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Determinants of Mortality in Respiratory Intensive Care Units

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ABSTRACT

Objective: Respiratory intensive care units (RICUs) play a critical role in managing patients with severe respiratory conditions, including acute and chronic respiratory failure, severe lung infections, and pulmonary edema. Mortality-related factors in these specialized units may differ from those observed in general intensive care units. This study aims to identify these distinctions.

Methods: We conducted a retrospective analysis of 406 patients admitted to a tertiary-level RICU. Data collected included scoring metrics-such as the Acute Physiology and Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment, Glasgow Coma Scale (GCS), and Charlson comorbidity index-along with the hospital department from which cases were transferred, biochemical blood test results, and the types of respiratory support administered. These variables were assessed to identify factors associated with mortality.

Results: Mortality occurred in 69.1% of cases (n=244), while 30.9% (n=109) survived. Independent risk factors for mortality included higher APACHE II scores, lower GCS scores, the need for endotracheal intubation, inotropic support, reduced albumin levels, low hemoglobin levels, and elevated D-dimer levels. Notably, exacerbations of chronic obstructive pulmonary disease were associated with increased mortality compared to other primary pulmonary conditions (p=0.001). Furthermore, patients transferred from the emergency department demonstrated lower mortality than those transferred from other departments (p=0.001).

Conclusion: Mortality risk factors in RICUs share similarities with those in other intensive care units. However, RICUs also have unique risk determinants related to underlying respiratory disorders and specific biomarkers, such as D-dimer, underscoring the need for targeted management strategies in this patient population.

Keywords: Intensive care, mortality, risk factors, chronic obstructive pulmonary disease, D-dimer, respiratory

INTRODUCTION

Intensive care units (ICUs) are medical facilities, characterized by the intensive use of invasive interventions, advanced monitoring techniques, and the implementation of multidisciplinary treatment approaches, that admit patients with critically threatened vital functions. Respiratory ICUs, in particular, are critical areas for the treatment of respiratory diseases, including acute or chronic respiratory failure, severe lung infections, and pulmonary edema (1). The success of treatments administered in these units depends on numerous factors that directly influence patients' survival and quality of life. Key factors influencing the prognosis of patients receiving treatment in the ICU include age, underlying diseases, the need for and duration of mechanical ventilation, organ failure, the presence of infection, and comorbidities (2,3). However, various scoring systems have been developed to predict the prognosis of ICU patients. Scoring systems such as Acute Physiology and Chronic Health Evaluation II (APACHE II) Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score II aim to estimate the risk of mortality based on patients' physiological parameters (3). In recent years, the advancement of data science and artificial intelligence-supported models has enabled more precise methods for predicting mortality in ICU patients (4). However, the widespread adoption of these new methods in clinical practice may take time, highlighting the need to update existing scoring systems. Additionally, the number of specific studies focusing on respiratory ICU patients is limited, and the factors influencing mortality have not been fully elucidated in the literature (5).

Understanding the factors that predict disease prognosis and adverse outcomes can assist physicians in providing more effective guidance to patients regarding the expected course of their illness. The effectiveness of treatment and medical care is directly

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related to reducing patient mortality. Therefore, each clinic should aim to identify both favorable and unfavorable prognostic factors to reduce mortality rates among its patients.

In this study, we aimed to identify all clinical and biochemical risk factors affecting mortality in respiratory ICUs and to develop a model composed of the independent risk factors that influence mortality.

METHODS

This study was conducted with ethical approval from the University of Health Sciences Türkiye, Ankara Atatürk Sanatory Training and Research Hospital Scientific Research Ethics Committee, under (number: 2024-BÇEK/7, date: 28.02.2024). This study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants included in the study. In the study, the data of 406 patients who were admitted and monitored in the Respiratory ICU of University of Health Sciences Türkiye, Ankara Atatürk Sanatory Training and Research Hospital between December 1, 2021, and December 1, 2022, were retrospectively examined. Patients aged 18 and older were included in the study. In this context, a total of 353 patients for whom complete data were available were included in the study. Since exacerbations of respiratory diseases exhibit seasonal variability, all patients who were admitted to and discharged from the ICU or who died over the course of one year were included in the study. This approach aimed to minimize the impact of seasonal infectious processes on the overall risk factors for mortality in respiratory diseases. All patients who died due to their primary respiratory disease, either in the ICU or within 48 hours after discharge from the ICU, were classified under ICU mortality.

The ICU where our study was conducted did not admit patients infected with coronavirus disease-2019 (COVID-19). Additionally, patients who tested positive for COVID-19 by polymerase chain reaction after ICU admission were transferred to a dedicated COVID-19 ICU, and these patients were excluded from the study.

Surviving and deceased patients were compared, and the mortality rates and factors affecting mortality in the tertiary chest diseases ICU were analyzed. Patient data were retrieved from the hospital's healthcare database system.

The following variables were recorded: patients' ages, genders, primary diagnosis [chronic obstructive pulmonary disease (COPD) exacerbation, pneumonia, lung cancer (LC), interstitial lung disease (ILD), bronchiectasis, acute pulmonary thromboembolism, pulmonary tuberculosis, acute respiratory distress syndrome, and other pulmonary diseases], comorbidities [hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD)-arrhythmia, congestive heart failure, non-pulmonary malignancies, chronic kidney disease, neurological diseases, thyroid disorders, and other diseases], length of stay, mortality status, and the department from which the patient was transferred to the ICU (emergency department, other departments of the hospital, or other hospitals).

The status of endotracheal intubation (admitted intubated, intubated during follow-up, or re-intubated due to extubation failure), duration of intubation, tracheostomy status (admitted with tracheostomy or underwent tracheostomy), and type of respiratory support [non-invasive mechanical ventilation (NIMV), IMV, high-flow nasal oxygen, nasal oxygen, or transitioned from NIMV to IMV due to NIMV failure] were also documented. The following scores were calculated: APACHE II, SOFA, Glasgow Coma Scale (GCS), and modified Charlson comorbidity index (mCCI). Additionally, whether the patient received inotropic support during the ICU stay was recorded.

Laboratory parameters obtained at ICU admission were also collected, including arterial blood gases, creatinine, glomerular filtration rate, and blood urea nitrogen (BUN). Other parameters included aspartate aminotransferase, alanine aminotransferase, magnesium, calcium, chloride, sodium, potassium, and white blood cell (WBC) count. Additionally, lymphocyte and neutrophil counts, hemoglobin (Hgb), hematocrit, platelet count, procalcitonin, C-reactive protein (CRP), lactate dehydrogenase, brain natriuretic peptide, D-dimer, and troponin levels were recorded.

The scoring systems were calculated based on the worst values obtained within the first 24 hours of ICU admission using data from the hospital's healthcare database system.

Statistical Analysis

Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Descriptive statistical methods, including mean, standard deviation, median, frequency, percentage, and interquartile range (IQR) were employed to evaluate the study data. The normality of the distribution of quantitative variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, as well as skewness-kurtosis tests and graphical methods. Following normality tests, continuous variables with normal distribution were presented as mean ± standard deviation, while those not normally distributed were expressed as median (IQR). For comparing two groups, the independent sample's t-test was used for quantitative variables with a normal distribution, while the Mann-Whitney U test was applied for variables that did not exhibit a normal distribution. For categorical variable comparisons, Pearson's chi-square test and Fisher's exact test were employed. To determine cut-off values for the parameters, diagnostic screening tests (sensitivity, specificity, positive predictive value, and negative predictive value) and receiver operating characteristic (ROC) curve analysis was performed. To assess the statistical significance of differences between area under the curve (AUC) values, pairwise post hoc comparisons were conducted using Z-tests calculated from the standard errors of the AUC estimates. For multivariate analysis, the effects of other risk factors on mortality were evaluated using logistic regression analysis. For multivariate analysis, backward stepwise logistic regression was used to evaluate the effects of various risk factors on mortality, ensuring focus on the most relevant predictors while minimizing collinearity. A confidence interval of 95% was adopted for all statistical analyses, and a p-value of <0.05 was considered statistically significant.

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RESULTS

Between December 2021 and December 2022, a total of 406 patients were admitted to the Level 3 Respiratory ICU at University of Health Sciences Türkiye, Ankara Atatürk Sanatory Training and Research Hospital. Of these, 12 patients were readmissions, and 41 were transferred to other hospitals, resulting in the exclusion of 53 patients from the study. Consequently, the study was conducted with 353 patients, of whom 34% (n=120) were female and 66% (n=233) were male. The ages of the patients ranged from 20 to 95 years, with a mean age of 70.21±11.64 years. Comorbid conditions among the patients were assessed, revealing, the three most common as follows: HT in 43.1% (n=152), CAD or arrhythmia in 30% (n=106), and DM in 27.8% (n=98) (Table 1).

Table 1. Descriptive variables

		n	%
Age (year)	Mean±SD	70.21±11.64	
Gender	Female	120	34.0
	Male	233	66.0
Source of admission to the intensive care unit	Emergency department	151	42.8
	The other department of hospital	139	39.4
	Another hospital	63	17.8
Primary pulmonary disease	COPD exacerbation	141	39.9
	Pneumonia	93	26.3
	Lung cancer	47	13.3
	ILD	24	6.8
	Bronchiectasis	5	1.4
	Acute PTE	18	5.1
	PTB	5	1.4
	ARDS	7	2.0
	Sepsis	7	2.0
	Other	6	1.7
•Comorbidities	HT	152	43.1
	DM	98	27.8
	CAD-arrhythmia	106	30.0
	CHF	65	18.4
	Extrapulmonary malignancies	27	7.6
	CRF	32	9.1
	Neurological diseases	38	10.8
	Thyroid diseases	16	4.5
	Other diseases	40	11.3

•Multiple diseases are observed
SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, ILD: Interstitial lung disease, PTE: Pulmonary thromboembolism, PTB: Pulmonary tuberculosis, ARDS: Acute respiratory distress syndrome, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CHF: Congestive heart failure, CRF: Chronic renal failure, IQR: Interquartile range

The APACHE-II scores of the patients ranged from 3 to 47, with a mean of 18.03±7.82 and a median of 17. The SOFA scores ranged from 0 to 17, with a mean of 4.81±3.70 and a median of 4. The results of the other intensive care scoring systems, including their mean and median values, are presented in Table 2. A total of 147 patients (41.6%) underwent IMV, including patients intubated upon ICU admission (n=55) and those intubated during their ICU stay (n=92). Additionally, NIMV was applied to 112 patients (32.3%). Forty-five patients were intubated and subsequently switched to IMV due to the failure of NIMV. The duration of intubation ranged from 1 to 45 days, with a mean of 7.18±7.66 days and a median of 5 days. The duration of ICU stay ranged from 1 to 54 days, with a mean of 6.94±7.73 days and a median of 4 days. 69.1% of the patients (n=244) survived, while mortality occurred in 30.9% (n=109) (Table 2). In patients transferred to the ICU from the emergency department, mortality rates were found

Table 2. The distrubition of clinical data

		n	%
APACHE-II Score	Median (IQR)	17 (11)	
SOFA Score	Median (IQR)	4 (5)	
Modified Charlson comorbidity index	Median (IQR)	4 (3)	
GCS	Median (IQR)	15 (2)	
Duration of intubation (day) (n=147)	Median (IQR)	5 (3)	
İntubation	No	206	58.4
	Patients intubated upon ICU admission	55	15.6
	Patients intubated in the ICU	92	26.0
Patients with tracheostomy upon ICU admission	No	346	98.0
	Yes	7	2.0
Patients who underwent tracheostomy in the ICU	No	340	96.3
	Yes	13	3.7
Reintubation	No	329	93.2
	Yes	24	6.8
Respiratory support (n=347)	IMV	102	29.3
	NIMV	112	32.3
	HFNO	13	3.8
	Nasal O_2	75	21.7
	NIMV>IMV	45	12.9
Inotropic support	No	245	69.4
	Yes	108	30.6
Length of ICU stay (day)	Median (IQR)	4 (6)	
Mortality	No	244	69.1
	Yes	109	30.9

APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow Coma Scale, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation, HFNO: High-flow nasal oxygen NIMV>IMV: Patients who were intubated and followed with IMV due to NIMV failure

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to be significantly lower than those admitted from other hospital departments (p=0.001). Upon examining the primary respiratory disease diagnoses of the patients, it was observed that mortality rates were significantly higher in patients with a primary diagnosis of LC, while mortality rates were significantly lower in patients with a primary diagnosis of COPD exacerbation (p=0.001) (Table 3). As expected, mortality rates were significantly higher in patients who were already intubated upon arrival at the ICU, those who were intubated during their stay, and those who were re-intubated after extubation (p=0.001) (Table 4). The descriptive values and statistical significance of the biochemical blood test results between the groups with and without mortality are presented in Table 5.

The mCCI, APACHE II, SOFA, and GCS scoring systems were found to be effective in predicting mortality in patients in the respiratory ICU, similar to other intensive care populations. Higher scores on mCCI, APACHE II, and SOFA, along with a lower GCS, were significantly associated with mortality. The cut-off values derived from ROC analysis using these scoring systems, along with the AUC values, specificity, sensitivity, and negative and positive predictive values, are presented in Table 6, alongside the p-values. Based on binary logistic regression analyses conducted using the calculated cut-off values for these scoring systems, the risk of mortality was 2636 times higher in cases with a CCI level of 5 or above, 4896 times higher in cases with an APACHE II score of 20 or above, 3282 times higher in cases with a SOFA score of 5 or above, and 6841 times higher in cases with a GCS of 14 or below.

Post hoc comparisons of AUC values between the scoring systems were performed using a Z-test based on the standard error of AUC estimates. The comparison revealed that the APACHE-II score had a significantly higher AUC than the mCCI (p=0.045), whereas the differences between other scoring systems were not statistically significant (Table 7).

Table 3. Descriptive characteristics by mortality

n (%)		Mortality (-) (n=239)	Mortality (+) (n=114)	p-value
		n (%)		
Age (year)	Mean ± SD	70.03±11.52	70.57±11.94	[a]0.686
Gender	Female	88 (36.8)	32 (28.1)	[b]0.105
	Male	151 (63.2)	82 (71.9)	
Source of admission to the intensive care unit	Emergency department	117 (49.0)	34 (29.8)	[b]0.001**
	The other department of hospital	74 (31.0)	65 (57.0)	
	Another hospital	48 (20.1)	15 (13.2)	
Primary pulmonary disease	COPD exacerbation	110 (46.0)	31 (27.2)	[b]0.001**
	Pneumonia	65 (27.2)	28 (24.6)	[b]0.599
	Lung cancer	18 (7.5)	29 (25.4)	[b]0.001**
	ILD	12 (5.0)	12 (10.5)	[b]0.055
	Bronchiectasis	4 (1.7)	1 (0.9)	[c]1.000
	Acute PTE	15 (6.3)	3 (2.6)	[b]0.146
	PTB	2 (0.8)	3 (2.6)	[c]0.334
	ARDS	5 (2.1)	2 (1.8)	[c]1.000
	Sepsis	3 (1.3)	4 (3.5)	[c]0.219
	Other	5 (2.1)	1 (0.9)	[c]0.668
•Comorbidities	HT	107 (44.8)	45 (39.5)	[b]0.347
	DM	72 (30.1)	26 (22.8)	[b]0.151
	CAD-arrhythmia	73 (30.5)	33 (28.9)	[b]0.760
	CHF	47 (19.7)	18 (15.8)	[b]0.380
	Extrapulmonary malignancies	15 (6.3)	12 (10.5)	[b]0.160
	CRF	24 (10.0)	8 (7.0)	[b]0.355
	Neurological diseases	28 (11.7)	10 (8.8)	[b]0.404
	Thyroid diseases	9 (3.8)	7 (6.1)	[b]0.316
	Other diseases	29 (12.1)	11 (9.6)	[b]0.491

[a]Independent Samples t-test, [b]Pearson chi-square test, [c]Fisher's exact test
**p<0.01, •Multiple diseases are observed, COPD: Chronic obstructive pulmonary disease, ILD: Interstitial lung disease, PTE: Pulmonary thromboembolism, PTB: Pulmonary tuberculosis, ARDS: Acute respiratory distress syndrome, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CHF: Congestive heart failure, CRF: Chronic renal failure, IQR: Interquartile range

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Table 4. Clinical data by mortality

n (%)		Mortality (-) (n=239)	Mortality (+) (n=114)	p-value
		n (%)		
APACHE-II score	Median (IQR)	15 (8)	22 (10.5)	[d]0.001**
SOFA score	Median (IQR)	3 (4.75)	6 (6)	[d]0.001**
Modified Charlson comorbidity index	Median (IQR)	4 (2)	5 (4.5)	[d]0.001**
GCS	Median (IQR)	15 (0)	13 (7)	[d]0.001**
Duration of intubation (day) (n=147)	n	39	108	
	Median (IQR)	5 (0)	5 (9)	[d]0.308
Intubation	No	206 (84.1)	0 (0)	[b]0.001**
	Patients intubated upon ICU admission	23 (9.3)	32 (29.6)	
	Patients intubated in the ICU	16 (6.6)	76 (70.4)	
Patients with tracheostomy upon ICU admission	No	232 (97.1)	114 (100)	[c]0.101
	Yes	7 (2.9)	0 (0)	
Patients who underwent tracheostomy in the ICU	No	233 (97.5)	107 (93.9)	[c]0.128
	Yes	6 (2.5)	7 (6.1)	
Reintubation	No	236 (98.7)	93 (81.6)	[b]0.001**
	Yes	3 (1.3)	21 (18.4)	
Respiratory support (n=285)	MV	3 (1.5)	37 (46.8)	[b]0.001**
	NIMV	108 (52.4)	4 (5.1)	
	HFNO	13 (6.3)	0 (0)	
	Nasal O_2	72 (35.0)	3 (3.8)	
	NIMV>MV	10 (4.9)	35 (44.3)	
Inotropic support	No	214 (89.5)	31 (27.2)	[b]0.001**
	Yes	25 (10.5)	83 (72.8)	
Length of ICU stay (day)	Median (IQR)	4 (5)	6.5 (12.5)	[d]0.116

[b]Pearson chi-square test, **p<0.0, [c]Fisher's exact test, [d]Mann-Whitney U test
APACHE-II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow Coma Scale, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation, HFNO: High-flow nasal oxygen, NIMV>IMV: Patients who were intubated and followed with IMV due to NIMV failure, IQR: Interquartile range

Table 5. Laboratory findings by mortality

		Mortality (-) (n=239)	Mortality (+) (n=114)	p-value
pH	Mean±SD	7.38±0.10	7.34±0.15	[a]0.005**
PO_2 (mm/Hg)	Median (IQR)	47 (32.5)	44.5 (30.5)	[d]0.230
PCO_2 (mm/Hg)	Median (IQR)	53 (34.75)	56 (35)	[d]0.360
HCO_3	Mean±SD	31.50±8.62	30.80±10.40	[a]0.532
BE	Median (IQR)	5 (10)	3 (13)	[d]0.080
Creatinine (mg/dL)	Mean±SD	1.15±0.62	1.27±0.87	[a]0.214
GFR (mL/min)	Mean±SD	70.30±28.39	67.65±30.68	[a]0.425
BUN (mg/dL)	Median (IQR)	23 (17)	30 (32.5)	[d]0.001**
ALT (IU/L)	Median (IQR)	16 (18)	23.5 (54.5)	[d]0.002**
AST (IU/L)	Median (IQR)	21 (20)	32.5 (43.5)	[d]0.001**
LDH (IU/L)	Median (IQR)	258 (134.75)	330.5 (255.5)	[d]0.001**
Albumin (g/L)	Mean±SD	32.00±5.20	27.49±5.55	[a]0.001**
Magnesium (mg/dL)	Mean±SD	2.03±0.54	2.06±0.43	[a]0.646
Sodium (mmol/L)	Mean±SD	138.89±4.64	139.47±6.53	[a]0.394
Potassium (mmol/L)	Mean±SD	4.42±0.68	4.50±0.99	[a]0.422
Chloride (mmol/L)	Mean±SD	98.57±8.49	98.47±8.14	[a]0.920
Calcium (mg/dL)	Mean±SD	8.60±0.83	8.31±1.08	[a]0.013*

Table 5. Continued

		Mortality (-) (n=239)	Mortality (+) (n=114)	p-value
CRP (mg/L)	Median (IQR)	44 (80.75)	116 (129)	[d]0.001**
WBC (µL)	Median (IQR)	10000 (6902)	13030 (7810)	[d]0.001**
Lymphocytes (µL)	Median (IQR)	880 (755)	715 (765)	[d]0.028*
Monocytes (µL)	Median (IQR)	510 (457.5)	530 (510)	[d]0.238
Neutrophils (µL)	Median (IQR)	8460 (6710)	11275 (7905)	[d]0.001**
Eosinophils (µL)	Median (IQR)	10 (50)	10 (20)	[d]0.052
HGB (g/dL)	Mean±Sd	11.96±2.69	11.52±2.36	[a]0.134
HCT (%)	Mean±Sd	38.39±8.31	37.11±7.20	[a]0.159
Platelets (µL)	Median (IQR)	236000 (123750)	241000 (169500)	[d]0.398
Procalcitonin (µg/L)	Median (IQR)	0.1 (14)	0.4 (31)	[d]0.001**
BNP (ng/L)	Median (IQR)	181 (407.75)	142 (802)	[d]0.961
D-dimer (ng/mL)	Median (IQR)	1620 (2080)	3625 (6675)	[d]0.001**
Troponin (ng/L)	Median (IQR)	14 (40)	27 (91)	[d]0.001**

[a]Independent Samples t-test, [d]Mann-Whitney U test, *p<0.05, **p<0.01
IQR: Interquartile range, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BE: Base excess, BUN: Blood urea nitrogen, GFR: Glomerular filtration rate, HCO_3: Bicarbonate, LDH: Lactate dehydrogenase, PCO_2: Partial Pressure of carbon dioxide, PO_2: Partial pressure of oxygen, BNP: B-type natriuretic peptide, CRP: C-reactive protein, HCT: Hematocrit, HGB: Hemoglobin, WBC: White blood cells

Table 6. Diagnostic screening tests and ROC curve results of mCCI, APACHE II score, SOFA score, and GCS measurements by mortality

	Diagnostic scan					ROC curve		p-value
	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	AUC	95% Confidence interval	
mCCI	≥5	57.02	66.53	44.83	76.44	0.667	0.605-0.730	0.001**
APACHE-II	≥20	60.53	76.15	54.76	80.18	0.736	0.679-0.792	0.001**
SOFA	≥5	63.16	65.69	46.75	78.89	0.727	0.671-0.782	0.001**
GCS	≤14	57.89	83.26	62.26	80.57	0.711	0.650-0.772	0.001**

**p<0.01
APACHE-II: Acute Physiology and Chronic Health Evaluation II, GCS: Glasgow Coma Scale, mCCI: Modified Charlson comorbidity index, SOFA: Sequential organ failure assessment, AUC: Area under the curve, ROC: Receiver operating characteristic

Table 7. Post hoc comparison of AUC values between scoring systems (Z-test results)

Model 1	Model 2	Z Score	p-value
mCCI	APACHE-II	-2.009	0.045*
mCCI	SOFA	-1.738	0.082
mCCI	GCS	-1.264	0.206
APACHE-II	SOFA	0.270	0.787
APACHE-II	GCS	0.743	0.458
SOFA	GCS	0.501	0.617

*p<0.05
mCCI: Modified Charlson comorbidity index, APACHE-II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, GCS: Glasgow Coma Scale

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Table 8. Logistic regression analysis of risk factors affecting the presence of mortality

	p-value	Odds ratio	%95 CI	
			Lower	Upper
APACHE-II score	0.021*	1.069	1.010	1.130
GCS	0.001**	1.211	1.084	1.354
Intubation (yes)	0.001**	95.437	27.755	328.160
Inotropic support (yes)	0.006**	3.278	1.415	7.589
Albumin	0.013*	1.106	1.022	1.198
Hemoglobin	0.028*	1.227	1.023	1.472
D-dimer	0.001**	1.005	1.003	1.010

**p<0.01, *p<0.05
APACHE-II: Acute Physiology and Chronic Health Evaluation II, GCS: Glasgow Coma Scale, CI: Confidence interval

For the presence of mortality, factors that were significant or approaching significance in the univariate analysis were included in the logistic regression analysis, to develop a model with high significance and explainability. Accordingly, the effects of the following factors were subjected to backward stepwise logistic regression analysis: the presence of primary respiratory disease diagnoses of COPD exacerbation, LC, and ILD; APACHE II score, SOFA score, mCCI, and GCS; presence of intubation, administration of inotropic support, length of stay in ICU; and measurements of BUN, albumin, CRP, lymphocytes, Hgb, procalcitonin, D-dimer, and troponin. The model generated at the end of step 12 for the risk factors affecting mortality is presented in Table 8. After step 12 of the analysis, it was observed that the APACHE II score, GCS, presence of intubation, administration of inotropic support, and measurements of albumin, Hgb, and D-dimer significantly contributed to the model that affects mortality. The explanatory power of the model, with a coefficient of 91.7%, is considered very good. Accordingly, in patients monitored in respiratory ICUs, a high APACHE II score, low GCS, presence of intubation, administration of inotropic support, low albumin levels, low Hgb levels, and high D-dimer values are independent risk factors for mortality.

DISCUSSION

The mortality rates of patients in the respiratory ICU vary according to several factors. These factors include age, gender, the source of ICU admission, the primary diagnosed disease, comorbid diseases, laboratory parameters, and prognostic scoring systems. Various studies have demonstrated that age is a significant factor, increasing mortality in the ICU. Seferian and Afessa (6) reported that ICU admission rates in the older age group (over 85 years) were significantly higher compared to younger age groups, and these patients had more comorbidities. ICU admissions during the last six months of life were found to be much higher in patients aged 85 years and above compared to those in the 18-44 age group (6). In the study by Chung et al. (5), it was stated that age did not directly affect acute mortality; however, older patients had longer ICU stays and an increased need for long-term care after discharge. However, this study found no statistically significant difference in the mean age between surviving and deceased patients. This finding, which appears to contradict the literature, may be due to the high number of young patients with terminal LC in the respiratory ICU where the study was conducted. The literature supports that age alone is not a determining factor for mortality, and that patients' comorbidities and treatment processes should be evaluated along with their age (5,7).

The literature presents varying results regarding the impact of gender on mortality in patients admitted to the ICU. Seferian and Afessa (6) reported that male gender is associated with a higher rate of ICU admissions among elderly patients and that males tend to have longer ICU stays. However, in another study by Ceriana et al. (8), the mortality rates of female patients in respiratory ICUs were observed to be higher than those of males, although this difference was not statistically significant. In our study, despite the higher proportion of male patients, the effect of gender on mortality was not found to be statistically significant. Considering that Romo et al. (9) study identified female gender as a high-risk factor for mortality, while Ursavaş et al. (10) reported higher mortality rates in males, it can be concluded that the impact of gender on ICU mortality remains unclear, and further research is needed to clarify these findings (6-10).

In our study, mortality was higher in patients transferred from hospital clinics compared to those admitted from the emergency department. The literature also contains studies supporting this finding. Motzkus et al. (11) demonstrated that patients diagnosed with sepsis had higher mortality rates when admitted from hospital clinics. A similar finding was reported in the study by Valentini et al. (12) on patients in respiratory ICUs. However, Parpucu et al. (13) found that mortality rates were higher among patients admitted from the emergency department compared to those transferred from hospital clinics. These conflicting results may be due to differences in patient groups, patient profiles, and the severity of illness at the time of initial admission. In our study, we attribute the higher mortality observed in patients admitted to the ICU from hospital clinics because these patients did not respond well to initial treatments, making the management of the respiratory patients admitted from the clinics considerably more challenging.

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Respiratory diseases are prominent among the reasons for ICU admissions, and our study identified COPD exacerbation, pneumonia, and LC as the most common causes of admission. Our findings indicate that the mortality rate is lower in patients with COPD exacerbation, but it is higher in patients with LC. No significant increase in mortality was detected in patients diagnosed with pneumonia. The literature supports some of our findings; for instance, Ursavaş et al. (10), demonstrated that the mortality rates of patients admitted to the ICU due to LC were higher than other patients. Çağlar et al. (14) reported that pneumonia has a significant impact on mortality. We believe that the strict protocols for treating respiratory failure, which have been implemented in our respiratory ICU for many years, may have contributed to the low mortality rates observed in COPD exacerbation patients in our study. These protocols include the use of new-generation non-invasive ventilation devices.

Comorbid conditions are known to be significant factors affecting mortality in the ICU. In our study, HT, CAD/arrhythmia, and DM were among the most common comorbidities; however, their impact on mortality was not found to be statistically significant. These findings are consistent with the study by Antonelli Incalzi et al. (15), which indicated that comorbidities do not increase mortality in patients with COPD.

Prognostic scoring systems are widely used to predict mortality in the ICU. The APACHE-II and SOFA scores are the most commonly utilized systems for assessing patients' mortality risk. In our study, we found that high APACHE-II and SOFA scores were significantly associated with mortality. The literature also supports these results. For instance, Godinjak et al. (16) noted that patients with an APACHE-II score above 27.5 had a significantly increased risk of mortality. Similarly, Naqvi et al. (17) found that both APACHE-II and SOFA scores were associated with mortality. In Naqvi et al. (17) study, it was shown that mortality significantly increased in patients with high APACHE-II scores, and SOFA scores also predicted mortality in a similar manner. Some studies have demonstrated that the SOFA score has higher discriminative power compared to the APACHE-II score, and both scoring systems aid in predicting mortality risk by assessing organ function and overall clinical status (18,19). Our study confirms the effectiveness of APACHE-II and SOFA scores in predicting mortality, and these findings are consistent with the existing literature. These scoring systems play a critical role in predicting mortality risk and managing patients in the ICU. Although the median APACHE II score (17) and median SOFA score (4) would correspond to expected mortality rates of approximately 20-25% and 15-20%, respectively, the observed mortality rate in our study was 30.9%. This discrepancy may be attributed to several factors, including the specific characteristics of the respiratory ICU population, the presence of underlying comorbidities, delayed referrals, disease severity not fully captured by the scoring systems, and post-COVID-19 pandemic effects on ICU admission profiles.

D-dimer and troponin levels are particularly associated with thromboembolic events and cardiac injury. Hu et al. (20) reported that D-dimer levels show a strong relationship with mortality, especially in patients admitted due to COPD exacerbations. An increase in D-dimer levels indicates that the coagulation system is activated and that the patient is at risk for thrombotic complications, which subsequently raises the risk of mortality. In our study, elevated D-dimer levels in patients were also found to be associated with higher mortality.

Study Limitations

Our study had several limitations. It was a single-center, retrospective study not specific to any disease. Patients' biochemical parameters were assessed with a single measurement at the time of ICU admission, and serial measurements were not performed. Vital signs at admission were not recorded. We did not have detailed information regarding disease severity, nutritional status, and quality of life prior to admission.

CONCLUSION

In our study, factors affecting mortality in the ICU were examined and compared with the literature. It was found that age, gender, the source of patient admission to the ICU, primary respiratory diagnosis, certain laboratory parameters, and prognostic scoring systems are significant in predicting mortality in respiratory ICUs. Our study produced results that are largely consistent with similar studies in the literature. However, differences in patient profiles and some results that vary according to clinical conditions indicate that such studies should be conducted with larger sample sizes and a focus on primary respiratory diseases. A better understanding of these factors may guide strategies aimed at reducing mortality in respiratory ICUs.

Ethics

Ethics Committee Approval: This study was conducted with ethical approval from the University of Health Sciences Türkiye, Ankara Atatürk Sanatory Training and Research Hospital Scientific Research Ethics Committee, under (number: 2024-BÇEK/7, date: 28.02.2024).

Informed Consent: Informed consent was obtained from all participants included in the study.

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Footnotes

Author Contributions: Surgical and Medical Practices - M.Y.; Concept - M.Y.; Design - M.Y.; Data Collection and/or Processing - M.A.; Analysis and/or Interpretation - O.M.; Literature Search - M.A.; Writing - M.A.

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Vestibular Exercises Combined with Table Tennis Exercises May Yield More Effective Outcomes: A Preliminary Randomized Study

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ABSTRACT

Objective: Conventional vestibular exercises (CVE) for patients with dizziness are sometimes not beneficial enough for the patients. It is thought that table tennis exercises may be beneficial in these patients, especially to improve the vestibular system and posture. The objective of our original study was to assess the vestibular exercises combined with table tennis exercises that can be done comfortably at home, are fun and cost-effective method on body posture.

Methods: In this preliminary study, healthy subjects with balance scores close to normal were recruited. CVE (n=36) and conventional vestibular exercises combined with table tennis (CVE-TT) (n=36) program was performed on two different groups for a 6-weeks. Individuals were evaluated with Sensory Organization Test pre and post the study.

Results: In the CVE-TT group, a statistically significant difference was found between Strategy 5-6, composite (COM) and vestibular (VEST) data scores before and after the study ($p<0.05$). There was a statistically significant difference between Strategy 6 and preference (PREF) data scores in the CVE group in the pre-post comparison ($p<0.05$), while there was a non-significant decrease in the CVE-TT group.

Conclusion: The findings demonstrate that the CVE-TT exercise programme leads to a more significant enhancement in balance performance when compared with CVE exercises. For individuals with dizziness (e.g., residual dizziness) it will be more efficient and entertaining to apply this new method that they can apply at home instead of the classical rehabilitation program.

Keywords: Balance, computerized dynamic posturography, table tennis, vestibular rehabilitation

INTRODUCTION

Balance is essential for many activities of daily living and balance problems (e.g., falls) are major public health problem. To prevent falls, individuals must control their center of mass location over the base of support during both voluntary movements, and in response to external, destabilizing forces (1). Postural stability is achieved by integrating vestibular, visual and somatosensory inputs to produce a motor response (2). The vestibular system plays various roles in postural control. The role it plays in the postural task varies according to the nature of the task and environmental conditions. Similarly, in situations where somatosensory information is less available and visual information is not available in the moment, vestibular information may play a dominant role in maintaining postural control (3).

Vestibular rehabilitation exercises improve quality of life by reducing the degree of handicap, improving the ability to perform daily tasks, and providing long-term postural stability. Rehabilitation programs offer a variety of benefits, including improvements in overall health and balance, a safer gait, and reduced disability due to dizziness (4). Rehabilitation strategies have been applied successfully in the last few decades to initiate central compensation of the tonus imbalance and facilitate substitution in different types of peripheral vestibular dysfunction (5).

Table tennis is an Olympic sports branch and one of the most widely played racquet sports. It requires complex visuospatial perception and movements, including balance control. Table tennis players have been shown to have shorter visual reaction

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times, better executive functions and visuospatial working memory than healthy individuals (6). Recreational table tennis has been associated with improved bone health, physical function and muscle strength. Positive cognitive effects of table tennis training have also been demonstrated (7).

Christensen et al. (8) demonstrated that a 6-week vestibular exercise program improved vestibular function on healthy adolescents. Cone et al. (1) demonstrated in their study, which included 40 healthy young, that a 6-week Wii Fit training improved dynamic balance. These studies are rare studies with normal individuals. To our knowledge, there are no studies on the effect of vestibular exercises combined with table tennis on balance.

There are studies in literature showing the effect of sports on balance (9). However, despite the results of these studies, there are very few studies in which these sports are added to balance exercises. In this study, we studied table tennis, a sport that has not been added to balance exercises before. Since table tennis has a fun aspect as well as positive effects on multisensory systems, we hypothesized that combining it with CVE would yield better results. Our study has a unique value in this respect.

METHODS

Study Population

The study was conducted between March 2023 and April 2023 on healthy individuals aged 18-21 years. The study was explained to each participant, and written informed consent was obtained. All described procedures were conducted following the Declaration of Helsinki. Ethical approval was obtained from the Non-Invasive Clinical Research Ethics Committee of İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee Presidency University with the decision no: 380 and date: 27.06.2018.

Nineteen female and nineteen male individuals (ages: 20.4±1.3 years) were included in the CVE group. Twenty female and sixteen male individuals (ages: 20.2±1.1 years) were included in the study group (F. The individuals did not have any major illness (otologic or neurologic pathology) and/or extensive experience in physical exercises. None of the test subjects were diagnosed with balance disorders, and none of them needed glasses, contact lenses, or hearing aids.

Sample Size and Randomization

Power analysis was performed using G*Power to ascertain whether the sample size would sufficiently detect significant differences. The power analysis revealed a power of 90% with an effect size of 0.50 (large) at a significance level of 0.05, indicating that a sample size of 36 (10). However, since we have two groups, the minimum sample size is calculated as 36*2=72. The effect size equals 0.5 according to Effect size index dz. After this, we randomly assigned a total of 40 patients to the CVE group and 40 patients to the CVE-TT group. A total of 6 people (4 in the CVE group and 2 in the CVE-TT group) dropped out of the study for personal reasons (Figure 1).

Balance Training Program

The exercise program of both groups consisted of three phases. Each phase of the exercise program was performed twice a week for six weeks. Exercises of both groups are shown in Tables 1 and 2. The exercises of the CVE-TT group are demonstrated in Figure 2. In this study, two cushions, one small ball, one table tennis racket and ball, one balance board, one pilates ball and two pilates mats were used. Balance status of the individuals was evaluated with CDP pre and post the study.

Measurements of Postural Control

A NeuroCom Balance Manager (Natus Medical Inc., Seattle, WA) was used to assess postural stability. Sensory Organization Test (SOT), which are subtest of Computerized Dynamic Posturography (CDP), was performed to objectively assess postural stability. This test is used to assess the individual's use of somatosensory, visual, and vestibular input to maintain balance.

Participants were secured in a safety harness and positioned barefoot on the NeuroCom Balance Manager, with their foot placement standardized relative to their height. Data collectors followed standardized written instructions for the SOT protocol, including verbal cues for each trial of each condition. Individuals stood with arms relaxed at their sides, looking straight ahead as still as possible. Participants performed all six SOT conditions, repeating each 20-second trial three times. The individual is presented with six conditions of varying sensory input including eyes open with fixed support (Condition 1), eyes closed with fixed support (Condition 2), sway surround with fixed support (Condition 3), eyes open with sway support (Condition 4), eyes closed with sway support (Condition 5), and sway surround with sway support (Condition 6). In this way, different SOT conditions create sensory discrepancies. The systems (somatosensory, visual and vestibular) that the patient actively uses while maintaining balance, the overall balance score (composite) and the preference for the visual system while maintaining balance are shown at the

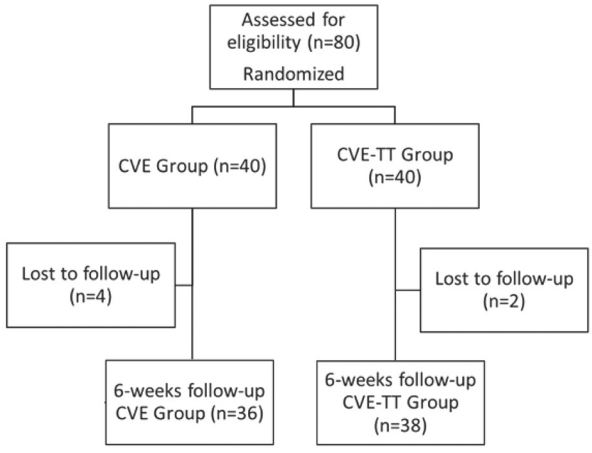

Figure 1. Participants at each stage of the trial
CVE-TT: Conventional vestibular exercises combined with table tennis

Table 1. Conventional vestibular exercises program
EXERCISE PROGRAM 1 (1st-2nd week)
1. Walking back and forth on the soft surface (e.g. cushion, mat) with eyes closed.
2. Standing on one foot on firm surface.
3. Standing on a cushion, with eyes closed, and sitting down standing up continuously.
4. Shaking the head while standing on firm surface with gaze fixation (Rotates the head side to side horizontally with gaze fixed on a stationary target. Side-to-side head movement of w60 at a speed of 90/s, 1.5 hz).
5. Shaking the hand while standing on firm surface with gaze fixation (Extends one arm forward and make the thumb-target-up and turn the arm side to side while focusing on the thumb. Keep the head still and moves only the eyes).
EXERCISE PROGRAM 2 (3rd-4th week)
1. March in place with eyes closed.
2. Standing on the balance board with eyes open.
3. Shaking the head while standing on the soft surface (e.g. cushion, mat) with eyes closed.
4. Standing on the mat with one leg with hands on waist and eyes closed.
5. Walking back and forth on a soft surface (e.g. cushion, mat) with gaze fixation.
EXERCISE PROGRAM 3 (5th-6th week)
1. Walking to the right and left with sharp or wide turns with eye closed.
2. Standing on the balance board with eyes closed.
3. Shaking the head while walking back and forth on the soft surface (e.g. cushion, mat) with gaze fixation (Rotates the head side to side horizontally with gaze fixed on a stationary target. Side-to-side head movement of w60 at a speed of 90/s, 1.5hz).
4. Shaking the head while standing on a soft surface (e.g. cushion, mat) with eyes closed.
5. Shaking the head while sitting on a pilates ball on a soft surface (e.g. cushion, mat) with eyes closed

Table 2. Conventional vestibular exercises combined with table tennis exercises program
EXERCISE PROGRAM 1 (1st-2nd week)
1. Walking back and forth on the soft surface (e.g. cushion, mat) with eyes closed.
2. Standing on a firm surface on a one leg.
3. Standing on a cushion, with eyes closed, and sitting down standing up continuously.
4. Shaking the head while standing on firm surface, (Rotates the head side to side horizontally with gaze fixed on a stationary target. Side-to-side head movement of w60 at a speed of 90/s, 1.5 hz).
5. Table tennis ball bounce with table tennis racket.
EXERCISE PROGRAM 2 (3rd-4th week)
1. March in place with eyes closed.
2. Standing on the balance board with eyes open.
3. Shaking the head while standing on the soft surface (e.g. cushion, mat) with eyes closed.
4. Standing on the mat with one leg with hands on waist and eyes closed.
5. Playing table tennis between a table and a wall (see picture).
6. Controlling the ball on the racket and walking without bouncing it.
EXERCISE PROGRAM 3 (5th-6th week)
1. Walking to the right and left with sharp or wide turns with eye closed.
2. Standing on the balance board with eyes closed.
3. Shaking the head horizontally with gaze fixation on a stationary target while walking back and forth on the soft surface (e.g. cushion, mat) (Side-to-side head movement of w60 at a speed of 90/s, 1.5 hz).
4. Shaking the head while standing on a soft surface (e.g. cushion, mat) with eyes closed.
5. Bouncing the ball between the racket and the table (see the picture).
6. Bouncing a ball with a racket against the wall (without using the table) (see the picture).

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end of the test. Participants must compensate for these sensory discrepancies and maintain their balance. Each person completed the tests as shown in Figure 3.

A balance score is obtained based on staying within 8.5 degrees in the anterior direction and 4 degrees in the posterior direction, previously determined on the SOT and measured by the automatic device. Less postural sway indicates better postural stability in the sagittal plane and produces a proportional balance score (greater is better). If the participant falls or gets a negative value by swaying out of a total of 12.5 degrees, they receive 0 balance points for that trial. More difficult conditions (3-6) receive larger weights and an overall COM score uses a weighted average of all scores. A higher COM score indicates better postural control. Specific sensory systems are identified using ratio combinations of the average balance scores for each condition. Postural strategy scores are determined between 0-and 100, with 0 indicating the usage of only hip strategy, while 100 indicates the usage of sole ankle strategy. The better one maintains balance (i.e., the less sway), the more ankle is used.

Figure 2. Table tennis exercises samples. A) Bouncing the ball between the racket and the table (CVE-TT/3rd Exercise Program/5th exercise). B) bouncing a ball with a racket against the wall (without using the table) (CVE-TT/3rd Exercise Program/6th exercise). C) Controlling the ball on the racket and walking without bouncing it (CVE-TT/2nd Exercise Program/6th exercise). D) Playing table tennis between a table and a wall (CVE-TT/2nd Exercise Program/5th exercise)

CVE-TT: Conventional vestibular exercises combined with table tennis

Statistical Analysis

Statistical analysis was performed using SPSS IBM 22.0 program. The normal distribution of the values was assessed using the One-Sample Kolmogorov-Smirnov test. The descriptive statistics are reported as mean and standard deviaton for normally distributed variables and median and interquartile ranges for non-normally distributed variables. Paired Student's t-test was used to determine whether there was a significant difference between the groups for normal distribution, otherwise Wilcoxon test is used. The significance value was taken as 0.05 (8). A randomized Two-Group Pretest-Posttest Design was performed. Mann-Whitney U test was performed to see that the pre-exercise values of the CVE group and CVE-TT group were similar. Wilcoxon test was used to investigate whether there was a significant difference between the CVE and CVE-TT groups for the pre- and post-study groups.

RESULTS

In the CVE-TT, a statistically significant difference was found between Strategy 5, Strategy 6, COM and VEST data scores pre and post the study ($p<0.05$, $p<0.01$). No significant difference was found in Strategy 1, Strategy 2, Strategy 3, Strategy 4, somatosensorial (SOM), visual (VIS) and PREF data scores pre- and post the study ($p>0.05$) (Table 3, Figure 4).

In the CVE, a statistically significant difference was found between Strategy 6 and PREF data scores pre and post the study ($p<0.05$). No significant difference was found in Strategy 1, Strategy 2, Strategy 3, Strategy 4, Strategy 5, COM, SOM, VIS, and VEST data scores pre and post the study ($p>0.05$) (Table 3).

Post study results between CVE and CVE-TT were compared, a statistically significant difference was found between Strategy 4 scores of CVE and CVE-TT post study ($p<0.05$). Although the post study scores of CVE-TT were higher than those of CVE, no significant difference was found in the post-study Strategy 1, Strategy 2, Strategy 3, Strategy 5, Strategy 6, COM, SOM, VIS, PREF and VEST scores of CVE and CVE-TT ($p>0.05$) (Table 3).

DISCUSSION

Vestibular, visual, and somatosensory systems provide information to the central nervous system (CNS) to orient the body relative to itself and the external environment. This information is highly integrated into multiple CNS levels, allowing the system to modify the output based on the reliability of the input received (11). Preliminary researches have demonstrated that vestibular rehabilitation positively affects cognitive skills, especially for patients with central disorders (12). In the study of Schaefer and Scornaienchi (13) it was seen that playing table tennis for a long time provides cognitive benefits. Because of these results, we thought that table tennis might also be cognitively beneficial in vestibular rehabilitation. The increase of COM data in our study may be associated with this hypothesis.

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Table 3. Comparison between conventional vestibular exercises group and conventional vestibular exercises with table tennis exercises group of vestibular data and composite data in sensory organization test sensory analysis

Mean				p-value			
	CG Pre-exercise	CG Post-exercise	TG Pre-exercise	TG Post-exercise	Pairwise pre- and post-exercise of CG	Pairwise pre-and post-exercise of TG	Pairwise post-exercise of CG and TG
COM					0.340	0.004**	0.096
Mean±SD	78±3.74	79.50±4.74	77.80±5.89	84.28±5.41			
SOM					0.893	0.224	0.815
Median (IQR)	97 (1.91)	96 (2.32)	95 (3.40)	100 (3.40)			
VIS					0.917	0.204	0.102
Median (IQR)	71 (10.39)	86 (14.35)	80 (10.00)	93 (7.50)			
PREF					0.028*	0.821	0.710
Median (IQR)	93 (6.90)	100 (6.52)	94 (10.85)	98 (11.40)			
VEST					0.249	0.003**	0.066
Mean±SD	68.79±9.14	72.06±8.39	70.68±9.37	81.45±8.63			
Strategy I					0.705	0.113	0.182
Median (IQR)	93 (3.00)	92 (3.12)	91 (3.10)	97 (1.00)			
Strategy II					0.140	0.968	0.053
Median (IQR)	93 (2.50)	90 (2.60)	93 (2.50)	98 (2.10)			
Strategy III					0.892	0.588	0.349
Median (IQR)	93 (4.25)	91 (2.75)	90 (2.95)	95 (2.55)			
Strategy IV					0.104	0.465	0.046*
Median (IQR)	89 (2.37)	85 (6.05)	87 (5.60)	94 (4.10)			
Strategy V					0.893	0.023*	0.085
Median (IQR)	77 (12.62)	79 (10.82)	77 (8.80)	85 (7.70)			
Strategy VI					0.028*	0.008**	0.540
Median (IQR)	78 (9.00)	84 (7.80)	77 (8.75)	88 (8.80)			

*p<0.05; **p<0.01, CG: Conventional vestibular exercises group, COM: Composite data, IQR: Interquartile range, PREF: Preference data, SD: Standard deviation, SOM: Somatosensorial data, TG: Conventional vestibular exercises combined with table tennis group, VEST: Vestibular data, VIS: Visual data

In the 1940s, Cawthorne-Cooksey's early studies in vestibular rehabilitation revealed that physical exercise positively affected balance function. However, the repetition of the study and the patients' boredom during these studies led the academicians to develop other various exercises. We thought that table tennis exercises, which can be done comfortably at home, are fun and cost-effective, could be the solution. It has been thought that table tennis is a beneficial sport for balance, mainly because of its quick response to sudden reactions and the requirement of rapid eye follow-up, directing the eye to ball-tracking instead of the task of balance control, thus increasing the effectiveness of the vestibular system in maintaining balance.

In this study, there was an increase in vestibular data due to our use of CVE-TT. Our main theme is to design CVE-TT for those whose balances did not develop sufficiently only through vestibular rehabilitation exercises. In addition to the development of the vestibular system, the increase in the results of the SOT strategy score for fifth and sixth conditions indicates that the person uses the ankle strategy better while balancing and has been effective in decreasing the oscillation of the person, and this showed that when vestibular exercises are used in combination with table tennis, it is associated with less oscillation as the vestibular system develops in difficult balance conditions.

While there was a significant difference in VEST and COM values in the study group, COM and VEST values increased in the group where only vestibular exercises were performed, but this increase was not statistically significant. This shows that CVE-TT significantly improve the vestibular system and posture control. In the CVE group, the increase in PREF data showed an increased dependence on the visual system, and this shows that in the absence of table tennis, trust in the visual system comes to the fore rather than the vestibular system.

There was a significant increase in PREF values in the CVE group in the pre-post comparison, while there was a decrease in the CVE-TT group. The reason for this is that the PREF data is to rely on eye information. In other words, we increased confidence in the vestibular system and decreased eye dependence in line with the CVE-TT exercises we performed.

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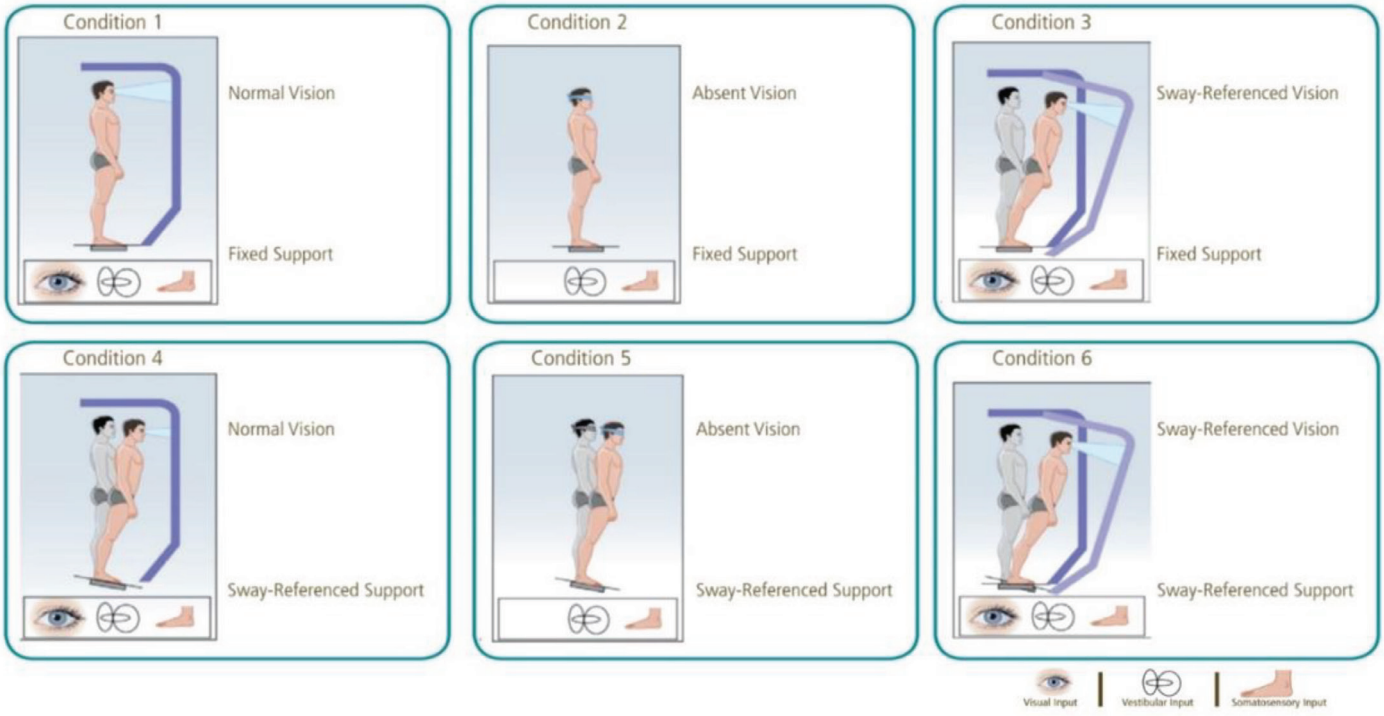

Figure 3. Sensory organization test conditions

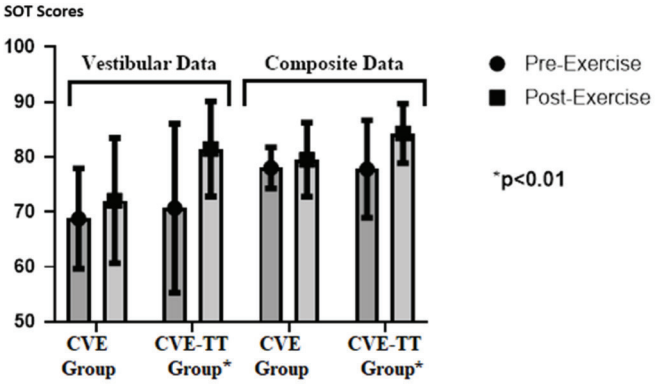

Figure 4. Comparison between CVE group and CVE-TT group of vestibular data and composite data in sensory organization test sensory analysis

Tekin Dal et al (14). compared the effects of activity-based home program and Cawthorne Cooksey exercises in 75 patients aged 18-65 years with chronic unilateral peripheral vestibular disorders. They found a statistically significant improvement in Strategy 5, Strategy 6 and composite data scores in the activity group compared to the exercise group (15). In our study, we found a statistically significant difference between pre- and post-study Strategy 5-6, COM and VEST data scores in the CVE-TT group. Although the two studies have similar and different aspects, the advantages of activity-based programs that can be applied at home have emerged. In our study, unlike the study of Tekin Dal et al. (14) table tennis was applied as the main component of the program.

In their study on adolescents, Christensen et al. (8) showed that a 6-week vestibular exercise program improved vestibular function. While the VEST data improved significantly in the group in which CVE-TT were applied, the difference was not statistically significant in the group where only CVE were applied, and this has shown that table tennis exercises can be a helpful method for the development of the vestibular system of individuals.

Rogge et al. (15) study shows that balance training leads to neuroplasticity in brain regions associated with visual and vestibular self-motion perception. Because these regions (especially the hippocampus) are known for their role in spatial orientation and memory, stimulating visual-vestibular pathways during self-movement can mediate the beneficial effects of physical exercise on cognition (15). Therefore, since table tennis and balance exercises stimulate visual-vestibular pathways, it is predicted that the patient's balance would benefit from this interaction. Elite expert table tennis players show stronger cortico-cortical communication between right-temporal and premotor areas than amateurs (16). In addition to these findings on coincidence anticipation performance, visuomotor reaction experiments revealed faster reaction times in table tennis players when compared to non-athletes as well as experienced tennis players (6). These results prove that table tennis activates different structures in the brain and makes the person more balanced depending on mobility. This situation supports the increase in our study's COM score.

Öztürk et al. (17) evaluated individuals with VEMP and vHIT tests in the presence of visual illusions. According to this study, an increase was observed in the VEMP amplitudes of the individuals when the visual illusion was given, and significant increases were observed in the gains of some semicircular canals. This showed that the vestibular system works more efficiently with the stimulation of the visual system. Consistent with this study, the better output of vestibular data can be explained by the inclusion of a sport such as table tennis, where visual attention is critical in vestibular rehabilitation (17).

Study Limitations

There are several limitations in this study. In this study, young adults were included as the age group. These individuals were university students. However, considering that BPPV is more common in middle and older age groups, healthy individuals in this age group could have been included.

This is a preliminary study. Thus, instead of testing a study of unknown effects on patients, we first tested it on healthy subjects so that we could see improvement even in healthy subjects whose data were within normal limits. The use of healthy subjects may not be a weakness for this study, but these results may not be reflective for a sample of people with persistent postural perceptual dizziness (PPPD) or residual dizziness (RD). Therefore, its application to these patient groups is recommended as a suggestion for further studies.

CONCLUSION

As a result, it has been shown that table tennis exercises, which are not difficult to implement, are low cost, can be played alone (against the wall or table), and will be more beneficial for general balance and vestibular system development than conventional methods. This method assumes that people who do not have a pathological condition in objective tests but still feel unbalanced (dizzy) can also develop. In this period, especially for individuals with balance problems, a rehabilitation program that they can implement at home rather than going to the clinic will be more efficient, amusing, and risk-free. We think that the rehabilitation program, will be a healthy option for individuals with subjective balance problems. For further research, it is suggested that this approach may objectively benefit patients with subjective dizziness such as PPPD or RD.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-Invasive Clinical Research Ethics Committee of Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee Presidency University with the decision no: 380, date: 27.06.2018.

Informed Consent: The study was explained to each participant, and written informed consent was obtained.

Footnotes

Author Contributions: Concept – K.E.; Design – K.E., C.Y., M.B.Ş.; Data Collection and/or Processing – K.E., C.Y., Analysis and/or Interpretation - K.E., C.Y., S. E., M.B.Ş.; Literature Search – K.E., C.Y., S. E., M.B.Ş.; Writing – K.E., C.Y., S. E., M.B.Ş.

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

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Investigation of the Relationship between Tinnitus Severity, Tinnitus Loudness, Hyperacusis and Anxiety Level in Individuals with Tinnitus

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ABSTRACT

Objective: The relationship between the effect of tinnitus on the individual and anxiety and hyperacusis should be investigated. The aim of the study is to examine the relationship between tinnitus loudness, tinnitus handicap level, hyperacusis level, and state and trait anxiety levels in individuals with subjective chronic tinnitus.

Methods: A cross-sectional approach was employed in this study. The study included 44 participants, consisting of 24 men and 20 women. The mean age of the participants was 53.7±16.6 years. The loudness of tinnitus was assessed using the visual analogue scale (VAS), while its severity was evaluated with the Tinnitus Handicap Inventory (THI). The Khalfa hyperacusis scale (HQ) was employed to determine the degree of hyperacusis, and the State and Trait Anxiety Inventory (STAI) was utilized to assess anxiety levels in 44 individuals experiencing subjective chronic tinnitus. Correlation and comparison analyses were conducted between the scales.

Results: A significant statistical correlation was observed between THI and VAS, HQ, and STAI ($p<0.05$). Anxiety levels differed significantly between individuals with and without hyperacusis ($p<0.05$).

Conclusion: Tinnitus severity is associated with tinnitus loudness, hyperacusis, anxiety scores. Accordingly, it can be said that as the tinnitus handicap score increases, perceived tinnitus loudness, hyperacusis, and state and trait anxiety also increase.

Keywords: Subjective tinnitus, tinnitus severity, tinnitus loudness, hyperacusis, state and trait anxiety

INTRODUCTION

Tinnitus refers to the perception of sound in the absence of an identifiable external acoustic source (1). An estimated 10%-15% of the population experiences tinnitus, with 5% of these individuals reportedly having clinically significant and distressing symptoms (2).

Although the majority of individuals with tinnitus adapt well, one in five reports emotional distress (3). Those affected often find tinnitus particularly intrusive, with common coexisting issues such as concentration difficulties, depression, anxiety, irritability, and sleep disturbances (4).

Studies indicate that individuals with tinnitus exhibit a higher prevalence of depression, anxiety, and somatic symptom disorders compared to those without tinnitus. Additionally, a positive correlation has been observed between tinnitus perception and depression levels (5). While hearing loss is recognized as a risk factor for tinnitus, research suggests that it does not play a significant role in the association between tinnitus and depression, anxiety, or somatic symptom disorders (6).

Another condition commonly observed in individuals with tinnitus is hyperacusis. Hyperacusis is characterized by a decreased tolerance to sounds that are typically perceived as normal by the majority of the population or that were previously considered normal by the individual before the onset of hyperacusis (7). Sixty percent of tinnitus patients are reported to experience significantly reduced sound tolerance, with 30% of these individuals also suffering from hyperacusis (8).

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Hyperacusis has been shown to negatively affect various aspects of life, including quality of life, emotional well-being, hearing ability, sleep patterns, and concentration; in some cases, it may even lead to psychiatric disorders (9). A study found that participants with tinnitus accompanied by hyperacusis exhibited higher levels of stress, anxiety, depression, reduced quality of life, tinnitus distress, discomfort from sound, and heightened awareness of their symptoms (10).

Tinnitus and hyperacusis are difficult to assess because of their subjective perception, and the use of various assessment scales is crucial to evaluate the effects of tinnitus and hyperacusis on the individual. The Tinnitus Handicap Inventory (THI) is a well-established tool used to assess how tinnitus affects an individual's everyday life (11). The hyperacusis questionnaire (HQ), created by Khalfa, is designed to evaluate the presence, severity, and impact of sound sensitivity symptoms (12). Anxiety and depression are commonly observed in individuals with tinnitus (5). The State and Trait Anxiety Inventory (STAI) is a commonly used scale to measure the individual's level of anxiety (13). Research has indicated a connection between the results of the THI and the STAI (14).

The chronicity of tinnitus and its effects on individuals are shaped not only by auditory factors but also by cognitive-emotional and psychological components. However, studies evaluating the level of tinnitus severity holistically with perceived loudness, hyperacusis, and anxiety levels are limited. This study aims to reveal the dynamic relationships between the subjective and psychological components of tinnitus by analyzing the determinants of tinnitus handicap level in individuals with subjective chronic tinnitus. In this study, it is hypothesized that the level of handicap caused by tinnitus is related to the perceived tinnitus loudness, hyperacusis, and state and trait anxiety levels. The findings may shed light on individualized assessment and intervention approaches in tinnitus management.

METHODS

This research was designed as a cross-sectional study. It was approved by the İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee (decision no.: 1560, date: 17.04.2024) and conducted in compliance with the principles outlined in the Helsinki Declaration. All participants provided written informed consent prior to their inclusion in the study.

Participants

The sample size was determined based on an effect size of 0.5, a power of 0.90, and a significance level of 0.05 (Type I error) with analysis based on the t-test method using the G*Power program, reaching 44 participants (15). The study involved 44 patients who visited the Hearing, Speech, and Balance Unit of the Department of Otorhinolaryngology at Dokuz Eylül University Hospital, reporting subjective, chronic tinnitus complaints. Two patients diagnosed with Meniere's disease were excluded due to the exclusion criteria of the study. A detailed history of tinnitus was taken from each patient. The data obtained were recorded in the information form. The study included patients who had chronic subjective tinnitus for a minimum of three months and presented with a Type A tympanogram. Individuals with psychological, neurologic, and otologic complaints; systemic diseases that may cause objective tinnitus; and hearing aid users were excluded.

Audiological Assessment

Air and bone conduction hearing thresholds were measured through pure tone audiometry using the MADSEN clinical audiometer (Madsen Astera 2, Otometrics, Denmark). Air conduction testing was carried out with TDH39 supra-aural headphones, and bone conduction testing was performed using the B71 bone conduction vibrator, both in a soundproof booth. Air conduction thresholds were assessed at octave frequencies ranging from 250 to 8000 Hz, while bone conduction thresholds were measured at octave frequencies between 500 and 4000 Hz, following the modified Hughson-Westlake method.

Acoustic immittance measurements were performed using the Otometrics Diagnostic Clinical device (Otometrics, Denmark). Middle ear pressure, compliance, and the equivalent volume of the external ear canal were measured using an acoustic stimulus at 226 Hz and an intensity of 85 dB sound pressure level. The type of tympanogram was classified according to the Jerger classification.

Scales

The visual analogue scale (VAS), THI, HQ, and STAI were administered to the individuals included in the study.

VAS

The VAS was employed to evaluate the perceived loudness of tinnitus. Participants rated the intensity of their tinnitus on a scale from 0 (no tinnitus) to 10 (extremely loud). Higher scores reflect a stronger perception of tinnitus loudness.

Tinnitus Handicap Inventory

This scale evaluates the effect of tinnitus on quality of life, offering insights into its severity and intensity. The scale was originally developed in 1996 (16), and its Turkish validity and reliability were assessed in 2007 (11). The THI contains 25 questions, categorized into three subscales: functional, emotional, and catastrophic. Responses are scored as follows: "No" = 0 points, "Sometimes" = 2 points, and "Yes" = 4 points, with the total score reflecting the sum of these values. Higher scores represent a greater burden of tinnitus and a more pronounced negative effect on quality of life (11).

Hyperacusis Questionnaire

The scale comprises 14 items in a 4-point Likert format, divided into three subscales: attention, social, and emotional. Responses are rated as follows: "No" (0 points), "Yes, a little" (1 point), "Yes, quite a lot" (2 points), and "Yes, a lot" (3 points). The total score is obtained by adding the individual responses, and hyperacusis is evaluated based on this score.

The highest possible score on the scale is 42. A score below 15 suggests no hyperacusis, a score between 15 and 28 indicates

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suspected hyperacusis, and a score of 29 or above signifies complete hyperacusis. The scale's Turkish validity and reliability were assessed previously (17).

State and Trait Anxiety Inventory

The inventory comprises two subscales, each consisting of 20 items, aimed at evaluating an individual's state and trait anxiety. The State Anxiety Scale gauges how a person feels at a specific moment under particular conditions, while the Trait Anxiety Scale measures how they generally feel, regardless of their immediate environment or situation. Developed by Spielberger in 1983 and later adapted into Turkish by Öner and Le Compte in 1985, the scale uses a 4-point Likert format. It includes both direct and reverse-scored items. For reverse-scored items, responses with a weight of 1 are changed to 4, and those with a weight of 4 are changed to 1, before calculating the total score. The score range for each subscale is from 20 to 80. Higher scores reflect higher anxiety levels, while lower scores indicate lower anxiety levels (13).

Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics V26. Descriptive statistics were reported as frequency and percentage for categorical variables, and as median, interquartile range, mean, and standard deviation for numerical variables.

The normality of numerical variables was evaluated using the Shapiro-Wilk test, along with histogram and box plot visualizations. Relationships between numerical variables were examined using the Pearson correlation coefficient, as the normality assumption was met. Comparisons between two independent groups were conducted using the t-test. A significance level of 0.05 was established.

RESULTS

Among the 44 participants in the study, 24 were male (54.5%) and 20 were female (45.5%). The average age of the participants was 53.7±16.6 years. Table 1 provides an overview of the demographic characteristics of the participants.

No significant correlation was observed between age and the VAS, THI, HQ, STAI-S, or STAI-T scores ($p>0.05$). Additionally, there were no gender-based differences in the scale scores ($p>0.05$).

The correlation analysis exploring the relationships between VAS, THI, HQ, STAI-S, and STAI-T scores revealed a low but statistically significant positive correlation between THI and VAS scores (r=0.340, p=0.024). As the level of tinnitus severity increases, the perceived tinnitus loudness increases. A moderate, statistically significant positive correlation was observed between the THI and HQ scores (r=0.423, p=0.004). As the tinnitus severity increases, the severity of hyperacusis also increases. A statistically significant positive correlation was observed between the THI score and the STAI-S score at a low level (r=0.388, p=0.009), and between the THI score and the STAI-T score at a moderate level (r=0.510, $p<0.001$). As the tinnitus severity increases, both the state and trait anxiety levels also increase.

A moderate statistically significant positive correlation was observed between the HQ score and the STAI-S score (r=0.474, p=0.001), as well as between the HQ score and the STAI-T score (r=0.501, p=0.001). There is a positive relationship between the level of hyperacusis and both state and trait anxiety levels. As the level of hyperacusis increases, anxiety levels also increase. A moderate, statistically significant positive correlation was observed between the STAI-T and STAI-S scores (r=0.548, $p<0.001$). Table 2 presents the correlations among VAS, THI, HQ, STAI-S, and STAI-T.

When hyperacusis scores were grouped, 25 participants (56.8%) were in the no hyperacusis group, 16 participants (36.4%) were

Table 1. Information about the participants

	Mean±SD	Median (IQR)
Age (years)	53.7±16.6	
Duration of tinnitus (month)		48 (114.75)
Tinnitus localization	n	%
Left	17	38.6
Right	11	25.0
Both (right and left ears)	14	31.8
Head	2	4.5

n: Number of participants, SD: Standard deviation, IQR: Interquartile range

Table 2. Correlation between VAS, THI, STAI-S, STAI-T

Variables	VAS	THI	HQ	STAI-S
THI				
r	**0.340***			
p	**0.024**			
n	44			
HQ				
r	-0.040	**0.423****		
p	0.796	**0.004**		
n	44	44		
STAI-S				
r	-0.041	**0.388****	**0.474****	
p	0.794	**0.009**	**0.001**	
n	44	44	44	
STAI-T				
r	0.056	**0.510****	**0.501****	**0.548****
p	0.716	**<0.001**	**0.001**	**<0.001**
n	44	44	44	44

r: Correlation coefcient, n: Number of participant, VAS: Visual analog scale, THI: Tinnitus Handicap Inventory, HQ: Hyperacusis questionnaire, STAI-S: State Trait Anxiety Inventory- State, STAI-T: State Trait Anxiety Inventory-Trait, *Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level

in the suspected hyperacusis group, and 3 participants (6.8%) were in the complete hyperacusis group. Since the participants were not equally distributed across the hyperacusis groups, no statistical analysis was conducted among the three groups. The suspected hyperacusis and complete hyperacusis groups were combined to form a hyperacusis group. The scale results were compared between the group without hyperacusis and the group with hyperacusis. No significant difference was found in the VAS and THI scores between the groups, but anxiety levels differed significantly ($p<0.05$). The group with hyperacusis had higher mean state and trait anxiety scores than the other group. Consequently, anxiety levels tend to be higher in individuals with hyperacusis. The t-test comparison of the scales in patients with and without hyperacusis is presented with a box plot in Figure 1. Scale comparisons of the groups with and without hyperacusis are presented in Table 3. In addition to statistically significant group differences in STAI-S and STAI-T scores, effect size calculations indicated large effects, (Cohen's d=0.95 and 0.81, respectively), suggesting clinically meaningful differences in anxiety levels between groups.

The average air conduction hearing thresholds of individuals with tinnitus in the 250-8000 Hz range are presented in Table 4. Eight participants had bilateral air conduction hearing thresholds below 25 dB in the 250-8000 Hz range, indicating normal hearing. In 22 participants, thresholds were normal according to the pure-tone air conduction average at four frequencies (0.5, 1, 2, 4 kHz) in both ears, but hearing loss increased towards higher frequencies. In 14 participants, mild-to-moderate sensorineural hearing loss progressively worsening at higher frequencies was observed bilaterally. Overall, participants exhibited hearing loss that became more pronounced at higher frequencies, as indicated by their average hearing thresholds. Pure-tone averages were created for both ears at 0.5, 1, 2, and 4 kHz. The relationship between pure-tone averages and the VAS, THI, HQ, and STAI scales was examined, but no statistically significant correlation was observed ($p>0.05$).

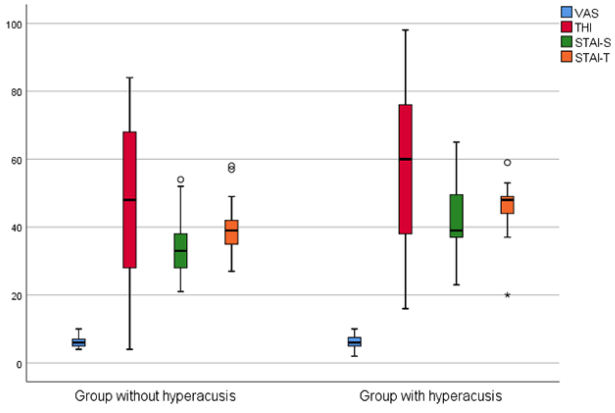

Figure 1. T-test comparison of scales in patients with and without hyperacusis box-plot
VAS: Visual analogue scale, STAI-S: State Trait Anxiety Inventory-State, STAI-T: State Trait Anxiety Inventory-Trait, THI: Tinnitus Handicap Inventory

DISCUSSION

This study examined the connection between tinnitus severity, perceived tinnitus loudness, hyperacusis, and anxiety in individuals with subjective chronic tinnitus. The goal was to assess the impact of tinnitus on daily life and explore associated factors.

A study examining potential risk factors for tinnitus in patients with anxiety disorder found that the lifetime prevalence of tinnitus was greater in individuals with anxiety disorder compared to those without it (18). Several studies indicate that personality traits, as well as anxiety and depression, might worsen tinnitus symptoms. According to Andersson and Vretblad, anxiety sensitivity could be a contributing factor to tinnitus-related distress (19). A study reported that individuals with high anxiety sensitivity experienced greater tinnitus discomfort and more negative life impacts than those with normal sensitivity, regardless of hearing loss level. Tinnitus distress and tinnitus handicap have been shown to be predictable based on elevated levels of anxiety sensitivity (20).

A study comparing individuals with chronic tinnitus and normal hearing to healthy controls found significantly higher depression levels in the tinnitus group, with no differences in anxiety or personality traits. However, within the tinnitus group, tinnitus severity was positively correlated with anxiety, anxiety sensitivity, and neurotic personality traits (21). In a study measuring anxiety and depression levels in individuals with tinnitus, both state and trait anxiety were found to be associated with the THI (22). Crocetti et al. (14) found that THI and STAI-T were associated with VAS, which measures tinnitus severity. The studies examining the link between anxiety

Table 3. T-test comparison of scales in patients with and without hyperacusis

Variables	Group without hyperacusis (n=25)		Group with hyperacusis (n=19)		p-value	Cohen's d
	Mean	SD	Mean	SD		
VAS	6.2	1.8	5.8	2.2	0.572	0.19
THI	47.1	21.8	57.8	26.8	0.149	0.43
STAI-S	33.6	8.5	42.7	10.8	**0.010***	0.95
STAI-T	39.3	7.7	45.7	8.1	**0.004****	0.81

n: Number of participants, SD: Standard deviation, VAS: Visual analog scale, THI: Tinnitus Handicap Inventory, HQ: Hyperacusis questionnaire, STAI-S: State Trait Anxiety Inventory-State, STAI-T: State Trait Anxiety Inventory-Trait, Cohen's d values represent effect sizes for group comparisons. Small effect: d=0.2, medium: d=0.5, large: d=0.8 (Cohen, 1988). *p<0.05, **p<0.01 (Group differences are statistically significant)

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Table 4. 250-8000 Hz mean air conduction hearing thresholds

Mean hearing thresholds of all participants		
	Right median (IQR)	Left median (IQR)
250 Hz	10 (10)	10 (10)
500 Hz	10 (15)	10 (15)
1000 Hz	15 (15)	15 (15)
2000 Hz	20 (25)	20 (20)
4000 Hz	32.5 (40)	32.5 (42.5)
6000 Hz	40 (38.75)	45 (38.75)
8000 Hz	45 (53.75)	52.5 (40)

IQR: Interquartile range

and tinnitus in individuals with tinnitus reveal a significant association between anxiety and tinnitus severity. In our study, a statistically significant positive correlation was found between tinnitus severity and both state and trait anxiety. The study findings also show that state and trait anxiety levels are positively correlated. It can be stated that as the tinnitus handicap level increases, both state and trait anxiety levels also increase.

Yakunina and Nam (23) found that tinnitus loudness measured by VAS did not correlate with psychoacoustically matched tinnitus loudness and minimum masking level (MML). However, it correlated with subjective tinnitus distress measures such as the THI score, daily tinnitus duration measured by VAS, discomfort and distress levels, and depression score. It has been reported that tinnitus loudness determined by VAS is influenced much more by emotional distress and depression than by hearing loss. Rating the perceived tinnitus loudness is associated with the extent to which an individual is affected by tinnitus, and patients who are more disturbed by tinnitus tend to rate its loudness higher (23). In the study by Cho et al. (22), it was shown that VAS loudness is associated with THI, but not with depression or STAI. In our study, the VAS score shows a significant positive relationship with THI but not with the HQ and STAI scales. While perceived tinnitus loudness is related to the impact of tinnitus on daily life, it may not be directly related to hyperacusis and anxiety levels. As the negative impact of tinnitus on daily life intensifies, the VAS score correspondingly increases.

Psychological distress, including anxiety and depression, is considered a crucial factor in the accurate diagnosis and effective treatment of hyperacusis. Regardless of normal hearing function, it is recommended that patients presenting to the clinic due to hyperacusis should also be evaluated for psychological distress for an accurate diagnosis. Research has demonstrated that individuals with hyperacusis exhibit higher anxiety and depression scores than those in the control group (24). In the study by Erinc and Derinsu (17), participants who scored lower on the Beck Anxiety Scale had lower hyperacusis scores, while those who scored higher had higher hyperacusis scores. Jacquemin et al. (25) found that the group with hyperacusis scored higher on the Tinnitus Functional Index, Hospital Anxiety and Depression Scale, and VAS (loudness) than the group without hyperacusis. As a result, it has been proposed that the presence of hyperacusis may signal a greater need for treatment. Clinicians should be mindful of the increased risk of comorbid anxiety and depression in patients with hyperacusis (25). Individuals with hyperacusis complaints exhibit greater tinnitus distress along with more pronounced symptoms of anxiety and depression. These findings highlight the impact of hyperacusis on emotional well-being (26).

A study utilizing the Tinnitus Primary Function Questionnaire (TPFQ) to assess the functional impact of tinnitus found a positive correlation between the TPFQ and HQ. The findings of this study indicate that hyperacusis may affect the severity of tinnitus. Additionally, having an HQ score of 28 or higher significantly increases the likelihood of reporting tinnitus (27). Cederroth et al. (10) found a significant association between hyperacusis and tinnitus, especially in cases of severe tinnitus. In this study, participants with both tinnitus and hyperacusis exhibited worse outcomes across various factors, including stress, anxiety, depression, quality of life, tinnitus distress, sound loudness, discomfort, and awareness, compared to those without hyperacusis (10).

In our study, a positive significant relationship was found between HQ and THI, STAI-S, and STAI-T. As the level of hyperacusis increased, both the tinnitus severity and anxiety scores also increased. Consistent with findings in the literature, this study also shows that hyperacusis is associated with tinnitus and emotional state. In our study, anxiety scores were higher in the group with hyperacusis than in the group without hyperacusis. No significant differences were observed in the VAS and THI scores between the groups with and without hyperacusis. The lack of differences in other scales between the groups could be due to the small number of participants in the complete hyperacusis group and the merging of this group with the suspected hyperacusis group to form the "group with hyperacusis". It is recommended that evaluations be repeated in a larger sample with a more balanced distribution of the complete hyperacusis and no hyperacusis groups. Our findings highlight the importance of assessing anxiety levels in individuals with hyperacusis.

Aazh et al. (28) found that THI is related to VAS, HQ, and HADS, which measures anxiety and depression. In the same study, age was not found to be significantly related to THI and HQ. Furthermore, no significant correlation was observed between THI scores and the hearing thresholds of the better or worse ear. Udupi et al. (29) showed that the perceived tinnitus handicap level is related to depression but not to hearing loss, age, or gender. Although tinnitus is highly prevalent among patients with hearing loss, other studies have found no significant correlation between tinnitus

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severity and hearing thresholds (30). Our study's finding of no correlation among age, gender, average hearing thresholds, and the scales aligns with results reported in the literature.

Study Limitations

In our study, a three-category comparison was not possible due to the uneven distribution of data across the hyperacusis scale categories. Specifically, the complete hyperacusis group included only three individuals, which would have compromised statistical power and generalizability. Therefore, the suspected hyperacusis and complete hyperacusis groups were combined for analysis. It is recommended to compare scale scores in a larger sample with a more balanced distribution across categories. Additionally, a categorical evaluation between those with and without hearing loss could not be performed. Although the participants' hearing configuration was generally characterized by high-frequency hearing loss, there were individual differences. Future studies could better evaluate the impact of hearing loss on the scales by focusing on participants with specific degrees and configurations of hearing loss, which may help reduce its potential effects. In our study, the age range was 18-81, covering a broad span. More specific findings could be obtained by narrowing the age range and focusing on a specific age group.

CONCLUSION

In conclusion, the tinnitus severity experienced by individuals with subjective chronic tinnitus is positively correlated with VAS, HQ, and STAI. Therefore, it is important to consider common comorbidities such as hyperacusis and anxiety when evaluating individuals with tinnitus. It is suggested that a holistic approach should be adopted in the treatment for individuals with tinnitus.

Ethics

Ethics Committee Approval: It was approved by the İzmir Bakırçay University Non-Interventional Clinical Research Ethics Committee (decision no: 1560, date: 17.04.2024).

Informed Consent: All participants provided written informed consent prior to their inclusion in the study.

Footnotes

Author Contributions: Concept - E.A.Ö.A., S.M.D.; Design - E.A.Ö.A., S.M.D.; Data Collection and/or Processing - E.A.Ö.A.; Analysis and/or Interpretation - E.A.Ö.A., S.M.D., S.A., G.K.; Literature Search - E.A.Ö.A.; Writing - E.A.Ö.A., S.M.D., S.A., G.K.

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

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Evaluation of the Relationship between Bladder Wall Thickness and Pathological Findings in Patients with Hematuria

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ABSTRACT

Objective: This study aimed to evaluate the relationship between bladder wall thickness (BWT), measured via ultrasonography, and histopathological findings in patients presenting with hematuria, and to determine the predictive value of BWT for urothelial malignancy.

Methods: Patients diagnosed with hematuria and who underwent bladder biopsy between January 2010 and June 2023 were retrospectively analyzed. Patients were categorized into benign and malignant pathology groups. Demographic data, BWT measurements, and biopsy results were compared.

Results: Benign pathology was detected in 86.8% and urothelial carcinoma in 13.2% of 175 patients. The malignant group was older (median 67.0 vs. 44.5 years; $p<0.001$) and had a higher proportion of males compared to the non-malignant group ($p=0.002$). No significant difference in BWT was observed between the groups ($p=0.132$).

Conclusion: Although increased BWT may indicate an underlying pathological process in patients with hematuria, it is not sufficient alone to predict malignancy. BWT should be assessed alongside clinical evaluation and advanced diagnostic methods.

Keywords: Bladder cancer, bladder wall thickness, biopsy, chronic cystitis, hematuria

INTRODUCTION

Hematuria is a prevalent symptom of both urological and nephrological disorders, with a prevalence ranging from 2.5% to 20% in the general population (1). In normal urine, fewer than three red blood cells per high-power field are expected, and any value exceeding this threshold is classified as hematuria. This condition is indicative of a range of benign and malignant diseases affecting the urinary system, necessitating a comprehensive investigation for accurate diagnosis and management. Hematuria has a wide spectrum of etiologies. The urological causes include urinary tract infections, nephrolithiasis, trauma, benign prostatic hyperplasia, and urothelial malignancies (2). Nephrological hematuria is associated with glomerular damage, vascular diseases, and inflammatory kidney disorders (3). Patients presenting with macroscopic hematuria are at an elevated risk of malignancy, making prompt and effective evaluation imperative (4). Various diagnostic methods have been used to assess hematuria. The dipstick test, commonly used in the initial phase, is favored for its rapid and straightforward application. However, it may produce false-positive results owing to the presence of free hemoglobin or myoglobin in the urine. Consequently, microscopic examination and additional laboratory tests are recommended to confirm hematuria (5). Ultrasonography (USG) is a critical imaging modality for the evaluation of patients with hematuria. The measurement of bladder wall thickness (BWT) can yield valuable insights into differentiating between benign and malignant pathologies. An increase in BWT is typically associated with chronic inflammatory processes and bladder outlet obstruction, whereas a thinner bladder wall structure is observed in malignancies (6,7). Nonetheless, studies exploring the relationship between BWT and pathological findings are limited. This study examined the relationship between BWT measured using ultrasound and pathological findings obtained from biopsy in patients presenting with hematuria. This study aimed to ascertain whether BWT serves as a predictive parameter for urothelial malignancies and other benign pathologies, thereby contributing to the clinical management of patients with hematuria.

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METHODS

This study was approved by the local Ethics Committee of Hisar Intercontinental Hospital (decision no: 25-26, date: 28.02.2025). This study involved a retrospective analysis of patients who presented to the urology outpatient clinic with various symptoms between January 2010 and June 2023, and were diagnosed with hematuria during their evaluations. Cystoscopy and bladder biopsy results of these patients were reviewed. Patients who were diagnosed with hematuria and subsequently underwent bladder biopsy were included in the study. A comprehensive retrospective analysis of clinical and laboratory data was performed. The exclusion criteria were as follows: a history of urinary tract infection, presence of proteinuria, use of aspirin or other anticoagulants (e.g., warfarin), detection of suspicious or malignant cells in urine cytology prior to cystoscopy, presence of lesions causing filling defects in the ureters or bladder, detection of tumors in the upper urinary tract, and incomplete or insufficient patient data.

In the selected cohort, detailed retrospective data extraction was carried out, encompassing demographic characteristics, clinical presentations, and diagnostic work-up findings. Laboratory evaluations included complete blood count, coagulation parameters (international normalized ratio and activated partial thromboplastin time), renal function markers (urea, creatinine, electrolytes), urine cultures, and cytological analysis. USG measurement of BWT was recorded in all patients, while contrast-enhanced computed tomography urography was performed when further evaluation of suspected structural or tumor pathology was warranted.

Cystoscopic examinations were systematically reviewed in conjunction with histopathological analysis of bladder biopsy specimens. The pathological findings were subsequently classified into four main categories: (1) chronic cystitis, (2) squamous metaplasia or dysplasia, (3) urothelial carcinoma (low-grade or high-grade), and (4) other rare entities such as glandular cystitis, eosinophilic cystitis, and papilloma.

Statistical Analysis

The normality of continuous variables was assessed using the Shapiro-Wilk test. Variables that were not normally distributed were reported as median [interquartile range, (IQR)] and compared between groups using the Mann-Whitney U test. Results were expressed in the tables as median (IQR) format for central tendency and dispersion, and p-value for significance testing. Categorical variables were analyzed using Pearson's chi-square test. In cases where expected cell counts were below 5, Fisher's exact test was used to ensure accurate results. A p-value <0.05 was considered statistically significant for all comparisons. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 175 patients diagnosed with hematuria who underwent bladder biopsy were included in the study. Histopathological analysis revealed benign lesions in 86.8% (n=152) of patients and malignant pathology, specifically urothelial carcinoma, in 13.2% (n=23) (Table 1). The most common benign diagnosis was chronic non-specific cystitis, identified in 77.1% (n=135) of patients. Among these, 40 cases were classified as mild, 27 as unspecified, and 13 as erosive cystitis. Squamous metaplasia or dysplasia frequently coexisted with chronic cystitis. Urothelial dysplasia was observed in 10.3% (n=18) of patients, predominantly mild (n=14) and moderate (n=4), all associated with chronic inflammation. Rare benign pathologies included urothelial papilloma, inverted papilloma, and bladder amyloidosis, each detected in one patient (0.6%). Other specific cystitis subtypes were glandular cystitis (4.0%), eosinophilic cystitis (2.9%), and cystitis cystica (3.4%).

All malignant cases (n=23) were diagnosed as urothelial carcinoma. The majority were non-muscle-invasive papillary tumors, with 78.2% (n=18) staged as pathological tumor (pT) stage 1 (lamina propria invasion) and 21.8% (n=5) as pT stage a (non-invasive). High-grade tumors were present in 52.2% (n=12), compared to 47.8% (n=11) that were low-grade. Notably, no cases exhibited muscle invasion (pT stage 2 or higher) or carcinoma in situ.

Patients were categorized into benign and malignant groups for comparative analysis. The median age was significantly higher in the malignant group than in the benign group [67.0 (61.0-74.0) vs. 44.5 (32.0–53.0) years, p<0.001]. Additionally, the proportion of male patients was significantly greater in the malignant group (87.0% vs. 50.7%, p=0.002). However, there was no statistically significant difference in BWT between the two groups [4.5 (3.975-5.0) mm vs. 4.3 (3.5-4.8) mm, p=0.132] (Table 2).

Table 1. Demographic, preoperative, and postoperative characteristics of the patients

Parameter	p-value
Number of patients, n	175
Age (years) ± SD	46.75±15.77
Sex, n (%)	
Male	97 (55.4%)
Female	78 (44.5%)
Bladder wall thickness (mm) ± SD	4.51±1.08
Histopathological diagnosis, n (%)	
Benign	152 (86.8%)
Malignant	23 (13.2%)

SD: Standard deviation

Table 2. Patient characteristics in benign and malignant pathology groups

Characteristic	Benign (n=152)	Malignant (n=23)	p-value
Age (years) (median, IQR)	44.5 (32.0-53.0)	67.0 (61.0-74.0)	<0.001[a]
Male gender, n (%)	77 (50.7%)	20 (87.0%)	0.002[b]
Bladder wall thickness (mm) (median, IQR)	4.5 (3.975-5.0)	4.3 (3.5-4.8)	0.132[a]

IQR: Interquartile range, [a]: Mann-Whitney U test, [b]: Chi-square test

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DISCUSSION

In this study, we investigated the diagnostic value of BWT, measured via ultrasound, in distinguishing between malignant and benign lesions in patients presenting with hematuria. Although our findings revealed significant differences between malignant and benign pathologies in terms of age and sex, no statistically significant difference was observed in BWT. This suggests that BWT alone may not be a reliable predictive parameter for bladder cancer.

Numerous studies have evaluated the diagnostic value of ultrasonographic findings in bladder tumors. Mostafaloo et al. (8) reported that USG in patients with hematuria has relatively high specificity but low sensitivity. The literature indicates that benign pathologies are associated with notable thickening of the bladder wall, whereas malignant conditions, such as urothelial carcinoma, typically manifest as focal lesions (9). Previous studies have demonstrated that benign inflammatory processes result in diffuse thickening of the bladder wall, particularly in conditions such as chronic cystitis, glandular cystitis, and eosinophilic cystitis (10,11). In the literature, BWT in healthy adults is generally reported to be less than 3 mm (12). In our study, BWT was increased in the benign group, with a median of 4.5 mm, relative to that of a normal bladder, which is consistent with the literature. However, there was no statistically significant difference between the benign and malignant groups, indicating that BWT is insufficient as a predictive marker for malignancy.

The impact of sex on the incidence of bladder cancer has been the subject of extensive research. Epidemiological studies suggest that men are at a greater risk of developing bladder cancer than women. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program report an incidence rate of 31.6 per 100,000 men and 7.8 per 100,000 women, resulting in a male-to-female ratio of approximately 4:1 (13). In the present study, 87% of the malignant cases were male, which is consistent with these findings.

The research conducted by Kluth et al. (14) revealed that although men exhibit a higher risk of developing bladder cancer, female patients are frequently diagnosed at more advanced stages. This delay in diagnosis is associated with poor oncological outcomes in women. The elevated incidence of bladder cancer in men is not yet fully understood; however, factors such as smoking, exposure to environmental toxins, and hormonal influences are considered contributory (13).

Our study revealed a statistically significant difference in age between patients with malignant and benign bladder pathologies, with older age being strongly associated with malignancy ($p<0.001$). This finding aligns with previous epidemiological data indicating that bladder cancer is predominantly a disease of older adults. Age-related accumulation of genetic mutations, prolonged exposure to environmental carcinogens such as tobacco and industrial chemicals, and a decline in immune surveillance are among the key factors believed to contribute to the increased risk of malignancy in elderly individuals (13,15).

This study highlights the potential utility of measuring BWT using ultrasound as a diagnostic parameter in the assessment of patients presenting with hematuria. While increased BWT may reflect an underlying pathological process in patients with hematuria, it cannot be solely relied upon to exclude malignancy. This should be considered in conjunction with the clinical findings, laboratory tests, and advanced imaging techniques. Notably, none of the patients with BWT exceeding 5 mm were diagnosed with malignancy in this study, indicating that inflammatory processes in benign conditions may contribute to more pronounced thickening. However, given that urothelial carcinoma often manifests as small superficial lesions in its early stages, cystoscopic evaluation remains essential for patients with hematuria.

Study Limitations

This study represents one of the most comprehensive retrospective analyses examining the relationship between BWT and pathological diagnoses in patients presenting with hematuria. The retrospective design of the study constitutes a limitation, as a prospective approach could yield more robust and generalizable results. Additionally, subjectivity in the measurement of BWT should be considered, including potential interobserver variability among radiologists and factors such as the degree of bladder filling at the time of measurement.

CONCLUSION

While ultrasonographic measurement of BWT offers valuable insights into underlying bladder pathology in patients with hematuria, it falls short as a standalone predictor of urothelial malignancy. Our findings emphasize that reliance solely on BWT may lead to missed or delayed diagnoses of bladder cancer. Therefore, BWT should be considered a complementary tool within a multidisciplinary diagnostic approach. Integrating USG findings with cystoscopy and clinical assessment remains essential for timely and accurate detection of malignancies. Prospective studies are needed to refine non-invasive diagnostic strategies in hematuria management.

Ethics

Ethics Committee Approval: This study was approved by the local Ethics Committee of Hisar Intercontinental Hospital (decision no: 25-26, date: 28.02.2025).

Informed Consent: This study involved a retrospective analysis of patients who presented to the urology outpatient clinic with various symptoms between January 2010 and June 2023, and were diagnosed with hematuria during their evaluations.

Footnotes

Author Contributions: Surgical and Medical Practices - B.Ç.; Concept - C.T.G., B.Ç.; Design - C.T.G., B.Ç.; Data Collection and/or Processing - B.Ç.; Analysis and/or Interpretation - C.T.G.; Literature Search - C.T.G., B.Ç.; Writing - C.T.G., B.Ç.

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The Impact of Screen Exposure on Attention Development in Preschool Children in Türkiye

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ABSTRACT

Objective: Excessive screen exposure that negatively affects a person's life is called problematic media use. Problematic media uses in healthy children is associated with a sedentary lifestyle and negative health outcomes. Problematic media use and its negative effects on attention are a subject of debate.

Methods: We screened children between the ages of 5 and 6 who visited the pediatric department. One hundred and eighty-six children were included in the study. Demographic data were collected from the patients and their families. Additionally, daily screen exposure times were evaluated. The long form of the Problematic Media Use Scale (screen addiction scale), which is valid for ages 4-11, and the Frankfurter Concentration Test for 5-6 Year Old Children (FTF-K) were applied to all participants.

Results: Children using multiple screens had significantly higher problematic media use scores and screen time compared to those using only television (p=0.003, p=0.017). No statistically significant relationship was found between children's age, screen addiction scale scores, screen exposure duration, and final FTF-K test scores (p>0.05). A significant positive correlation was found between the number of siblings and screen addiction scale scores, and screen exposure duration; (r=0.19, p=0.010), (r=0.20, p=0.007).

Conclusion: Problematic media use and exposure duration in preschool children were not found to have a direct relationship with attention.

Keywords: Screen exposure, attention development, FTF-K test, screen addiction, children, problematic media use

INTRODUCTION

The rapid development of digital technologies in recent years has significantly increased children's interaction with media, leading to the emergence of new concepts such as problematic media use (1). Problematic media use is defined as excessive dependency on media content, which negatively affects daily life activities and causes psychosocial issues (2).

The widespread use of media at an early age has made it even more critical to examine its effects on children's cognitive, emotional, and social development (3). Excessive media use has been shown to lead to negative outcomes in children, such as externalizing behaviors, decreased academic performance, and sleep disorders (4).

The rapid development of digital technologies has further increased children's media interaction, making the relationship between attention development and screen exposure more significant (5). Research suggests that early and prolonged screen exposure is associated with issues such as attention

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deficit and impairments in executive functions (6). Given that the study involves older children, the observed outcomes may reflect cumulative exposure effects. However, the specific age at which such problematic media use begins remains unidentified. However, there are also studies that do not show a relationship between attention deficit and screen exposure (7).

Attention development plays a crucial role in children's academic and social lives, with lower attention spans being linked to learning difficulties and behavioral problems later in life (8). Factors that determine children's screen time, such as parental control, the nature of media content, and the child's age, play a significant role in this development (9).

For children over the age of two, screen time should be limited to two hours. However, many studies have shown that this two-hour limit is often exceeded. It is also known that boys are exposed to more screen time than girls, and older children and adolescents spend more time on screens than younger children (10).

This study aims to investigate the effects of screen exposure on attention development in preschool children in Türkiye. Türkiye is a developing country. In developing countries, people generally face no significant economic barriers to accessing various video devices. This situation suggests that screen addiction may be prevalent. Therefore, examining their effects on children was deemed necessary. It is important to anticipate the negative effects that potential attention disorders may have on academic and social life. Our aim is to investigate whether screen exposure and problematic media use cause attention deficits in children with normal motor and social development. Therefore, the need for this research has been recognized.

METHODS

Design

Our study was designed as a single-center, cross-sectional study. We screened children between the ages of 5 and 6 who visited our pediatric department's outpatient clinics and emergency room. The study period was set from September 2024 to February 2025. A total of 327 children without chronic illness were identified, and 214 agreed to participate in the study. The Denver II test was administered to the participating children. Among the 214 participants, 28 children were excluded from the study due to delays in personal-social development, fine motor-adaptive development, and language development. Our study was completed with 186 children. Demographic data were collected from the patients and their families. Additionally, daily screen exposure times were evaluated. Since our study involved a young age group, parents were asked to record in writing the total duration of active and passive media use over one week. The daily average duration was then calculated. Due to the high amount of passive use (such as watching videos and television), a comparison between the two types of use could not be conducted. However, both active use (such as playing games) and passive use were commonly observed among most participants. Additionally, the usage types include videos, television, and games that are watched or played solely for entertainment purposes. The long form of the Problematic Media Use Scale, which is valid for ages 4-11, and the Frankfurter Concentration Test for 5-6 Year Old Children (FTF-K) were applied to all participants. Families were selected from individuals living in the Gaziosmanpaşa district of Istanbul with similar income levels. Our study includes participants from the middle and lower income groups according to the standards of our country.

Ethics

The parents or guardians of the children provided informed consent, and the local Ethics Committee of the University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital approved the study (desicion no: 81, date: 08.01.2025). The study adhered to the ethical principles outlined in the Declaration of Helsinki.

Participants

Children with chronic neuropsychiatric disorders or other chronic illnesses were excluded from the study. Children who had regular medication use were excluded.

Problematic Media Use Scale Long Form

The scale, originally developed by Domoff et al. (11) in 2019 to assess problematic media consumption (PMC) in children aged 4-11, consists of a 27-item long form and a 9-item short form. Its Turkish adaptation, including validity and reliability analyses, was conducted by Furuncu and Öztürk (12) in 2020. The long form (problematic media use scale - long form) follows a single-factor structure and is rated on a 5-point Likert scale (1= never, 5= always). The total score is calculated by averaging the responses across all items, with higher scores indicating greater levels of problematic media use. The Cronbach's alpha coefficient for the long form of the scale is reported as 0.97 (12).

The Frankfurter Concentration Test for 5-6 Year Old Children

FTF-K is a commonly utilized psychological assessment designed to evaluate the attention and concentration skills of children between the ages of 5 and 6. This test is especially valuable in educational and psychological contexts, as it helps assess a child's capacity to maintain focus on tasks that require sustained attention and cognitive regulation. FTF-K has been supported by various studies, confirming its strong reliability in assessing attention skills in young children. Its standardized structure allows for objective evaluation, making it a significant instrument in developmental psychology and educational assessments. The test is administered in a quiet setting with minimal distractions to ensure optimal concentration. The child is provided with a pencil and a standardized test sheet, while the examiner gives clear instructions before initiating the timed task. The child's performance is assessed based on response accuracy and speed, offering insights into his or her attentional capabilities (13-15).

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Statistical Analysis

In this study, statistical analyses were conducted using the IBM SPSS software (version 23, Chicago, IL, USA, 2015). While evaluating the study data, descriptive statistical methods (mean, standard deviation, frequency) were used. Normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For normally distributed parameters, comparisons were made using the Independent Samples t-test and one-way analysis of variance (ANOVA). For non-normally distributed parameters, the Mann-Whitney U test and Kruskal-Wallis test were applied. Additionally, the Spearman rank correlation test was used to examine relationships between two parameters. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

The reliability of the scales, commonly used to determine whether the information provided by the survey has stable characteristics, and whether the same results would be obtained from a second measurement conducted for the same purpose, was assessed using the Cronbach's alpha reliability coefficient for the screen addiction questionnaire applied to 186 children aged 5-6 years. The scale was found to have high reliability with a coefficient of 0.85 ($0.81<\alpha<1.00$) (16). The first validity and reliability studies of the FTF-K in the Turkish sample were carried out by Kaymak (17). The reliability of the test was evaluated by senior students enrolled in the Clinical Psychology Applications course at Ankara University Faculty of Educational Sciences, by applying it to 30 children aged 5-6 years by senior students enrolled in the Clinical Psychology Applications course at Ankara University Faculty of Educational Sciences. The test-retest method was used to determine the reliability. Based on the analysis, the correlation value between the test-retest applications was found to be over 0.70, indicating that the test is considered a reliable and valid data collection tool (17).

A post-hoc power analysis was conducted using the G*Power 3.1.9.7 software to assess the power of the accessible sample size (18). In the post-hoc analysis, assuming a medium effect size of $d=0.5$ and a significance level of $\alpha = 0.05$, the statistical power was calculated for an independent samples t-test with 99 participants in group 1 and 87 participants in group 2, yielding a power ($1-\beta$) of 0.959. For the Mann-Whitney U test under the same conditions, the power ($1-\beta$) was found to be 0.952.

For a one-way ANOVA with a small to medium effect size ($d=0.25$), a significance level of $\alpha=0.05$, and a total sample size of 186 across four groups, the calculated power ($1-\beta$) was 0.818.

In the correlation analysis, assuming an effect size of $p=0.3$, a significance level of $\alpha=0.05$, and a sample size of 186, the statistical power ($1-\beta$) was determined to be 0.989.

Demographic findings are presented in Table 1.

The final FTF-K test scores were obtained by summing the raw and adjusted scores. These final scores allow for a comparison of the child with peers of the same age in months (see Table 2).

Among the 186 children aged 5-6 who took the FTF-K test, 88 (47.3%) had concentration levels above 75% of their peers. A total of 67 children (36%) had concentration levels above those of 51% of their peers, while 31 children (16.7%) had concentration levels below those of 74% of their peers.

When comparing age, screen exposure, screen addiction scale scores, and FTF-K test scores by gender, the results showed no statistically significant difference between boys and girls ($p>0.05$) (see Table 3).

When children were categorized into four groups based on screen use (multiple devices, television only, tablet only, phone only), and their ages were compared across these groups, the results showed no significant difference ($p>0.05$) (see Table 4).

Table 1. Demographic cohort

Total (n, %)	**186 (100%)**
Age (month) (mean ± SD)	**66.13±3.90**
Sex (n, %)	**186 (100%)**
Female	99 (53.2%)
Male	87 (46.8%)
Number of siblings (mean ± SD)	**1.60±1.16**
Screen exposure (hour) (mean ± SD)	**2.72±1.62**
Screen addiction scale score (mean ± SD)	**57.36±21.11**
FTF-K test (raw) score (mean ± SD)	**28.33±9**
FTF-K test (final) score (mean ± SD)	**32.17±9**
FTF-K test (final) score comparison (n, %)	**186 (100%)**
Below average (0-22 score)	31 (16.7%)
Average (23-32 score)	67 (36%)
Above average (33-48 score)	88 (47.3%)
Screen exposure (n, %)	**186 (100%)**
Multiple	108 (58.1%)
Only TV	30 (16.1%)
Only tablet	10 (5.4%)
Only smartphone	38 (20.4%)

n: Number of children, SD: Standard deviation, FTF-K: Frankfurter Concentration Test for 5-6 Year Old Children

Table 2. FTF-K test (final) score distribution

(n, %)	Final score	Percentage	Assessment
31 (16.7%)	0-22	26%	Below average
67 (36%)	23-32	49%	Average
88 (47.3%)	33-48	25%	Above average

n: Number of children, FTF-K: Frankfurter Concentration Test for 5-6 Year Old Children

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However, when comparing screen addiction scale scores among these four groups, the results indicated a statistically significant difference: χ^2 (3, n=186) =12.690, p=0.005. Post-hoc comparisons using the Bonferroni-corrected Dunn method revealed that children using multiple screens had significantly higher screen addiction scale scores compared to those using only television (p=0.003). However, no significant differences were found among the other groups (p>0.05) (see Table 4).

Similarly, when screen exposure levels were compared among these four groups, a significant difference was observed; χ^2 (3, n=186) =8.939, p=0.030. Post-hoc comparisons using the Bonferroni-corrected Dunn method showed that children using multiple screens had significantly higher screen exposure than those using only television (p=0.017). However, no significant differences were found among the other groups (p>0.05) (see Table 4).

Lastly, when comparing the mean final FTF-K test scores among these four screen-use groups, the results indicated no statistically significant difference; F (3,182) =0.777, p=0.508 (see Table 4).

When children were categorized into three groups based on their final FTF-K test scores (below average, average, and above average) and compared in terms of age, number of siblings, screen addiction scale scores, and screen exposure, the results showed no statistically significant differences among the groups (p>0.05) (see Table 5).

Spearman's rho correlation coefficients were calculated to assess the relationships between children's age, number of siblings, screen addiction scale scores, screen exposure duration, and final FTF-K test scores. The results showed no statistically significant relationship between children's age, screen addiction scale scores, and screen exposure duration, and final FTF-K test scores (p>0.05).

However, a significant positive correlation was found between the number of siblings and screen addiction scale scores (r=0.19, p=0.010). Additionally, a significant positive correlation was observed between the number of siblings and screen exposure duration (r=0.20, p=0.007). Furthermore, a strong positive correlation was identified between screen addiction scale scores and screen exposure duration (r=0.97, p<0.001) (see Table 6).

Table 3. Age, screen exposure, screen addiction scale score, and FTF-K test score comparison between females and males

	Female	Male	p-value
Age (month) (mean ± SD); (median)	66.11±3.86; (65)	66.15±3.96; (66)	0.980[a]
Screen exposure (ho) (mean ± SD); (median)	2.62±1.54; (2)	2.84±1.7; (2)	0.454[a]
Screen addiction scale score (mean ± SD); (median)	55.82±19.15; (54)	59.11±23.13; (54)	0.493[a]
FTF-K test (final) score (mean ± SD)	32.54±8.72; (33)	31.75±9.36; (31)	0.887[b]

[a]: Mann-Whitney U test, [b]: Independent Samples t test, FTF-K: Frankfurter Concentration Test for 5-6 Year Old Children

Table 4. Age, number of siblings, screen exposure, screen addiction scale score, and FTF-K test (final) score comparison in terms of screen utilization

	Multiple	Only Tv	Only tablet	Only smartphone	p-value
Age (month) (mean ± SD); (median)	66.22±4.03; (66)	65.37±3.51; (65)	65.9±4.51; (67)	66.53±3.72; (68)	0.579[a]
Number of siblings (mean ± SD); (median)	1.60±1.01; (2)	1.50±1.25; (1.5)	1.70±1.83; (1.5)	1.66±1.30; (1.5)	0.923[a]
Screen addiction scale score (mean ± SD); (median)	61.19±22.0; (56.5)	45.7±14.0; (44)	56.8±15.55; (62)	55.82±20.47; (49.5)	0.005[a]
Screen exposure (h) (mean ± SD); (median)	2.96±1.69; (3)	1.93±1.11; (2)	2.7±1.42; (3)	2.66±1.63; (2)	0.030[a]
FTF-K test (final) score (mean ± SD)	32.92±8.58	30.3±9.56	30.7±8.1	31.89±9.98	0.508[b]

[a]: Kruskal-Wallis test, [b]: One-Way ANOVA test, SD: Standard deviation, FTF-K: Frankfurter Concentration Test for 5-6 Year Old Children

Table 5. Comparison of evaluation groups formed according to the final FTF-K test score in terms of age, number of siblings, screen addiction scale score, and screen exposure

	Below average (0-22 score range)	Average (23-32 score range)	Above average (33-48 score range)	p-value
Age (month) (mean ± SD); (median)	66.90±3.74; (68)	66.07±3.82; (66)	65.90±3.82; (65)	0.458[a]
Number of siblings (mean ± SD); (median)	1.97±1.22; (2)	1.48±1.33; (1)	1.57±0.97; (2)	0.054[a]
Screen addiction scale score (mean ± SD); (median)	54.52±22.80; (51)	57.46±20.55; (51)	58.28±21.08; (57)	0.518[a]
Screen exposure (h) (mean ± SD); (median)	2.55±1.73; (2)	2.70±1.61; (2)	2.80±1.59; (3)	0.661[a]

[a]: Kruskal-Wallis test, FTF-K: Frankfurter Concentration Test for 5-6 Year Old Children, SD: Standard deviation

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Table 6. Correlation coefficients of children's ages, number of siblings, screen addiction scale scores, screen exposure durations, and FTF-K test (final) scores

	M	SD	Age (month)	Number of siblings	Screen addiction scale score	Screen exposure (h)	FTF-K test (final) score
Age (month)	66.13	3.9	-				
Number of siblings	1.60	1.16	0.01	-			
Screen addiction scale score	57.36	21.11	0.10	0.19*	-		
Screen exposure (h)	2.72	1.62	0.09	0.20*	0.97**	-	
FTF-K test (final) score	32.17	9	-0.13	-0.07	0.01	-0.01	-

*p<0.05, **p<0.001; M: Mean, SD: Standard deviation, n:186, FTF-K: Frankfurter Concentration Test for 5-6 Year Old Children Spearman's rho correlation coefficent

DISCUSSION

Problematic media use has emerged as a significant issue in the rapidly advancing technological age. It can lead to social relationship problems, promote sedentary lifestyles, and negatively affect cognitive functions. However, there are many factors that mitigate the negative effects of time spent in front of screens. It is stated that the impact of time spent actively or passively on cognition differs (19). There are studies showing that extended screen time has adverse effects on attention. Studies argue that screen time does not necessarily lead to attention deficits. The complexity of this issue seems to arise from the influence of many different factors (6,7). The aim of our study is to investigate this issue in preschool children. However, when designing our study, we included children who had normal development in language, personal-social skills, and fine motor skills by applying a developmental test. The goal here is to examine the isolated effect of screen exposure on attention. It is likely that children with deficits in personal-social development, language delay, or motor skills would exhibit lower attention performance. To explore the direct impact of problematic media use on attention, our study was structured to focus on this relationship.

Our examination of the study results revealed that the participants' final FTF-K test scores were above average. This rate, which was 47.3%, indicates that the participants had higher levels of attention. One possible reason for this could be the selection of participants based on a developmental test. When comparing age, screen exposure, screen addiction scale scores, and FTF-K test scores by gender, no significant differences were found in our study. The literature suggests that executive functions (such as self-control and inhibition) are higher in adolescent girls than in boys (20). However, while no behavioral differences have been observed in the preschool period, stronger prefrontal activity has been identified in girls (21). In our study, no significant differences were found in screen addiction and attention scores.

Our findings indicate that children exposed to multiple digital devices had higher problematic media use scale scores and greater screen exposure compared to children who only watched television. This suggests that phones and tablets may have a higher addictive potential. Our study concluded that exposure to multiple digital devices increases the risk of addiction (Table 4). However, when examining attention test scores, no differences were found between children using multiple screens and those using a single digital device. Since television is considered a more passive form of screen exposure, our study indirectly suggests that active and passive participation do not create a significant difference. While in preschool children, not only television but also tablets and phones may serve as passive engagement tools (such as watching videos), some studies indicate that active or passive participation affects cognition in adolescents (19). This may explain the absence of differences in attention test scores.

No significant differences were found when children were categorized into three groups based on their final FTF-K test scores (below average, average, and above average) and examined in terms of age, number of siblings, screen addiction scale scores, and screen exposure. This suggests that even children with below-average attention levels do not necessarily have a connection with screen addiction. However, in our study, as the number of siblings increased, the "problematic media use scale" scores and screen exposure duration also increased. This may be due to reduced parental attention in families with multiple children. This situation may also result from neglect of the children when there are many siblings. Perhaps we did not encounter this situation because siblings may encourage each other to use videos, television, and games. The risk of screen addiction appears to be higher in preschool children from large families, making this an important finding in our study (Table 6). Additionally, a strong correlation was observed between the problematic media use scale and screen exposure time, which supports the reliability of the responses provided by families.

In summary, our study did not find a direct relationship between screen addiction and attention in preschool children. Studies suggesting such a relationship likely indicate that screen exposure, affecting personal social development, fine motor skills, and language development, leads to secondary attention-related problems. This suggests that screen exposure alone may not cause an attention disorder. The contradictory findings may be due to the differing effects of the content that children were exposed to. Additionally, we were unable to assess the positive or negative effects of active media use in this age group, as passive

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use was predominantly observed. Moreover, negative impacts on attention may increase cumulatively with age, which could explain why we did not detect significant effects in our study. However, the literature on this topic remains controversial (6,7) as multiple factors play a role in this relationship. The effects of screen addiction may vary depending on cultural factors. As Türkiye is a Middle Eastern country with strong family and kinship ties, the negative effects of screen exposure may have been less apparent in our study. Since our study specifically focused on the impact of screen exposure on attention, it contributes valuable insights to the literature. Conducting future studies with children who have developmental delays may provide more guidance. It is likely to observe the negative effects of problematic media use in children with developmental delays (such as language delay and social delay).

Study Limitations

Future studies with larger sample groups could further examine developmental delays and their association with attention, providing additional contributions to this field. The cross-sectional nature of our study presents a limitation. Longitudinal studies with extended follow-up periods could provide more comprehensive insights. Since data were recorded by parents, some subjectivity may have been introduced. However, considering the large number of recordings and the fact that they were collected in the home environment, this method was the most feasible. Additionally, since passive media use was more commonly observed in this age group, we were unable to clearly differentiate between active and passive use among our participants.

CONCLUSION

Problematic media use and exposure duration in preschool children were not found to have a direct relationship with attention. However, they may have negative effects on attention when accompanied by developmental delays. Problematic media use and screen exposure are more prevalent among children in large families. However, no significant impact on attention has been identified.

Ethics

Ethics Committee Approval: Ethics Committee of the University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital approved the study (desicion no: 81, date: 08.01.2025).

Informed Consent: The parents or guardians of the children provided informed consent.

Footnotes

Author Contributions: Concept - O.C.; Design - O.C.; Data Collection and/or Processing - O.C., S.K., Ö.S., U.T., E.A., B.T., Ş.K.; Analysis and/or Interpretation - O.C.; Literature Search - O.C.; Writing - O.C., S.K.

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The Effect of Dimethyl Fumarate on Tissues in Methanol Poisoning

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ABSTRACT

Objective: This study aimed to investigate the effects of an antioxidant, dimethyl fumarate (DMF), on methanol (MeOH)-induced liver, kidney, testicular, and ocular toxicity in Wistar rats.

Methods: Six experimental groups were established: a control group; a group receiving (DMF; 100 mg/kg); a group receiving methotrexate [(MTX); 0.3 mg/kg/day]; and three groups receiving MTX followed by MeOH (3 g/kg, oral, 20% solution) with either 30 mg/kg or 100 mg/kg DMF, or no DMF. MTX was administered for seven days prior to MeOH, and DMF was administered two hours before MeOH, on the eighth day. Animals were sacrificed eight hours after MeOH administration.

Results: Minimal changes were seen in the urine test, such as a high protein score and increased pH value in the MTX + MeOH group, and a significant level of bilirubin excretion in the MTX + MeOH + DMF100 group. Only the liver weight/body weight X100 index was lower in the DMF group. There were no histopathological changes in liver, kidney, testicular, and eye tissues.

Conclusion: DMF was found to be safe for the liver, kidney, testicular, and ocular tissues. However, it was not possible to achieve the MeOH toxicity model in the specified doses and routes in the rats, contrary to the related literature. Future studies are needed to develop a reliable model for MeOH toxicity in rats.

Keywords: Alcohol, animal experimentation, antioxidant, ocular toxicity, methotrexate, toxicology

INTRODUCTION

Methanol (MeOH) is used in a wide range of consumer products, such as model car fuel, aviation fuel, fragrances, gas line antifreeze, and copy machine fluid. Unfortunately, MeOH is sometimes illegally substituted for ethanol due to its lower cost and easier availability (1). Inhalation of carburetor cleaner is another source of MeOH poisoning. Notably, in India, Türkiye, and Tunisia, a large proportion of MeOH poisoning cases result from the absorption of fragrances and colognes (1). Accidental or intentional ingestion of MeOH-containing substances, is an important public health problem as its toxicity may cause severe morbidity and mortality (1-3). The enzymatic activity of alcohol dehydrogenase on MeOH first produces formaldehyde, which is then converted to formic acid by aldehyde dehydrogenase. This process decreases nicotinamide adenine dinucleotide (NAD+) concentrations. When the conversion of NAD+ to NADH diminishes, anaerobic respiration is promoted. These metabolic changes can lead to hypoglycemia and lactic acidosis (4). Acidosis leads to oxidative stress, production of reactive oxygen species, lipid peroxidation, cell damage, and mitochondrial dysfunction in many organs, especially in the optic nerve (1,3). Formic acid itself is also considered responsible for ocular toxicity (1,2). Meanwhile, several antioxidants have been reported as effective medications against tissue damage of MeOH poisoning (2,3,5).

Dimethyl fumarate (DMF) is an immunomodulatory, anti-inflammatory, and antioxidant, pharmaceutical agent indicated for the therapeutic management of inflammatory pathologies, specifically psoriasis and multiple sclerosis (6,7). Evidence suggests that DMF facilitates a cascade of processes, leading to the final expression of a variety of antioxidant and detoxifying genes. Furthermore, systemic administration of this agent for psoriasis treatment reduced levels of several cytokines, including interleukin

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(IL)-6, IL-17, IL-22, granulocyte-macrophage colony-stimulating factor, transforming growth factor-alpha, and interferon-gamma, while conversely increasing IL-10 levels. Similarly, the anti-inflammatory mechanism of multiple sclerosis treatment on glial cells involves inhibiting the release of various pro-inflammatory molecules, such as nitric oxide, IL-1 beta, IL-6, and tumor necrosis factor (TNF)-alpha (7). The findings of Sangineto et al. (6) demonstrated that DMF protected mice from ethanol-induced liver damage, steatosis, and inflammation by specifically reducing hepatic triglyceride and alanine aminotransferase levels, downregulating the hepatic expression of inflammatory cytokines (TNF-α, IL-1β, CXCL11), and decreasing the presence of neutrophils and macrophages in the liver tissue of ethanol-fed mice. A recent review provided several examples of the benefits of DMF in ocular diseases, such as age-related macular degeneration, uveitis, cystoid macular edema, light-induced photoreceptor loss in mice, and corneal transplantation in rats (7).

Nevertheless, research has not yet examined the effects of DMF on MeOH toxicity at the organ level, especially considering the significant side effects on the retina. Therefore, this study aims to investigate the efficacy of DMF as an antioxidant and anti-inflammatory agent in MeOH poisoning.

METHODS

Since no human embryos, fetuses, tissues derived from them, or other human cells and tissues were used in any part of this study, obtaining a patient consent form is not required. Animal experiments were conducted at the Animal Center of Aydin Adnan Menderes University, and all animal protocols were approved by the Animal Ethics Committee for Experiments at Aydin Adnan Menderes University (decision no: 64583101/2024/32, date: 21.03.2024) before the experiments were conducted. The study used 54 male Wistar albino rats that were 10-12 weeks old and were kept in a room with a temperature of 22±2 degrees celsius, 40-50% humidity, and a 12-hour light-dark cycle. Because rats are resistant to MeOH toxicity, methotrexate was given to establish the animal model (2,3). Each group consisted of 9 animals; the groups were as follows:

Control: The control group was administered intraperitoneal saline solution for 7 days, followed by 1 mL of oral saline solution on the 8th day.

DMF100: The group receiving a single high dose of DMF by gavage in the study was intended to demonstrate the safety of the treatment agent at this dose and route.

Methotrexate (MTX): The group administered methotrexate (0.3 mg/kg/day) by gavage for 7 days.

MTX + MeOH: The group administered methotrexate (0.3 mg/kg/day) by gavage for 7 days, followed by methyl alcohol (3 g/kg, 20%) by gavage on the 8th day.

MTX + MeOH + DMF30: The group was administered methotrexate (0.3 mg/kg/day) by gavage for 7 days, then DMF (30 mg/kg) by gavage on the 8th day, and finally oral methyl alcohol (3 g/kg, 20%) administered 2 hours later.

MTX + MeOH + DMF100: The group was administered methotrexate (0.3 mg/kg/day) by gavage for 7 days, followed by DMF (100 mg/kg) by gavage on the 8th day. Subsequently, oral methyl alcohol (3 g/kg, 20%) was given 2 hours later.

The animals were euthanized 8 hours after MeOH intoxication (2,8), using a combination of 50 mg/kg ketamine and 5 mg/kg xylazine anesthesia. Liver, kidney, testicular, and eye samples were placed in the 10% formalin solution.

Clinical Follow-up

All animals' body weights were assessed to adjust the drug doses. Liver, kidney and testicular wet weights have been adjusted according to body weight: [(sum of liver weights)/body weight] × 100; [(sum of kidney weights)/body weight] × 100, and [(sum of testicular weights)/body weight] × 100. To identify organ changes, such as edema, vasoconstriction and necrosis, in cases of acute organ damage where body weight remained unchanged, organ weights were compared to body weight. Blood glucose level was measured with a glucometer (Clever Chek, Istanbul, Türkiye) from the tail blood sample.

The urine samples were collected just prior to the sacrifice, to perform the strip test. Using a monitor (Hua 90M portable urine monitor, China), numeric data was obtained to show kidney and liver functions for urinary density, pH alteration, presence of leukocytes, nitrite, urobilinogen, calcium, blood ketone, bilirubin, creatinine, and glucose (9).

Pathological Evaluation

In the pathological examination, tissues were fixed in 10% neutral buffered formalin and subjected to routine tissue processing. Following this procedure, 4 µm thick sections were prepared from the tissue samples embedded in paraffin blocks using a rotary microtome. These sections were stained with hematoxylin and eosin (HE) and evaluated under a light microscope (BX51, Olympus, Tokyo, Japan) at 10x, 20x, and 40x magnifications. For findings that were present, semi-quantitative scoring was applied based on severity: mild (1), moderate (2), or severe (3).

For the liver: portal inflammation, confluent necrosis, spotty necrosis, piecemeal necrosis, and fibrosis were evaluated as either present or absent.

In the kidney tissues, interstitial inflammation, glomerular sclerosis, tubular necrosis, and vascular changes were evaluated as present/absent (0).

In the testicular tissues, necrosis and spermatogenesis arrest, as present/absent (1/0), were evaluated.

In the ocular tissues, damage findings in the cornea, retina, and optic nerve, including edema, inflammation, hemorrhage, increased vascularity, and necrosis, were evaluated as present or absent, with 0 indicating absence.

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Statistical Analysis

The conformity of quantitative variables to normal distribution was examined by the Kolmogorov-Smirnov test. One-Way Analysis of Variance or Kruskal-Wallis test were used, according to the distribution structure of the variables. Pathologic examination results were analyzed using chi-square tests. Descriptive statistics were given as mean ± standard error, median (25^{th}-75^{th} percentiles), or frequency (%). For all statistical analyses, $p<0.05$ was accepted as the significance level.

RESULTS

Clinical findings

None of the rats died during the study. The presence of leukocytes, nitrite, urobilinogen, protein, calcium, blood, ketone, creatinine, and glucose in the urine was not significantly different among the groups. The MTX + MeOH group had a urine protein score of 3.33, which was higher than the control group's 2.75. However, no significant differences were observed among the other groups: DMF (2.13), MTX (2), MTX + MeOH + DMF30 (2.25), and MTX + MeOH + DMF100 (2.88).

Bilirubin excretion score of MTX + MeOH + DMF100 group was 0.78, significantly higher than the control group score, which was 0 (p=0.014). The MTX group score was 0.44 and the MTX + MeOH + DMF30 group score was 0.25; both scores showed a tendency to increase.

Urine density was the same in all groups. The urine pH values in the DMF treatment groups (30 mg/kg and 100 mg/kg) were found to be similar to the control group, respectively, with measurements of 6.06±0.42, 6.89±0.16, and 6.88±0.25. Only DMF-taken group's urine pH was 6.44±0.11. In the MTX + MeOH group, the pH value increased to 7.31±0.25, but there was no statistically significant difference when compared to the control group. Blood sugar was not different among the groups, although it tended to be lower with MeOH. The animals' kidney to body weight and testicular weight to body weight ratios were insignificant (Table 1).

A significant reduction in the liver weight/body weight ratio was observed when compared to the Control group (3.53±0.11) in the DMF100 group (3.17±0.06, p=0.010), the MTX + MeOH + DMF30 group (3.14±0.06, p=0.035), and the MTX + MeOH + DMF100 group (3.01±0.06, p=0.014). (Table 1).

Pathological Evaluation

Pathological evaluations were performed on the liver (inflammation, necrosis, fibrosis); kidney (inflammation, sclerosis, necrosis, vascular changes); testes (necrosis, spermatogenesis arrest); and eyes (edema, inflammation, hemorrhage, increased vascularity, necrosis in cornea, retina, optic nerve) using HE staining. No abnormalities were detected in any group across these tissues. (Figure 1).

DISCUSSION

In an effort to replicate and extend previous findings, we applied DMF within our experimental model, using the same setup and strictly adhering to published techniques. Regrettably, we could not demonstrate that this route and dose of administration, with HE staining, produced MeOH toxicity, or that DMF attenuated systemic inflammation in a rat model of MeOH toxicity. MeOH had minimal effects on the systems in our rats.

In a previous study, male Wistar rats exposed to 3 g/kg of a 50% w/v solution of MeOH showed the highest increase in liver lipid peroxide products, 24 hours later (5). Similarly, Nugrahanti et al. (8) induced liver toxicity in 2-3 month-old male Wistar rats by administering 3.5 and 7 g/kg of a 20% w/v MeOH solution and sacrificing them 8 hours later, without MTX pretreatment. This dosage resulted in an abnormal liver condition. In contrast, Sahin et al. (2) examined retinal and optic nerve damage, administering 3 g/kg of a 20% w/v MeOH solution intraperitoneally after 7 days of MTX (0.3 mg/kg/d) treatment, and sacrificing the rats 8 hours post-MeOH. They noted that rats are less susceptible to MeOH poisoning than humans due to higher liver folic acid and rapid formic acid metabolism, the latter of which can be compromised by nitrous oxide or MTX. MTX treatment impairs folate-dependent

Table 1. Biochemical findings of all experimental groups

	Urine pH	Urine density	Blood sugar	Liver weight /BW X100	Kidney weight /BW X100	Testicular weight /BW X100
Control	6.5 (6.5-7.0)	1030 (1030-1037.5)	198 (168.5-219.5)	3.53±0.11	0.83 (0.83-0.89)	0.87 (0.81-0.88)
DMF100	6.5 (6.13-6.5)	1030 (1030-1037.5)	201.5 (160-228.75)	3.17±0.06*	0.91 (0.83-0.96)	0.89 (0.85-0.98)
MTX	7 (5.75-7.25)	1030 (1030-1030)	189 (168.5-240)	3.51±0.09	0.89 (0.85-0.96)	0.89 (0.88-0.93)
MTX+MeOH	7 (6.75-8.0)	1030 (1030-1030)	172 (156-189)	3.37±0.10	0.90 (0.84-0.99)	0.97 (0.92-1.01)
MTX+MeOH+ DMF30	5.75 (5.0-7.38)	1030 (1030-1055)	174 (155.5-191.75)	3.14±0.06**	0.88 (0.83-0.97)	0.92 (0.84-0.97)
MTX+MeOH+ DMF100	7 (6.5-7.25)	1030 (1030-1035)	166 (161-177)	3.01±0.06***	0.87 (0.81-0.94)	0.93 (0.89-0.97)
p-value	0.122	0.428	0.252	<0.001	0.586	0.058

*: DMF100 (p=0.010), **: MTX + MeOH + DMF30 (p=0.035) and ***: MTX + MeOH + DMF100 (p=0.014) are statistically different from the Control group.
DMF100: Dimethyl fumarate (100 mg/kg), MTX: Methotrexate (0.3 mg/kg/7 days), MeOH: Methyl alcohol (3 g/kg, 20%), DMF30: Dimethyl fumarate (30 mg/kg), DMF100: Dimethyl fumarate (100 mg/kg)

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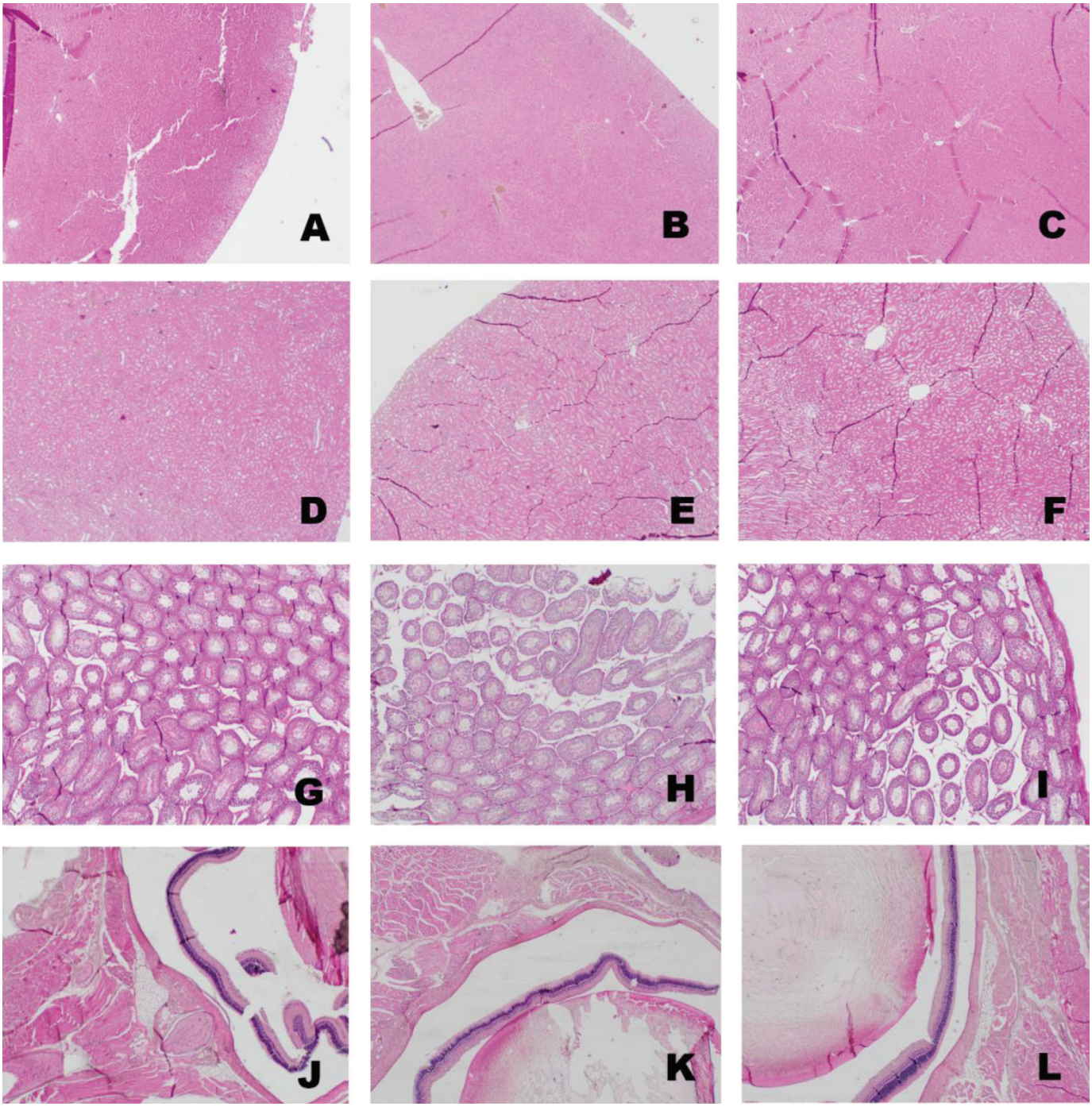

Figure 1. Pathological appearance of liver (A, B, C), kidney (D, E, F), testis (G, H, I) and eye (J, K, L) tissues. A, D, G, J are the Control groups; B, E, H, K are the 100 mg/kg Dimethyl Fumarate groups; C, F, I, L are Methotrexate+ Methanol groups

formate metabolism and facilitates MeOH poisoning in rats (3). Human livers contain approximately half the tetrahydrofolate levels found in rat livers. Furthermore, the activity of the enzyme 10-formyl tetrahydrofolate dehydrogenase is lower in human livers than in rat livers. Consequently, rats metabolize formate twice as quickly as humans. This rapid metabolism prevents the accumulation of formic acid in rats, protecting them from acidosis, ocular damage, and other toxic effects observed in human MeOH poisoning (1). Yazgan et al. (10) and Gursul et al. (3) also reported that they successfully used this MTX/MeOH model for liver injury. Therefore, to mitigate the risk of sudden death or gastric hemorrhage associated with a 3.5 or 7 g/kg MeOH dose alone, we pretreated rats with MTX for 7 days and applied 3 mg/kg of a 20% w/v MeOH solution, strictly adhering to established protocols. We have also used 10-12 week old male Wistar rats according to previous literature. These previous reports have evaluated the MeOH exposure samples through electron microscopy (5) and by measuring the leakage of alanine aminotransferase and aspartate

aminotransferase into the blood (3,5). Additionally, they have assessed malondialdehyde and total (anti)oxidant status (3) and conducted docking affinity studies for alcohol dehydrogenase (2). Unlike previous studies, we employed urine tests and pathological examinations to evaluate toxicity in the liver, kidneys, testicles, and eyes.

Silva et al. (9) demonstrated that a urine test strip, used in semiquantitative biochemical urinalysis, is a straightforward and safe technique for evaluating urinary and systemic function in ischemia and reperfusion injury in the kidney and in streptozotocin diabetes models. Similar to their technique, we placed the animals on the bench and waited for spontaneous urination. They reported an average urine pH of 8.5 in their mouse model. Conversely, our experiments with normal rats showed a significantly lower urine pH, averaging 6.88. The application of MTX + MeOH to rats increased the urine pH to 7.31 (a 6.25% increase). This group also showed a high protein score in urine 3.33 (a 21% increase over the control value), indicating an early sign of kidney stress; however, prominent kidney pathology was not detected using HE staining following the administered MeOH dose. Our urine analyses also supported these normal histological findings, which showed creatinine within normal levels and no hematuria in the urine samples.

Bilirubin is typically absent from urine. However, some animals showed bilirubin excretion in urine following treatment with MTX and MTX + MeOH + DMF30, while the MTX + MeOH + DMF100 group exhibited a significant increase. This effect was not observed in the control or DMF groups, suggesting that it is related to MTX. As MTX can indirectly affect bilirubin levels due to its potential impact on the liver (11), this side effect may be more pronounced when used in combination with MeOH or DMF. Nugrahanti et al. (8) reported that liver specimens exposed to only, 3.5 and 7 g/kg of MeOH exhibited inflammatory cells, necrosis, cell degeneration, and fibrosis. This was similar to findings in a previous study, where 3 g/kg of a 20% w/v MeOH solution, administered with MTX for 7 days, resulted in severe pyknosis, hemorrhage, hydropic degeneration, and mononuclear cell infiltration in the hepatocytes of the MeOH + MTX group (3). However, we did not observe any of these signs in HE staining of our liver samples.

In our study, testicular tissue was not damaged by this route and dose in the MeOH + MTX group, as evaluated through histopathological examination of HE staining.

Hypoglycemia and lactic acidosis are known consequences of MeOH poisoning (4). However, it has been reported that inducing the severe acidosis seen in human MeOH poisoning is not possible in rodents (1). This limitation might explain why our study did not show severe urine and blood parameter changes. While blood glucose levels slightly decreased, this difference was not statistically significant compared to the control group.

Sahin et al. (2) showed that MeOH + MTX exposure caused oxidative stress in rat retinas and optic nerves, leading to retinal ganglion cell loss. This damage was prevented by the antioxidant caffeic acid phenethyl ester. Although we used the same MeOH + MTX protocol, we did not observe, using HE staining, edema, inflammation, hemorrhage, increased vascularity, or necrosis in the cornea, retina, or optic nerve.

In this study, DMF was determined to be safe for the liver, kidney, testicular, and ocular tissues, based on the parameters inspected. DMF has been shown to be effective against ethanol-induced hepatic injury, steatosis, and inflammation in mice (6). Furthermore, its beneficial effects have been proposed in many experimental eye models (7). Similarly, we would like to evaluate its potential, especially in ocular tissue in MeOH toxicity. Unfortunately, we could not prove our hypothesis. At least we could prove its safety in this dose and route on four tissues. First, an additional replicable MeOH model should be established.

Study Limitations

A key limitation of this study is that the model did not produce expected toxicity symptoms in urine and tissue samples. Furthermore, only HE staining was used to evaluate the four tissue samples, unlike previous research that employed electron microscopy for more detailed damage assessment.

CONCLUSION

DMF was found to be safe for the liver, kidney, testicular, and ocular tissues. The administered dose and route of MeOH, in conjunction with MTX, did not result in toxicity in rats, as has been observed in previous reports. Our study provides foundational techniques and ideas for future research.

Ethics

Ethics Committee Approval: Animal Ethics Committee for Experiments at Aydin Adnan Menderes University (decision no: 64583101/2024/32, date: 21.03.2024).

Informed Consent: Since no human embryos, fetuses, tissues derived from them, or other human cells and tissues were used in any part of this study, obtaining a patient consent form is not required.

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Footnotes

Author Contributions: Surgical and Medical Practices - A.A.U., B.D.; Concept - A.I.A.U., I.M., B.D.; Design - A.I.A.U., A.A.U., B.D.; Data Collection and/or Processing - A.A.U., I.M., B.D.; Analysis and/or Interpretation - A.I.A.U., I.M., B.D.; Literature Search - A.I.A.U., A.A.U., B.D., Writing - A.I.A.U., B.D.

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The Effectiveness of Shear-wave Elastography in Childhood Hepatosteatosis Grading and Comparison with Sonographic Grading

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ABSTRACT

Objective: To assess acoustic radiation force impulse (ARFI) elastography-measured liver stiffness with respect to its relationships with hepatic steatosis presence and severity in pediatric non-alcoholic fatty liver disease (NAFLD), while identifying clinical factors associated with altered liver elasticity.

Methods: This cross-sectional observational study included 31 children with ultrasonographically diagnosed NAFLD and 12 healthy controls aged 7-16 years. Clinical, anthropometric, laboratory, and imaging data were obtained from hospital records. Laboratory parameters included alanine aminotransferase, aspartate aminotransferase, fasting glucose, insulin, lipid profile, and homeostasis model assessment of insulin resistance. Liver stiffness was assessed using ARFI elastography by a single operator, with shear wave velocity (SWV) measurements acquired from segments 5-8 of the liver, excluding the left lobe.

Results: Mean age was 12.94±3.20 years in the hepatosteatosis group and 11.00±2.73 years in the control group (p=0.072); females comprised 35.5% and 58.3% of each group, respectively (p=0.309). The hepatosteatosis group had significantly higher body mass index (BMI) (p=0.001), height (p=0.001), and liver craniocaudal length (p=0.002) than controls. Among hepatosteatosis patients, those with grade 2 steatosis had significantly higher BMI (p=0.001) and liver size (p=0.004) than those with grade 1. ARFI SWV values were similar between groups and steatosis grades, and SWV values did not correlate with anthropometric or laboratory parameters.

Conclusion: ARFI elastography measurements are unaffected by hepatic steatosis severity in pediatric NAFLD and values do not correlate with clinical or laboratory parameters. As such, ARFI is a reliable non-invasive tool for fibrosis assessment, irrespective of other patient characteristics.

Keywords: Non-alcoholic fatty liver disease, elasticity imaging techniques, ultrasonography, pediatrics, biomarkers

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), which causes steatosis and inflammatory fibrosis, is a prevalent condition that has the potential to progress into end-stage liver disease (1). It is also closely associated with obesity and insulin resistance (2,3). With rising childhood obesity rates, NAFLD has become the most common pediatric liver disorder, affecting 5-10% of children in Western countries and up to 30% in obese populations (4-6).

Ultrasonography (US) is widely used for NAFLD screening because of its accessibility and affordability, with a sensitivity of 60-94% and specificity of 66-95% for detecting hepatic steatosis (7,8). However, US relies on subjective echogenicity assessments with significant inter-observer variability (7,9). Liver biopsy is the gold standard but is invasive, costly, and carries risks (e.g., bleeding, pain), with up to 3% of pediatric cases requiring hospitalization due to complications (10). Moreover, histological grading systems lack universal standardization, making biopsy impractical for routine follow-up (10). These limitations of different methods warrant the study of other non-invasive alternatives that can be used for diagnostic and prognostic purposes in NAFLD.

Elastography techniques have revolutionized hepatic assessment by quantifying tissue stiffness as a surrogate marker of disease severity. Among these, acoustic radiation force impulse (ARFI) elastography has had considerable success in pediatric applications (11). This modality employs conventional US devices and does not require external compression or specialized probes

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(11). The technology measures shear wave velocity (SWV) in meters/second, with values increasing proportionally to hepatic fibrosis stage (12). Emerging pediatric data suggest ARFI may also detect early changes associated with steatosis before US-detectable signs appear (13,14). However, it is unclear if the presence of steatosis could independently elevate ARFI values without the presence of actual fibrosis, potentially leading to overestimation of fibrosis (13,14). Addressing potential confounders impacting ARFI measurement reveal if the results are reliably utilized for the assessment of steatosis and fibrosis (early or overt). The sensitivity of ARFI may also be useful for assessing treatment response, as US findings are often delayed. At present, pediatric ARFI applications remain limited by unresolved steatosis-stiffness interactions, lack of standardized cut-offs, and segmental measurement variability (13).

This study aims to investigate the relationship between both ARFI-measured liver stiffness and the presence and severity (grade) of hepatic steatosis in pediatric NAFLD, and to identify potential factors associated with altered liver elasticity. By establishing these relationships, we seek to validate ARFI elastography as a reliable non-invasive tool for pediatric steatosis assessment while elucidating clinical and metabolic determinants of liver stiffness in this population.

METHODS

Study Design and Ethical Approval

This study was designed as a cross-sectional, observational study conducted at the Department of Pediatric Radiology, İstanbul Faculty of Medicine, İstanbul University, İstanbul, Türkiye. The study was carried out between January 2014 and June 2014, with the approval of the Ethics Committee of İstanbul University (decision no:16, date: 26.09.2014). Written informed consent was obtained from all participants and their legal guardians.

Study Population

The study population consisted of two groups: a hepatosteatosis group and a control group. The hepatosteatosis group included 31 school-aged children who were followed at the general pediatric outpatient clinic due to US-diagnosed NAFLD. The control group comprised 12 healthy school-aged children without any clinical or radiological signs of hepatic steatosis. Inclusion criteria for the hepatosteatosis group were: age between 7 and 16 years, diagnosis of hepatic steatosis based on ultrasound, and absence of acute or chronic viral hepatitis, autoimmune liver disease (e.g., autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis), drug-induced or herbal hepatotoxicity, and inherited or metabolic liver diseases (e.g., Wilson's disease, hemochromatosis, glycogen storage disorders). The control group included children aged 7-16 years with normal liver echogenicity on US and no history of metabolic syndrome or liver disease.

Data Collection and Laboratory Parameters

Clinical data of the participants were retrospectively collected from patient files and our hospital's digital database. The available data were based on records from clinical examination, laboratory analysis, and imaging studies. These included demographic and anthropometric data, biochemical parameters, liver size measurements, hepatic steatosis grading, and liver stiffness measurements obtained *via* ARFI elastography. Weight and height were measured using calibrated digital scales and stadiometers. Body mass index (BMI) was calculated using the standard formula (weight in kilograms divided by height in meters squared).

Venous blood samples were obtained in the morning after an 8-hour fasting period. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting glucose, cholesterol, and triglyceride levels were measured in the central laboratory using standard automated chemical analyzers. Serum insulin levels were measured by radioimmunoassay. Insulin resistance was evaluated by calculating the homeostasis model assessment of insulin resistance (HOMA-IR) using the formula: HOMA-IR = (glucose × insulin) / 405 (15).

Ultrasound and ARFI Measurements

All imaging was performed using the Siemens ACUSON S3000™ ultrasound system (Siemens Healthcare, Erlangen, Germany) with a 4 MHz transabdominal convex probe. Scans were conducted in the morning after at least 8 hours of fasting. Initially, a routine upper abdominal US was performed to assess liver morphology and measure the craniocaudal length of the liver. Patients with space-occupying lesions or extrahepatic abnormalities identified during the scan were excluded. Hepatosteatosis was graded as described previously (16). For ARFI elastography, cases were scanned in the supine position through the intercostal space. Measurements were obtained from segments 5, 6, 7, and 8 of the liver, avoiding vascular and biliary structures (Figure 1). For each segment, two measurements were taken by placing a 5-10 mm rectangular region of interest at a depth of 2-5 cm from the capsule. Measurements taken outside the specified depth range (2-5 cm from the capsule) were excluded from analysis. Mean velocity values in meters per second (m/s; SWV) were recorded for each segment and an average liver stiffness value was calculated. The left lobe was excluded due to motion and cardiac pulsation artifacts. All measurements were performed by the same radiologist with experience in abdominal sonography.

Statistical Analysis

Analyses were performed using Number Cruncher Statistical System 2007 and Power Analysis and Sample Size 2008 statistical software (Utah, USA). Descriptive statistics, including mean, standard deviation, median, 1st quartile, 3rd quartile, frequency, and percentage, were used to summarize the data. The normality of the data distribution was assessed. For comparisons of quantitative variables between two independent groups, the

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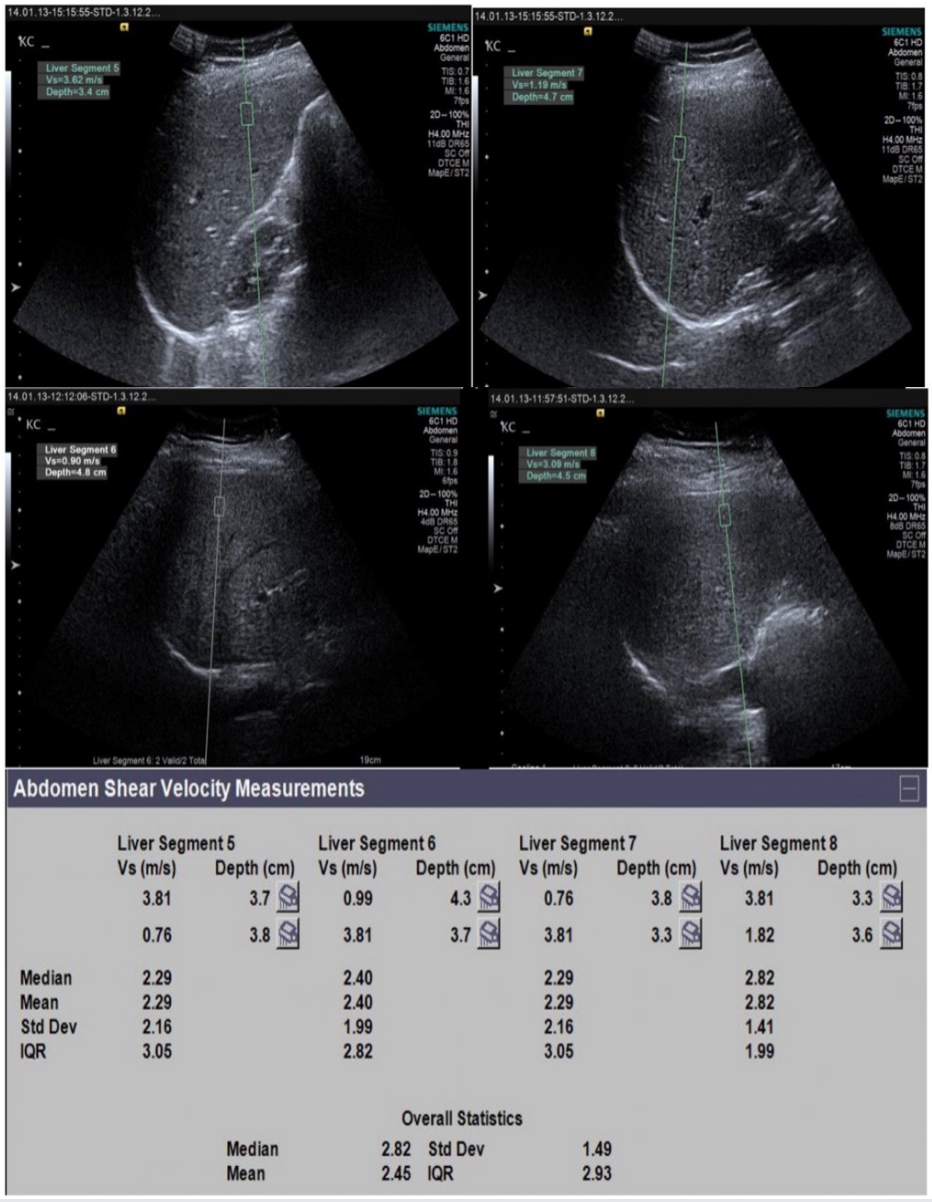

Figure 1. Measurement of shear wave velocity (SWV) using ARFI elastography. The image demonstrates the calculation of mean and median SWV values (ms) from multiple region-of-interest measurements across different liver segments
ARFI: Acoustic radiation force impulse

Mann-Whitney U test and independent t-test was used due to non-normal distribution of the data. Categorical variables were compared using the Yates' corrected chi-square test. Correlations between continuous variables were evaluated using Spearman's rank correlation coefficient. A p-value of less than 0.05 was considered significant.

RESULTS

The mean age of the hepatosteatosis group was 12.94±3.20, while the control group's mean age was 11.00±2.73 (p=0.072). In the hepatosteatosis group, 35.5% were female, compared to 58.3% in the control group (p=0.309). The median weight and BMI of the hepatosteatosis group were significantly higher than those of the control group (p=0.001). The liver craniocaudal length in the hepatosteatosis group was also significantly greater than that in the control group (p=0.002). No significant differences were observed between groups regarding any ARFI measurements (Table 1).

Among patients with grade 2 hepatosteatosis, both liver craniocaudal length (p=0.004) and BMI (p=0.001) were significantly higher than in patients with grade 1 hepatosteatosis (Table 2). ARFI measurement values did not differ significantly between grade 1 and grade 2 hepatosteatosis groups (Table 2).

There were no significant correlations between mean SWV and liver craniocaudal length (r=0.009, p=0.961), ALT levels (r=-0.173, p=0.325), AST levels (r=-0.186, p=0.283), HOMA-IR (r=-0.179, p=0.361), cholesterol levels (r=-0.103, p=0.633), or triglyceride levels (r=-0.273, p=0.056) (Table 3).

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Table 1. Demographic, clinical, and ARFI elastography characteristics of study participants

	Hepatosteatosis group (n=31)	Control group (n=12)	p-value
Age, years	12.94±3.20	11.00±2.73	0.072
Sex			
Female	11 (35.5%)	7 (58.3%)	0.309
Male	20 (64.5%)	5 (41.7%)	
Height, cm	157.74±17.32 (162)	146.25±16.15 (144)	0.054
Weight, kg	(54-89)	(32-49)	**0.001**
BMI, kg/m^2	30 (26-33)	19 (15-21)	**0.001**
ALT, U/L	26 (34-82)		
AST, U/L	31 (24-44)		
Insulin, µIU/mL	52 (39-112)		
Glucose, mg/dL	92 (86-109)		
HOMA-IR	16 (12-41)		
Cholesterol, mg/dL	169 (146-201)		
Triglyceride, mg/dL	56-302 (136.59±63.35)		
Hepatosteatosis grade			
Grade 1	26 (83.9%)		
Grade 2	5 (16.1%)		
Liver craniocaudal Length, mm	138.16±18.87	118.08±12.75	**0.002**
ARFI measurements			
Mean liver velocity, m/s	1.5(0.9-2.1)	1.3 (0.7-1.9)	0.163
Segment 5 mean velocity, m/s	1.4 (0.6-2.2)	1.2 (1.0-1.4)	0.056
Segment 6 mean velocity, m/s	1.4 (0.8-2.3)	1.3 (0.9-2.6)	0.350
Segment 7 mean velocity, m/s	1.3 (0.9-2.0)	1.3 (0.8-2.3)	0.323
Segment 8 mean velocity, m/s	1.3 (1.1-1.6)	1.3 (1.0-1.6)	0.498

Data are presented as mean ± standard deviation or median (1st - 3rd quartile) for continuous variables depending on their distribution and n (%) for categorical variables. P-values were obtained from independent t-tests (normal distribution) or Mann-Whitney U tests (non-normal distribution) for continuous variables and chi-square tests for sex comparison. Bolded p-values indicate statistical significance ($p<0.05$). ARFI: Acoustic radiation force impulse, BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HOMA-IR: Homeostatic model assessment of insulin resistance

DISCUSSION

The current study investigated the impact of hepatic steatosis on ARFI elastography measurements in pediatric NAFLD. Our results demonstrated that children with NAFLD exhibited significantly higher BMI and liver craniocaudal length compared to healthy controls, confirming the association between obesity and hepatomegaly in this population. However, ARFI-derived SWV measurements showed no significant differences between NAFLD patients and controls, nor between grade 1 and grade 2 steatosis subgroups. Furthermore, SWV values did not correlate with liver size, aminotransferase levels (ALT/AST), insulin resistance (HOMA-IR), or lipid profiles (cholesterol/triglycerides).

The increasing prevalence of pediatric NAFLD necessitates reliable non-invasive tools for fibrosis assessment, since this can improve the prediction of cirrhosis risk (17). ARFI elastography has proved considerable efficacy for this purpose, with SWV measurements acting as a surrogate for fibrosis severity (18). Hanquinet et al. (19) 32 demonstrated significantly higher SWV in chronic liver disease (1.99 m/s) versus controls (1.12 m/s), with 100% sensitivity for severe fibrosis at a cut-off <2 m/s. Noruegas et al. (20) validated the utility in different fibrosis stages, while Marginean and Marginean (21) noted elevated SWV in pediatric NAFLD and correlations with AST and inflammation. Despite this level of evidence, it is still unclear whether hepatic steatosis alone (regardless of fibrosis) influences ARFI results. Our study addresses this gap, revealing no significant SWV differences between NAFLD patients and healthy controls, indicating that steatosis presence alone does not intrinsically alter ARFI-derived stiffness measurements in pediatric NAFLD. Our results are supported

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Table 2. Comparison of clinical and ARFI elastography parameters between Grade 1 and Grade 2 hepatosteatosis patients

	Grade 1 (n=26)	Grade 2 (n=5)	p-value
Liver craniocaudal length, mm	133.46±15.79	162.60±14.84	**0.004**
ARFI measurements			
Mean velocity for overall liver, m/s	1.4 (0.8-2.0)	1.9 (1.3-2.8)	0.361
Segment 5 mean velocity, m/s	1.4 (0.5-2.2)	1.6 (0.8-2.0)	0.788
Segment 6 mean velocity, m/s	1.4 (0.7-1.8)	1.7 (1.5-2.0)	0.747
Segment 7 mean velocity, m/s	1.3 (0.6-2.2)	1.7 (0.8-1.9)	0.227
Segment 8 mean velocity, m/s	1.3 (0.6-2.3)	1.7 (1.0-2.0)	0.347
BMI (kg/m^2)	29 (21-32)	42 (32-47)	**0.001**
ALT, U/L	18 (14-38)	32 (19-49)	0.085
AST, U/L	22 (15-39)	26 (18-51)	0.893
Cholesterol, mg/dL	175 (151-192)	154 (146-174)	0.065
Triglyceride, mg/dL	(79-151)	(101-132)	0.977
HOMA-IR	5 (3-12)	8 (7-22)	0.085

Data are presented as mean ± standard deviation or median (1st - 3rd quartile), and independent t-tests (normal) and Mann-Whitney U (non-normal) were performed accordingly. Bold p-values significant ($p<0.05$)
ARFI: Acoustic radiation force impulse, BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HOMA-IR: Homeostatic model assessment for insulin resistance

Table 3. Correlation analysis between mean liver ARFI velocity and clinical parameters

Mean liver velocity, m/s		
	r	**p**
Liver craniocaudal length, mm	0.009	0.961
ALT, U/L	-0.173	0.325
AST, U/L	-0.186	0.283
HOMA-IR	-0.179	0361
Cholesterol, mg/dL	-0.103	0.633
Triglyceride, mg/dL	-0.273	0.056

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HOMA-IR: Homeostatic model assessment of insulin resistance, r: Spearman correlation coefficients

by data from several studies. Motosugi et al. (22) showed no differences in SWV values between adults with fatty liver (SWV: 1.02±0.12 m/s) and those without (1.03±0.12 m/s). Similarly, Rifai et al. (23) found no association between steatosis and SWV in biopsy-proven cases. Taken together, these studies indicate that fibrosis is the primary factor altering SWV, particularly in human steatosis, as animal studies appear to show varying findings (24). It is also crucial to note that tissue-specific and methodological factors may alter the results. This alteration includes the varying impact of inflammation and lipids on the microenvironment (25), as well as the differences in results based on the site of SWV measurement in the liver (13). These variations might be unavoidable given the technical limitations of US-based analyses versus magnetic resonance imaging (MRI) (14). Nonetheless, while steatosis may indirectly influence stiffness via altering inflammation or fibrosis, our evidence suggests it does not systematically bias ARFI measurements. Despite this reliability for fibrosis screening in pediatric NAFLD, combining it with biomarkers like AST/ALT ratios could optimize diagnostic precision (26).

The relationship between hepatic steatosis severity and ARFI-derived liver stiffness remains controversial, with conflicting evidence regarding whether fat accumulation grade independently influences SWV measurements (27). In our study, we observed no significant differences in SWV values between children with Grade 1 and Grade 2 steatosis, suggesting that steatosis severity alone may not directly alter ARFI-based stiffness assessments. The literature on this topic reveals contrasting results. Yoneda et al. (28) reported an inverse relationship between steatosis grade and SWV, with decreasing velocities in higher grades (Grade 1: 1.38 m/s; Grade 2: 1.14 m/s; Grade 3: 1.08 m/s). This is an unexpected decline, and it raises questions regarding the application of ARFI; however, such an intriguing finding could also be demonstrating the technical limitations of SWV in different disease states and progression. Oana et al. (13) documented elevated SWV in the right lobe (segment 8: 1.982±0.85 m/s) compared to segment 1 (1.325±0.27 m/s) in obese children, implying regional stiffness variations driven by uneven fat distribution rather than global grading. This is partially supported by data from pediatric patients showing higher SWV in obese children with steatosis (1.746±0.49 m/s) versus controls (1.080±0.27 m/s), despite the absence of correlations between SWV and BMI (13). Animal models further complicate interpretation: Guzmán et al. (24) demonstrated that diet-induced steatosis markedly increases SWV, with strong histological correlation. However, species-specific metabolic responses limit extrapolation to humans. Crucially, Rifai et al. (23)

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found no statistical impact of steatosis grade on ARFI in clinical cohorts. This latter result aligns with our findings and suggests steatosis grade does not confound elastography measurements. There are several possible explanations the inconsistent results in the literature. Regional heterogeneity in fat distribution can significantly influence localized SWV readings, as fat accumulation can alter tissue mechanics (13). Inflammation and its differing impacts on tissues and lesion microenvironments could also confound interpretations, as different histological outcomes in different sites (e.g., ballooning hepatocytes, lobular inflammation) may alter stiffness and SWV outputs (21,23). Finally, technical limitations of US-based steatosis grading, which lacks the precision of MRI or histology, may obscure subtle fat-stiffness relationships due to inconsistent fat quantification and threshold definitions (14). While severe steatosis appears to have the potential to influence ARFI results, current evidence does not support a consistent, grade-dependent effect on SWV measurements in pediatric NAFLD.

The robustness of ARFI elastography in pediatric NAFLD is reported to be influenced by several other clinical and biochemical variables (29); however, we did not find any significant correlations between SWV and liver size, aminotransferase levels, insulin resistance (HOMA-IR), or lipid profiles. Indeed, available literature largely suggests that ARFI results are unassociated with age, sex, and BMI (12,30-32). However, Rifai et al. (23) reported positive correlations between ARFI values and hepatomegaly/splenomegaly, suggesting that portal hypertension or volumetric changes in advanced disease may influence liver stiffness. Similarly, Takahashi et al. (32) observed that SWV data correlated with AST/ALT levels in patients with chronic liver disease; however, again, these relationships might easily be attributed to concurrent inflammation rather than NAFLD pathophysiology, which is supported by another study demonstrating that SWV results correlated with AST (but not ALT) in patients with malignancy, as well as those with NAFLD (21). This could indicate that AST elevation is a result of excessive inflammation-induced hepatocellular injury rather than being directly associated with NAFLD. Metabolic factors like BMI have been shown to influence ARFI measurements in otherwise-healthy children with obesity (21), but this relationship does not exist in patients with established NAFLD. Considering available evidence and our results, it is evident that ARFI-measured SWV results are not strongly altered by metabolic fluctuations. Nevertheless, interpretation of results might necessitate awareness of disease stage, progression, treatment characteristics and response, and tissue-level or systemic complications.

Study Limitations

The present study focuses on ultrasound-measured results and does not utilize gold standard methodology (biopsy) in the determination of steatosis and fibrosis. This is an important limitation as US-based grading remains inferior to biopsy or MRI. Second, our small sample size may be considered limited in terms of the comparison of groups with regard to steatosis grades (in fact, grade 3 was entirely absent). Further, the single-center design may limit the generalizability of our findings to other pediatric populations with varying ethnic, geographic, or comorbidity profiles. Furthermore, all ARFI measurements were performed by a single radiologist. Although this prevented possible biases due to inter-observer variability, it must be noted that all ultrasound-based outputs have some level of subjectivity.

CONCLUSION

This study demonstrates that ARFI elastography measurements are unaffected by the presence or severity of hepatic steatosis in pediatric NAFLD and show no significant correlations with anthropometric, biochemical, or metabolic parameters. ARFI-based measurements appear to be a crucial tool for allowing non-invasive fibrosis assessment in children without steatosis-related confounding. However, further large-scale studies performing analyses with respect to histopathological data are needed. Based on present findings and prior literature, integrating ARFI with clinical and biomarker data could optimize the utility of this tool in the diagnosis and follow-up of children with NAFLD.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of İstanbul University (decision no: 16, date: 26.09.2014), and ethical permission was obtained prior to its initiation.

Informed Consent: Written informed consent was obtained from all participants and their legal guardians.

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Footnotes

Author Contributions: Surgical and Medical Practices - M.S.Ç.; Concept - M.S.Ç., B.A.; Design - M.S.Ç., B.A.; Data Collection and/or Processing - M.S.Ç.; Analysis and/or Interpretation - M.S.Ç.; Literature Search - M.S.Ç.; Writing - M.S.Ç., B.A.

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

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Evaluation of the Combined Effectiveness of Transforaminal and Facet Joint Injections in Low Back and Leg Pain Unresponsive to Conservative Treatment

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ABSTRACT

Objective: This study evaluates the short- to mid-term effectiveness of simultaneous transforaminal anterior epidural injection (TAEE) and facet joint injections (FJI) in patients with acute low back and leg pain and assesses the impact of obesity on treatment outcomes.

Methods: Sixty-seven patients (22 males, 45 females) underwent TAEE and FJI. Pain levels were assessed using the visual analog scale (VAS) and Oswestry Disability Index (ODI) before treatment and at the 6-month follow-up. Non-parametric tests and logistic regression were used for statistical analysis.

Results: A total of 105 TAEE and 302 FJI procedures were performed. Significant reductions in VAS and ODI scores were observed at 6 months ($p<0.05$). Obese patients had significantly higher VAS scores at follow-up ($p=0.002$ for low back pain, $p=0.019$ for radicular pain). However, logistic regression analysis showed that obesity was not an independent predictor of post-treatment VAS scores ($p=0.211$, $p=0.168$).

Conclusion: TAEE and FJI effectively reduce pain in patients with low back and leg pain unresponsive to conservative treatment. While obesity may delay pain relief, it does not independently affect treatment success.

Keywords: Low back pain, radiculopathy, facet joint injection, transforaminal anterior epidural injection, steroids, obesity

INTRODUCTION

Low back pain is a significant problem that causes dysfunction in the musculoskeletal system, leading to socio-economic losses in all societies. Epidemiological studies have shown that 65-80% of the general population suffers from low back pain at some point in their lives. It can generally be managed with bed rest, medical treatment, and physical therapy. However, it can become chronic and reduce patients' quality of life. One of the most important causes of chronic low back pain is intervertebral disc degeneration (1). In patients with low back pain, specific cases of lumbar disc herniation (LDH) and lumbar spinal stenosis account for only 15%, while the remaining 85% are diagnosed with "non-specific low back pain" (2).

Minimally invasive methods can be applied to reduce pain and improve quality of life for patients who do not respond to conservative treatment, have failed surgical treatment, or do not require surgical intervention. Lumbar transforaminal anterior epidural and facet joint injections (FJI) are the most well-known ones among these methods. Transforaminal anterior epidural injection (TAEE) is a safe method for the non-surgical treatment of spinal stenosis and can also support the indications for surgical treatment (3). Anterior epidural steroid injections performed under fluoroscopy are commonly used for the treatment of low back and lower extremity radicular pain. These procedures have been shown to be effective in relieving pain in the short term and are relatively safe (3).

Although the primary indication for transforaminal anterior epidural steroid injection is symptomatic disc herniation that does not require surgery, it is also widely and effectively used for lumbar canal stenosis, failed back surgery syndrome, postoperative

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epidural fibrosis, spondylolisthesis, infectious radiculitis, and neuralgic pain (4,5).

This study aims to retrospectively analyze the data of 67 patients, in a single center, with low back and radicular pain who underwent combined TAEE and facet joint injection, without having had lumbar surgery, evaluating short- to mid-term clinical efficacy and reliability.

METHODS

This retrospective study was conducted with ethics approval granted by the Institutional Ethics Committee of a University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital (approval number: 19, date: 03.07.2024), and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Sixty-seven patients who underwent combined transforaminal epidural and FJI, and had pre- and post-procedure six-month records were included in the study. Patients were included in the study if they had not responded to previous conservative treatments and experienced low back and radicular pain lasting more than two months. Additionally, their visual analog scale (VAS) pain scores were higher than 4, and Oswestry Disability Index (ODI) scores were above 18. Those excluded from the procedure were pregnant or had a suspected pregnancy history, were candidates for surgery or had previously undergone surgery, had wounds in the procedure area, had bleeding disorders, allergies to the medications administered, serious chronic illnesses, low Karnofsky scores, or any form of organ failure. The sex, height, weight, body mass index (BMI), complaint, and neurological signs were noted. Before the procedure, VAS and ODI scores were recorded for all patients.

All the patients were evaluated again six months after the procedure. VAS and ODI scores were measured to objectively assess changes in pain levels. For the VAS, the scores ranging between 0 and 2 were classified as optimal responses to the treatment, the scores of 3 and 4 as suboptimal responses, and the scores of 5 and above as insufficient responses.

Surgical Procedure

The patients were taken to the operating room, and procedures were performed under sterile conditions. A fluoroscopy device was used for imaging. The patient was placed in a prone position on the operating table, aligned with the fluoroscopy device. The area to be injected was cleaned according to asepsis-antisepsis rules and covered with a sterile drape. Local anesthesia (0.5-1 ml of 1% lidocaine) was applied to the area before the procedure. Using fluoroscopy, the entry point for foraminal injection was targeted from anteroposterior (AP), lateral, and oblique angles, aiming for the triangle described by Kambin and Gellman (6), which lies between the facet joint posteriorly, the exiting nerve root laterally, and the vertebral pedicle inferiorly. A 24-G spinal needle was used for all foraminal injections. When the target point was reached as confirmed by fluoroscopic control, the accuracy of the needle position was checked with 0.5 mL of non-ionic contrast material. The contrast material should spread in a straight line in the anterior epidural space in the lateral view (Figure 1). After confirming the correct spread of the contrast material on fluoroscopy, a total of 5 mL of drug consisting of 3 mL of bupivacaine, 1 mL of isotonic solution, and 1 mL containing 40 mg of methylprednisolone was administered. Additionally, FJI were performed in these patients. For the facet joint injection, the needle was placed in the target facet joint using AP-lateral fluoroscopy control (Figure 2). No contrast control was performed for the facet joint injection. Similar to the transforaminal injection, a 5 mL drug solution consisting of 3 mL of bupivacaine, 1 mL of isotonic solution, and 1 mL/40 mg of methylprednisolone was administered for the facet joint injection. After the procedure, the patients were monitored for 2 hours before being mobilized and discharged on the same day.

Statistical Analysis

SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The results indicated that the data did not follow a normal distribution ($p<0.05$ for all key variables); therefore, non-parametric tests were used. The Mann-Whitney U test was applied for pairwise comparisons, and the Kruskal-Wallis test was used for

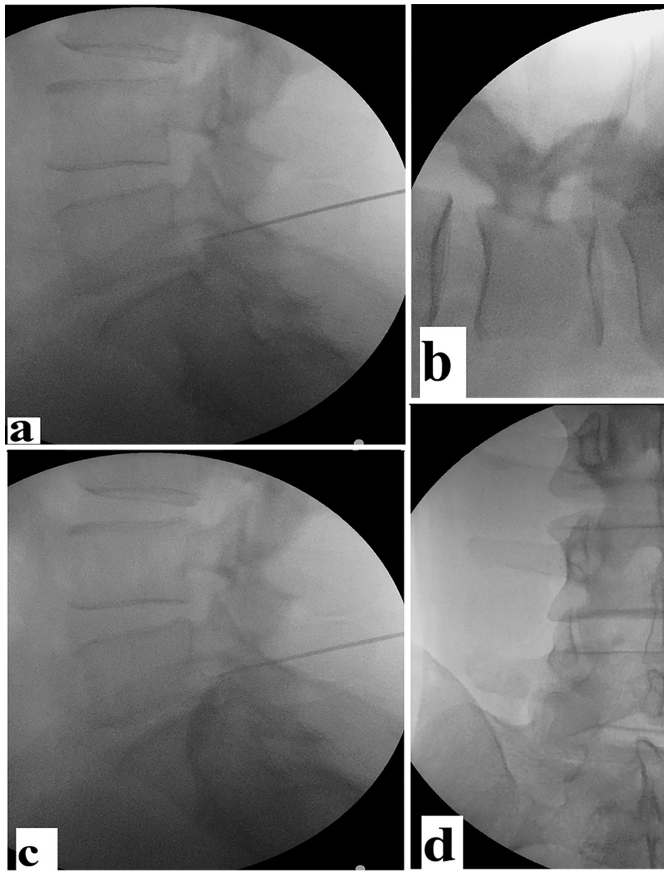

Figure 1. Staining the root and epidural space with contrast material in the ap/lateral view in transforaminal injection (a, b, c, d)

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multi-group analyses. Categorical variables were analyzed using the chi-square test.

A post-hoc power analysis was performed, considering the sample size and effect size, revealing that the study had a statistical power of 1.0, indicating a high probability of detecting significant differences.

A logistic regression analysis was conducted to determine whether obesity significantly influenced post-treatment VAS scores. The dependent variable was converted into a binary outcome (VAS ≤3 as successful, VAS >3 as unsuccessful). Independent variables included obesity status (BMI ≥30 categorized as obese) and age. A p-value <0.05 was considered statistically significant.

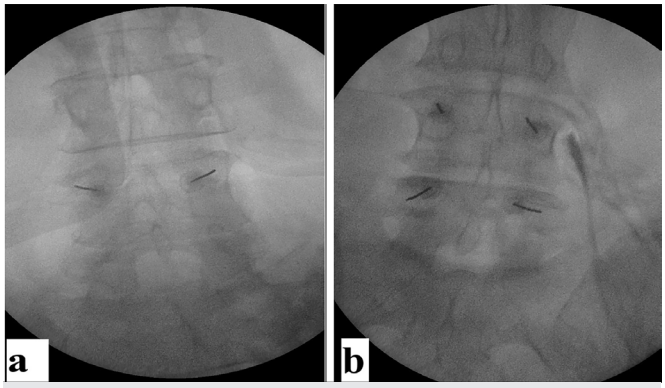

Figure 2. Needle localization in facet injection (a and b)

Table 1. Demographic and clinical characteristics of the patients

Variable	p-value
Patients (N)	67
Sex (M/F)	22/45
Age (years)	51.95±10.65
Height (cm)	165.51±7.18
Weight (kg)	79.02±12.05
BMI	28.81±3.85
Low back pain, n (%)	67 (100)
Radicular pain, n (%)	67 (100)
Right	26 (38.8)
Left	33 (49.3)
Bilateral	8 (11.9)
Facet injections, n (%)	
L3-L4	20 (29.9)
L4-L5	64 (95.5)
L5-S1	67 (100)
Transforaminal injections, n (%)	
L3-L4	13 (19.4)
L4-L5	58 (86.6)
L5-S1	24 (35.8)

M: Male, F: Female, BMI: Body mass index

RESULTS

A total of 67 patients were included in this study, comprising 22 men (32.8%) and 45 women (67.2%). The mean age of the patients was 51.95±10.65 years (25-76 years). The mean height and weight of the patients were 165.51±7.18 cm (146-180 cm) and 79.02±12.05 kg (53-102 kg), respectively. When calculating BMI, 12 patients (17.9%) were classified as normal weight, 28 patients (41.8%) as overweight, and 27 patients (40.3%) as obese. In the pre-procedural assessment of the patients, low back pain and signs of lumbar tenderness were found in all patients. Additionally, 26 patients (38.8%) had right leg pain, 33 patients (49.3%) had left leg pain, and 8 patients (11.9%) had pain in both legs (Table 1).

All patients underwent facet joint injection and anterior epidural transforaminal injection. Only 3 patients (4.5%) received a single-level facet joint injection, whereas 64 patients (95.5%) received multiple-level FJI. A single-level transforaminal injection was performed in 59.7% of the patients (40 patients), while 43.3% (27 patients) received multiple-level transforaminal injections. Injections to the facet joints were applied bilaterally at every level. Twenty patients (29.9%) received injections at the L3-L4 level, 64 patients (95.5%) at the L4-L5 level, and 67 patients (100%) at the L5-S1 level. In transforaminal injections, the side with leg pain was selected. In 8 patients (11.9%), bilateral injections were performed. Transforaminal injections were given at the L3-L4 level in 13 patients (19.4%), at the L4-L5 level in 58 patients (86.6%), and at the L5-S1 level in 24 patients (35.8%) (Table 2).

The VAS and ODI scores reported by the patients for low back pain before the procedure were 8.31±0.99 (6-10) and 32.09±7.41 (18-47), respectively. The VAS and ODI scores reported for radicular pain before the procedure were 8±0.87 (7-10) and 31.06±6.16 (19-45), respectively. At the 6-month follow-up after the procedure, the VAS and ODI scores for low back pain were found to be 2.18±1.54 (0-5) and 11.88±3.62 (6-21). For radicular pain, they were 2.03±1.11 (0-5) and 12.08±3.30 (5-21) (Table 3, Figure 3).

The normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, which indicated that the data did not follow a normal distribution ($p<0.05$ for all key variables). Therefore, non-parametric tests were used in the analysis. The Mann-Whitney U test was applied for pairwise comparisons, and the Kruskal-Wallis test was used for multi-group comparisons.

The Mann-Whitney U test showed that obese patients had significantly higher VAS scores for low back pain compared to non-obese patients at the 6th-month follow-up ($p=0.002$). However, for radicular pain, the difference was not statistically significant in the preoperative assessment ($p=0.73$), but became significant by the 6th month ($p=0.019$) (Table 3).

The Kruskal-Wallis test demonstrated significant differences among normal weight, overweight, and obese groups in terms of VAS scores for low back pain ($p=0.024$ preoperatively, $p=0.0002$ postoperatively). Post-hoc analysis showed that normal weight and overweight patients had significantly lower VAS scores compared

Table 2. Comparison of preoperative and 6-month postoperative VAS and ODI scores
Mann-Whitney U test was used for comparisons

Pain scores	Before procedure (mean ± SD)	Sixth month after procedure (mean ± SD)	p-value
VAS for low back pain	8.31±0.99	2.18±1.54	0.001
VAS for radicular pain	8.00±0.87	2.03±1.11	0.001
ODI for back pain	32.09±7.41	11.88±3.62	0.001
ODI for radicular pain	31.06±6.16	12.08±3.30	0.001

VAS: Visual analog scale, ODI: Oswestry Disability Index, SD: Standard deviation

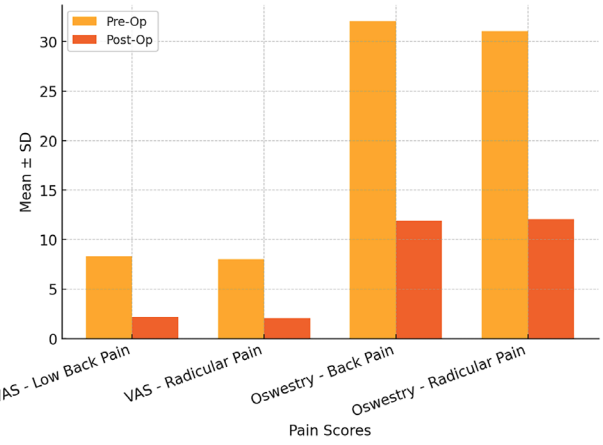

Figure 3. Comparison of preoperative and 6-month postoperative VAS and ODI scores
VAS: Visual analog scale, ODI: Oswestry Disability Index, SD: Standard deviation

Table 3. Comparison of treatment response in VAS scores between obese and non-obese patients
Mann-Whitney U test was used for comparisons

VAS score category	Non-obese (BMI <30) n (%)	Obese (BMI ≥30) n (%)	Total n (%)	p-value
VAS for low back pain				
Optimal	29 (72.5)	9 (33.3)	38 (56.7)	**0.002**
Suboptimal	10 (25.0)	12 (44.4)	22 (32.8)	-
Insufficient	1 (2.5)	6 (22.3)	7 (10.5)	-
VAS for radicular pain				
Optimal	31 (77.5)	14 (51.9)	38 (56.7)	**0.019**
Suboptimal	9 (22.5)	12 (44.4)	22 (32.8)	-
Insufficient	0 (0.0)	1 (3.7)	1 (1.5)	-

VAS: Visual analog scale

to obese patients (p=0.002 and p=0.021, respectively). For radicular pain, only normal weight patients showed a significant difference compared to obese patients (p=0.036).

A logistic regression model was used to evaluate the effect of obesity on post-treatment VAS scores. The dependent variable was converted into a binary outcome (VAS ≤3 as successful, VAS >3 as unsuccessful). The results showed that obesity was not a statistically significant predictor of post-treatment VAS scores (p=0.211 for low back pain, p=0.168 for radicular pain). Age was also not found to have a significant effect (p=0.168) (Table 4).

DISCUSSION

With advancing technology, TAEE and FJI are frequently utilized as alternative treatment methods for cases of low back and leg pain caused by LDH, spinal stenosis, and facet joint degeneration. Particularly in cases where pain is the primary issue, surgical treatment is unnecessary unless methods such as physical therapy, medical treatment, TAEE, or FJI are applied. In approximately 90% of patients with LDH, radicular pain responds to conservative treatment; however, surgical intervention is required for 10-15% of cases (7,8). Among patients whose radiculopathy persists following LDH surgery, recurrent disc herniation is the most common cause. In such cases, medical and/or physical therapy may be insufficient. Selective nerve root blocks and/or combined interventions can provide additional relief in these scenarios. Today, it is well-known that inflammation and irritation in the nerve root play a significant role in the development of radicular pain (9). Any disc herniation affecting the nerve root not only exerts pressure but also causes localized inflammation. The chemical mediators released due to this inflammation further intensify radicular pain by irritating the nerve root.

In our study, we compared pain levels before and after the application of TAEE combined with facet joint steroid injection, in patients with acute and subacute low back and leg pain. It was observed that TAEE, combined with FJI, known for its effectiveness in lumbar radicular pain and effective in controlling pain caused by degenerated facet joints, is a more efficient method for pain palliation.

Transforaminal anterior epidural nerve root block reduces pain by suppressing inflammation in the nerve root and epidural space at the procedure site. In addition to their anti-inflammatory effects, corticosteroids also have membrane-stabilizing properties. This combined effect minimizes radicular pain by reducing the impact of external stimuli on sensitive root ganglia and damaged nerve roots (10). Lutze et al. (11) demonstrated a relative reduction in pain following periradicular anesthetic and depot steroid injections in 40 patients with radicular pain due to LDH (12,13). In another study, 33 procedures were performed via the transforaminal route followed for 16 months and divided into treatment and placebo groups. The success rate was 84% in the transforaminal selective

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Table 4. Logistic regression analysis for predicting post-treatment VAS scores
Dependent variable: Post-treatment VAS ≤3 (success) vs. VAS >3 (failure)

Variable	OR	95% CI	p-value
Obesity (BMI ≥30)	1.153	0.654 – 2.961	0.211
Age	1.066	0.972 – 1.169	0.168

VAS: Visual analog scale, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index

nerve root block group and 48% in the placebo group. The success rate of transforaminal anterior epidural and facet joint steroid injections in patients with low back and leg pain has been reported to be around 65%. These procedures yield better results in the short term, and moderate efficacy is reported for the long term (14,15).

In our study, the short- to mid-term effectiveness and safety of transforaminal epidural injection combined with facet joint steroid injection were evaluated and found to be consistent with the literature. Additionally, the literature indicates that while transforaminal nerve root block achieves good short-term outcomes for radicular pain, the results for selective nerve root blocks are moderate in patients with persistent low back and leg pain after failed back surgery. The effectiveness of transforaminal and facet injections in obese patients has been observed to be short-term and limited. This highlights the significant impact of obesity on treatment response.

In this study, we found that obese patients had significantly higher post-treatment VAS scores for low back pain compared to non-obese patients at the 6-month follow-up. However, logistic regression analysis showed that obesity was not a statistically significant predictor of post-treatment VAS scores (p=0.211 for low back pain, p=0.168 for radicular pain). These findings suggest that while obesity may influence short-term treatment outcomes, it does not independently predict long-term pain relief.

Previous studies have reported that obesity can negatively affect spinal interventions due to altered biomechanics, increased inflammation, and technical challenges during injections. However, our results indicate that the combined transforaminal and FJI provide substantial pain relief in both obese and non-obese patients, although obese individuals tend to have slightly higher residual pain levels.

The effect of obesity on spinal interventions remains controversial. While some studies suggest that obese patients respond less effectively to epidural steroid injections, others indicate that the outcomes are comparable to non-obese patients when proper technique and medication dosage are applied. Our findings align with studies demonstrating that while obesity may delay pain relief, it does not significantly alter overall treatment success rates.

Mavrocordatos and Cahana (16) reported moderate outcomes for transforaminal epidural root blocks in treating failed back surgery syndrome. Another study injected steroids and hyaluronidase via the transforaminal route in patients with persistent low back and leg pain following failed back surgery. Approximately half of these patients experienced a 50% improvement one month after treatment, with long-term benefits reported to persist (17).

Study Limitations

The limitations of the study included its retrospective nature, a limited sample size, and its conduct at a single center.

CONCLUSION

In conclusion, TAEE combined with facet joint steroid injection is a safe and effective method for alleviating pain and improving the quality of life in patients with low back and radicular pain unresponsive to medical and physical therapy. It is considered a viable alternative to surgery in appropriate cases.

Ethics

Ethics Committee Approval: Institutional Ethics Committee of a University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital (approval number: 19, date: 03.07.2024).

Informed Consent: Written informed consent to participate was obtained from all participants.

Footnotes

Author Contributions: Surgical and Medical Practices - O.B.; Concept - O.B., E.C.S., S.K.; Design - O.B., E.C.S., Ö.Ö., S.K.; Data Collection and/or Processing - O.B., O.Ö., E.C.S.; Analysis and/or Interpretation - O.B., O.Ö., S.K.; Literature Search - O.B., G.B.S. Ö.Ö.; Writing - O.B., G.B.S.

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