologies and indexing standards may complicate keyword normalization. However, the study's strength lies in its methodological rigor and visualization of thematic trends. Future research should consider alternative impact indicators, use machine learning for semantic analysis, and include diverse scholarly contributions. The Bibliometrics program may make mistakes in the analysis of some expressions. In our study, the expressions "magnetic resonance imaging" and "mri" were evaluated as two different concepts.

CONCLUSION

In conclusion, this bibliometric analysis of brain tumor research over the past four decades represents a seminal contribution to the scientific understanding of global research trends, intellectual structure, and emerging thematic frontiers within the field. Through the rigorous application of science mapping methodologies, this study unveils pivotal shifts in research foci, influential scholarly networks, and the evolution of key conceptual frameworks that have shaped contemporary neuro-oncology. The originality of this work lies in its comprehensive synthesis of an extensive body of literature, offering an unprecedented panoramic view of scientific progress while identifying critical knowledge gaps and future research trajectories. By illuminating the intricate interplay between innovation, collaboration, and knowledge dissemination, this study not only advances bibliometric scholarship but also provides an indispensable reference for researchers, policymakers, and funding bodies seeking to optimize research strategies in the relentless pursuit of breakthroughs in brain tumor diagnosis, treatment, and patient outcomes.

Ethical Statement

Ethical approval is not required for this study. There are no human or animal elements in our study. Obtained from open sources on the internet.

Authors' Contribution

Study Conception: TK; Study Design: TK; Supervision: TK; Funding: TK; Materials: TK; Data Collection and/or Processing: TK; Statistical Analysis and/or Data Interpretation: TK; Literature Review: TK; Manuscript Preparation: TK and Critical Review: TK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2025;11(3):654-660 Review

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A clinical perspective towards oropharyngeal dysphagia management in neurological conditions: a brief literature review

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ABSTRACT

Dysphagia is a condition affecting the passage of solid and liquid food into the stomach due to impaired swallowing mechanisms caused by neurological factors like stroke, progressive diseases, and brain injury. Symptoms usually manifest within seconds of swallowing. In this brief review, the clinical perspective towards oropharyngeal dysphagia management from a speech and language therapist's point of view in neurological conditions will be outlined. This review was carried out by a brief literature screening. This review includes swallowing performance assessment and oropharyngeal dysphagia therapy techniques. Instrumental evaluation techiques were typically used to determine dysphagia presence in the clinical settings. Based on the findings of instrumental evaluation, clinicians must decide the therapy plan. In dysphagia, treatments contain behavioral interventions, central nervous system stimulation, and postural techniques. Behavioral therapy approaches include maneuvers, swallowing exercises, and postural techniques. Electrical stimulation approaches, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), improve the brain's ability to change and adapt, known as neural plasticity. In conlusion, the significance of evidence-based treatment in swallowing therapies is essential to enhance the comprehension of dysphagia therapy efficacy, particularly through randomized controlled trials.

Keywords: Neurogenic dysphagia, swallowing, behavioral therapy, speech and language therapy

Swallowing is a result of the complex operation of the oral, pharyngeal, and esophageal structures [1]. Consequently, it facilitates the passage of solid and liquid food into the stomach. Dysphagia is linked to a higher likelihood of malnutrition and pneumonia, and results in longer hospitalization, unfavorable prognosis, and mortality [2]. Swallowing mechanisms could be impaired by various neurological factors such as stroke, progressive neurological diseases, and acquired brain injury [3]. Additionally, a normal swallowing mechanism could be negatively affected by other ethiologies and known as anatomical disorders [4], esophageal dysphagia [5], rheumatological disorders [6] and dysphagia and medication-induced dysphagia [7]. Dysphagia is a prevalent and perilous symptom associated with numerous neurological disorders. In this patient group, dysphagia is correlated with a considerably prolonged duration of

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mechanical ventilation and an extended requirement for artificial nourishment. Neurogenic dysphagia significantly increases the risk of pneumonia, the primary cause of mortality in these patients [8]. Moreover, swallowing problems in these patients correlate with diminished quality of life, inadequate pharmacological efficacy, and malnutrition [9]. 20-30% of dementia patients experience severe dysphagia accompanied by silent aspiration, which often remains unrecognized by the individuals themselves [10]. Swallowing difficulties escalate with the advancement of cognitive decline [11].When negatively affected by these conditions, the preceding result is named as dysphagia. Dysphagia, a multidimensional condition that results from a variety of etiological factors, has the potential to disrupt swallowing function, thereby presenting individuals with nutritional challenges. Oropharyngeal dysphagia is characterized by difficulty in starting the swallowing process and the impeded movement of food from the oral cavity to the esophagus. The patients frequently report drooling, coughing, nasal regurgitation, aspiration, or choking, and symptoms of oropharyngeal dysphagia typically manifest within seconds of swallowing [12].

The evaluation and diagnostic methods used to assess dysphagia are subject to variation and are typically determined by the patient's reported symptoms and risk factors. Instrumental evaluations are gold standart evaluations that are employed to ascertain the etiology of dysphagia. Modified barium swallow study (MBSS) and fiberoptic endoscopic evaluation of swallowing (FEES) are procedures that are most frequently employed in the clinic to diagnose the patients with dysphagia [13-15].

After the dysphagia diagnosis, the severity of the dysphagia should be determined and therapy procedure should commence promptly. Thus, the patient's quality of life is increased. Therapies for oropharyngeal dysphagia include behavioural interventions and central nervous system stimulation [16,17]. Behavioral interventions for oropharyngeal dysphagia include motor behavioral techniques, oromotor exercises, adjustments to body and head posture, swallowing maneuvers to improve food movement and protect the airway, sensory and neuromuscular electrical stimulation, and modifying the consistency of the food bolus. In addition to these approaches, Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are employed to activate the central nervous system and address dysphagia [18, 19].

The present research reviews the current therapy and intervention options for oropharyngeal dysphagia induced by neurological disorders such as stroke, traumatic brain injury, and dementia.

This brief review was carried out by screening the dysphagia and dysphagia management in the literature.

BEHAVIORAL THERAPY APPROACHES

While dealing with oropharyngeal dysphagia, clinicians use maneuvers, swallowing exercises and postural techniques to either rehabilitate the dysphagic patients or redirect the movement of bolus in the oropharyngeal cavities.

Swallowing Therapy Techniques

Effortful swallowing, Mendelsohn, supraglottic swallow and super-supraglottic swallow maneuvers are the most commonly used techniques in the clinical settings. Effortful swallowing maneuver increases the supraglottic pressure and improve base of tongue retraction in the patients [20]. The patient executes swallowing by forcefully pressing the tongue on the hard palate, propelling it posteriorly while engaging the neck muscles. This technique is useful in the patients with decreased submental muscles. Effortful swallowing is also thought to increase laryngeal vestibule movement and UES opening [21]. Mendelsohn maneuver is one the most effective techniques used in the patients with oropharyngeal dysphagia to prevent bolus from falling into the airway thus protecting the patients from choking and premature falling [22]. The patient is expected to consciously control the elevation of the larynx to the greatest extent possible during swallowing. The patient is instructed to elevate the larynx as high as possible for 2-3 seconds. However, it is fairly a difficult technique in the patients with impaired cognitive abilities and motor functions. Both in supraglottic swallow and super-supraglottic maneuvers, it is aimed that the patients protect their airway by holding their breath voluntarily before and during a swallow. After a successful swallow, the patients are asked to form a cough to clear any bolus residue left in the supraglottis [23].

Swallowing Therapy Maneuvers

In addition to swallowing maneuvers, swallowing exercises are utilized by healthcare professionals to rehabilitate the patients. Laryngeal elevation, Masako, Shaker exercises and resistive lingual isometric exercises are included in these exercises. In laryngeal elevation, speech and language therapist wants the patient to produce a prolonged high pitch /i/ sound so that the patient can elevate their larynx and get used to contol it in the elevated position. Then, the patient does laryngeal elevation exercises to raise and sustain the larynx in a heightened posture. This enables the patient to protect airway from any bolus getting in the larynx. Swallowing physiology can be improved using this technique [24]. Masako or tongue hold is another exercise which is used in the patients with dysphagia. With the speech and language therapist's instructions, the patient protrudes the tongue anteriorly between the teeth during the process of swallowing and makes a voluntary swallow. Masako is performed without any bolus presence in the oral cavity. The purpose of this is to enhance the mobility and strength of the posterior pharyngeal wall during the process of swallowing [25]. One of the most important swallowing exercises used in the clinical setting is Shaker exercise. This exercise could be performed both dynamically and statically by the patients. In dynamic type, the patient lies on a horizontal plane. They lie without any support for their necks. They elevate their head to look at their toes by using their neck muscles and thereafter drop their head without pausing to view the toes. In static type, The patient is positioned on a horizontal surface. They lay down without any neck support. They raise their head to observe their toes by engaging their neck muscles and are instructed to maintain this position for a minimum of one minute. The Shaker exercise involves the contraction of the thyrohyoid, mylohyoid, geniohyoid, and anterior belly of diagastric muscles, which causes the hyolaryngeal structures to move upward and forward. The Shaker exercise effectively decreases the occurrence of postswallow aspiration by prolonging UES opening and strengthening muscles that pull the larynx and hyoid up and forward [26]. Last but not least, resistive lingual isometric exercises are used as a treatment to enhance reduced tongue pressure strength and endurance in the patients suffering from oropharyngeal dysphagia since tongue is crucial for the process of swallowing due to its complex muscular structure, which enables rapid and flexible movements during oral activities [27]. Isometric exercises include generating resistance with the tongue, which remains stationary or moves minimally.

Swallowing Therapy Postural Techniques

In oropharyngeal dysphagia management, postural techniques are used. They the mobility of the bolus in the mouth and pharynx and change the size of it. Postural treatments are also suitable for the patients with neurological problems. Postural adjustment can aid in the rehabilitation of the patients with dysphagia by influencing the movement of food bolus to enhance the speed and safety of swallowing through the closing of airways to prevent the inhalation of foreign substances [28]. Chin-down posture, chin-up posture, head rotation, head tilt are the postural techniques used in dysphagia management. In chin-down posture, the chin is brought down towards the neck, which can result in the tongue base moving closer to the back wall of the throat, narrowing the passage to the airway, and expanding the space in the vallecular region during swallowing [29] while chin is elevated, which may aid in the passage of the bolus from the mouth in chin-up posture [30]. The act of maintaining a chin-up posture has the potential to enhance the movement of food bolus through the mouth cavity which could lessen oral residue. Head rotation and head tilt are used to make sure bolus stays in the stronger side of the pharynx by turning the head [31]. This will also limit the amount of bolus residue in the weakened lateral for the patient.

ELECTRICAL STIMULATION APPROACHES

Traditional oropharyngeal dysphagia management is written above. This part will deal with techniques which stimulates patients' central and peripheral nervous system. In recent times, there has been a growing body of research focusing on alternative interventions that try to improve the brain's ability to change and adapt, known as neural plasticity, through the use of non-invasive brain stimulation (NIBS) techniques [32-34] . There are two types of NIBS method. Repetitive transcranial magnetic stimulation (rTMS) and tran-

scranial direct current stimulation (tDCS) are non-invasive brain stimulation (NIBS) treatments that are applied to the cortex or core areas of the brain. NIBS treatment enhances cortical plasticity through direct stimulation of the cortex. rTMS utilizes electromagnetic induction to induce depolarization of post-synaptic connections [35], while tDCS employs direct electrical current to alter the polarity of nerve cells. Generally, rTMS can be categorized into two primary treatment regimens based on the frequency of stimulation: low frequency (≤ 1 Hz) and high frequency (> 1 Hz). Low frequency repetitive transcranial magnetic stimulation (LF-rTMS) suppresses the level of cortical excitability, whereas high frequency repetitive transcranial magnetic stimulation (HF-rTMS) enhances the level of cortical excitability [36]. rTMS can hinder the development of harmful changes in the brain's cortex, enhance beneficial changes in brain activity, and facilitate the restoration of neurological function following a stroke [37]. rTMS has a positive impact on the ability to swallow in those suffering from dysphagia following a stroke. Nevertheless, other elements can impact the effectiveness, including the frequency and location of stimulation. Additional investigation into the mechanism of rTMS and the determination of appropriate parameters will be crucial for the advancement of this innovative intervention in the clinical practice [18]. tDCS, a type of non-invasive brain stimulation, has been found to enhance motor performance following a stroke [38]. This will help the patients with weakened motor functions. tDCS alters the level of cortical excitability in a manner that depends on the polarity. Anodal transcranial direct current stimulation (tDCS) enhances cortical excitability by depolarizing the resting membrane potential, while cathodal tDCS reduces cortical excitability by hyperpolarizing the resting membrane potential [39].

On the other hand, treatments such as pharyngeal electrical stimulation (PES) and neuromuscular electrical stimulation (NMES) specifically focus on the peripheral neuronal pathways by using electrical stimulation. NMES, or neuromuscular electrical stimulation, is a technique that enhances the force of muscle contractions during the process of swallowing. It achieves this by applying electrical stimulation to the anterior neck muscles through electrodes implanted on the skin [40]. NMES is a conventional therapeutic approach for dysphagia. Additionally, NMES is a conventional therapy for dysphagia. The long-term therapeutic benefits of NMES (2-4 weeks) can enhance swallowing function by strengthening the muscles involved in swallowing, rehabilitating the reflex responsible for swallowing, and controlling the excitability of the cerebral cortex [2]. Moreover, NMES can amplify the sensory input in the oral pharyngeal area and improve the responsiveness of muscle contraction [41]. NMES has prompt effects on the onset of swallowing without elevating the likelihood of unfavorable incidents [42]. This stimulation activates sensory pathways in the body. Lastly, PES is an innovative therapy for oropharyngeal dysphagia caused by neurological factors like stroke [43]. It has been demonstrated that PES stimulates neuroplasticity in the pharyngeal motor cortex by directly stimulating the pharyngeal mucosa using intraluminal catheters [44]. PES stimulates the sensory feedback pathways that are essential for ensuring the safety and efficiency of swallowing. Having been implemented, it leads to a higher occurrence of voluntary swallowing and improved management of pharyngeal secretions. Evidence demonstrates that PES is a secure and effective therapeutic approach for managing dysphagia in individuals suffering from stroke and brain injury [45-47].

The techniques utilized in swallowing difficulties differ based on the specific symptoms reported. Not all techniques employed in swallowing therapy are behavioral therapies. Alongside behavioral therapy techniques, video-based feedback methods that enhance the patient's awareness of their swallowing and electrical stimulation approaches are also employed. It would be inappropriate to consider the approaches employed in swallowing therapy in isolation or separately. Diverse therapeutic modalities should be employed concurrently based on the patient's condition to maximize the outcome [48-50].

CONCLUSION

This study examines the existing treatment and intervention choices for oropharyngeal dysphagia caused by neurological conditions. Oropharyngeal dysphagia management is sustained using both behavioral therapy approaches and technological instruments, most

of which are still yet to be clinically proven effective. However, a standart dysphagia therapy protocol has not yet been established. Implementing a dysphagia therapy procedure seems to be quite vital. Therapy procedures could be fully maintained if only dysphagia could be handled by means of an interdisciplinary approach. In this approach, speech and language therapists play a very importan role in rehabilitation process of the dysphagic patients. Both before and during therapies, each dysphagia therapy team member has to be aware of the importance of patient safety to avoid any unnecessary mistakes which could endanger the patients' health. To further understand the efficacy of dysphagia therapies, especially research involving randomized controlled trials is needed, and evidence-based treatment in swallowing therapies is really important.

Ethical Statement

Ethical approval is not required for this study. There are no human or animal elements in our study. This review was carried out by a brief literature screening.

Authors' Contribution

Study Conception: ST, FSK, NÇ; Study Design: ST, FSK, NÇ; Supervision: ST, FSK, NÇ; Funding: ST, FSK, NÇ; Materials: ST, FSK, NÇ; Data Collection and/or Processing: ST, FSK, NÇ; Statistical Analysis and/or Data Interpretation: ST, FSK, NÇ; Literature Review: ST, FSK, NÇ; Manuscript Preparation: ST, FSK, NÇ and Critical Review: ST, FSK, NÇ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2025;11(3):661-665 Case Report

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A rare case of bilateral Preiser's disease originating from the distal pole of the scaphoid

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ABSTRACT

The scaphoid bone – os naviculare manus – is an important bone in that it is located within the proximal row of carpal bones and articulates with both the radius and other carpal bones. Preiser's disease is a rare entity and is commonly associated with avascular necrosis of the scaphoid without fracture or trauma. This case study describes a 55-year-old female patient who visited our outpatient clinic complaining of five months' worth of pain and swelling on both of her wrists. The patient had no history of trauma or prolonged steroid use. The patient had pain around the thenar region and anatomical snuff box on both wrists. On a 2-directional wrist radiograph, the distal part of the scaphoid bone showed signs of subchondral sclerosis. Magnetic Resonance Imaging (MRI) was performed to verify the diagnosis. MRI of the patient's wrist revealed bone edema at the distal pole of the scaphoid which was associated with Preiser's disease. In this case study, we present a patient who had bilateral Preiser's illness that began at the distal pole.

Keywords: Preiser's disease, non-traumatic, bilateral, scaphoid edema, distal pole

Preiser's disease is a rare condition and is commonly associated with avascular necrosis of the scaphoid and repetitive microtraumas are thought to play a role in its pathophysiology [1]. In 1910, Preiser described a ''rarefying osteitis'' of the scaphoid in a series of 5 cases. He thought that the cause of this condition was an interruption of the scaphoid blood supply at the scaphotrapezial area, which led to central rarefaction, and the fractures were probably secondary [2]. According to radiography and Computerised Tomography (CT) scan pictures, Herbert and Lanzetta [3] classified patients in 1994. Later, Moran [4] *et al*. added signals from MRI images to this categorization, further developing it.

Extrinsic factors such as corticosteroid therapy, alcoholism, trauma, and repetitive microtrauma along with intrinsic factors like genetics are believed to contribute to the pathogenesis of Preiser's disease, affecting the coagulation and fibrinolysis processes leading to ischemia and consequently a bone infarct [5]. Restoring the wrist joint range of motion, reducing pain, and delaying the onset of arthritis are the main goals of treatment.

Pain in the radial compartment of the wrist, swelling, and decreased range of motion are always present in Preiser's disease [1, 5]. An early diagnosis is challenging with radiographs. Therefore when a diagnosis is suspected, an MRI is performed [5, 6].

When a section of the proximal pole of the scaphoid and the adjacent subchondral bone separates,

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Fig. 1. **Radiographs show bone edema in the distal pole of both scaphoids. Anteroposterior (A) and lateral (B) view.**

it is referred to as scaphoid osteochondritis. This condition only affects the proximal pole and is never seen in the distal portion of the bone [7].

CASE PRESENTATION

A 55-year-old right-handed female primary school teacher complained of pain that had been present for 5 months in the thenar region of both wrists. The patient did not have any mechanical stress, systemic disease, or trauma history.

Clinically, the patient's range of motion was normal but painful, and there was local tenderness over the thenar region bilaterally. Finkelstein's test was negative and there were no physical examination findings supporting de Quervain's tenosynovitis.

At the same time, Tinel sign and Phalen's test were evaluated as negative bilaterally. No findings supporting median nerve entrapment were found in the Electromyography (EMG) study. Watson test, also called the scaphoid shift test, a test for assessing the dynamic stability of the scapholunate ligament was evaluated as negative.

Clinically, the patient had tenderness over the anatomical snuff box on both wrists. Bone edema at

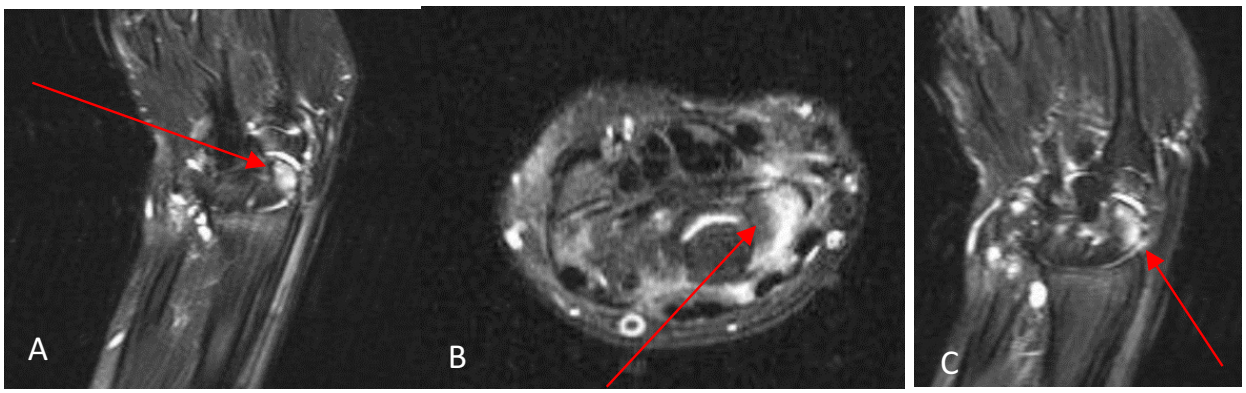

Fig. 2. **MRI Sections showing effusion at the intercarpal joint (A) and bone edema (B, C) in the distal scaphoid of the right wrist shown with arrows.**

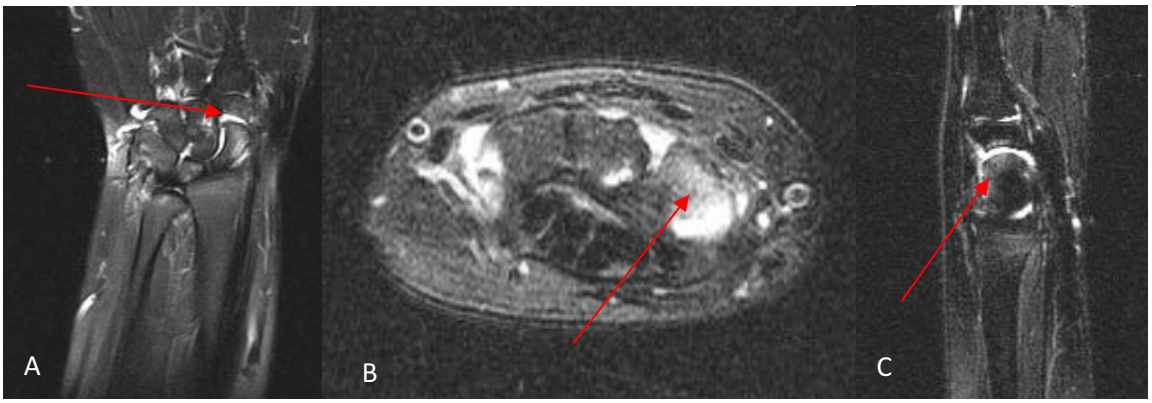

Fig. 3. MRI sections demonstrating effusion in the intercarpal joint (A) and bone edema (B, C) in the distal scaphoid of the left wrist shown with arrows.

the distal pole of the scaphoid (Figs. 1A and 1B) supporting Preiser's disease was seen on X-rays of both wrists. Because there was no separation in the scaphoid's proximal pole and the pathology was in the distal pole rather than the proximal pole, we were able to distinguish Preiser's disease from scaphoid osteochondritis.

The diagnosis was verified by an MRI showing effusion at the intercarpal joint (Figs. 2A and 3A) and bone edema in the distal scaphoid (Figs. 2B, 2C, 3B and 3C) of both wrists.

The patient underwent bilateral wrist CT to classify the disease. The CT scan showed subchondral sclerosis (Figs. 4A and 5A) and a cyst (Figs. 4B and 5B) at the distal pole of the scaphoid, which was diagnosed as Stage 2.

Due to the patient's early Preiser's disease, history of gastric bleeding, and nonsteroidal anti-inflammatory drugs (NSAID) allergy, immobilization treatment was performed. (Figs. 6A and 6B).

At the end of the 3rd week, the right wrist cast was removed and a re-examination was performed. Bone edema was found to be reduced by 85% in the MRI of the wrist (Figs. 7A, 7B and 7C) and patients' pain was greatly reduced.

DISCUSSION

Oxidative stress factors have an effect on diseases based on avascular necrosis bone pathophysiology such as Preiser. Antioxidants have an important role in maintaining a normal bone remodeling process and protecting bone health [8, 9].

There are no prospective, long-term trials evaluating the various therapy options for Preiser illness,

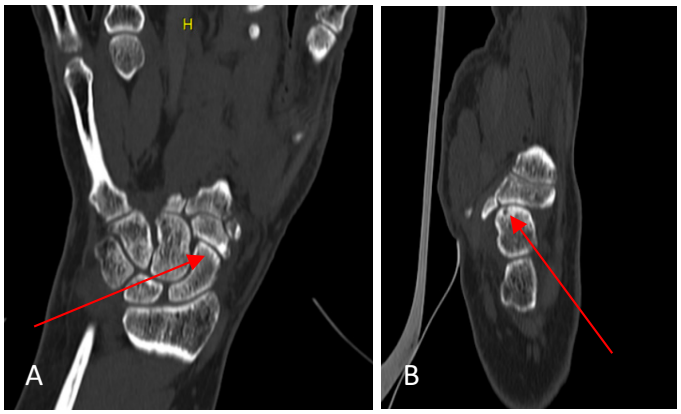

Fig. 4. Subchondral sclerosis (A) and cyst (B) of the distal scaphoid of the right wrist are shown with red arrows.

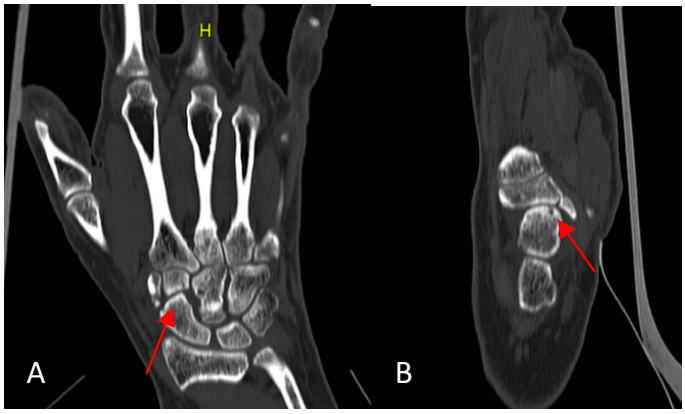

Fig. 5. Subchondral sclerosis (A) and cyst (B) of the distal scaphoid of the left wrist are shown with red arrows.

Fig. 4. Short cast of right arm with thumb support. Antero-posterior (A) and lateral (B) views.

making treatment controversial [10]. Treatment is therefore mostly determined by the surgeon's preference. Electrical stimulation, immobilization, steroid infiltration, and non-steroidal anti-inflammatory medications are examples of conservative or nonoperative treatment [11,12]. Early immobilization and non-operative conservative treatment methods are used in the initial treatment of these patients. In the late stage, a choice has to be made between proximal row carpectomy, four-corner's fusion with scaphoid resection, or denervation of the wrist [13, 14].

This case report details a 55-year-old female patient who came to our outpatient clinic with complaints of swelling and pain in both of her wrist joints that had persisted for five months. The patient had pain around the thenar region and anatomical snuff box on both wrists. The imaging revealed no signs of a scaphoid fracture, this eliminated the possibility of scaphoid proximal pole avascular necrosis which typically results from a fracture. Once the diagnosis was made, the illness was staged radiologically to determine the treatment plan. Using a plain radiograph as a guide, Herbert and Lanzetta divided Preiser illness into four stages according to the scaphoid area involved [3] Based on the degree of scaphoid involvement in MRI, Kalainov recently classified two categories of Preiser disease [11]. Our patient is classified as type 2 both according to Herbert and Lanzetta classification and the Kalainov classification.

According to Herbert and Lanzetta, the process starts in the proximal pole and moves on to the remaining scaphoid. However, in our patient, the disease onset was in the distal pole and spread proximally. Due to the early stage of the disease and patient compliance, our choice of treatment was immobilization. In the treatment algorithm proposed by Sokolov and Bourcheix vascularized bone grafting is the recommended treatment method for Herbert stages 1 and 2 [7]. However, we were able to obtain satisfactory results with a 3-week plaster treatment on both wrists with stage 2 Preiser's disease according to Herbert's classification [7, 15].

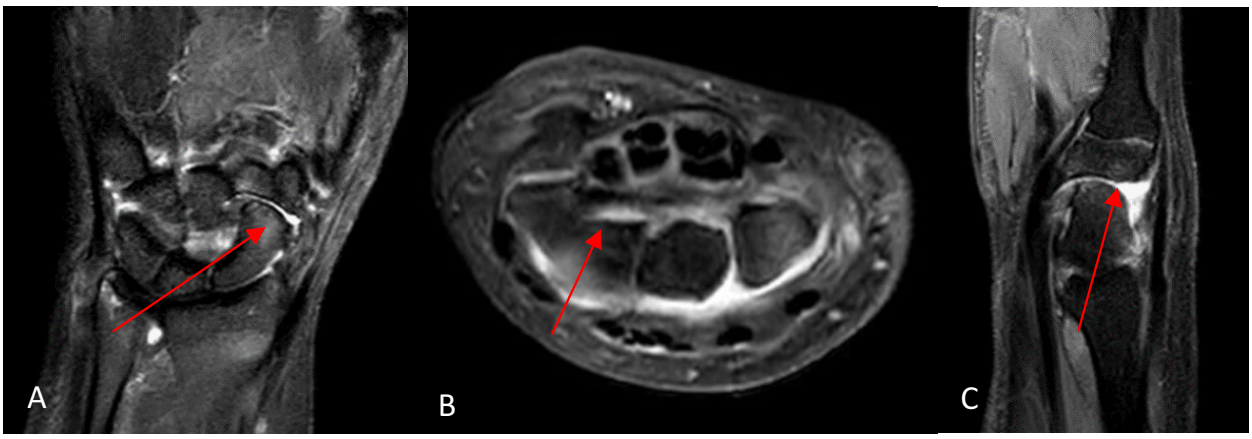

Fig. 7. Significant reduction in bone edema of right scaphoid bone after treatment with circular cast splint. The reduction area is shown with red arrows. (A) Coronal, (B) Axial, and (C) Sagittal.

CONCLUSION

Preiser's disease is a rare condition that lacks a definitive treatment guideline. In this case report we reported a case of bilateral Preiser's disease at stage 2 with unusual presentation that was treated conservatively with immobilization for 3 weeks and reached satisfactory results. This case stands out because disease processes were initially seen at the distal pole and were resolved with a relatively short treatment of only 3 weeks of immobilization, and highlights the potential of conservative treatment options when pain and disturbance to the patient at presentation are manageable and when disease is detected at an early stage.

Ethical Statement

Ethical approval is not required for this study. This study is a case report

Patient' Consent

Patient was informed about the purpose of the case report, and informed consent was obtained from the patient for this publication (Consent date:09/09/2024).

Authors' Contribution

Study Conception: CÇ; Study Design: BÖŞ; Supervision BÖŞ; Funding: CÇ; Materials: CÇ; Data Collection and/or Processing: SI; Statistical Analysis and/or Data Interpretation: SI; Literature Review: SI; Manuscript Preparation: SI and Critical Review: CÇ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Editor's note

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Letter to the editor for the article entitled "The importance and prognostic effect of thyroid hormones in patients with transposition of the great arteries"

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Dear Editor,

We read the article by Arslanoğlu et al. [1] entitled "The importance and prognostic effect of thyroid hormones in patients with transposition of the great arteries" with great interest. First of all, we congratulate the authors for their valuable contribution to the literature. We would like to point out some issues and ask some questions to the authors about the content of the article.

Serum thyroid hormone levels are known to be associated with the prognosis after pediatric heart surgery. Regular monitoring of thyroid hormone levels is of utmost importance especially in pediatric patients undergoing congenital heart surgery, since thyroid hormone levels are depressed in this patient group after the surgeries under cardiopulmonary bypass [2]. The authors presented their experiences on the arterial switch operations in cases with transposition of the great arteries and emphasized that regular monitoring of thyroid hormone levels and follow-up of thyroid function could improve the health status and prognosis of this patient group, as a conclusion of the study [1]. However, in their study population, serum thyroid hormone levels were studied only in the preoperative period, and no knowledge exists of the postoperative course of thyroid hormone levels.

Extracorporeal membrane oxygenation (ECMO) ensures efficient cardiopulmonary support in cases of cardiopulmonary failure in pediatric patients undergoing congenital heart operations. In these patients, it is known that correct timing, appropriate management, and careful patient selection for ECMO are important issues for achieving satisfactory outcomes with ECMO support [3]. The authors indicated that the need for ECMO was decided by an intensive care team and all ECMOs were placed centrally. However, in their study population, no knowledge exists on how many cases received ECMO support, and its relationship with perioperative mortality.

We think that the most interesting finding of the study was that greater preoperative thyroid-stimulating hormone levels affected the severity of aortic regurgitation and mortality. However, no emphasis was placed on this situation in the conclusion section of the article. In our opinion, it would be better to emphasize the important findings of the study rather than the general information about the topic provided in this section of the article.

Finally, in the article, it was seen that the patients

Keywords: Thyroid hormones, prognosis, pediatric heart surgery

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were not categorized as those who developed mortality (the mortality group) and those who did not (the surviving group), and thus since no such categorization and subsequent comparison was made between the two groups. However, the authors indicated that there was no significant relationship between mortality and several factors such as gender and postoperative degree of aortic regurgitation in the results section of the article. We would like to receive the authors' valuable opinions on this subject.

Ethics Statement

Ethical approval is not required for this study. This study is a letter to the editor

Authors' Contribution

Study Conception: MSA, A.M; Study Design: MSA, A.M; Supervision: MSA, A.M; Funding: N/A; Materials: N/A; Data Collection and/or Processing: N/A; Statistical Analysis and/or Data Interpretation: N/A; Literature Review: MSA, A.M; Manuscript Preparation: MSA and Critical Review: A.M.

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Editor's note

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Author's Response to Letter to the Editor

Dear Editor,

We would like to express our gratitude for the valuable comments and constructive feedback regarding our article titled *"The Importance and Prognostic Effect of Thyroid Hormones in Patients with Transposition of the Great Arteries."* We see this feedback as an opportunity to enhance the understanding of our study and to clarify certain points. Although the submitted critique's suitability as a "Letter to the Editor" may be questionable, below we have addressed each question in detail.

1. Why were postoperative thyroid hormone levels not included in the study?

The primary aim of our study was to evaluate the prognostic impact of preoperative thyroid hormone levels. Postoperative thyroid hormone dynamics were intentionally excluded from the scope of this study. However, the existing literature highlights significant changes in T3 levels during and after cardiopulmonary bypass (CPB) procedures, which can impact clinical outcomes. Indeed, some pediatric cardiovascular surgery centers routinely monitor and manage postoperative thyroid hormone levels. Considering this feedback, we acknowledge the importance of investigating postoperative thyroid hormone changes and their influence on clinical outcomes. A follow-up study exploring these dynamics in detail may be planned, which would provide a more comprehensive understanding of the role of thyroid hormones during the perioperative period.

2. Why was detailed information about ECMO use and its relationship with mortality not included?

In our study, only a small number of patients (n=3) required extracorporeal membrane oxygenation (ECMO) support. Consequently, conducting a statistically meaningful analysis of ECMO use in relation to mortality was not feasible. However, ECMO remains a critical treatment modality for high-risk patients undergoing congenital heart surgery. Decisions regarding ECMO initiation in our cohort were made by a multidisciplinary intensive care team based on specific clinical indicators, such as left ventricular function, hemodynamic stability, and lactate clearance. While a more detailed evaluation of variables like ECMO timing, duration, and weaning success could yield valuable insights, incorporating such data into this study would have shifted its primary focus. Therefore, we chose not to include these variables. Future studies with larger sample sizes may explore the impact of ECMO on outcomes more comprehensively.

3. Why was the relationship between elevated preoperative TSH levels, aortic regurgitation, and mortality not emphasized in the conclusion?

The relationship between elevated preoperative TSH levels, advanced aortic regurgitation, and mortality represents a significant finding of our study. However, this specific association may not have been sufficiently highlighted in the conclusion. This omission was a result of our attempt to present the general prognostic effects of thyroid hormones rather than emphasizing individual findings. We appreciate this feedback and agree that such key observations deserve greater emphasis. In future revisions or related publications, we will ensure that these findings are more explicitly discussed, particularly in the conclusion section.

4. How were relationships between mortality and other factors evaluated without categorizing patients into mortality groups?

Although we did not explicitly divide patients into "mortality" and "surviving" groups, statistical analyses were performed on the entire cohort to assess the relationships between various preoperative and perioperative variables and mortality. Multivariate regression analyses were used to identify the independent effects of factors such as gender, coronary artery anatomy, and postoperative aortic regurgitation on mortality. Our approach allowed us to evaluate mortality-related factors comprehensively. However, we acknowledge that stratifying patients into more distinct subgroups could provide additional clarity. This suggestion will be considered in the design of future studies.

5. Why did the conclusion focus on general information rather than highlighting the study's specific findings?

The conclusion was designed to contextualize the clinical importance of thyroid hormone regulation in congenital heart disease, particularly in transposition of the great arteries (TGA). However, we acknowledge that findings unique to our study, such as the association between preoperative TSH levels and adverse outcomes, could have been more prominently featured. While we view this as a matter of personal preference, future publications will aim to achieve a better balance between general insights and study-specific contributions. This approach will help researchers who are interested in our findings focus on these critical aspects more effectively.

CONCLUSION

We are grateful for these thoughtful comments, which have allowed us to refine our interpretation of the study's findings and identify avenues for future research. We hope that our responses adequately address the questions and concerns raised. We also thank the reviewers and editorial team for their contributions to the improvement of our work.

Yours sincerely,

Ergin Arslanoğlu