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EDITORIAL

Dear Colleagues,

We are honored to present the release of the first issue of the Journal of Medicine and Palliative Care (JOMPAC) in 2024, which is published bi-monthly under the umbrella of Medihealth Academy. We express our gratitude to every author, researcher, reviewer, and editorial board member who made a contribution to this publication. We also like to express our gratitude to the publishing team for their hard work getting the journal ready for publishing.

The blind evaluation processes of articles sent to our journal are transparent and ethics and scientificity are always at the forefront. Our main purpose is to maintain these values of the journal and create an alternative pathway for the resarchers to contribute to the literature in the fields of Medicine and Palliative Care. Our another goal for JOMPAC is to be indexed in international indexes such as SCI-Expanded, Scopus, ESCI, and Pubmed.

There are twelve original research articles and a review in this 2024 first launch issue. Journal writers and readers create and popularize journals. We express our gratitude to everyone who, in any way, contributes to the publication.

Sincerely,

Assoc. Prof. Deniz Çelik
Editor in Chief

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Does the prevalence of subclinical coronary atherosclerosis increase in primary hyperparathyroidism; coronary flow reserve and plasma aterogenic index in patients with primary hyperparathyroidism?

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ABSTRACT

Aims: The coronary flow reserve (CFR) is a sign of early-stage coronary artery disease (CAD). Plasma atherogenic index (PAI) is related to atherosclerosis and cardiovascular mortality. Therefore, our aim was to determine CFR and PAI in patients with primary hyperparathyroidism (PHPT) and investigate whether PAI can be used in the detection of early-stage CAD.

Methods: The sample was comprised of 44 patients with PTHT and 33 healthy volunteers. We defined CFR as the ratio of the hyperemic diastolic peak velocity to the baseline diastolic peak velocity. PAI values were calculated with the formula of log 10 triglyceride (TRG)/high-density lipoprotein (HDL).

Results: The comparison of the groups for PAI and CFR demonstrated that PAI levels were significantly higher while CFR levels were significantly lower in the PTHT patients ($p<0.01$, $p=0.01$, respectively). The correlation analysis revealed that CFR was negatively correlated with PAI and TRG (PAI- $p<0.0001$ $r=-0.537$). The multivariate logistic regression analysis showed that only a high PAI level (OR: 151.6, 95% confidence interval (CI): 4.1-5480, $p=0.006$) was an independent predictor of reduction in CFR in PHPT patients.

Conclusion: Overall, we found an independent correlation between PAI and CFR values. Hence, PAI may be useful in identifying PHPT patients facing a high risk of adverse cardiovascular events and may also allow early diagnosis of subclinical atherosclerosis.

Keywords: Primary hyperparathyroidism, plasma atherogenic index, atherosclerosis, coronary flow reserve

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a clinical condition characterized by hypercalcemia caused by excessive parathyroid hormone (PTH) secretion from the parathyroid gland and the most prevalent cause of hypercalcemia in outpatient clinics.[1,2] It has been detected more frequently in the last 40 years due to more frequent measurement of serum calcium (Ca) levels.[3] Therefore, PHPT is a relatively common endocrine disease with an incidence of 1/1000 among patients.[4] Recently, there has been an increasing interest in cardiac evaluation in patients with PHPT because various studies showed that PHPT elevates cardiac morbidity and mortality.[5]

Coronary flow reserve (CFR) is calculated by dividing the absolute values of hyperemic and resting myocardial blood flows and primarily refers to coronary microvascular function. A decrease in CFR is an indicator of atherosclerosis and, therefore, early coronary artery disease (CAD) with impaired endothelial functions. It was previously shown to have a prognostic value for cardiovascular events in different systemic diseases.[6-8] Transthoracic echocardiography can be used to measure CFR; it is preferred because of its high diagnostic accuracy, versatility, low cost, and especially not being exposed to radiation.[9]

Although conventional atherogenic lipid parameters are used to assess the risk of CAD, many extensive epidemiological studies revealed that novel lipid indices, such as the plasma atherogenic index (PAI), have better predictive value for atherosclerotic CAD risk assessment than conventional ones.[10-12]

PAI is a newly popular lipid index obtained by logarithmic conversion of triglyceride (TRG) / high-

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density lipoprotein cholesterol (HDL-C) ratio. Relevant literature host studies having shown that it is associated with atherosclerosis and subclinical coronary artery disease and may be a marker for cardiovascular mortality.[13,14]

Ultimately, we aimed to determine CFR, an indicator of subclinical atherosclerosis, and PAI levels for risk assessment of CAD in patients with PHPT. We also explored whether PAI can be used for the early detection of CAD.

METHODS

Ethics

We conducted the study strictly complying with the principles of the Declaration of Helsinki and ensured all participants sign an informed consent form before enrollment. The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethical Committe (Date:03.09.2020, Decision No: 146).

Sample

We prospectively carried out the study with 44 PHPT patients who were followed up in the Endocrinology Clinic of Kayseri City Training and Research Hospital between September and March 2021. We noted down physical examination findings, medical records, and laboratory findings of the patient and control groups. The control group consisted of age- and sex-matched 33 individuals with normal blood PTH levels who were not considered to have coronary artery disease upon their medical records, physical examination, ECG, and echocardiography findings.

Yet, we excluded those under 18 years of age, those with a history of stroke, congestive heart failure, CAD, dilated/hypertrophic or restrictive cardiomyopathies, severe valve disease, hypertension (HT), diabetes/impaired glucose tolerance, hypothyroidism and hyperthyroidism, smoking, obstructive sleep apnea, dyslipidemia, morbid obesity (body mass index >35 kg/m²), excessive alcohol consumption (>120 g/day), and diseases that may affect coronary blood flow such as kidney or liver failure, and those with concomitant systemic disorders. In addition, we excluded asthmatic patients for safety reasons and those with suboptimal image quality or arrhythmias that would preclude the acquisition of adequate images to measure CFR.

Biochemical Parameters and Atherogenic Index of Plasma

Venous blood samples were taken from both the patient and control groups in the morning after 10-12 hours of fasting. We noted down their fasting blood sugar, total cholesterol, HDL-C, total cholesterol (TC), and TRG levels and obtained their complete blood counts, basic biochemistry parameters, and total calcium (Ca), albumin-adjusted Ca, phosphorus, thyroid-stimulating hormone, and PTH levels. Then, we measured their plasma levels of high sensitivity C-reactive protein (hsCRP). Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald formula (TC=LDL+HDL+TRG/5), while PAI values were obtained using the log10 TRG/HDL formula. Non-HDL cholesterol was reached by subtracting HDL from TC. We calculated Castelli risk indices (CRI) I and II as TC/HDL and LDL/HDL, respectively. The atherogenic coefficient (AC) was calculated by dividing non-HDL by LDL. When calculating PAI, we first converted TRG and HDL values into their molar equivalents and then used the log (TRG/HDL-C) formula.

Echocardiographic and Coronary Flow Reserve Assessment

We performed imaging on the basis of second-harmonic imaging using the Vivid-6 (GE Medical Systems, Horten, Norway) ultrasound device. All findings were stored digitally and analyzed by an experienced cardiologist blind to the clinical and laboratory data. Conventional echocardiographic examinations of the patients and healthy volunteers were performed according to the standards defined by the American Society of Echocardiography. We calculated left ventricular mass with the Deveraux formula using end-diastolic left ventricular wall thickness and left ventricular diameter. Left ventricular ejection fraction was calculated through the apical windows using the modified Simpson's method.

We assessed CFR with the patient lying in the left lateral position, using a modified two- or four-chamber window to visualize the left anterior descending (LAD) artery by positioning the transducer in the fourth and fifth intercostal spaces, close to the mid-clavicular line. We continuously monitored the patients' ECG and heart rates. Transducer frequencies for B-mode and Doppler imaging were set to 8 MHz and 1.00-2.50 kHz, respectively. All subjects received 0.56 mg/kg of dipyridamole infusion for 4 minutes, and we administered an additional dose of 0.28 mg/kg to the subjects when the target heart rate was not reached. CFR was measured using the pulse-wave Doppler method in the patient and control groups, considering baseline diastolic flow velocity and peak flow velocity after dipyridamole infusion. We averaged at least three cycles of measurements (at rest, during maximum dipyridamole infusion, and three minutes after dipyridamole was discontinued) to obtain diastolic peak flow velocity (DPFV). We defined CFR as the

ratio of the hyperemic diastolic peak velocity to the baseline diastolic peak velocity, and a CFR≥2.0 was considered normal. All echocardiographic procedures were performed by a single researcher, and the intraclass correlation coefficient for CFR measurement was determined to be 0.903.15

Statistical Analysis

We performed all statistical analyses on the SPSS package program (version 26, Chicago, IL, USA). Kolmogorov-Smirnov test was used to evaluate whether the data showed a homogenous distribution. For the homogeneously distributed variables, we compared the groups using the Student's T-test and presented the results as mean±standard deviation. On the other hand, we used the Mann-Whitney U test to compare the groups where the variables did not show a homogeneous distribution, and the findings were given as minimum-maximum values.

We used Pearson's correlation analysis to reveal the associations between the variables and accepted a p-value below 0.05 as statistically significant. For bivariate correlation analyses, an r-value of <0.30 indicates no or very weak correlation. A value of 0.30<r<0.50 indicates a weak correlation, while a value of r≥0.50 indicates a moderate to good correlation between the variables.

RESULTS

Baseline clinical, demographic, and laboratory characteristics of the groups are presented in Table 1. Accordingly, we could not find any significant difference between the groups by gender, age, smoking, diabetes, and hypertension (p>0.05). Both groups were similar in terms of systolic and diastolic blood pressure measurements. Yet, PHPT patients had significantly higher CRP, total Ca, albumin-adjusted Ca, and PTH levels than the control group, while they had significantly lower phosphorus levels (p<0.001). Other blood parameters were also similar between groups.

CFR levels were found to be significantly lower in the patient group (2.21±0.45 vs. 3.01±0.5, p<0.001) (Figure 1). While there was no difference between the groups in terms of conventional lipid parameters such as TC, HDL, LDL, and non-HDL (p>0.05), we detected TRG level to be significantly higher in patients with PHPT (p=0.012) (Table 1).

In terms of novel lipid indices, we found no difference between the groups by CRI-1, CRI-2, and AC (p>0.05), while PAI levels were found to be significantly higher in the patient group (p=0.01) (Table 1).

As in Table 2, baseline echocardiographic parameters

Table 1. Baseline clinical and demographic features and laboratory measurements of the study groups

Variables	Control group (n=33)	PHPT (n=44)	P value
Age (years)	58.7±10.9	56±11.3	.284
Male/female	3/32	5/43	.778
HT	15	21	.935
DM	3	5	.778
Smoke	1	1	.986
SBP (mm/Hg)	119.5±10.2	122.6±11.5	.201
DBP (mm/Hg)	73.7±7.2	74.7±6.3	.507
Glucose (mg/dl)	91.2±5.7	93.7±7.2	.110
BMI	27.61±1.83	27.42±2.26	.680
Kreatinin (mg/dl)	0.84±0.19	0.83±0.15	.730
Aspartat aminotransferaz (U/L)	19.8±6.3	19.6±6.8	.920
Alanin aminotransferaz (U/L)	19.05±6.8	20.95±10.4	.355
Albumin	4.06±0.5	4.02±0.35	0.748
Albumin-corrected calcium (mg/dl)	9.2±0.43	11.1±0.63	.0001
Phosphorus (mg/dl)	3.82±0.44	2.52±0.45	.0001
PTH	33.7±8.4	220.7±146	.0001
TSH	1.88±1.11	2.11±0.83	.413
Vitamin D	22.11	18.1±7.98	0.321
WBC (10^3/ul)	7.78±1.47	7.71±1.73	.847
Hemoglobin (g/L)	14.01±1.6	13.8±1.29	.448
Platelet (/mm^3)	264.2±68.0	259.2±62.6	.729
Hs CRP	2.49±1.5	5.12±3.2	0.001
TC	180.3±27.4	184.2±37	0.602
TRG	105.1±50.6	142.3±74	0.012
HDL	45.1±9.1	42.8±13.7	0.393
LDL	114.5±25	109.8±29.9	0.451
Non HDL	135.2±25.7	141.8±39	0.387
AC	3.1±0.8	3.6±1.40	0.072
PAI	0.32±0.2	0.49±.3	0.010
CRI-1	4.11±0.86	4.60±1.4	0.077
CRI-2	2.61±0.6	2.76±1	0.435
CFR	3.01±0.5	2.21±0.45	<0.001

PHPT: Primary hyperparathyroidism, DM: Diabetes mellitus, HT: Hypertension, SBP: Sistolic blood pressure, DBP: Diastolic blood pressure, WBC: white blood cell, PTH: Parathyroid hormone, TSH: Thyroid stimulating hormone, PAI: Plasma atherogenic index, AC: Atherogenic coefficient, CRI: Castelli risk indice, hsCRP: High-sensitivity C-reactive protein TC: Total cholesterol, TRG: triglyceride, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein, BMI: Body mass index.
Data are expressed as mean±standard deviation for normally distributed data and percentage (%) for categorical variables

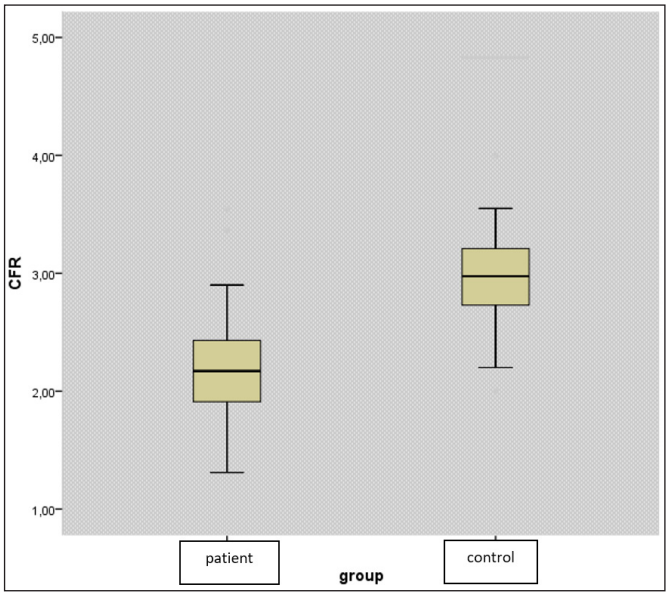

Figure 1. Comparison of CFR levels of PHPT patients and control groups
CFR: Coronary flow reserve, PHPT: Primary hyperparathyroidism

did not differ significantly between the groups

Table 2. Echocardiography characteristics of the study population

Variables	Control Group (N=33)	PHPT (N=44)	P value
LVEDD	4.68±0.41	4.80±0.44	.198
LVESD	3.11±0.41	3.05±0.32	.463
IVSD	1.05±0.97	1.05±0.18	.871
PWD	1.01±0.84	1.01±0.17	.915
LVEF	62.3±3.1	63.3±4.1	.214

PHPT: Primary hyperparathyroidism, LVEDD: Left Ventricular End Diastole Diameter, LVESD: Left Ventricular End Systole Diameter, IVSD: İnterventricular Septal Diameter, PWD: Posterior Wall Diameter, LVEF: Left Ventricular Ejection Fraction, Data are expressed as mean±standard deviation for normally distributed data and percentage (%) for categorical variables.

The results of the correlation analysis revealed a negative correlation between CFR and novel lipid indices (except CRI-2), including TRG and PAI (p<0.0001, r=-0.537 for PAI; p=0.026, r=-0.244 for CRI-1; p=0.023, r=-0.250 for AC; p>0.05 for CRI-2) in PHPT patients. However, there was no correlation between CFR and other conventional lipid parameters other than TRG (p>0.05 for all) (Table 3). Besides, CFR was negatively correlated with PTH and albumin-adjusted Ca levels, while positively correlated with phosphorus (p<0.001, r=-0.610 for Ca; p<0.001, r=-0.494 for PTH; p<0.001, r=0.553 for phosphorus).

Table 3. Correlation analysis of non-CFR parameters between CFR in PHPT patients

	CFR	
	r values	p values
PAI	-0.537	<0.001
AC	-0.250	0.023
CRI-1	-0.244	0.026
CRI-2	-0.120	0.282
hsCRP (mg/dl)	-0.409	<0.001
TC	-0.077	0.488
TRG (mg/dl)	-0.363	0.001
HDL (mg/dl)	0.135	0.223
LDL (mg/dl)	0.080	0.473
Non-HDL (mg/dl)	-0.133	0.231
Albumin-corrected calcium	-0.610	<0.001
Phosphorus	0.553	<0.001
PTH	-0.494	<0.001

CFR: Coronary flow reserve, PTH: Parathyroid Hormone, PAI: Plasma atherogenic index, AC: Atherogenic coefficient, CRI: Castelli risk indice, hsCRP: High-sensitivity C-reactive protein TC: Total cholesterol, TRG: triglyceride, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein

When CFR measurements were divided into two groups (CFR<2 and CFR≥2 and above; CFR=2 is considered the cut-off value for being a predictor of atherosclerosis), CRP, PTH, Ca, and TRG levels were significantly higher in the group with lower CFR levels (p=0.032, p=0.011, p=0.023, and p=0.019, respectively) (Table 4). Yet, among the novel lipid indices, only PAI level was significantly higher in this group (p=0.001) (Figure 2). The groups did not differ by other demographics, examination findings, and lipid parameters and indices (Table 4). Then, we found a negative correlation between CFR and PAI (Figure 3).

Table 4. Comparison of demographic, clinical and laboratory values between subgroups with low and high CFR levels (cut-off value 2 for CFR)

	CFR <2 (n=19)	CFR ≥2 (n=25)	p
CFR	1.7±0.2	2.39±0.33	<0.001
Age (years)	56.6±11.2	55.6±11.5	0.768
BMI (kg/m²)	25.9±3.7	25.8±2.8	0.94
SBP (mmHg)	129.6±8.2	131.3±5.6	0.459
DBP (mmHg)	78.2±4.1	80.3±4.2	0.130
TC (mg/dl)	186.5±37.1	182.4±37.5	0.706
TRG (mg/dl)	170.4±76.3	120.4±65.6	0.019
HDL (mg/dl)	42.3±17.1	43.2±10.6	0.836
LDL (mg/dl)	105.8±33.9	113±26.6	0.416
Non-HDL (mg/dl)	145.1±37.8	139.2±40.4	0.607
PAI	0.66±0.17	0.40±0.25	0.001
AC	3.78±1.3	3.48±1,5	0.484
CRI-1	4.75±1.3	4.4±1.54	0.521
CRI-2	2.74±0.9	2.78±1.04	0.892
hsCRP (mg/dl)	6.6±4.4	3.97±3.7	0.032
PTH	296.7±214	161.5±105.5	0.011
Albumin-corrected calcium	11.3±0.74	10.9±0.46	0.023
Phosphorus	2.44±0.4	2.57±0.4	0.315

CFR: Coronary flow reserve, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index TC: Total cholesterol, HDL: High-density lipoprotein cholesterol, TRG: Triglyceride, LDL: Low-density lipoprotein, PAI: Plasma atherogenic index, CRI: Castelli risk indice, AC: Atherogenic coefficient, hsCRP: High-sensitivity C-reactive protein, PTH: Parathyroid hormone

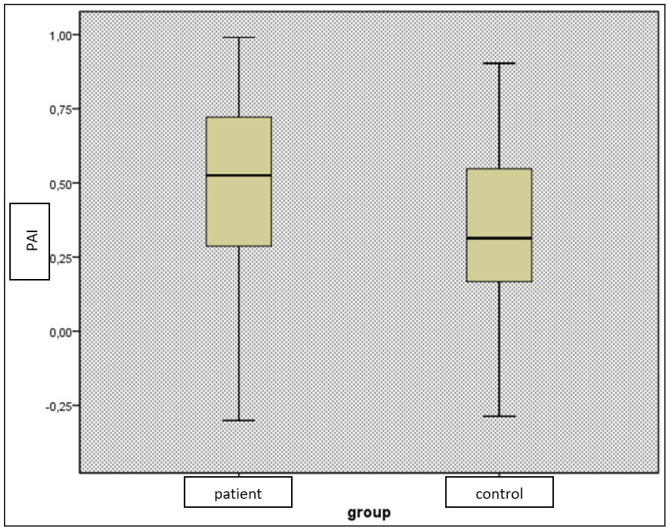

Figure 2. Comparison of PAI levels of PHPT patients and control groups
PAI: Plasma atherogenic index, PHPT: Primary hyperparathyroidism

We analyzed the role of some risk factors for the reduction in CFR levels using multivariate analysis. In the univariate analysis, we found a correlation between CFR levels and increased PAI, PTH, albumin-adjusted calcium, and hsCRP levels. The multivariate logistic regression analysis, on the other hand, showed that only a high PAI level was an

Table 5. Univariate and multivariate logistic regression analysis to identify the independent predictors of coronary flow reserve in patients with PHPT

	Univariate analysis			Multivariate analysis		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
PAI	159.3	7.1-3525.5	0.001	151.6	4.1-5480	0.006
PTH	1.005	1.000-1.009	0.031			
Albumin-corrected calcium	3.397	1.083-10.653	0.036			
hsCRP (mg/dl)	1.172	1.007-1.365	0.041			

PAI: Plasma atherogenic index, PTH: Parathyroid Hormone, hsCRP: High-sensitivity C-reactive protein

independent predictor of reduction in CFR levels in PHPT patients (OR: 151.6, 95% confidence interval (CI): 4.1-5480, p=0.006) (Table 5).

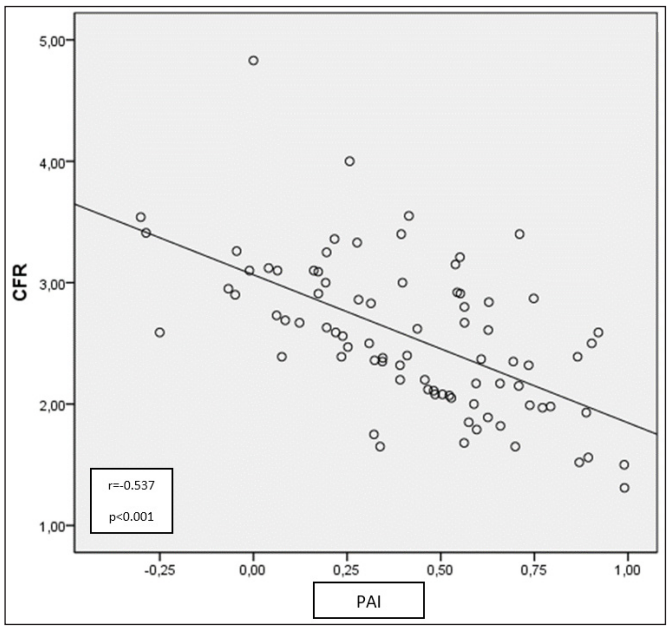

Figure 3. Relationship between PAI and CFR in patients with PHPT
CFR: Coronary flow reserve, PAI: Plasma atherogenic index, PHPT: Primary hyperparathyroidism

DISCUSSION

In this study, we investigated the association between CFR, which can be easily measured echocardiographically, and various lipid parameters and novel lipid indices, which have become increasingly popular in recent years, in PHPT patients. The main results of our study can be listed as follows: 1) we found significantly higher PAI values in PHPT patients compared to healthy controls; 2) we showed that CFR levels were significantly lower in PHPT patients compared to the control group; 3) we found a negative correlation between CFR and PAI, AC, and CRI-1 levels. There was a similar correlation between CFR and hs-CRP, PTH, and Ca levels; 4) PHPT patients with CFR<2.0 had significantly higher serum hs-CRP, PAI, PTH, Ca levels compared to those with CFR≥2.0; 5) PAI was the parameter with the best predictive value in showing a change in CFR in PHPT patients; 6) Our results suggest that PAI may be an indicator of subclinical atherosclerosis in PHPT patients.

Some studies previously showed that mortality rates due to all-cause and cardiovascular events are higher in PHPT patients. In addition, serum Ca and PTH levels were determined to be independent predictors of mortality and CAD.[16,17] A wealth of evidence from experimental and clinical studies suggests that both Ca and PTH levels may be causally involved in cardiovascular disease processes through the development of vascular dysfunction, atherosclerosis, and inflammation.[18-21] In their study, Hagström et al.[22] showed that increased PTH levels were associated with atherogenesis both directly through its receptors on the vessels and indirectly with vascular calcification and vascular remodeling.

Moreover, recent studies found independent predictors of atherosclerosis, such as HT, hyperlipidemia, and glucose metabolism disorder, to be more prevalent in PHPT patients.[23] In addition to all these variables, Stamatelopoulos et al.24 found higher levels of CRP and Interleukin-6 (IL-6) in patients with PHPT, which contributes to the atherogenic process in such patients. Several small-scale studies with PHPT patients showed an association between various atherosclerotic mediators, such as a decrease in brachial vasoreactivity, an increase in carotid intima-media thickness (IMT), and an increase in abdominal aortic IMT, reinforcing the claim of endothelial dysfunction and early atherogenesis in these patients.[22,25,26] CFR is used to evaluate microvascular endothelial functions and, previously, was found to be a more decisive test than other early atherosclerosis predictors used.[27] CFR can be used in the evaluation of moderately severe coronary artery lesions, as well as in the evaluation of coronary blood flow regulation and prognosis in conditions such as post stent placement and post-acute myocardial infarction.[28,29] We could not find a study investigating CFR levels in patients with PHPT in the literature. In our study, we reported impaired CFR in patients with PHPT. We also found a negative correlation between CFR and Ca and PTH levels, which was consistent with the results of previous studies in the literature showing the link between increased Ca and PTH levels and the development of atherosclerosis. Our result also suggests that PHPT patients are at risk for CAD.

Although dyslipidemia or hypercholesterolemia is

reported to be more prevalent in PHPT patients, there are still conflicting results regarding the levels of conventional lipid parameters (TC, LDL-C, HDL-C, and TRG) in studies conducted so far.[23,30] In our study, TRG was found to be significantly higher in the patient group with PAI, which we can call atherogenic dyslipidemia, and PAI was negatively correlated with CFR. In recent studies, it is claimed that newly created lipid indices, such as PAI, Framingham risk scoring, CRI I-II, and AC, are better than conventional lipid parameters (TC, LDL, TRG, and decreased HDL) in predicting cardiovascular events.[31-33] Substantial evidence suggests that changes in serum lipid levels cause deterioration in CFR and that treatment of dyslipidemia may restore CFR.[15,34,35] Two mechanisms come to mind while explaining why PAI, the logarithmic value of TRG/HDL, causes endothelial dysfunction. In the first mechanism, small-density LDL (sdLDL) was previously shown to be a more robust predictor of atherosclerosis than LDL, associated with coronary events, and its clinical use is now suggested.[36,37] Since sdLDL is an expensive and complicated method to measure, and because it was found to be well correlated with PAI in recent studies, the idea that PAI can be used instead of sdLDL is now popular. In the literature, it was reported that PAI can be a good marker for the early detection of subclinical atherosclerosis in diseases such as Behçet's disease, rheumatoid arthritis, and systemic lupus erythematosus.[38] Increased systemic inflammatory activity in PHPT patients was shown in previous studies, and it is not far from mind to expect more LDL oxidation in environments with inflammation.[23] As a result, it can be speculated that oxidized LDL is associated with a decrease in CFR.[39] Regarding the other mechanism, increased TRG levels were shown in previous studies to impair endothelium-dependent vasodilation. Increased PAI levels due to elevated serum TRG may directly affect CFR.[40,41] Kul et al.[36] found an inverse correlation between PAI and CFR in their study in which they used CFR to evaluate patients with inflammatory bowel disease. Uslu et al.[42] showed that high PAI levels were associated with increased carotid IMT in SLE patients. In our study, we found a negative correlation between CFR and AC, CRI-1, and PAI in patients with PHPT. Since CFR≥2 was considered normal in previous research, we divided the patient group into 2 groups by this cut-off level and found PAI levels to be significantly higher in the group with low CFR, although there was no difference by other novel lipid indices. In the multivariate analysis, we found that only PAI levels affected CFR. Our results suggest that PAI, which can be detected by simple laboratory testing, may be a much better predictor of CFR, which is used to evaluate early atherosclerosis in PHPT patients.

Limitations

The first is the low number of participating patients. Second, although CFR is predictive for coronary artery disease, the lack of long-term follow-up of our patients creates uncertainty about how much of our findings will be projected in daily practice. Third, we measured CFR only in the LAD artery. Other vessels may have led to lower CFR measurements, but we may have been considered them normal. Fourth, we used only CRP as a marker of inflammation, but it may not represent the full spectrum of inflammatory activity.

CONCLUSION

A high atherogenic plasma index may be useful both to identify PHPT patients at high risk for adverse cardiovascular events and allow early detection of subclinical atherosclerosis. However, further studies are needed to elucidate the precise mechanisms of early atherogenesis in PHPT patients and understand the full impact of atherogenic dyslipidemia on cardiovascular outcomes in this subset of patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethical Committe (Date:03.09.2020, Decision No: 146).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Safety of partial selective COX-2 inhibitors in patients with cross-reactive NSAID hypersensitivity and factors affecting safety

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ABSTRACT

Aims: Partial selective COX-2 inhibitors, such as nimesulide, or meloxicam are tolerated by the majority of the patients with cross-reactive NSAID hypersensitivity. This study aimed to obtain more information about the safety of partial selective COX-2 inhibitors; nimesulide and meloxicam in non-immunologic type, cross-reactive NSAID hypersensitivity and to detect risk factors for intolerance to these drugs.

Methods: This is a retrospective study of patients with suggestive of cross-reactive NSAID hypersensitivity who admitted to our clinic over a period of 10 years. Patients who had a reliable history of immediate type NSAIDs hypersensitivity with at least 2 chemically unrelated class and/or positive ASA provocation test and who underwent alternative drug provocation test with partial selective COX-2 inhibitors (nimesulide and/or meloxicam) were included to study. Patients' demographics, comorbidities, atopy status, duration of NSAID hypersensitivity, total number of reactions, reaction grades, clinical phenotypes, pulmonary function test parameters and results of alternative drug provocation test results are recorded. Patients with and without reactions during alternative provocation tests with nimesulide and/or meloxicam were compared in terms of these data.

Results: A total of 560 patients were included in the study, 378 (67.5%) of them were female. Allergic comorbidities were detected in 394 (72.6%) patients. Asthma, other drug allergies and nasal polyp were the most common comorbidities. Alternative drug provocation test positivity with nimesulide and/or meloxicam was detected in 50 of 560 (8.9%) patients. Provocation test positivity was 33/541 (6.1%) with nimesulide, 30/517 (5.8%) with meloxicam and 13/498 (2.3%) with both nimesulide and meloxicam. Duration of NSAID hypersensitivity was shorter and allergic comorbidities, asthma, nasal polyp and the coexistence of asthma and nasal polyp were more common in patients with a positive provocation test.

Conclusion: The partial selective COX-2 inhibitors nimesulide and meloxicam are well tolerated alternatives in patients with cross-reactive NSAID hypersensitivity. Hypersensitivity to these drugs is significantly higher in patients with asthma and/or nasal polyp than other group of cross-reactive NSAID hypersensitive patients and also in patients with a shorter duration of NSAID hypersensitivity.

Keywords: NSAID, hypersensitivity, COX-2 inhibitor, nimesulide, meloxicam, safety

Our study has been presented previously as an poster presentation in XXVI. Ulusal Alerji ve Klinik İmmünoloji Kongresi (poster number P-130) (2019).

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are most frequently prescribed medicines worldwide and they are the drugs most commonly involved in drug hypersensitivity reactions (DHRs).[1-3]

The NSAID-induced hypersensitivity reactions involve different mechanisms and current classification is based on these mechanisms as allergic (immunologic) or nonspecific pharmacologic (non-immunologic) mechanisms. Non-immunologically mediated or cross-reactive NSAID hypersensitvity involves NSAIDs-exacerbated respiratory disease (NERD), NSAIDs-exacerbated cutaneous disease (NECD) and multiple NSAIDs-induced urticaria/angioedema (NIUA).[1-3]

Underlying mechanism is important for the management of patients with NSAID hypersensitivity. The mechanism of non-immunologic hypersensitivity is related to cyclooxygenase-1 (COX-1) inhibition. COX is an enzyme that metabolizes arachidonic acid to prostaglandins, thromboxanes and prostacyclin. Inhibition of COX-1 by NSAIDs may lead to a decrease in protective prostaglandins production which is normally act as a brake on the production of cysteinyl leukotrienes and lead to activation of mediator release from inflammatory cells such as mast cells and eosinophils.[1-5]

In case of a history of reactions with more than one chemically unrelated COX-1 inhibitor, the cross-reactive type can be suspected and the mechanism of the reaction is not immunological.[2]

NSAIDs have different chemical structures that share the capacity for inhibiting COX enzymes (COX-1 and COX-2). According to the 'COX' hypothesis, inhibition

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of COX-1 (but not COX-2) by asetyl salicylic acid (ASA) or other NSAIDs triggers mechanisms leading to symptoms[3,6] NSAIDs that are strong COX-1 inhibitors induce reactions in patients with cross-reactive NSAID hypersensitivity and should be avoided in these patients. Weak COX-1 inhibitors (e.g acetaminofen) in low doses or selective COX-2 inhibitors are generally well tolerated.[2-4] Partial selective COX-2 inhibitors, such as nimesulide, or meloxicam are tolerated by the majority of the patients and may be used as safe alternative analgesic drugs if tolerated on the provocation tests.[7]

Most of the previous studies evaluating the safety of partial selective COX-2 inhibitors in NSAID hypersensitivity have been done before the current classification and that do not fully account for cross-reactivity. The aim of this study was to obtain more information about the safety of partial selective COX-2 inhibitors; nimesulide and meloxicam in non-imunologic type, cross-reactive NSAID hypersensitivity and to detect risk factors for intolerance to these drugs.

METHODS

Ethics

This is a retrospective study of patients with suggestive of cross-reactive NSAID hypersensitivity who admitted to our clinic over a period of 10 years; between January 2009 and January 2019. The study was approved by local ethics committee (Date: 12.10.2021, Decision No: 2012-KAEK-15/2373). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Inclusion Criterias

A total of 1140 patient data reviewed. A total of 560 patients who had a reliable history of immediate type NSAIDs hypersensitivity with at least 2 chemically unrelated class and/or positive ASA provocation test (n=27) and who underwent alternative drug provocation test with partial selective COX-2 inhibitors (nimesulide and/or meloxicam) were included to study.

NSAIDs hypersensitivity is characterized by the development of any symptoms including urticaria, angioedema, bronchospasm, nasoocular symptoms or anaphylaxis induced by at least two NSAIDs with different chemical groups.

Exclusion Criterias

A total of 580 patients who had delayed type NSAID hypersensitivity (n:34), negative ASA provocation test (n=235), only one reaction history (n=174), more than one reaction but within the same chemical class (n=48), unreliable history (n=71), unavailable records (n=18) were excluded from study.

Patient Characteristics

Patients' demographics, concomitant diseases, atopy status, duration of NSAID hypersensitivity, total number of reactions, reaction severities, clinical phenotypes, pulmonary function test (PFT) parameters and results of alternative drug provocation test results are recorded. Patients with and without reactions during alternative provocation tests with nimesulide and/or meloxicam were compared in terms of these data.

Presence of atopy was defined by measurement of allergen spesific IgE or skin prick test (SPT) positivity to at least one of the following aeroallergens; Dermatophagides pteronyssinus (der p); Dermatophagoides farinae (der f); cockroach; grass, tree, weed pollens; cat; dog; Alternaria; Cladosporium and Aspergillus antigens. Positive (histamine, 10 mg/mL) and negative (saline solution) controls were included. SPT was considered positive when the skin reaction was a wheal at least 3mm diameter greater than control solution with a surrounding erythema. An allergen-specific IgE level >0.35 kU/L was accepted as positive.

Drug Provocation Tests

Single blinded, placebo-controlled, oral, drug provocation tests with partial selective COX-2 inhibitors (nimesulide and/or meloxicam) were performed to assess the tolerance to these drugs. All patients gave an informed written consent before each challenge session.

On the first day divided doses of one-quarter and three-quarters placebo tablets (lactose) were given at 1 hour intervals. If the placebo challenge was negative divided doses of one-quarter and three-quarters of the therapeutic doses of nimesulide and/or meloxicam were given at 1 hour intervals on different days. Total challenge doses were 100 mg for nimesulide and 7.5 mg for meloxicam.

All drug challenges were performed under close observation of patient in the allergy unit. Emergency equipment was available during all challenges. Patients were observed at hospital for at least two hours after last dose administration and were seen in the outpatient department on the next day to determine whether any delayed reactions had occurred.

All patients were challenged at least 4 weeks after their most recent adverse reaction. None of the patients presented significant cutaneous or respiratory symptoms at the time of testing, Patients with chronic urticaria were challenged during a period of clinical remission of the disease. Antihistamines had been discontinued seven days or more before challenges.

During the challenge procedure blood pressure, pulse, nasoocular, respiratory and cutaneous symptoms were monitored before and every hour after each dose was given. Forced expiratory volume in 1 second (FEV1) was measured before each dose and any time if respiratory symptoms occurred.

Challenge test was accepted as positive if one of the following symptoms existed: conjunctival reaction; the upper and lower respiratory tract reactions such as sneezing, rhinorrhea, nasal blockage, dyspnea, wheezing, and cough with a 20% decrease in FEV1; cutaneous reactions such as erythema, pruritus with erythema, urticaria, angioedema; hypotension and/or anaphylactoid reaction.

The severity of culprit and alternative drug hypersensitivity reactions were classified according to Ring and Messmer Classification.[8]

Statistical Analysis

All statistical analyses were performed using the SPSS (statistical package of social sciences) for Windows 18,0 software package. In the evaluation of the data, mean and standard deviation for normally distributed variables, median and interquartile range for non-normally distributed variables, values and percentages for ratios were determined by descriptive statistical method. In univariate analyses, Chi-square, Fischer, Student's t-test and Mann-Whitney U tests were used, as appropriate. All p values lower than 0.05 were considered to be statistically significant.

RESULTS

A total of 560 patients; 378 (67.5%) female and 182 (32.5%) male with mean age 43±13.29 were included to study.

Median duration of NSAID hypersensitivity was 36 (1-420) months. 184 patients had two, 376 patients had three or more reactions. The highest reaction grades with culprit NSAIDs were grade 1 in 197 (35.2%), grade 2 in 162 (28.9%), grade 3 in 200 (35.7%), grade 4 in 1 (0.2%) patients.

Atopy was detected in 141 of 449 (31.4%) patients; 52 (36.9%) had polysensitization and 89 (63.1%) had monosensitization.

In the evaluation of comorbidities, non-allergic comorbidities were detected in 198 (36.9%) patients and allergic comorbidities were detected in 394 (72.6%) patients. Allergic comorbidities were shown in Table 1. Asthma, other drug allergies and nasal polyp were the most common comorbidities. Median duration of asthma and nasal polyp was 48 (0-480) months and 36 (0-240) months respectively. Seventy-two patients (68.6%) had a history of nasal polyp operation with median 2 (1-10) operations.

None of the patients experienced any reaction to placebo challenge. Alternative drug provocation test was performed with nimesulide in 541 patients, meloxicam in 517 patients, both nimesulide and meloxicam in 498 patients. Alternative drug provocation test positivity with nimesulide and/or meloxicam was detected 50 of 560 (8.9%) patients. Provocation test positivity was 33/541 (6.1%) with nimesulide, 30/517 (5.8%) with meloxicam and 13/498 (2.3%) with both nimesulide and meloxicam.

Table 1. Allergic comorbidities of study group

Allergic comorbidity	n (%)
Asthma	199 (36.9)
Other drug allergy	159 (29.3)
Nasal polyp	123 (22.8)
Asthma+nasal polyp	106 (18.9)
Allergic rhinitis	100 (18.6)
Chronic urticaria / angioedema	90 (16.7)
Non-allergic rhinitis	13 (2.4)
Venom allergy	18 (3.4)
Food allergy	12 (2.2)
Contact dermatitis	5 (0.9)
Atopic dermatitis	2 (0.4)
Latex allergy	2 (0.4)
Idiopathic anaphylaxis	1 (0.2)

Most of the reactions occurred after full therapeutic dose administration; 25/33 (75.8%) of nimesulide and 26/30 (86.7%) of meloxicam reactions. The characteristics of reactions with nimesulide and meloxicam are shown in Table 2. No significant difference was detected in terms of provocation test positivity ratio, reaction severity, provocative dose, interval between the last administered drug dose and reaction and clinical symptoms (Table 2).

Table 2. The characteristics of reactions with nimesulide and meloxicam

Reaction Properties	Nimesulide n (%)	Meloxicam n (%)	p
Provocation test positivity	33 (6.1)	30 (5.8)	0.838
Reaction severity			0.244
Grade 1	13 (39.4)	16 (53.3)	
Grade 2	7 (21.2)	8 (26.7)	
Grade 3	13 (39.4)	6 (20)	
Provacative dose			0.271
One quarter tablet	8 (24.2)	4 (13.3)	
Three quarters tablet	25 (75.8)	26 (86.7)	
Interval between last drug dose and reaction			0.405
<1 hour	10 (30.3)	7 (23.3)	
1-2 hours	12 (36.4)	8 (26.7)	
>2 hours	11 (33.3)	15 (50)	
Clinical symptoms			
Pruritus with erythema	13 (39.4)	12 (40)	0.964
Urticaria	10 (30.3)	11 (36.7)	0.593
Angioedema	6 (18.2)	6 (20)	0.854
Dyspnea	14 (42.4)	7 (23.3)	0.108
Bronchospasm	13 (39.4)	6 (20)	0.094
Rhinitis	10 (30.3)	10 (33.3)	0.796
Conjunctivitis	2 (6.1)	2 (6.7)	1.000
Nausea	1 (3)	3 (10)	1.000
Vomiting	1 (3)	1 (3.3)	1.000
Difficulty swallowing	2 (6.1)	2 (6.7)	1.000
Hypotension	2 (6.1)	-	0.494
Tachycardia	2 (6.1)	-	0.494
Dizziness	1 (3)	3 (10)	1.000
Hypertension	1 (3)	1 (3.3)	1.000
Tremor	1 (3)	-	1.000
Buzzing in the ear	3 (9.1)	-	0.240

Comparision of patients with positive (n:50) or negative (n:510) drug provocation test with nimesulide and/or meloxicam revealed that duration of NSAID hypersensitivity was shorter and allergic comorbidities, asthma, nasal polyp and the coexistence of asthma and nasal polyp were more common in patients with a positive provocation test (Table 3).

No significant difference was detected in alternative drug provocation test positivity in asthma patients according to PFT parameters (Table 4).

Table 4. Pulmonary function test parameters of asthma patients according to drug provocation test results

Variables	Positive DPT (n=173)	Negative DPT (n=26)	p
FVC (%)	92.72±14.79	95.20±14.74	0.439
FEV1 (%)	88.48±15.86	88.64±10.21	0.947
FEV1 (ml) median (min-max)	2410 (740-5200)	2680 (1640-4010)	0.242
FEV1/FVC	83 (50-94)	83 (56-91)	0.381
MMFR	75.05±24.10	69.36±20.87	0.270

DPT: Drug provocation test, FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capasity, MMFR: Maximum mid flow rate

Table 3. Comparision of the patients with positive or negative drug provocation test with nimesulide and/or meloxicam

Variables	All patients (n=560)	Patients with negative DPT (n=510)	Patients with positive DPT (n=50)	p
Age (years)	43.00±13.29	43.29±13.37	40.40±12.30	0.143
Gender Female, n (%) Male, n (%)	 378 (67.5) 182 (32.5)	 343 (67.3) 167 (32.7)	 35 (70) 15 (30)	0.692
Atopy, n (%)	141 (31.4)	127 (31.2)	14 (33.3)	0.777
NSAID hypersensitivity duration, months median (min-max)	36 (1-420)	36 (1-420)	18 (1-180)	0.017
NSAID reaction number 2 ≥3	 184 (32.9) 376 (67.1)	 170 (33.3) 340 (66.7)	 14 (28.0) 36 (72.0)	0.444
NSAID reaction severity Grade 1 Grade 2 Grade 3 Grade 4	 197 (35.1) 162 (28.9) 200 (35.7) 1 (0.2)	 183 (35.9) 143 (28.0) 183 (35.9) 1 (0.2)	 14 (28.0) 19 (38.0) 17 (34.0) 0 (0.0)	0.474
Non-allergic comorbidity, n (%)	198 (36.9)	179 (36.8)	19 (38)	0.870
Allergic comorbidity, n (%)	394 (72.6)	349 (88.6)	45 (90.0)	0.004
Asthma, n (%)	199 (36.9)	173 (35.4)	26 (52.0)	0.020
Nasal polyp, n (%)	123 (22.8)	102 (20.8)	21 (42.0)	0.001
Asthma and nasal polyp, n (%)	106 (18.9)	87 (17.1)	19 (38.0)	<0.001
Other drug allergy	159 (29.3)	143 (29.0)	16 (32.0)	0.553
Chronic urticaria / angioedema	90 (16.7)	81 (16.6)	9 (18.0)	0.800
Allergic rhinitis	100 (18.6)	90 (18.5)	10 (20.0)	0.793
Non-allergic rhinitiis	13 (2.4)	11 (2.3)	2 (4.0)	0.345
Venom allergy	18 (3.4)	16 (3.3)	2 (4.0)	0.680
Food allergy	12 (2.2)	12 (2.4)	0 (0.0)	0.613
Asthma duration, months median (min-max)	48 (0-480)	54 (0-480)	48 (0-240)	0.608
Nasal polyp duration,months, median(min-max)	36 (0-240)	48 (0-240)	24 (0-240)	0.259
Presence of polyp operation n (%)	72 (68.6)	59 (69.4)	13 (65.0)	0.702
Polyp operation number median (min-max)	2 (1-10)	2 (1-10)	1.5 (1-3)	0.062
Asthma and nasal polyp coexistence Respiratory symptoms, n (%) Systemic symptoms, n (%)	 56 (54.4) 47 (45.6)	 47 (56.0) 37 (44.0)	 9 (47.4) 10 (52.6)	0.498
Underlying chronic urticaria Urticarial exacerbation, n (%) Systemic symptoms, n (%)	 60 (65.9) 30 (33.3)	 54 (65.9) 27 (33.3)	 6 (66.7) 3 (33.3)	1.000

DPT: Drug provocation test, NSAID: Nonsteroidal anti-inflammatory drug

Drug provocation tests with both nimesulide and meloxicam were performed in 498 patients. Of these patients 29 had positivity with one drug and 13 had positivity with both drugs. No statistically significant difference was observed between cases with positive provocation tests with one or both drugs (Table 5).

Asthma and nasal polyp coexistence were observed in 106 patients. Of these patients 56 (52.8%) had only respiratory symptoms with culprit NSAIDs and 47 (44.3%) had systemic symptoms in addition to respiratory symptoms. No respiratory symptoms was observed in 3 (2.8%) patients with culprit NSAIDs. Median number of previous nasal polyp surgeries was found to be higher in patients who had systemic symptoms than in patients who had only respiratory symptoms; 2 (1-6) vs 1 (1-4) respectively (p=0.013).

Underlying chronic urticaria was present in 90 patients. Of these patients 60 (66.7%) had exacerbation of urticaria with NSAIDs, however 30 (33.3%) had systemic symptoms in adition to urticarial exacerbation after NSAID intake. Allergic rhinitis was more common in patients with urticaria and systemic symptoms than in patients with only urticarial exacerbation; 9 of 30 (31%) vs 6 of 60 (10%) respectively (p=0.018).

No statistically significant difference was detected in alternative drug provocation test positivity in NERD and NECD patients depending on whether there was a systemic response to NSAIDs or not (Table 3 and Table 5).

DISCUSSION

This study, which includes data from a large patient population, demonstrated that nimesulide and meloxicam are well tolerated alternatives in patients with cross-reactive NSAID hypersensitivity. Provocation test positivities with nimesulide and meloxicam were 6.1% and 5.8% respectively.

Table 5. Characteristics of patients with single or double positivity on nimesulide and meloxicam provocation test

Variables	Single positivity (n=29)	Double positivity (n=13)	p
Age (years)	41.48±12.45	36.62±9.57	0.219
Gender Female, n (%) Male, n (%)	 20 (69.0) 9 (31.0)	 9 (69.2) 4 (30.8)	1.000
Atopy, n (%)	6 (25.0)	5 (41.7)	0.446
NSAID hypersensitivity duration, months median (min-max)	18 (1-180)	18 (2-180)	0.643
NSAID reaction number 2 ≥3	 7 (24.1) 22 (75.9)	 4 (30.8) 9 (69.2)	0.713
NSAID reaction severity Grade 1 Grade 2 Grade 3 Grade 4	 8 (27.6) 12 (41.4) 9 (31.0)	 4 (30.8) 3 (23.1) 6 (46.2)	
Non-allergic comorbidity, n (%)	12 (41.4)	4 (30.8)	0.733
Allergic comorbidity, n (%)	27 (93.1)	12 (92.3)	1.000
Asthma, n (%)	13 (44.8)	9 (69.2)	0.143
Nasal polyp, n (%)	10 (34.5)	6 (46.2)	0.510
Asthma and nasal polyp, n (%)	9 (31.0)	6 (46.2)	0.488
Other drug allergy	11 (37.9)	2 (15.4)	0.278
Chronic urticaria / angioedema	5 (17.2)	2 (15.4)	1,000
Allergic rhinitis	4 (13.8)	3 (23.1)	0.657
Non-allergic rhinitiis	1 (3.4)	1 (7.7)	0.528
Venom allergy	1 (3.4)	1 (7.7)	0.528
Food allergy	0 (0.0)	0 (0.0)	1.000
Asthma duration,months median(min-max)	60 (0-240)	24 (0-60)	0.164
Nasal polyp duration,months, median(min-max)	36 (0-240)	12 (0-36)	0.108
Presence of polyp operation n (%)	7 (70.0)	2 (33.3)	0.302
Polyp operation number median(min-max)	2 (1-3)	2 (2-2)	0.857
Asthma and nasal polyp coexistence Respiratory symptoms, n (%) Systemic symptoms, n (%)	 4 (44.4) 5 (55.6)	 3 (50.0) 3 (50.0)	1.000
Underlying chronic urticaria Urticarial exacerbation, n (%) Systemic symptoms, n (%)	 3 (60.0) 2 (40.0)	 2 (100.0) 0 (0.0)	1.000

NSAID: Nonsteroidal anti-inflammatory drug

Previous studies evaluating the safety of nimesulide and meloxicam in cross-reactive NSAID hypersensitivity reported variable reaction rates. In studies conducted with a total provocative dose of 100 mg nimesulide reaction rates between 8.1% and 21.2% were reported.[9-12] On the other hand different reaction rates were reported in studies conducted with different provocative doses of meloxicam; reaction rates have been reported between 4.76% and 16.4% with a total provocative dose of 7.5 mg, and between 3.92% and 14.3% with a provocative dose of 15 mg.[9-15] Considering studies conducted with higher doses of meloxicam Inomata et al.[16] reported a reaction rate of 33% (2 of 6 patients) with a provocative dose of 18.5 mg meloxicam in patients with multiple NIUA. Quinones Estevez et al.[17] reported provocation test positivity in all of 8 patients with cross-reactive NSAID hypersensitivity after a provocative dose of 22.5 mg meloxicam and noted that COX-2 selectivity decreased with increasing doses.

Although there are publications in the literature reporting that meloxicam is safer than nimesulide in cross-reactive hypersensitivity, no statistical difference was found in our study.[12]

In our study 42 of the patients whose alternative drug provocation tests were positive were challenged with both nimesulide and meloxicam and 13 of them (31%) reacted to both drugs. Similarly in a study including patients with cross-reactive NSAID hypersensitivity reported that 6 of 19 (31.6%) patients had reactions with both drugs.[12] In another study that included only patients with NERD, reactions to both drugs were reported in 7 out of 8 (88%) patients and they also stated that the rate of reactions with nimesulide, meloxicam and paracetamol was higher in NERD patient group compared to some studies in the literature.[9]

NERD is defined as a chronic eosinophilic inflammatory disorder of the respiratory tract occurring in patients with asthma and/or rhinosinusitis with nasal polyps, which symptoms are exacerbated by NSAIDs, including aspirin. Clinical reaction is typically manifested by upper and/or lower respiratory symptoms.[18] In our study 106 patients had coexistence of asthma and nasal polyps. We observed that 45.6% of these patients developed systemic symptoms in addition to respiratory symptoms after NSAID intake and median number of previous nasal polyp surgeries was higher in patients accompanied by systemic response. We also observed that 33.3% of the NECD patients had systemic symptoms in addition to cutaneous symptoms after NSAID intake and allergic rhinitis was more common in patients describing systemic symptoms.

It is known that NSAID hypersensitivity is higher in asthma and nasal polyp patients than in the general population.[18] In this study we showed that partial selective COX-2 hypersensitivity is also significantly higher in patients with asthma and/or nasal polyp than other group of cross-reactive NSAID hypersensitive patients. We also showed that partial selective COX-2 hypersensitivity were significantly more common in the group of patients with a shorter duration of NSAID hypersensitivity.

Previous studies examining risk factors for reactions to alternative NSAIDs have reported different results. Pastorello et al.[19] reported that atopy and reaction to antimicrobial drugs increase the likelihood of intolerance of nimesulide and acetaminophen. However in their study the frequency of cross-reactive NSAID hypersensitivity in the patient group was not specified. Tepetam et al.[20] reported that the presence of atopy and reaction to antimicrobial drugs did not seem to influence the reactions to nimesulide in a patient group consisting of 37.9% of the patients described intolerance to multiple analgesics. Asero et al.[21] aimed to detect risk factors for intolerance to alternative drugs such as acetaminophen and nimesulide in different groups of patients with a history of adverse skin reactions (urticaria/angioedema, or anaphylaxis) after the ingestion of aspirin and other NSAIDs in their study. Sixty-nine of the 256 patients had underlying chronic urticaria. They reported that history of anaphylactoid reactions induced by NSAID represented a risk factor for urticaria after the ingestion of the alternative study drugs and atopic status was associated with a higher risk of reactivity to nimesulide. However history of intolerance to antibacterial drugs was not found to be associated with a higher prevalence of reactivity against acetaminophen and/or nimesulide. Terzioğlu et al.[11] reported that the anaphylaxis due to NSAID intake was a risk factor for intolerance to paracetamol and partial selective COX-2 inhibitors in a cross-reactive patient group.

In our study, we did not detect any difference between the groups in terms of reaction development with nimesulide and/or meloxicam in terms of atopy, NSAID grade, previous drug allergy, and underlying diseases other than asthma and/or nasal polyp.

In this study we observed that the time between the first NSAID hypersensitivity reaction and application allergy clinic was quite long (median 36 months), and that other accompanying drug allergies were at a significant level of 29.3%. These results suggest the necessity of public education about drug allergies.

Limitations

However, there were several limitations of this study. First limitation is the retrospective design of the study. Second limitation is the aspirin provocation test was not performed on all patients to confirm cross-reactivity.

CONCLUSION

The partial selective COX-2 inhibitors nimesulide and meloxicam are well tolerated alternatives in patients with cross-reactive NSAID hypersensitivity. Hypersensitivity to these drugs is significantly higher in patients with asthma and/or nasal polyp than other group of cross-reactive NSAID hypersensitive patients and also in patients with a shorter duration of NSAID hypersensitivity. Although they are highly tolerable drugs they can also cause grade 3 severe reactions so drug provocation tests should be carried out under supervision.

Abbreviations

ASA: Asetyl salicylic acid, COX: Cyclooxygenase (COX), DHR: Drug hypersensitivity reaction, FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capasity, NECD: NSAIDs-exacerbated cutaneous disease, NERD: NSAIDs-exacerbated respiratory disease, NIUA: NSAIDs-induced urticaria/angioedema, NSAID: Nonsteroidal anti-inflammatory drug, PFT: Pulmonary Function Test, SPT: Skin prick test

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.10.2021, Decision No: 2012-KAEK-15/2373).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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Prediction of long-term ischemic stroke with estimated whole blood viscosity in heart failure patients

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ABSTRACT

Aims: Heart failure (HF) and stroke often coexist and share common risk factors, including atrial fibrillation. Whole blood viscosity (WBV), one of the most significant indicators of endothelial stress, is a fundamental determinant of blood flow and is involved in the aetiology of atherosclerosis and thrombosis. The purpose of this study was to assess the association between estimated WBV and long-term ischemic stroke (IS) risk in patients hospitalized for acute HF.

Methods: A total of 409 patients with reduced ejection fraction HF hospitalized with acute HF were included. The primary outcome was IS post-discharge follow-up.

Results: IS occurred in 26 (6%) patients during a follow-up. In the IS group, older age, diabetes mellitus frequency and WBV were higher, left ventricular end-diastolic and left atrial anteroposterior diameter were increased and left ventricular ejection fraction was lower. In multivariate regression analysis, WBV was found to be a predictor of long-term IS (OR, 2.68; 95% CI, 1.96-3.12, p=0.008). In the receiver operating characteristic curve, the optimal cut-off value of WBV for one-year IS was 6.28 with 61.5% sensitivity and 70.2% specificity (area under the curve: 0.748).

Conclusion: WBV is a novel, easily measurable, cost-effective, non-invasive risk marker for the prediction of long-term IS in patients with HF, independent of traditional risk factors.

Keywords: Heart failure, ischemic stroke, whole blood viscosity

Our research's data was presented in 2nd National Heart Failure Congress as 'Oral Presentation' on June 2023.

INTRODUCTION

Heart failure (HF) is a rapidly growing global public health concern that affects almost millions of individuals globally and is a leading cause of mortality and re-hospitalization.[1] Moreover, stroke is the leading cause of death and disability worldwide after ischemic heart disease.[2] HF prognosis is significantly impacted by comorbidities related to HF.[1,3,4] Owing to its enormous prevalence, HF may significantly influence the occurrence of other illnesses, such stroke.[2-4] HF and stroke often coexist and share common etiological risk factors, including atrial fibrillation (AF).[1-4] Because of the increased activity of pro-coagulant factors and thromboembolic consequences, HF may raise the risk of an ischemic stroke (IS).[2-4] On the other hand, HF is commonly together with low blood pressure, which may prevent IS.[1,3-5] It have been still unknown whether HF directly causes the increased risk of IS, despite the fact that patients with HF had a two to three times greater risk of IS than general population.[3-7] This is due to the fact that the majority of stroke research with HF population does not accurately account for confounding factors or distinguish between patients with and without AF.[2,4-8] It is well known that current guidelines recommend the use of the CHA_2DS_2-VASc score to evaluate IS risk in HF patients with AF.[3,4] Anticoagulant treatment is indicated with a class I recommendation in cases with a CHA_2DS_2-VASc score ≥2.[3,4] Although some observational study data have been presented to determine stroke risk in HF patients without AF, anticoagulant or antiagregant treatment management has not been finalized.[5-10] In HF patients without AF, supportive parameters are needed to predict stroke risk and appropriate treatment management. Whole blood viscosity (WBV), one of the significant determinants of endothelial stress, was a strong parameter of blood flow and was revealed to involved in atherosclerosis and thrombosis.[11-13] Numerous studies have previously shown the association between elevated whole blood viscosity and adverse clinical outcomes, such as mortality, as well as its prognostic significance in cardiovascular diseases.[12-16]

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Because of significant role of WBV in the prediction of thrombogenicity and the uncertainty of research on stroke in HF patients, we aimed to evaluate the association between estimated WBV and long-term IS risk in patients hospitalized for acute HF.

METHODS

Ethics

The study was initiated with the approval of the Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 24.08.2022, Decision No: 266). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population and Design

In this retrospective observational research, 485 patients who applied to our center with HF symptoms between March 2020 and March 2023 were evaluated as New York Heart Association (NYHA) class 2-4 and were hospitalized for acute HF with reduced ejection fraction (HFrEF) were included. Those who satisfied at least one of the following criteria were excluded; diagnosis of with left ventricular (LV) thrombus and AF (n=20), receiving anticoagulant treatment (n=24), haemorrhagic stroke (n=5), active kidney infection, nephrotic syndrome or chronic kidney disease under hemodialysis treatment (n=10), active cancer (n=3), autoimmune disease (n=3), severe liver disease (n=6), hypo- or hyperthyroidism (n=5) (**Figure 1**). Following exclusion, 409 patients were included in final analysis. The hospital's medical database provided demographic, laboratory, and clinical data. Furthermore, telephone interviews or the national health registration system were used to collect follow-up data.

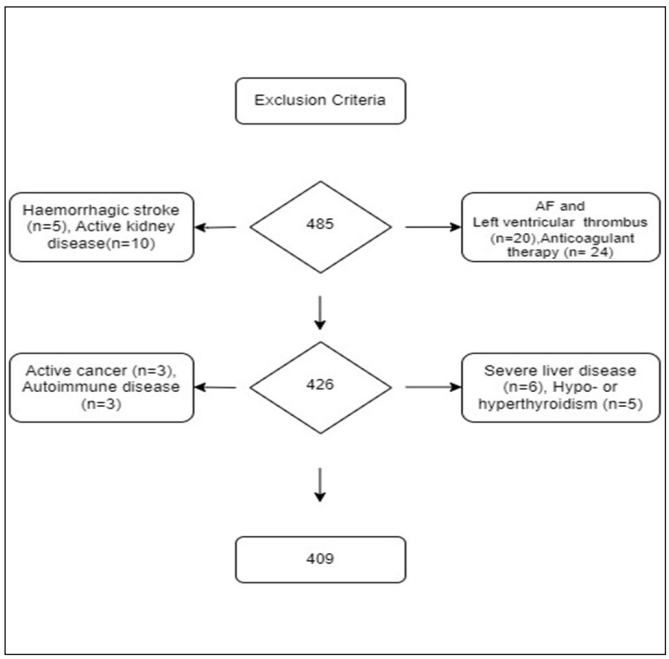

Figure 1. A flow chart for study inclusion and exclusion criteria

Definitions and Risk Factors

HFrEF was defined as the presence of symptoms or signs of HF and evidence of cardiac dysfunction: either LV ejection fraction (LVEF) <40% or increased plasma concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (>125 ng/l).[3,4] HF with a history of myocardial infarction, percutaneous coronary intervention, or coronary bypass surgery, as well as stenosis of greater than 70% in any vessel or more than 50% in the left main coronary artery, was desribed as ischemic cardiomyopathy.[3,4] Baseline laboratory parameters were meticulously documented for each patient during the emergency admission, encompassing a comprehensive set of analyses Assessments of complete blood counts were performed with the Beckman Coulter LH 750 device, which is situated in Fullerton, California, in the United States. The Cobas C7001 equipment from Roche Diagnostics in Rotkreuz, Switzerland was used to assess the lipid profile and other biochemical variables. According to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), patients were classified as having diabetes mellitus (DM), hypertension (HT), or hyperlipidemia if any of those disorders had been detected.[17] The formula for calculating body mass index (BMI) is weight in kilograms divided by height in meters squared (kg/m²). Smoking status was determined by considering a participant a current smoker if they were consistently smoking or had smoked in the 1 month leading up to the study. AF was diagnosed as the absence of irregular R-R interval and P-wave on hospitalization or follow-up electrocardiograms (ECGs).[18] Moreover, all patients had at least one 48-hour rhythm holter monitoring during a follow-up of approximately one year. Patients with a narrow QRS, irregular R-R interval of more than 30s, and irregular R-R interval on rhythm holter monitoring were considered to have AF.[18] A stroke was defined as a focal neurological deficit that was induced by a non-traumatic event and lasted for at least 24 hours.[19] It was categorized as either an ischemic, hemorrhagic, or undetermined type stroke based on the results of computed tomography or magnetic resonance imaging.[19]

WBV was calculated by the De Simone formula, which is rapid and simple to assess [WBV(s) (208 s-1)=(0.12×HCT)+0.17 (total protein-2.07)].[11] Following the recommendations of the American Society of Echocardiography, licensed cardiologists conducted echocardiographic assessments on participants using a Hitachi ultrasound cardiovascular system (Arietta 65, USA) with a 2.5-3.5 MHz transducer, without knowledge of any clinical data.[20] The modified biplane Simpson's rules were used to measure LVEF.

Follow up and Outcomes

The patients were monitored for a median of 15 (11-21) months. The primary outcome was IS post-discharge follow-up.

Statistical Analysis

The data were reported as median [interquartile range (IQR)] for continuous variables and as percentages (n) for categorical variables. The Kolmogorov-Smirnov test was used to determine if the continuous variable distribution was normally distributed. IS was the basis for stratifying the participants into two groups. The Mann-Whitney U-test was utilized to compare non-normally distributed continuous variables, and the Pearson Chi-square test was applied to evaluate the frequency of categorical variables across these groups. Both univariate and multivariate regression analyses included parameters that had significant differences between the two groups. The receiver operating characteristics curve (ROC) analysis was then used to evaluate the predictive performance of estimated WBV. For every analysis, a 95% confidence interval was taken into account and a significance level of $p<0.05$ was adopted. Statistical Package for the Social Sciences (SPSS version 22.0, SPSS Inc., Chicago, IL, USA) was utilized for these statistical analyses.

RESULTS

Baseline Characteristics

The total study population included 409 patients with a median age of 55 years (IQR: 47-63) years, 55 (72.4%) of whom were male. IS was observed in 6% of patients with HFrEF during a median follow-up period of 15 months. The IS (+) group had a higher median age than the IS (-) group [65 (60-71) vs 54 (46-63), $p<0.001$. Similarly, IS (+) group exhibited a statistically higher incidence of DM ($p=0.001$), left atrial anteroposterior diameter (LA-APD) ($p<0.001$), LV end-diastolic diameter (LVDD) ($p=0.009$), and LVEF ($p=0.001$). Male gender, HT, COPD, smoking and BMI were, on the other hand, comparable between the groups. In addition, IS (+) group had lower hemoglobin ($p=0.004$) and total protein levels ($p=0.025$). A total of 177 (43%) patients were on single antiplatelet therapy and 75 (18%) were on dual antiplatelet therapy. Table 1 provided comprehensive clinical, laboratory, and demographic characteristics of the research cohort which reported according to IS.

Independent Predictors of IS

Univariate analysis presented that age, DM, LA-APD, LVDD, LVEF and WBV were significantly associated with IS (respectively, age: OR, 1.09; 95% CI, 1.08 – 1.13, $p<0.001$; DM: OR, 3.63; 95% CI, 1.62-4.55, $p=0.002$; LA-APD: OR, 1.10; 95% CI, 1.03-1.17, $p=0.002$, LVDD: OR, 1.04; 95% CI, 1.07-1.08 $p=0.019$ and LVEF: OR, 0.91; 95% CI, 0.85-0.96, $p=0.003$) (Table 2). The WBV remained an independent predictor of IS even after several risk factors, including significant clinical variables in the univariate model, were included in the multivariate model for adjustment (OR: 2.68, 95% CI 1.96-3.12, $p=0.008$) (Table 2).

Diagnostic Performance of WBV for IS

The ability of WBV levels to predict IS was evaluated using ROC analysis. Figure 2 indicated that WBV had a respectable capacity to predict an IS (AUC: 0.748, $p<0.001$) according to the findings of the ROC analysis. The WBV cut-off value was found to be 6.28, resulting in a 61.5% sensitivity and a 70.2% specificity.

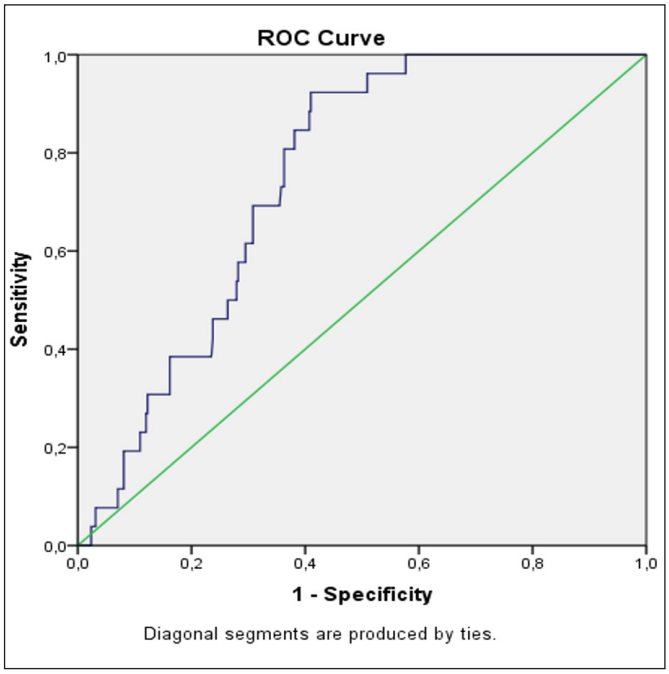

Figure 2. Receiver operating characteristic (ROC) curve analysis of total blood viscosity for ischemic stroke prediction (AUC:0.748 , Cut 6.28 , sensitivite 61.5% spesifite 70.2%)

DISCUSSION

There is a host of variables linked to stroke and other unfavorable outcomes in patients with HFrEF. These variables are grouped around treatment modalities, clinical characteristics, and laboratory parameters. We identified that DM, LA-APD, LVEF and WBV were independent predictors of IS prediction in patients with HFrEF. This was the first study to assess the association between WBV and the likelihood of a IS in HFrEF patients. The results of this investigation proved and verified that the elevated WBV values measured by De Simone formula were an independent, consistent measure of long- term IS prediction, regardless of other parameters in patients with HFrEF.

Table 1. Baseline characteristics of the study population

Variables	Overall (n= 409)	IS (-) (n=383)	IS (+) (n=26)	p-value*
Demographic features and risk factors				
Age, years; median, (IQR)	55 (47-63)	54 (46-63)	65 (60-71)	<0.001
Male; n (%)	332 (81.2)	309 (80.7)	23 (88.5)	0.326
DM; n (%)	107 (26.2)	93 (24.3)	14 (53.8)	0.001
HT; n (%)	181 (44.3)	165 (43.1)	16 (61.5)	0.067
HL; n (%)	102 (24.9)	94 (24.5)	8 (30.8)	0.699
Smoking; n (%)	109 (26.7)	101 (26.4)	8 (30.8)	0.624
Ischemic heart failure; n (%)	240 (58.7)	225 (58.7)	15 (57.7)	0.916
COPD; n (%)	43 (10.5)	41(10.7)	2 (7.7)	0.628
BMI; mean±SD	27±4.1	26.9±4.1	28±5.8	0.230
WBV; median (IQR)	5.9 (5.3- 6.3)	5.7 (5.2-6.3)	6.3 (6.1-6.6)	<0.001
LVDD, mm; median (IQR)	62 (56-67)	61 (56-66)	66 (59-74)	0.009
LA-APD, mm; median (IQR)	46 (42-49)	45 (42-49)	49 (47-52)	<0.001
LVEF, %; median (IQR)	30 (25-30)	30 (25-35)	26 (26-30)	0.001
Laboratory measurements				
Total cholesterol, mg/dl; median (IQR)	169 (146-188)	169 (145-188)	174 (153-189)	0.355
Trigliserid, mg/dl; median (IQR)	113 (92-140)	113 (92-140)	112 (88-134)	0.673
HDL-C, mg/dl; median (IQR)	35 (30-40)	35 (30-40)	37 (31-40)	0.571
LDL-C, mg/dl; median (IQR)	107 (87-120)	106 (87-120)	112 (97-135)	0.092
Creatinine, mg/dl; median (IQR)	1.03 (0.84-1.26)	1.01 (0.83-1.25)	1.1 (1.00-1.30)	0.076
BUN, mg/dl; median (IQR)	21 (16-29)	21 (16-29)	23 (16-32)	0.371
Glucose, mg/dl; median (IQR)	108 (92-141)	108 (92-142)	97 (89-120)	0.088
WBC count, 10^3/µl; median (IQR)	8.2 (6.9-10.1)	8.3 (6.9-10.1)	8 (6.8-10.4)	0.714
Hemoglobin, mg/dl; median (IQR)	13.1 (11.3-14.4)	13 (11.3-14.3)	13.6 (13.4-14.6)	0.004
Platelet count, 10^3/µl; median (IQR)	228 (196-292)	230 (196-292)	217 (195-315)	0.790
Lymphocyte count, 10^3/µl; mean±SD	2.1±0.93	2.09±0.32	2.3±1.17	0.342
Neutrophil count, 10^3/µl; mean±SD	5.4±2.22	5.4±2.25	5.4±1.79	0.478
CRP, mg/L; median (IQR)	0.9 (0.2-3.7)	0.9 (0.2-3.7)	1.0 (0.3-2.7)	0.885
Total protein, g/dl; mean±SD	7.3±2.4	7.3±2.4	8.4±1.07	0.025
Albumin, g/dl; mean±SD	3.9±1.4	3.9±1.4	4.1±0.49	0.140
Sodium, mEq/L; mean±SD	136 ±7.5	138±7.7	138±3.3	0.408
Potassium, mmol/L; median (IQR)	4.3 (4-4.6)	4.3 (4.0-4.7)	4.2 (4.8-4.4)	0.331
Magnesium, mg/dl; mean±SD	2±0.31	2±0.32	1.9±0.17	0.390
Calcium, mg/dl; median (IQR)	9.1 (8.7-9.6)	9.1 (8.7-9.6)	9.2 (8.7-9.5)	0.673
NT-proBNP, pg/ml; median (IQR)	925 (502-1816)	925 (511-1815)	960 (364-1862)	0.724
Medications prescribed before admission				
CCB; n (%)	34 (8.3)	32 (8.4)	2 (7.7)	0.903
B-blocker; n (%)	386 (94.6)	362 (94.8)	24 (92.3)	0.592
Antiaggregan; n (%)	252 (61.6)	234 (61.0)	18 (69.2)	0.585
ACE-I /ARB/ARNI, n (%)	341 (83.6)	319 (83.5)	22 (84.6)	0.883
MRA; n (%)	197 (48.3)	185 (48.4)	12 (46.2)	0.822
Thiazide; n (%)	73 (17.9)	66 (17.3)	7 (26.9)	0.214
Statin; n (%)	132 (32.4)	125 (32,7)	7 (26.9)	0.541

p<0.05 was considered statistical significance. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker;ARNI, angiotensin receptor/neprilysin inhibitor; BMI, body mass index; BUN, blood urea nitrogen; CPOD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; HL, hyperlipidemia; IQR, inter quartil range; IS, ischemic stroke; NT-proBNP, N-terminal pro b-type natriuretic peptide; LDL-C, low-density lipoprotein cholesterol; LA-APD, left atrium antero-posterior diameter; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; mm, millimeter; MRA, mineralocorticoid receptor antagonist; SD, standart deviation; WBC, white blood cell; WBW, whole blood viscosity

Table 2. Univariate and multivariate regression analysis for prediction ischemic stroke

Variable	Univariate Analysis			Multivariate Analysis		
	OR	CI (95%)	p value*	OR	CI (95%)	p value*
Age, years	1.09	1.08-1.13	<0.001	1.12	1.02-2.52	<0.001
LVEF, %	0.91	0.85-0.96	0.003	0.927	0.89-0.98	0.048
LVDD, mm	1.04	1.07-1.08	0.019	1.03	0.983-1.09	0.187
LA –APD, mm	1.10	1.03-1.17	0.002	1.14	1.12-1.67	0.006
DM	3.63	1.62-4.55	0.002	1.55	1.25-2.24	0.010
WBV	2.11	1.24-3.60	0.006	2.68	1.96-3.12	0.008

DM, diabetes mellitus; LA-APD, left atrium antero-posterior diameter; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; mm, millimeter; WBW, whole blood viscosity

Compared to most malignancies, HF has a higher death and morbidity rate.[1] Consequently, managing HF patients is critical to lowering the medical, social, and financial burdens associated with their condition.[1,3,4] In patients with HF, the heart cannot support the body with enough blood and oxygen to ensure systemic metabolism both at rest and during physical activity.[3-5] This results in a restriction of the perfusion of critical organs.[5] Limited cerebral perfusion in these patients can lead to cerebral ischemia and stroke.[5,7] Traditionally, thrombosis, hypoperfusion, and atherosclerosis have been identified as the causes of IS in individuals with HFrEF.[8-10] The two most often identified causes of cardioembolic stroke in people with HFrEF were LV hypokinesia or thrombus formation due to AF.[5,7,8] Virchow's triad (abnormalities of blood flow, vessel wall and blood components), a precondition for thrombogenesis, is unsurprisingly inevitable in patients with HFrEF.[5,8-10] Akinetic ventricular segments, dilated left atrium or ventricle, and decreased blood flow in HF patients may all contribute to increased thrombus formation by a mechanism similar to AF.[7-10] HF patients are in a pro-thrombotic state.[8-10] There is activation of the sympathetic nervous system and renin-angiotensin-aldosterone system, exaggerated inflammation, increased platelet aggregation, elevated von Willebrand factor levels, and impaired fibrinolysis.[5,7] Moreover, HF patients have functional and/or structural damage to blood vessels due to endothelial dysfunction, rheologic changes consistent with increased blood velocity, and atherosclerosis.[8-10] Impaired cerebral autoregulation is another significant condition that accompanies the etiology of stroke.[5,7] Together with all these factors, considering the causal relationship between HF and IS, comparable underlying etiologic risk factors including DM and HT are inevitable for this association.[6-8] As a result of all these aetiological and pathophysiologic mechanisms mentioned above, patients with HF are more susceptible to IS due to large artery atherosclerosis and small vessel occlusion.[5-10]

Due to the variability of HF patient clinical features and the diverse design of published research, epidemiological evidence about the prevalence and incidence of stroke in patients with HF is limited. Nonetheless, HF was thought to be the probable cause of stroke in approximately 9% of all patients.[21,22] According to a recent statement from the population-based, prospective Rotterdam Screening Study, IS was found in 4% of cases during 5 years of follow-up.[10] Other population-based investigations corroborated the Framingham Study's findings, which indicated that people with HF had a 2-3 times greater risk of IS than those without HF.[6-8] Another long-term cohort study described a notable correlation between HF and all stroke subtypes, even after adjustment for a number of different confounders, including AF or atrial flutter.[9] Patients with HF and AF more tended to develop stroke and had a 5-fold escalated risk compared to the general population.8 Despite the paucity of research on the connection between sinus rhythm HF and stroke, two recent population- community-based researches had shown that HF patients were more likely to experience an IS independent of AF compared with the general population.[8,9] During a mean follow-up of 15 months, almost 6% of the participants in this trial experienced an IS. Due to the exclusion of individuals with AF and those using anticoagulants, this incidence is lower than some of the studies described above and higher than others.

Available data on additional parameters of stroke risk in HF patients are based on retrospective cohort studies, post hoc analyses of several large clinical trials and their meta-analyses. Additional risk factors for HF patients were age, LVEF, DM, HT, prior stroke, and AF.[6-8,21-24] Although some evidence suggested that lower LVEF, older age and the presence of AF increase the risk of stroke, not all research revealed this correlation.[8-10,21-24] This shows the need for researches to identify HF patients at high risk for stroke as well as to determine the most appropriate therapeutic strategies for stroke prevention. Age, DM, LA-APD, LVEF, and WBV were found to be independent predictors of IS in this study. The fact that our research cohort included a relatively lower age group compared to previous studies could be the reason why age was a major predictor of IS in contrast to other studies. Due to conflicting data in patients with AF and the current clear recommendations for anticoagulant treatment in AF patients,[3,4,19] the analysis was performed without including AF patients.

WBV is the intrinsic resistance of blood to flow in vessels and is closely pertinent to blood flow velocity.[11,12] Because abnormal blood viscosity reduces tissue perfusion and interacts with other risk parameters, it is a crucial element in the advancement of atherosclerosis.[12,13] Red cell aggregation, haematocrit, plasma viscosity, and red cell deformation are the main determinants that affect blood viscosity.[1,12,13] In everyday practice, measuring and assessing blood viscosity with a viscometer can be challenging and complex. De Simone et al.[11] computed WBV with a straightforward equation using haematocrit and total protein levels and demonstrated the reliability of this formula by performing validation analyses with a viscometer.[12-16] WBV calculated by this formula has been shown to be a good parameter for determining adverse outcomes in many cardiovascular diseases such as stroke, HF, myocardial infarction and coronary slow flow phenomenon.[12-16] Moreover, HCT and plasma protein levels, which were used to calculate WBV, had a well-established association with adverse outcomes

in HF patients.[3,4,25] This study demonstrated that WBV could be a valuable parameter for the prediction of IS in HFrEF patients in sinus rhythm as an additional parameter. For these patients, the management of anticoagulant and antiaggregant therapy may be guided by elevated WBV.

Limitations

The limitations of this study included the retrospective design of our study, the inclusion of a single center and the possible effects of inter-observer variability despite the use of standard diagnostic methods. Nevertheless, the relatively large sample size and the fact that our center was a heart transplant center to which patients from other hospitals and cities were referred made the results of this study significant. Another limitation of the study was that the WBV value was not verified using a viscometer and the temporal variation of WBV was not evaluated. However, further extensive studies have verified the De Simone et al.11 formula and demonstrated that it offers a good substitute for the determination of direct viscosity measurement.

CONCLUSION

WBV is a novel, easily measurable, cost-effective, non-invasive risk marker for the prediction of long-term IS in patients with HF, independent of traditional risk factors. This results underscore the importance of clinical attention to IS risk in patients with HF and highlights the role of WBV as a supplement to potential prevention strategies in these patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 24.08.2022, Decision No: 266).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Examining the relationship between the atherogenic index of plasma and coronary plaque burden: insights from a retrospective intravascular ultrasound analysis

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ABSTRACT

Aims: In the context of coronary artery disease development, inflammation and lipid metabolism play significant roles. This study explores the link between the Atherogenic Index of Plasma (AIP) and plaque burden in intravascular ultrasound (IVUS) examined patients.

Methods: A retrospective analysis included seventy-six consecutive IVUS patients from June 2020 to May 2023. AIP, calculated as the log of plasma triglyceride divided by high-density lipoprotein cholesterol, measured atherogenicity. Plaque burden, a percentage, was determined by dividing the total plaque area by the total vessel area. Multivariate regression and Spearman's correlation analyzed the relationship between AIP and high plaque burden.

Results: The median age was 59 years, with 72.4% males. Univariate analysis identified age, diabetes mellitus (DM), smoking, and AIP as plaque burden predictors. Multivariate analysis showed AIP (OR=1.53, 95% CI:1.12-2.02, p=0.021) and DM independently predicted high plaque burden (OR=1.03, 95% CI:1.01-1.45, p=0.044). Spearman's correlation indicated a positive correlation between AIP and high plaque burden (rho: 0.682, p<0.05).

Conclusion: This study suggests AIP, a surrogate marker of atherosclerosis, may predict plaque burden in IVUS-examined patients.

Keywords: Atherogenic index of plasma, coronary plaque burden, intravascular ultrasound

INTRODUCTION

Coronary artery disease (CAD) manifests as a clinical outcome of atherosclerotic plaque formation, whether obstructive or non-obstructive, within the epicardial arteries.[1-3] In the complex process of atherogenesis, which is the main cause of CAD, basic risk factors such as inflammation, abnormal glucose metabolism and dyslipidemia contribute to the development of CAD.[4,5] The Atherogenic Index of Plasma (AIP) serves as a comprehensive metric, capturing the delicate balance between atherogenic and anti-atherogenic factors.[6] Previous studies have explored the connection between AIP, CAD and coronary plaque burden, revealing an association between elevated AIP levels, an increased risk of CAD, and a higher prevalence of coronary plaques.[7-9] Elevated AIP levels indicate an imbalance in lipid metabolism, characterized by heightened atherogenic lipids like low-density lipoprotein (LDL) cholesterol and diminished levels of anti-atherogenic lipids, including high-density lipoprotein (HDL) cholesterol.[10] This underscores the link between an unfavourable lipid profile, reflected by an increased atherogenic index, and the progression of atherosclerosis.[11]

Atherosclerosis, marked by the accumulation of fatty deposits within arteries, underscores the importance of assessing plaque burden to evaluate disease severity and its impact on vascular health.[12] Intravascular ultrasound (IVUS) serves as a sophisticated imaging modality, providing high-precision visualization and measurement of atherosclerosis and plaque burden.[13] Unlike conventional angiography's two-dimensional depiction of blood vessels, IVUS uses a catheter equipped with an ultrasound probe to generate real-time cross-sectional images of vessel walls. This capability not only facilitates the evaluation of plaque size but also enables the characterization of atherosclerotic plaques, aiding in precise disease assessment and guiding tailored treatment strategies. IVUS plays a pivotal role in interventional cardiology, offering detailed insights into plaque features and informing therapeutic decisions, including the optimal placement of stents or other interventions to optimize vascular health.[14,15]

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Despite existing research exploring the relationship between AIP and atherosclerosis, a distinct research gap exists concerning the utilization of IVUS, a modality celebrated for its heightened accuracy in assessing plaque burden. This study aims to bridge this gap by investigating the association between IVUS-measured plaque burden and the AIP. Our findings aspire to illuminate the predictive capacity of the AIP in the context of IVUS-measured plaque burden, providing valuable contributions to the understanding of vascular health and atherosclerotic conditions.

METHODS

Ethics

The study adhered to the ethical principles outlined in the Declaration of Helsinki, and Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee approved the study protocol on 13.12.2023 (Decision Number: 665). The retrospective nature of the study obviated the need for written informed consent.

This retrospective observational study enrolled 76 consecutive patients presenting to our outpatient clinic with stable angina pectoris and/or angina-equivalent symptoms, who subsequently underwent IVUS following conventional angiography between June 2020 and May 2023. IVUS examinations were conducted based on the following criteria: (i) presence of angiographically indeterminate left main CAD: This criterion is applied to cases demonstrating a 50% to 70% diameter narrowing of the left main coronary artery on angiography. (ii) IVUS guidance for coronary stent placement, especially in left main coronary artery stenting cases: IVUS was employed as a guiding tool both before and after coronary stent placement, with a particular focus on cases involving LMCA stenting.[16] Individuals who fulfilled any of the following criteria were not included in the study: those with endocrine disorders, individuals who had taken antihyperlipidemic medication in the last six months, those experiencing ongoing infections, individuals with current malignancies, advanced liver disease, or end-stage renal disease. Demographic, laboratory, and clinical data for the final analysis were subsequently retrieved from our institution's electronic medical record system for the remaining 76 individuals.

Coronary Angiography and IVUS

During coronary angiography and IVUS procedures, either radial or femoral access was employed for vascular entry. Following the administration of 300 mcg of perlinganite and 60/kg IU of unfractionated heparin to prevent thrombotic complications, imaging was initiated. IVUS images were subsequently analyzed by two independent reviewers. Plaque burden, denoted as a percentage, was calculated by dividing the total plaque area by the total vessel area. Individuals exhibiting a plaque burden surpassing 70% were categorized as having a high plaque burden, while those with a plaque burden below 70% were classified as having a low plaque burden. The study cohort consisted of a final group of 76 subjects, all of whom underwent IVUS using either a commercially available 40-MHz rotational transducer (OptiCrosss/Boston Scientific/Costa -Rica). The IVUS pullbacks were executed automatically. The images, acquired at a rate of 30 frames per second in digital format, adhered to DICOM standards and were stored in the picture archiving and communication system for subsequent analysis and reference.

Definitions and Risk Factors

Baseline laboratory parameters, including complete blood count using the Beckman Coulter LH 750 instrument in Fullerton, California, USA, and lipid profile analyzed with the Cobas C7001 system from Roche Diagnostics in Rotkreuz, Switzerland, were meticulously documented for each patient before the procedure. Renal function was assessed using the validated Modification of Diet in Renal Disease Study formula.[17] Hypertension (HT) was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or use of antihypertensive medication.[18] Diabetes mellitus (DM) was identified based on fasting glucose levels ≥126 mg/dl, postprandial levels ≥200 mg/dl, or antidiabetic therapy. Dyslipidemia was confirmed with patterns such as total cholesterol ≥240 mg/dl, LDL≥130 mg/dl, HDL<40 mg/dl (men) or <50 mg/dl (women), and triglycerides ≥150 mg/dl.[19] Body mass index (BMI) was calculated as the ratio of weight in kilograms to the square of height in meters (kg/m^2). Smoking status was determined by considering a participant a current smoker if they were consistently smoking or had smoked in the 1 month leading up to the study. The AIP was computed using the formula log (plasma TG/HDL),[20] providing a valuable metric for assessing the atherogenic risk profile of the participants.

Statistical Analysis

The data were summarized as median [interquartile range (IQR)] for continuous variables and as percentages (n) for categorical variables. The normality of the distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Participants were stratified into two groups based on plaque burden. Non-normally distributed continuous variables were compared using the Mann–Whitney U-test, while the Pearson Chi-square test was employed to compare the frequency of categorical variables between these groups.

Parameters demonstrating significant differences between the groups were included in both univariate and multivariate regression analyses. Subsequently,

the predictive performance of serum AIP was assessed through receiver operating characteristics curve (ROC) analysis. Spearman analysis was conducted to explore the correlation between plaque burden and AIP. A significance level of p<0.05 was applied to all analyses, and a confidence interval of 95% was considered. Statistical Package for the Social Sciences (SPSS version 22.0, SPSS Inc., Chicago, IL, USA) was utilized for these statistical assessments.

RESULTS

Baseline Characteristics

The total study population included 76 participants with a median age of 59 years (IQR:55-68) years, 55 (72.4%) of whom were male. The median age in the high plaque burden group was older than in the low plaque burden group [62 (55-69) vs 56.5 (52-61), p=0.041]. Similarly, the high plaque burden group exhibited a statistically higher incidence of DM (p=0.011) and smoking (p<0.031). Male gender, family history of CAD, and BMI were, on the other hand, comparable between the groups. In addition, the high plaque burden group had higher TG and low HDL levels (p<0.05, for all). **Table 1** presents a comprehensive overview of the demographic, clinical, and laboratory characteristics of the study population categorized by plaque burden.

Independent Predictors of Plaque Burden

Univariate analysis showed that age, smoking, DM and AIP were significantly associated with plaque burden (age: OR 1.03, 95% CI 1.01-1.05,p=0.049; smoking: OR 1.05,%95 CI 1.02-1.25, p=0.031; DM: OR 1.34, 95% CI 1.05-1.52, p=0.029; AIP: OR 1.71, 95% CI 1.41-2.5, p<0.001) (**Table 2**). The AIP (OR:1.53, 95% CI 1.12-2.02, p=0.021) and DM (OR=1.03, 95% CI:1.01-1.45, p=0.044) continued to be an independent predictor of plaque burden even after several risk factors, including important clinical variables in the univariate model, were included in the multivariate model for adjustment (**Table 2**).

Table 1. Baseline characteristics of the study population

Variables	Plaque Burden			p-value*
	Overall (n= 76)	Low (n=21)	High (n=55)	
Demographic features and risk factors				
Age; median, (IQR)	59 (55-68)	56.5 (52-61)	62 (55-69)	0.041
Male; n (%)	55 (72.4%)	10 (55.6)	45 (77.6)	0.068
DM; n (%)	45 (59.2)	6 (33.3)	39 (67.2)	0.011
HT; n (%)	52 (68.4)	12 (66.7)	40 (69.0)	0.855
HL; n (%)	56 (73.7)	13 (72.2)	43 (74.1)	0.872
Smoking; n (%)	38 (50.0)	5 (27.8)	33 (56.9)	0.031
Family history of CAD; n (%)	25 (32.9)	3 (16.7)	22 37.9)	0.093
BMI	23.6(22.7-24.6)	23.7(22.5-24.4)	23.7(23.0-24.3)	0.315
Angiographic results, n (%)				
Laboratory findings				
Total cholesterol, mmol/L; median [IQR]	4.33 (3.50-5.53)	4.14 (3.05-5.30)	4.33 (3.68-5.59)	0.337
Triglyceride, mmol/L; median [IQR]	1.54 (1.07-2.14)	1.07(0.85-1.46)	1.71 (1.32-2.23)	<0.001
HDL-C, mmol/L; median [IQR]	1.03 (0.82-1.26)	1.19(0.97-1.35)	0.99(0.80-1.21)	0.034
LDL-C, mmol/L; median [IQR]	2.59 (1.70-3.47)	2.61 (1.58-3.45)	2.59 (1.91-3.47)	0.574
Creatinine, mg/dl; median [IQR]	0.85 (0.74-1.04)	0.87 (0.71-0.98)	0.85 (0.7-0.104)	0.990
e-GFR, ml/min/1.73 m²; Median [IQR]	91 (72-99)	95 (71-99)	91 (71-99)	0.660
Glucose, mg/dl; median [IQR]	106 (90-151)	108 (96-122)	125 (114-157)	0.174
WBC,10^3/dl; median [IQR]	8.4 (7.2-10.5)	7.2 (6.2-9.4)	8.6 (7.2-10.8)	0.108
Haemoglobin, g/dl; median [IQR]	13.3 (12.0-14.6)	13.6 (12.4-14.5)	13.5 (11.9-14.5)	0.341
Platelet count,10^3/dl; median [IQR]	254 (204-300)	263 (220-296)	253 (205-309)	0.660
Lymphocyte, cells/µl, median [IQR]	2.0 (1.5-2.5)	2.0 (1.6-2.9)	2.1 (1.4-2.5)	0.696
Neutrophils, cells/µl; median [IQR]	4.9 (4.1-7.4)	5.2 (4.6-7.6)	4.8 (3.9-7.3)	0.396
CRP, mg/l; median [IQR]	3.95 (1.35-7.9)	4.9 (3.9-6.1)	7.6 (5.5-9.3)	0.305
Albumin, g/dl; median [IQR]	4.0 (3.7-4.3)	2.7 (0.75-8.0)	4.1 (2.0-8.1)	0.681
Medications prescribed at discharge, n (%)				
Antiplatelets, n (%)	58 (76.3)	16 (76.1)	48 (76.3)	0.901
B-blockers, n (%)	37 (48.6)	10 (47.6)	27 (49.0)	0.801
ACEIs or ARBs	22 (28.9)	6 (28.5)	16 (29.0)	0.755
OAD, n (%)	25 (32.8)	5 (23.8)	20 (36.3)	0.091

Values are presented as numbers (n) and percentages (%), mean±standard deviation, or median (interquartile range 25th-75th percentiles). For continuous data, the p-value was calculated using the Mann-Whitney U-test, and for categorical variables, the Chi-Square test or Fisher's exact test, as appropriate.
*p<0.05 was considered statistical significance. Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CRP, C-reactive protein;DM,diabetes mellitus;e-GFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; HL, hyperlipidemia; IQR, interquartile range, LDL-C, low-density lipoprotein cholesterol; OAD, oral antidiabetic drug; WBC, white blood cell.

Table 2. Univariate and multivariate regression analysis for predicting plaque burden

Variable	Univariate Analysis			Multivariate Analysis		
	OR	CI(95%)	p value*	OR	CI (95%)	p value*
Age	1.03	1.01-1.05	0.049	0.98	0.96-1.00	0.280
Smoking	1.05	1.02-1.25	0.031	1.01	0.99-1.05	0.080
DM	1.34	1.05-1.52	0.029	1.03	1.01-1.45	0.044
TG/HDL	1.75	1.41-2.5	<0.001	1.53	1.12-2.02	0.021

*p<0.05 was considered statistical significance. Abbreviations: DM, diabetes mellitus;e-GFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HT, hypertension;TG, Triglyceride.

Diagnostic Performance of AIP for Plaque Burden

ROC analysis was conducted to assess the predictive capability of AIP levels in estimating a high plaque burden. The results of the ROC analyses indicated that AIP exhibited a reasonable ability to predict a high plaque burden (AUC:0.897, p<0.001), as illustrated in Figure 1. The determined cut-off value for AIP was 0.25, providing a sensitivity of 78.8% and specificity of 83.7%.

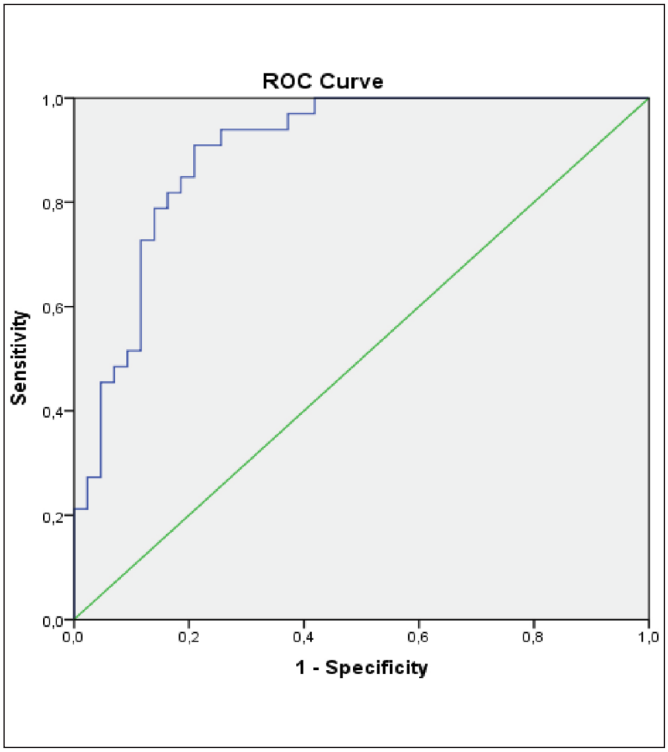

Figure 1. Receiver operating characteristics (ROC) curve analysis

Additionally, Spearman's analysis demonstrated a positive correlation between AIP and plaque burden (rho=0.682, p<0.001), as depicted in Figure 2. These findings suggest that AIP levels may serve as a valuable predictor for identifying individuals with a high plaque burden.

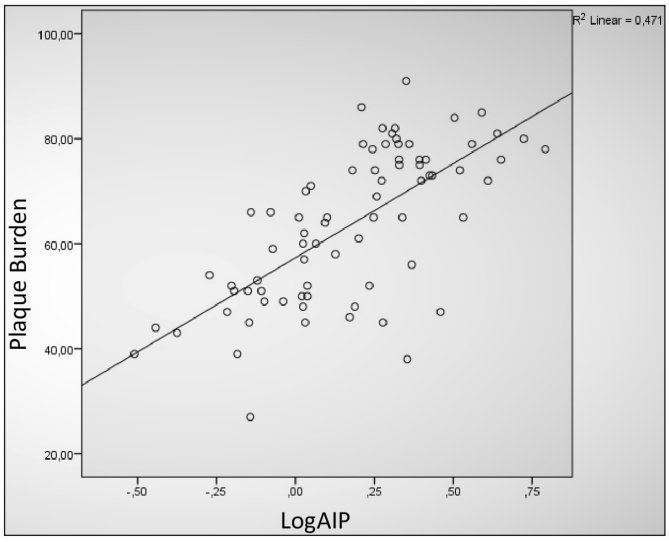

Figure 2. Spearman's correlation analysis

DISCUSSION

Our study revealed a robust positive correlation between AIP and plaque burden as detected by IVUS. These findings provide valuable insights into the intricate interplay among lipid metabolism, inflammation, and atherogenesis, particularly within the context of CAD.

Lipid accumulation in the arterial intima is the initial phase of the progression of atherosclerosis.[2] The relationship between LDL-C, HDL-C, total cholesterol, TG levels, and intimal lipid deposition is well demonstrated.[1,2,4] Moreover, small dense LDL (Sd-LDL) particles, resulting from the conversion of triglycerides, are more susceptible to oxidation, promoting the formation of foam cells. Oxidized apoprotein B and LDL-C are recognized as highly atherogenic.[21,22] Furthermore, Sd-LDL particles exacerbate atherosclerosis by activating oxygen radicals, promoting lipid peroxidation, and expressing adhesion molecules in endothelial cells, all of which are associated with endothelial dysfunction.[1,22] Contrary, HDL-C comprises antioxidant properties by transporting peripheral cholesterol to the liver and containing some antioxidant enzymes.[1] AIP is a new prognostic index associated with plasma TG and HDL-C levels.[23] AIP levels rise in response to elevated TG and/or decreased HDL levels.[10,21] An increase in AIP suggests a decrease in the diameter of LDL particles and a rise in sd-LDL levels.[4,21,24] AIP has also been shown to accurately reflect sd-LDL levels.[21,22] All current approaches for detecting sd-LDL are costly, have limitations, and are difficult to scale in clinical settings. AIP, on the other hand, is simple to calculate. Based on these findings, there is growing evidence that AIP might be a significant predictor of atherosclerosis and cardiovascular diseases.[6,7,24]

Our study has revealed a significant correlation between an elevated AIP and arterial plaque burden. Notably, this heightened risk of plaque burden persisted even after adjusting for traditional cardiovascular risk factors. Our findings align with prior research that has established a robust connection between the AIP index and atherosclerosis.[7,9,10] The incorporation of the AIP index into routine clinical diagnostic models holds promise for enhancing the precision of identifying atherosclerosis and plaque burden.

To the best of our knowledge, our study is the first to investigate plaque burden in patients diagnosed with CAD using the AIP in conjunction with IVUS. IVUS, offering a more comprehensive evaluation that goes beyond mere stenosis detection, provides superior insights into plaque structure, vulnerability, and burden compared to conventional angiography.[25] Despite technological advancements, IVUS has become pivotal in guiding invasive treatments for CAD through anatomical assessments. However, concerns persist about its widespread use, primarily due to potential invasive complications and associated costs. As emphasized in our study, a cost-effective, and reliable approach may involve integrating AIP indices with clinical findings. This combination could serve as a significant parameter for predicting atherosclerosis and plaque burden, providing a valuable tool for risk assessment and management in clinical practice.

Limitations

The findings of our study have several limitations. Firstly, inherent limitations are associated with the retrospective observational nature of the study. Secondly, the sample size may be considered insufficient, necessitating a larger cohort for more robust statistical analyses. Thirdly, in instances where IVUS image quality is suboptimal, accurately assessing plaque boundaries may pose challenges, potentially leading to measurement inaccuracies. Fourth, as automatic measurements are not feasible and rely on operator experience, the potential for bias exists. To mitigate all these limitations, our study was conducted by experienced operators who captured optimal images, revealing a strong relationship between AIP and plaque burden.

CONCLUSION

This investigation presents compelling evidence suggesting that the AIP, recognized as a surrogate marker for atherosclerosis, could function as a valuable predictive tool in evaluating plaque burden among patients undergoing IVUS examinations. These results enhance our comprehension of the interconnection between lipid metabolism, inflammation, and the development of atherosclerosis, offering potential assistance in the evaluation of risks and the management of the associated diseases.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date:13.12.2023, Decision No: 665).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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Comparison of three different doses of cis-atracurium under isoflurane anesthesia

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ABSTRACT

Aims: In this study; we compared the effects of three different doses of cis-atracurium, a nondepolarizing muscle relaxant agent, on neuromuscular blockade duration, endotracheal intubation quality and hemodynamic parameters under isoflurane anaesthesia.

Methods: A total of 60 patients (ASA I-II) were included in the study. Patients were premedicated with 10 mg diazepam intramuscularly 45 minutes before the operation. After the patients were transferred to the operating room, they were monitored noninvasively for heart rate and arterial blood pressure. Train of Four (TOF)-GUARD acceleration monitor was used for neuromuscular evaluation. All patients were administered 1 mg/kg fentanyl and 2 mg/kg propofol at induction, and anaesthesia maintenance was provided with 1.5% isoflurane+50% N2O+50% O2. The patients were divided into three groups according to the dose of cisatracurium administered: 0.15 mg/kg was administered to Group 1, 0.20 mg/kg was administered to Group 2, and 0.40 mg/kg cis-atracurium was administered to Group 3. Endotracheal intubation was performed at 120 seconds, and the block time of 99-100% (effect onset time) was recorded.

Result: Although the endotracheal intubation quality was evaluated as excellent and/or good in all three groups, the intubation quality of Group 3 was statistically higher than the other two groups ($p<0.05$). In hemodynamic measurements, no significant difference was observed within and between groups in all three groups. While the onset of effect was significantly shorter in the third group compared to the other two groups, the clinical effect duration was more prolonged. No significant difference was observed between all three groups regarding the postoperative recovery period and quality.

Conclusion: The 0.4 mg/kg application dose of cis-atracurium is superior to other recommended dose groups due to its high intubation quality, short onset of action, not causing any severe hemodynamic changes or side effects, and good recovery quality and duration.

Keywords: Cis-atracurium, neuromuscular block quality, general anaesthesia, nondepolarizing muscle relaxant

INTRODUCTION

The provision of anaesthesia is an essential component of healthcare worldwide. Access to safe anaesthesia is considered a fundamental individual right, and guidelines are published for its safe implementation.[1,2] Therefore, it is critical that the healthcare system can provide safe and effective anaesthesia for a wide range of surgical procedures in children and adults. However, many difficulties are encountered in providing anaesthesia, especially in the developing world, where facilities, equipment and staff training are often inadequate.[3] In general anaesthesia, patients are unconscious and do not realize their surroundings, but in practice, general anaesthesia is far beyond a state of unconsciousness. The components of general anaesthesia are analgesia, amnesia, muscle relaxation and limitation of autonomic reflexes.[4] There is no single drug used for general anaesthesia that provides all elements of general anaesthesia goals. Therefore, a combination of drugs, including volatile anaesthetics, opiates and at least muscle relaxants, is used during general anaesthesia.[4]

In anaesthesia, advances in neuromuscular muscle relaxants and the introduction of new drugs into clinical use have provided great flexibility for anesthesiologists.[5] None of the currently available muscle relaxants meets the criteria for an ideal neuromuscular blocking agent described by Savarese and Kitz.[6] Cis-atracurium Besylate (51W89 besylate, Nimbex) is the R-cis-R' isomer of Atracurium and is three times more potent. Although their muscle relaxant effects are similar, their onset of action initiates later.[7,8] Side effects observed with atracurium due to dose-dependent histamine discharge were not observed with cis-atracurium.[9]

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Although it has long been acknowledged that the onset of action of nondepolarizing muscle relaxants can be shortened by using large doses, use in these doses both increases the duration of clinical effects and increases the possibility of side effects.[10]

In our study, in isoflurane anaesthesia, using cis-atracurium at doses of 0.15 mg/kg, 0.20 mg/kg and 0.40 mg/kg, we evaluated intubation quality, maximum effect onset time, clinical effect duration, effects on hemodynamic parameters, effects on recovery and we aimed to compare side effects.

METHODS

Study Design

Our prospective thesis study, observational, single-centre study was initiated after obtaining the ethics committee's consent at the Anesthesiology and Reanimation Clinic of the Ministry of Health Ankara Training and Research Hospital. All procedures performed in our study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration (as revised in 2013) and its later amendments or comparable ethical standards.

Patients

Our study included 60 patients between the ages of 18-65, whose operating time did not exceed 2 hours, who did not have cardiovascular, pulmonary, renal, hepatic, neurological, psychiatric, neuromuscular, inflammatory or endocrine diseases and who did not use any medications that would affect the neuromuscular junction. Patients who were pregnant or suspected of pregnancy and who were taken as emergency cases were excluded from the study. Additionally, patients who required additional neuromuscular support other than induction during the operation were also excluded from the study.

Interventions and Clinical Definitions

All patients were premedicated with 10 mg diazepam intramuscularly 45 minutes (min) before the operation. Patients transferred to the operating theatre were monitored noninvasively for heart rate and blood pressure. For neuromuscular monitoring, the Train of Four (TOF)-GUARD INMT (Biometer, Denmark) acceleration monitor was placed on the arm ulnar nerve trace, the piezoelectric acceleration transducer on the thumb distal phalanx, and the skin temperature sensor on the adductor pollicis muscle, after the skin was cleansed with alcohol. Before induction of anaesthesia, the device was calibrated and then prepared to give quadruple stimulation at a frequency of 2 Hz every 12 seconds (sec). Fentanyl 1 mg/kg IV has been applied 3 min before induction. Induction was performed with propofol 2 mg/kg IV, and anaesthesia maintenance was provided with 1.5% isoflurane+50% N_2O+50% O_2. The patients were divided into three separate groups according to the dose of cis-atracurium used. 0.15 mg/kg was defined as Group 1, 0.20 mg/kg as Group 2, and 0.40 mg/kg as Group 3. The study participants were allocated to groups using the simple randomization method of sealed envelopes. Pre-operative patients were instructed to select one of the envelopes containing a group number. Cis-atracurium was administered based on the group number written inside the selected envelope. Endotracheal intubation was performed at 120 sec after neuromuscular agent application.

In the evaluation of intubation quality, the scoring system suggested by Aldrete et al.[11] was used. The intubation quality scoring tagging system is demonstrated in Table 1.

Heart rate per minute, ECG, and noninvasive pressure measurements monitored systolic and diastolic blood pressures. These hemodynamic data were recorded in the preoperative period, at the 1st, 5th, 15th, 25th, 35th and 55th minutes.

The time until 96% block developed following the administration of the muscle relaxant using the neuromuscular monitor was considered as the onset of effect time and was defined as T0 (sec). The time until 25% of the block was removed was considered the clinical effect time and was defined as T25 (min). The time until 75% of the block was removed was defined as T75 (min). The time from T25 to T75 was accepted as the recovery index and was defined as T25-75 (min).

Post-anaesthetic recovery (PAR) scoring was used to evaluate patient recovery.[11] Patients were evaluated and recorded with PAR scoring 10 min after extubation. The PAR scoring system is shared in detail in Table 2.

Table 1. Intubation quality scoring

Laryngoscopy	Vocal cords	Cough	Total score
Smooth (1)	Open (l)	None (l)	Excellent (3-4)
Medium difficulty (2)	Mobile (2)	Diaphragm movement (2)	Good (5-7)
Difficult (3)	Half sealed (3)	Straining (3)	Poor (8-10)
Impassable (4)	Fully sealed (4)	Severe cough (4)	Impassable (11-12)

Table 2. Post anaesthetic recovery (PAR) scoring		
Activity	a) The patient can move his four extremities voluntarily or on command b) The patient can move both extremities voluntarily or on command c) The patient cannot move his extremities voluntarily or on command	2 1 0
Respiratory	a) The patient can breathe deeply and cough. b) The patient is breathing intermittently or is dyspneic c) Patient is apneic	2 1 0
Circulation	a) Blood pressure is 20% different from pre-anesthesia value b) Blood pressure varies 20-50% from pre-anesthesia value c) Blood pressure is 50% different from pre-anesthesia value	2 1 0
Consciousness	a) The patient is awake b) The patient can be awakened by verbal stimuli c) Patient unresponsive to stimuli	2 1 0
Colour	a) Pink b) Pale yellow c) Cyanotic	2 1 0

Outcome

The primary outcome measure was the association of three different doses of cis-atracurium with the quality of endotracheal intubation. The secondary outcome measure was the relationship of three different doses of cis-atracurium with the duration of neuromuscular blockade and haemodynamic parameters.

Statistical Analysis

SPSS 22.0 package program was used to analyze the collected data statistically. Categorical variables were defined as number (n) and percentage (%). Continuous variables were described as mean, standard deviation, and minimum-maximum. The suitability of the variables to normal distribution was examined with the Kolmogorov-Smirnov/Shapiro-Wilk Test. The Chi-square and Fisher's Exact Test were used to compare categorical variables. Student-T test was used in groups with normal distribution, and Mann Whitney U Test was used in groups with non-normal distribution. Friedman analysis of variance was used for intragroup comparisons, and one-way analysis of variance was used for intergroup comparisons. In statistical calculations, the $p<0.05$ result was considered significant.

RESULTS

There was no significant difference in age, weight, height and gender distribution between the patients in three groups formed by applying three distinct doses of cis-atracurium. The demographic data of the patients are shared in **Table 3**.

A statistically significant difference was found between the groups regarding intubation quality ($p<0.05$). Intubation quality scores of patients in group 3 were higher than those in groups 1 and 2. Intubation score distributions between groups are demonstrated in **Table 4**.

Table 4. Intubation score distributions between groups				
Intubation quality	**Excellent, n (%)**	**Good, n (%)**	**Avarege, n (%)**	**Poor, n (%)**
Group 1	7 (35%)	11 (55%)	2 (10%)	-
Group 2	8 (40%)	9 (45%)	2 (10%)	1 (5%)
Group 3	19 (95%)	1 (5%)	-	-

The statistical studies conducted among the three groups regarding hemodynamic data measured at the 1st, 5th, 15th, 25th, 35th and 55th min after induction showed no significant difference in heart rate and mean arterial pressures ($p>0.05$). Hemodynamic data changes within the group are demonstrated in **Table 5**. Hemodynamic data changes within the group are demonstrated in **Table 5**.

Neuromuscular measurements and PAR scores of the three groups are demonstrated in **Table 6**. While there was no significant difference in the onset of effect times between the 1st and 2nd groups ($p>0.05$), a significant difference was detected between the 3rd group and the other two groups ($p<0.05$). When T25 was evaluated, the duration of the 3rd group was found to be significantly longer than the other two groups ($p<0.05$); there was no significant difference between the 1st and 2nd groups ($p>0.05$). There was no significant difference between the groups regarding T75, T25-75 and PAR recovery scores ($p>0.05$).

Table 3. The demographic data of the patients				
	Group 1 (0.15)	**Group 2 (0.20)**	**Group 3 (0.40)**	**P value**
Number of Cases, n	20	20	20	
Gender (F/M), n	14/6	11/9	16/4	
Age (year), mean±SD	39.94±11.47	49.70±13.81	40.82±12.19	0.163
Weight (kg), mean±SD	73.17±13.53	73.23±11.30	63.94±11.12	0.065
Height (cm), mean±SD	163.64±7.05	163.29±8.18	159.41±7.32	0.073

Table 5. Heart rate and mean arterial pressure changes according to time points within the group

	Group 1 n=20	Group 2 n=20	Group 3 n=20
Heart rate			
Preoperative, mean±SD	83.42±9.29	74.66±6.85	88.50±12,43
Ind. after 1 min., mean±SD	85.15±7.22	72.94±9.87	88.35±20.82
Ind. after 5 min., mean±SD	83.26±9.17	76.77±9.82	87.00±19.82
Ind. after 15 min., mean±SD	81.10±10.10	74.00±10.15	87.90±15.35
Ind. after 25 min., mean±SD	84.73±7.06	74.44±10.78	85.80±16.24
Ind. after 35 min., mean±SD	81.36±9.82	73.00±8.31	83.90±15.79
Ind. after 55 min., mean±SD	81.68±11.04	77.77±9.50	87.70±16.25
Intragroup P value	0.815	0.429	0.867
Mean arterial pressure			
Preoperative, mean±SD	98.94±11.97	100.89±11.90	89.96±17.02
Ind. after 1 min., mean±SD	92.37±16.14	86.06±22.17	83.88±15.92
Ind. after 5 min., mean±SD	86.49±15.75	90.88±20.69	92.59±20.37
Ind. after 15 min., mean±SD	86.54±13.97	93.94±20.59	86.60±17.28
Ind. after 25 min., mean±SD	88.38±14.00	93.11±17.20	82.21±18.89
Ind. after 35 min., mean±SD	88.38±14.82	93.67±13.60	87.39±16.99
Ind. after 55 min., mean±SD	92.67±14.81	89.61±17.13	86.76±14.33
Intragroup P value	0.056	0.124	0.829

Ind.: induction

Table 6. Neuromuscular measurement comparisons between groups

Group	T0, mean±SD	T25, mean±SD	T75, mean±SD	T25-75, mean±SD	PAR, mean±SD
1	199.78±52.54	56.26±12.34	90.84±32.58	15.05±10.34	8.36±1.46
2	181.11±39.97	63.44±8.48	95.16±19.60	13.27±7.58	8.61±1.42
3	102.25±34.32	78.45±18.93	99.60±17.76	10.35±5.80	8.75±1.37

DISCUSSION

One of the crucial developments in anaesthesia practice is the effort to find a muscle relaxant with ideal properties. The ideal features expected from ideal muscle relaxants are that they have a short onset time and high effectiveness, provide an excellent and good intubation quality, have minimal side effects and no cumulative effect, have no pharmacologically active metabolites, and can be entirely antagonised by anticholinesterases. Unfortunately, none of the muscle relaxants introduced into clinical practice to date contain all of these features. Cis-atracurium is also a product of these studies carried out to achieve the optimal. Our study aimed to find the most appropriate dose for the properties sought in an effective muscle relaxant by comparing different doses of Cis-Atracurium.

Littlejohn et al.[12] where they used thiopental or propofol and fentanyl as induction agents in their study, displayed that excellent and/or good intubation conditions were achieved in 120 sec with a dose of 0.15 mg/kg cis-atracurium. Bluestein et al.[13] conducted a similar study using midazolam in induction and obtained excellent intubation conditions in 120 sec with a dose of 0.15 mg/kg cis-atracurium. The results obtained by these two researchers at a dose of 0.20 mg/kg differ. While Littlejohn rated the intubation conditions at 90 sec as good/average, Bluestein found them to be excellent/good. The difference between the intubation conditions in these two studies was attributed to Bluestein's use of midazolam in induction.[12-14] Schmautz,[15] another researcher who investigated the intubation conditions of cis-atracurium, also found the 0.20 mg/kg dose for 90 sec to be weaker. Schmautz and Littlejohn, whose study results were similar, did not apply midazolam in induction. When evaluating the intubation conditions of cis-atracurium, the common opinion of all researchers is that better intubation conditions are provided at higher doses. Although this feature is valid for all muscle relaxants, the point to be considered is the undesirable effects of increasing the dose. Therefore, in our study, we paid attention to this issue and investigated the doses of 0.15 mg/kg, 0.20 mg/kg and 0.40 mg/kg of cis-atracurium. When perfect and good intubation conditions were compared in our study in which we used propofol/fentanyl in induction, we did not find a statistically significant difference between all three dose groups ($p>0.05$). However, when we evaluated only perfect intubation conditions, we found the 0.40 mg/kg dose of cis-atracurium superior to the other two dose groups. The difference was statistically significant ($p<0.01$). At the dose of 0.40 mg/kg, perfect intubation conditions were achieved in almost all patients in 95% (19/20), while at the dose of 0.20 mg/kg, perfect intubation conditions were achieved in 40% (8/20), and at the dose of 0.15 mg/kg, perfect intubation conditions were achieved in 35% (7/20).

It has been reported that a complete block of the adductor pollicis muscle is not required to ensure good intubation conditions, and relaxation in the vocal cords occurs before.[16-18] Non-depolarising block is based on a dynamic balance in which acetylcholine and muscle relaxant molecules compete for binding sites on the receptor. Thus, the frequency of activation of receptors by acetylcholine decreases as the concentration of the muscle relaxant increases.[16] In the 3rd group, the onset of the effect was shorter compared to the other two groups, and the block in the vocal cords started earlier, ensuring that the intubation conditions were excellent in this group.

As with every newly introduced drug, many studies have been conducted to reveal the dose-dependent hemodynamic and side effect profile of cis-atracurium. In the clinical studies conducted by Bryson and Faulds,[19] they detected 0.4% bradycardia, 0.2% hypotension, 0.2% flushing, 0.2% bronchospasm and 0.1% rash, and reported no side effects above 1%.[19] In Lepage and Lien's[9,14] studies in adult patients under thiopental sodium / fentanyl / midazolam anaesthesia, there were no significant changes in mean arterial pressure and heart rate at doses up to 4 mg/kg. In Lien's[9] study, changes in mean arterial pressure and heart rate were observed to increase or decrease by 3%.[9] In their study on patients with coronary artery disease, Reich and Konstadt,[20] who investigated the hemodynamic effects of cis-atracurium, found a decrease of at most 20% in mean arterial pressure with cis-atracurium at doses of 0.1 and 0.3 mg/kg. In studies investigating the hemodynamic changes of cis-atracurium compared to vecuronium, no difference was found between both agents, and both drugs' hemodynamic stability was demonstrated.[21,22] According to Lepage and Lien,[9,14] benzylisoquinoline compounds, metabolites of cis-atracurium, cause mild to moderate hemodynamic changes through stimulation of histamine release. Cis-atracurium at doses of 4 mg/kg and lower does not cause a significant change in dose-related mean plasma histamine levels, although there is a considerable variation between patients. In a study by Lepage,[14] a significant increase in mean plasma histamine concentration was observed 2 min after rapid administration of cis-atracurium. Although a two-fold or more increase in histamine levels was observed at doses of 1-2 mg/kg, histamine-related clinical findings did not occur. Our study evaluated the average arterial pressures and heart rates of all three dose groups. No significant difference was detected either within or between groups. No clinical or hemodynamic changes due to histamine discharge were found in the patients of all 3 groups. Accordingly, when we evaluate it together with the results of previous studies on this subject, we see that the results of our study are compatible with the literature.

A common use of cis-atracurium is in intensive care patients. In the studies conducted by Meretoja et al.[23] no central nervous system-related side effects or cerebral excitation were observed in any patients who underwent elective surgery or were hospitalised in the intensive care unit and received cis-atracurium infusion.[24] In our study, no side effects identified in the literature were observed in any of the three groups.

Another research conducted on cis-atracurium measured and evaluated data on dose-dependent neuromuscular blockade.[7,14] According to Lepage and Belmont,[7,14] depending on the dose, the degree and duration of neuromuscular blockade increases while the period to onset of effect decreases. During barbiturate or propofol anaesthesia, 99-100% pulse suppression was achieved in 4.6-5.8 min with a 0.1 mg/kg dose. The results of numerous studies on this subject have shown that higher doses of cis-atracurium provide maximum suppression in a shorter time. 0.15 mg/kg in 2.4-3.7 min,[13,15,25] 0.20 mg/kg in 2.7-3.8 min,[7,13-15] 0.40 mg/kg in 1.9 min[7] achieving maximum suppression is the dose-response times observed in the literature. A different study on this subject was prepared by Sorooshian.[26] In this study, based on healthy adults, the time required for a maximum block with 0.1 mg/kg Cis-Atracurium is prolonged by 1 minute in elderly patients and patients with renal insufficiency. At the same time, it is shortened by 1 minute in patients with end-stage liver disease. However, the maximum block is not affected in any of these patients during general anaesthesia.[26] In our study, in which we compared the maximum effect duration and clinical effect duration in 3 different doses of cis-atracurium using the TOF-GUARD monitor, we found the maximum effect duration significantly shorter and the clinical effect duration significantly longer in the patients in the 3rd group compared to the other two groups. The results we reached are consistent with those found in previous dose studies on this subject. However, in one patient each in the 1st and 2nd groups, we had to apply additional muscle relaxants even though the TOF-GUARD monitor showed maximum suppression at the 20th and 25th min of the operation. We found the post-tetanic count (PTC) responses we measured before drug administration to be 6 for the patient in group 1 and 7 for the patient in group 2. Afterwards, the operation continued and was completed. In our study, we excluded these two patients' hemodynamic data and neuromuscular block values from our statistical evaluations. Additionally, these patients also underwent abdominal surgery. The patient in the first group was a female patient weighing 95 kg, and the patient in the second group was a female patient

weighing 110 kg. We believe that multifactorial factors such as failure to comply with cold chain rules in storing muscle relaxants, difficulty in surgical manipulation in overweight patients, especially in abdominal operations, and insufficient anaesthetic depth for the patient during maintenance of general anaesthesia caused this incident.

The shortening of the maximum effect time and the prolongation of the clinical effect of the muscle relaxant used in higher doses are due to the fact that it creates more molecular load at the neuromuscular junction, and thus, its concentration in the plasma and synaptic gap is higher.[27] As suggested by Bowman et al.[28] according to the mass effect law, diffusion to binding points occurs rapidly, and the rate of first block development is faster. In their studies, Belmont and Lepage[7,14] found the average recovery time of 25-75% to be 8-13 min in adults for 0.1 mg/kg cis-atracurium and showed that the recovery time between doses of 0.1-0.4 mg/kg was independent of the dose. In another article on recovery time and quality, Brandom[29] reported that when an overdose of cis-atracurium (0.86 mg/kg) was given to an infant, recovery occurred within 10-15 min. In our study, no significant difference was found between the groups when clinical recovery times were compared, and recovery occurred within 10-15 min in all patients. Recovery from anaesthesia occurs with the return of the effects of the anaesthetic drugs and techniques used, and, in addition to the patient's physical characteristics, factors such as premedication dose and elimination of volatile agents used to affect the quality of recovery. In our study, we monitored the patients taken to the recovery room with PAR scoring 10 min later. Since the premedication and anaesthetic techniques of the patients were kept standard, the prolonged effects of muscle relaxants and the characteristics of the patients were effective in our follow-up. No significant difference was found in terms of recovery quality in the patients of all 3 groups.

Limitations

Among the limitations of our study is that it is single-centred and has a limited number of patients. Although our patients had similar demographic characteristics, they were not a single surgical unit patient undergoing the same operation. Failure to perform a similar surgical procedure may affect the need for muscle relaxants. Patients were not classified according to the surgical procedure. Additionally, we excluded patients who required additional muscle relaxants during the operation. We did not take these into consideration. More extensive prospective observational studies are needed on this subject.

CONCLUSION

As a result, although the 0.15 and 0.20 mg/kg application doses of cis-atracurium provide the mediocre conditions expected from a muscle relaxant, the 0.40 mg/kg dose provides excellent intubation conditions at a high rate (95%), medium clinical effect duration, significant hemodynamic effects, and significant hemodynamic effects. It is the most appropriate dose for clinical use as it does not cause any alterations, does not cause any complications during the recovery period and does not cause any significant side effects.

ETHICAL DECLARATIONS

Ethics Committee Approval

Since the study was old, local ethics were taken from the Ministry of Health Ankara Training and Research Hospital Ethics Committee at that time and published as a thesis. However, the records could not be accessed due to changes in hospital data processing.

Informed Consent

In this study, each patient provided informed consent prior to participation.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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The predictive role of systemic immune-inflammation index in non-ischemic cardiomyopathy

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ABSTRACT

Aims: The systemic immune-inflammation index (SII), a useful marker of systemic inflammation, has been shown to be associated with cardiovascular diseases in previous studies. Inflammation is known to have a significant role in heart failure, but no study has evaluated the relationship between inflammatory parameters and prognosis in patients with non-ischemic cardiomyopathy (NICM). This study aimed to explore the relationship between SII and long-term mortality in patients with non-ischemic cardiomyopathy.

Methods: The study enrolled 326 consecutive patients with NICM. The median 25-month follow-up mortality results of the patients were recorded retrospectively. SII, a combined index based on the count of three parameters, was calculated as follows: neutrophil count x platelet count/lymphocyte count. Patients with a higher SII value than the median SII were accepted as having a high SII, and the remaining patients were defined as having a low SII. The survival curves of the patients with high and low SII values during the study period were analyzed using the Kaplan-Meier method.

Results: The mean age of the participants was 46.6 years. The mean SII value was 598.4 in patients without mortality and 722.7 in those with mortality. In the multivariate logistic regression analysis, SII was found to be an independent predictor of mortality. The median SII value of the patients who participated in the study was 644. Upon dividing the patients into two groups according to the median SII value, the mortality rate was determined to be 48.4% in the high SII group and 27.4% in the low SII group.

Conclusion: High SII values were observed to be associated with long-term mortality in patients with NICM. SII, which is easily accessed and simply calculated, can be used to predict mortality risk in these patients. Prospective and larger cohort studies are needed to clarify the causality of this relationship.

Keywords: Heart failure, non-ischemic cardiomyopathy, systemic immune-inflammation index

INTRODUCTION

Non-ischemic cardiomyopathy (NICM) is a myocardial disease characterized by left ventricular dilatation and contractile dysfunction in the absence of previous myocardial infarction, pathologies obstructing coronary blood flow, and valvular disease associated with systolic dysfunction.[1,2] The incidence of NICM in the general population varies between 1/2,500 and 1/250.[3] Both genetic and environmental factors are involved in the etiopathogenesis of NICM, and the end point is systolic dysfunction with dilatation.[4] The most common symptoms in patients are circulatory disorders due to heart failure (HF), arrhythmias, and thromboembolic events.[5] NICM is more common in middle-aged individuals and men, and it is among the common causes of heart transplantation, especially in Western societies.[6,7] In recent years, favorable improvements in terms of survival have been observed due to advances in diagnosis, classification, and treatment methods (pharmacological, mechanical support, and heart transplantation).[8] Nevertheless, the risk of HF, ventricular arrhythmias, and related mortality is not low in this patient group, with a 10-year survival rate lower than 60%.[4,6,9,10] Risk stratification in patients with NICM is essential in predicting poor clinical outcomes. Therefore, it is important to investigate markers that will detect poor clinical outcomes at an earlier period and implement preventive treatment.

Patients with NICM, contrary to those with ischemic cardiomyopathy, are younger and have fewer comorbidities. Therefore, age and comorbidity have less effect on poor clinical outcomes in these patients,[10] and survival is more related to the aggravation of HF and the

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associated conditions.[9,10] Previous studies have shown that several parameters, such as low left ventricular ejection fraction (LVEF) and high brain natriuretic peptide (BNP) levels are associated with a poor prognosis.[10,11] However, there is limited data showing that some systemic inflammatory parameters are also associated with poor clinical outcomes in patients with NICM. Several studies conducted with these patients have shown a relationship between the degree of myocardial disease and biochemical parameters indicating an inflammatory response, such as C-reactive protein (CRP), C3 and C4 complement, and ceruloplasmin.[12,13] In addition, high CRP values have been associated with poor survival in these patients.[14] In recent years, the systemic immune-inflammation index (SII), which is a much better and easily accessible and calculable biochemical marker of systemic inflammation, has been investigated in various cardiovascular diseases. SII can be simply derived from the counts of neutrophils, lymphocytes, and platelets. These three immune cells are collected via a hemogram, which is a basic laboratory test.[15] SII has been previously investigated as a potential marker for various diseases such as cancer. In addition to cancer, several studies have been published on cardiovascular diseases such as chronic coronary syndrome, HF, and acute coronary syndrome in terms of poor clinical outcomes.[16-19] However, there is no scientific evidence that SII is an independent risk factor for poor prognosis in patients with NICM. The aim of the current study was to investigate the relationship between SII and mortality in patients with NICM.

METHODS

Ethics

The study was carried out with the permission of the Scientific Research Evaluation and Ethics Committee of Ankara City Hospital (Date: 12.09.2023, Decision No: E1-23-4000). We obtained an informed consent form from all patients for the procedure. All procedures were undertaken in accordance with ethical rules and the principles of the Declaration of Helsinki.

Study Population

The study sample consisted of 326 consecutive patients presenting to our hospital between March 2019 and February 2022, for whom severe coronary artery disease was excluded by diagnostic procedures and a diagnosis of NICM was established. Patients with an acute infection, hematological diseases, malignancies, systemic inflammatory and autoimmune diseases, severe valvular heart disease and/or prosthetic heart valves, chronic kidney disease, chronic liver disease, restrictive and hypertrophic cardiomyopathy, or antibiotic use, as well as those who had received blood or blood product replacement within the last three months, were excluded. The median 25-month follow-up mortality results of the patients were recorded retrospectively. Since the study was planned retrospectively, written informed consent could not be obtained from the patients.

Analysis of Patients' Data and Laboratory Analysis

Demographic characteristics, laboratory parameters, and cardiovascular risk factors were obtained from the hospital data system. Venous blood samples were collected at the time of presentation to the hospital. Biochemical measurements were performed using a molecular analyzer in the hospital's biochemistry laboratory. Complete blood count parameters were measured using an autoanalyzer. At presentation, transthoracic echocardiography was performed, and LVEF was calculated with the modified Simpson's method in the apical two and four-chamber views in both end-diastole and end-systole.

Definitions

SII is a combined index based on the count of three parameters: neutrophils, platelets, and lymphocytes. SII was calculated as follows: neutrophil count x platelet count / lymphocyte count. The diagnosis of NICM was based on the absence of severe stenosis of the coronary vessels by various imaging modalities, including conventional coronary angiography, coronary computerized tomography angiography, or cardiac magnetic resonance imaging, as well as the confirmation of reduced LVEF by echocardiography. Hypertension (HT) was defined as current antihypertensive use, a systolic blood pressure of 140 mmHg, or a diastolic blood pressure of ≥90 mmHg. Patients with a fasting blood glucose value of >126 mg/dl, those with a documented diabetes mellitus (DM) diagnosis, or those using oral antidiabetics or insulin at the time of presentation were accepted as diabetic. Current tobacco users were defined as smokers. Effort-induced dyspnea was classified according to the New York Heart Association (NYHA) functional classification.

Statistical Analysis

Analyses were performed using SPSS Statistics version 24.0 for Windows (SPSS Inc, Chicago, IL). The distribution patterns were defined using the Kolmogorov-Smirnov method. Data were presented as mean and standard deviation, median and interquartile range, or percentages as appropriate. While the Student's t-test was used to compare data with a normal distribution, the Mann-Whitney U test was used to compare the data without a normal distribution. Categorical variables were compared with the chi-square test. The effects of different variables on clinical outcomes were assessed by Cox regression analysis. The

variables for which the unadjusted P value was <0.10 in the univariate Cox regression analysis were identified as potential risk markers and included in the multivariable Cox regression model. Patients with a higher SII value than the median SII were accepted as having a high SII, and the remaining patients were defined as having a low SII. The survival curves of the patients with high and low SII values during the study period were analyzed using the Kaplan-Meier method, and statistical assessment was performed using the log-rank test. A p value of <0.05 was considered statistically significant for all analyses.

RESULTS

A total of 326 patients were included in the study. The patients were divided into two groups: those with and without mortality. The mean age of the patients was 46.6 years, and 188 (57.7%) were male. The median follow-up period of the patients was 25 (interquartile range: 20-38) months. Of the patients, 124 (38%) had mortality during the follow-up period. The patients' baseline demographics and clinical and laboratory parameters are shown in Table 1. A significant difference was found between the mortality and non-mortality groups in terms of gender (p=0.001). There was no significant difference in terms of age, DM, HT, or smoking between the groups. The group with mortality had a lower LVEF (24.5±12.4 vs. 22.1±11.9%; p=0.005). In addition, systolic pulmonary artery pressure (sPAP) was significantly higher in this group (40.32±15.5 vs. 45.4±12.6 mmHg; p=0.001). The NYHA functional capacity was lower in the mortality group (p<0.001). Blood urea nitrogen, BNP, and SII were significantly higher in the mortality group. The blood sodium level, neutrophil count, and lymphocyte count were significantly higher in the non-mortality group.

A stepwise multivariate COX regression analysis was performed to assess the independent predictors of mortality and revealed that SII was an independent predictor of mortality (hazard ratio: 3.566, confidence interval: 1.922-5.184; p<0.001). sPAP, NYHA functional class, blood sodium level, and BNP were other independent predictors of mortality (Table 2). The median SII value of the patients included in the study was 644, and the patients were further evaluated in high SII and low SII groups according to the median SII value. The mortality rate was 48.6% for the high SII group and 27.4% for the low SII group (p<0.001). Subsequently, the Kaplan-Meier mortality curves for the low and high SII groups revealed worse mortality for the patients with a high SII (log-rank p<0.001, Figure 1).

Table 1. Comparison of groups according to the baseline demographics and clinical and laboratory characteristics

Variables	Non-mortality group (n=202)	Mortality group (n=124)	p value
Age	46.5±11.8	46.9±9.8	0.244
Male, n (%)	111 (54.9)	77 (62.3)	0.001
Diabetes mellitus, n (%)	49 (24.3)	31 (25.0)	0.312
Hypertension, n (%)	43 (21.3)	27 (21.8)	0.285
Smoking, n (%)	25 (12.4)	15 (12.1)	0.683
LVEF (%)	24.5±12.4	22.1±11.9	0.005
sPAP (mmHg)	40.32±15.5	45.4±12.6	0.001
NYHA functional class	3 (2-4)	3 (3-4)	<0.001
Glucose (mg/dl)	101.12 ±24.54	102.43±12.56	0.874
Creatinine (mg/dl)	1.04±0.63	1.09±0.45	0.832
BUN (mg/dl)	43.23±11.12	46.23±13.11	0.003
Na (mEq/L)	141.2±8.3	135.4±6.7	0.001
K (mEq/L)	4.1±0.6	4.1±0.9	0.819
AST (U/L)	22.12±12.45	23.02±11.43	0.738
ALT (U/L)	19.14±11.62	20.85±10.55	0.629
BNP (ng/L)	869.1±342.6	1453.5±543.5	<0.001
Hemoglobin (gr/dl)	12.5±4.5	12.3±5.6	0.583
WBC count (10^9/L)	8.45 (6.45-10.23)	8.23 (6.94-9.25)	0.136
Neutrophil count (10^9/L)	5.36 (3.94-6.14)	5.24 (3.89-6.22)	0.045
Lymphocyte count (10^9/L)	1.95 (1.34-2.36)	1.67 (1.22-2.08)	0.001
Platelet count (10^9/L)	245.6 (191.2-276.4)	236.9 (188.4-268.4)	0.144
SII	598.4 (415.5-899.4)	722.7 (488.6-1033.5)	<0.001
ICD, n (%)	138 (68.3)	87 (70.1)	0.235
CRT-D, n (%)	78 (38.6)	47 (37.9)	0.433

LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; NYHA, New York Heart Association; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; BNP, brain natriuretic peptide; WBC, white blood cell; SII, systemic immune inflammation index; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy defibrillator.

Table 2. Results of univariate and multivariate logistic regression analyses for the prediction of mortality

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.007 (0.985-1.015)	0.267	-	
Male gender	2.143 (1.231-2.856)	0.002	1.879 (0.984-3.444)	0.088
LVEF	1.836 (1.114-2.563)	0.006	1.455 (0.934-2.544)	0.122
sPAP	2.345 (1.522-3.122)	<0.001	2.455 (1.655-3.655)	<0.001
NYHA functional class	2.834 (1.954-3.433)	<0.001	3.444 (2.421-4.124)	<0.001
BUN	1.243 (1.122-1.434)	0.004	1.199 (0.849-1.656)	0.188
Blood sodium	2.614 (1.399-3.256)	<0.001	2.433 (1.123-3.676)	0.001
BNP	3.623 (1.983-6.655)	<0.001	3.231 (1.844-5.624)	<0.001
SII	3.987 (2.124-5.733)	<0.001	3.566 (1.922-5.184)	<0.001

HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; NYHA, New York Heart Association, BUN, blood urea nitrogen; BNP, brain natriuretic peptide; SII, systemic immune-inflammation index.

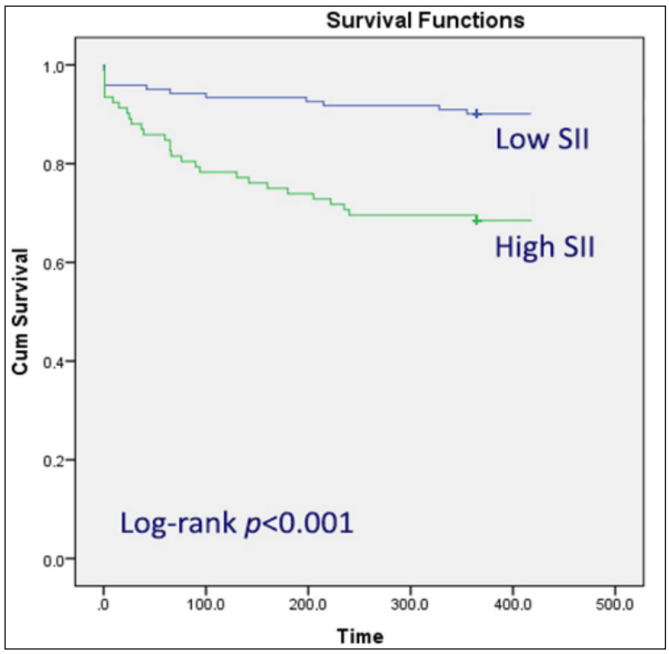

Figure 1. Kaplan-Meier survival curves (SII, systemic immune inflammation index)

DISCUSSION

The present study was designed to investigate the association between SII and long-term mortality in patients with NICM, and the results suggested that a high SII could predict mortality in this patient group regardless of other factors. We consider that our study is important because it is the first in the literature to reveal such an association and the potential of SII as a readily available marker for prognosis in NICM.

Heart failure is a chronic pathophysiological process with high mortality rate. Older age is one of the strongest determinants of mortality.[20] However, NICM patients are diagnosed at younger ages. This patient group has less comorbidities. Therefore, other predictors besides age and comorbidity should be investigated to predict mortality risk. In various studies, a relationship between heart failure and inflammatory parameters has been observed.[16,20,21] Therefore, identification of reliable inflammatory markers that reflect inflammatory burden and predict clinical outcomes is of great clinical importance. In another study, lower lymphocyte counts in patients with heart failure have a higher mortality rate.[22]

Despite advances in the treatment of patients with NICM, especially in the last decade, HF remains the most common cause of mortality.[23] Having simple markers that can be used to predict both early and late prognosis in NICM can allow clinicians to identify patients with poor prognosis and perform their treatment and follow-up more closely. BNP is one of the most powerful parameters for prognosis prediction in patients with HF.[21] Similar to the results of previous studies, our study showed a significant relationship between a high BNP value and mortality.[24] However, the difficulty of access to this parameter and its high cost limits its use in clinical practice. In addition, BNP values may be affected by differences in age, gender, body weight, and laboratory kits.[25] This has increased the importance of easily accessible and low-cost parameters in patient follow-up and led researchers to explore more possible parameters.

Recent studies have shown that HF, which is the main prognostic marker in patients with NICM, is closely related to the inflammatory response. In vitro and in vivo studies have shown that inflammation is a central pathophysiological process in the whole spectrum of HF, whether it is acquired or genetic and whether acute or chronic, and is associated with poor outcomes.[26,27] Studies have shown that cytokines such as tumor necrosis factor-alpha and interleukin-6 increase in relation to myocardial apoptosis and necrosis in these patients, and this is associated with poor clinical outcomes.[28] In another study, CRP, which is frequently used as an indicator of inflammatory response, was shown to be negatively associated with survival in patients with NICM.[14] Although these inflammatory parameters are highly predictive of the

prognostic outcomes of patients, their clinical use is limited due to their high costs and difficult access. SII, which has been associated with the prognosis of many cardiovascular diseases in recent years, is a new inflammatory biomarker that can be easily calculated based on a complete blood count analysis. In our study, high values of SII, which shows both immune and inflammatory responses, were found to be useful in predicting poor prognosis and increased long-term mortality in patients with NICM.

SII has been found to be an indicator in the prognosis prediction of some cardiovascular diseases.[16,19] This index is based on the counts of neutrophil, lymphocyte, and platelet cells, which are responsible for both inflammatory and immune-thrombotic responses in blood circulation. However, the mechanism of how this index has an adverse prognostic association with HF and other cardiovascular diseases is yet to be clarified.[16]

In the present study, the multivariate regression analysis performed showed that high SII, low blood sodium, high sPAP, lower NYHA functional capacity, and high BNP values were also independent risk factors in predicting poor prognosis in patients with NICM. These findings are consistent with previous studies.[21,24,29] A commonality among the independent risk factors in our study is that they are all typical characteristics of patients with severe HF. Given that HF is the most common cause of mortality in NICM, the detection of these risk factors in severe HF can explain the relationship observed in our study.

Limitations

This study has several limitations. The primary limitation is the absence of patient randomization and possible selection bias due to the retrospective design. Consecutive patients were included in the study to eliminate this bias. In addition, we did not have data on the causes of mortality, which would have made the study more powerful. Therefore, it was not possible to evaluate cardiovascular or non-cardiovascular mortality outcomes. Finally, the patients included in the study were not classified according to the NICM etiologies.

CONCLUSION

The results of this study showed that SII, which can be easily calculated with a hemogram routinely obtained at the time of presentation, could be used to predict long-term prognosis in patients with NICM. A high SII value was found to be an independent risk factor for long-term mortality. SII can be used as a practical biochemical marker for the prediction of poor prognosis in patients with NICM.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 12.09.2023, Decision No: E1/4000/2023).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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Evaluation of clinical characteristics and treatment patterns of patients infected with hepatitis B

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ABSTRACT

Aims: Chronic hepatitis B virus (CHB) infection causes chronic liver disease, cirrhosis, and hepatocellular carcinoma. Our study aimed to evaluate the effects of newly initiated tenofovir alafenamide fumarate (TAF) on clinical parameters in naïve and treatment-experienced patients with CHB.

Methods: This retrospective, single-center observational study was performed in the Department of Infectious Diseases and Clinical Microbiology, Kayseri City Hospital. Demographic and clinical characteristics of the cases were obtained from the outpatient clinic follow-up files. The change over time in the clinical data of all patients at the beginning, 3rd, 6th, and 12th months of TAF treatment was evaluated using One-Way Analysis of Variance in Repeated Measures (ANOVA) and Friedman Analysis of Variance in Repeated Measures, according to their compliance with normal distribution.

Results: The mean age of the patients was 56.5±12.2 years, and 59 (57.8%) were male. 70.6% of the patients had at least one additional disease, and the most common additional diseases were hypertension (29.4%) and Diabetes mellitus (23.5%). Of the 102 patients who started TAF treatment, 81 (79.4%) were treatment-experienced, and 21 (20.6%) were treatment-naïve patients. The reasons for switching to TAF treatment were osteoporosis (44.1%), the need for a more potent agent (34.3%), and low GFR (13.7). While the detectable HBV DNA rate was 38.2% at the beginning of treatment, this rate was 2.9% at the 12th month ($p<0.001$). While there was a statistically significant change in ALT, abnormal ALT, and detectable HBV DNA rates from all four follow-up periods within 12 months after the start of TAF treatment (p values <0.001), there was no significant change in AST ($p=0.081$). While the GFR level did not change statistically significantly during the follow-up period ($p=0.381$), the phosphorus level changed statistically significantly (p-value<0.001).

Conclusion: In our study, a significant improvement in detectable HBV DNA, ALT level, and phosphorus level was observed in both naive and treatment-experienced patients with the initiation of TAF.

Keywords: Chronic hepatitis B, tenofovir alafenamide fumarate, alanine transaminase, phosphorus

INTRODUCTION

According to the World Health Organization report, it was reported that approximately 296 million people were living with chronic hepatitis B (CHB) infection worldwide in 2019, and there were 1.5 million new infections every year.1 Chronic hepatitis B virus infection is the leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma.2

The main goals of HBV treatment are to stop disease progression and prevent disease-related complications by suppressing hepatitis B virus (HBV) DNA replication.3 Since complete elimination of the virus is impossible, treatment is usually lifelong. Nucleoside/nucleotide analogs approved to date for the treatment of HBV in humans include lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LdT), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF).4

Drugs with high barriers against the development of antiviral resistance in HBV treatment are ETV, TDF, and TAF. These are drugs with high treatment success that effectively suppress HBV-DNA in the majority of patients. TDF is converted to tenofovir by hydrolysis and then phosphorylated to tenofovir diphosphate by cellular enzymes.5 Side effects associated with TDF include lactic acidosis, severe hepatomegaly with steatosis, osteoporosis, and nephropathy. As the CHB population ages, more patients will likely develop bone loss.6-8

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TAF is the last licensed treatment option for HBV treatment in our country and in the world. Our country's reimbursement scope included it with the Health Implementation Communiqué dated June 2020. First, it is approved for use in patients whose use of TDF is limited due to osteoporosis and nephropathy. However, it can be used today in all CHB patients requiring treatment.9

This study aimed to evaluate the effect of TAF on some clinical parameters, GFR, and phosphorus levels in patients with CHB.

METHODS

This retrospective, single-center observational study was performed in the Department of Infectious Diseases and Clinical Microbiology, Kayseri City Hospital. The study was approved by the Kayseri City Hospital Clinical Researches Ethics Committee (Date: 28.11.2023, Decision No: 953). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

CHB patients aged 18 years and over who started TAF treatment with appropriate indications between January 2020 and October 2023 at the infectious diseases and clinical microbiology outpatient clinic of Kayseri City Hospital were retrospectively examined. Demographic and clinical characteristics of the cases were obtained from the outpatient clinic follow-up files. The criteria for conversion to TAF were determined as follows: 1. Hypophosphatemia; serum phosphorus level <2.5 mg/dl, 2. osteoporosis; T score on BMD <-2.5, 3. low GFR; creatinine clearance <60 ml/min and 4. detectable HBV DNA; HBV DNA level > 20 IU/ml. Elevated alanine aminotransferase (ALT) was defined according to AASLD criteria (>35 U/L in men, >25 U/L in women).10 Liver fibrosis staging and histological activity index (HAI) scores were evaluated using the Modified Ishak Scoring System.11

Statistical Analysis

Categorical data were presented as frequency distributions and percentages, and continuous variables were presented as mean (± standard deviation) and median (minimum and maximum). The chi-square test was used to compare categorical data. The normal distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test. Normally distributed glomerular filtration rate (GFR) and serum phosphate level were compared using the Paired-Samples T-test. AST, ALT, and normalized ALT that did not show normal distribution were compared using the non-parametric Wilcoxon test. Repeated measurements of normally distributed glomerular filtration rate (eGFR) and phosphate level were evaluated using "one-way analysis of variance in repeated measurements (ANOVA)." Mauchly's test of sphericity was used to test the ANOVA assumption of sphericity. In Mauchly's sphericity test, when p <0.05, the sphericity assumption was considered not fulfilled, and the epsilon value was checked. When the epsilon value was less than 0.75, the "Greenhouse-Geisser" value was used, and when it was more significant, the "Huynh-Feldt" value was used. The data were then evaluated at the 0.05 significance level using the Bonferroni correction. AST, ALT, and normalized ALT values that did not show normal distribution were assessed using "friedman analysis of variance in repeated measurements." In the data with a difference according to the friedman test, the "Wilcoxon paired two sample test" was used to find out which data caused the difference.

RESULTS

The average age of the patients was 56.5±12.2 years, and 59 (57.8%) were male. 70.6% of the patients had at least one comorbidity, and the most common comorbidities were hypertension (29.4%) and Diabetes mellitus (23.5%). Of the 102 patients who started TAF treatment, 81 (79.4%) were treatment-experienced, and 21 (20.6%) were treatment-naïve patients. The reasons for switching to TAF treatment were osteoporosis (44.1%), the need for a more potent agent (34.3%), and low GFR (13.7). The patient's baseline characteristics are presented in **Table 1**.

The change in HBV DNA detection over time in all patients at the beginning, 3, 6, and 12 months of TAF treatment is presented in **Figure 1**. While the detectable HBV DNA rate was 38.2% at the beginning of treatment, this rate was 2.9% at the 12th month (p<0.001).

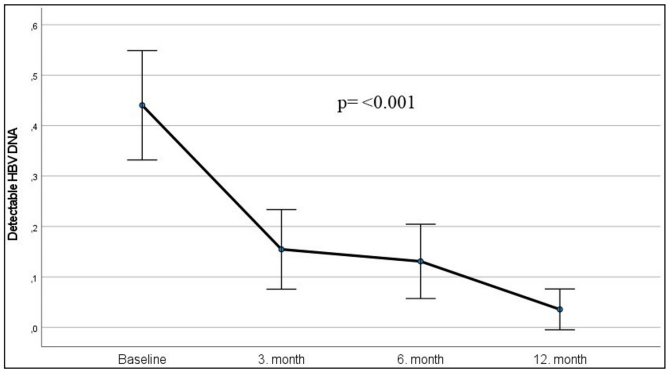

Figure 1. The changes in detectable HBV DNA over time

The change graph in the patients' AST, ALT, eGFR, and phosphorus levels at the beginning of TAF treatment and the 3rd, 6th, and 12th months is presented in **Figure 2**. While there was a statistically significant change in ALT, abnormal ALT, and detectable HBV DNA rates obtained from all four follow-up periods within 12 months after the start of TAF treatment (p values<0.001), there was no significant change in AST value (p=0.081) (**Table 2**). ALT level, abnormal ALT, and detectable HBV DNA rates decreased significantly during the follow-up period.

Table 1. Baseline characteristics of the patients (n=102)

Characteristics	n (%)
Age, years, (mean± Std)	56.5±12.2
Male mean	59 (57.8)
Comorbidities	72 (70.6)
Diabetes	24 (23.5)
Hypertension	30 (29.4)
COPD	10 (9.8)
Cardiovascular disease	9 (8.8)
CKD	5 (4.9)
Cirrhosis	5 (4.9)
Malignancy	13 (12.7)
Transplant patient	7 (6.9)
Rheumatological disease	19 (18.6)
Previous treatment	
Naïve	21 (20.6)
Tenofovir disoproxil fumarate	59 (57.8)
Entecavir	32 (31.4)
Lamivudine	22 (21.6)
Tenofovir disoproxil fumarate+entecavir	6 (5.9)
Causes for the initiation of TAF treatment	
Proteinuria	10 (9.8)
Osteoporosis	45 (44.1)
Phosphorus level <2.5, mg/dl	2 (2)
eGFR <60, mL/min/1.73 m²	14 (13.7)
Switching to a more potent drug	35 (34.3)
Detectable HBV DNA	39 (38.2)
Prevalence of high ALT	27 (26.5)
HAI (Mean± Std)	6.3±2.2
Fibrozis (Stage) (Mean±Std)	2.8±1.3
White blood cell count (10^3/mm³) (mean±Std)	7±1.9
Thrombocyte (10^3/mm³) (mean±Std)	234.7±71.5
eGFR (mL/min/ 1.73 m²) (mean±Std)	88.9±24.1
Phosphorus (mg/dl) (mean±Std)	3.2±0.68
Hemoglobin (mg/dl) (median, IQR)	14.9 (13.5-15.9)
AST (U/L) (Median, IQR)	21 (17-28)
ALT (U/L)(Median, IQR)	18 (15-30.5)

COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, HAI: Histological activity index, eGFR: Estimated glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, IQR: Interquartile ranges, Detectable HBV DNA: HBV DNA level >20 IU/ml, High ALT was defined according to AASLD criteria (>35 U/L in men, >25 U/L in women)

Table 2. Change in the AST, ALT values, and abnormal ALT level according to AASLD criteria

Factors (n)	Baseline, median (IQR)	3rd month, median (IQR)	6th month, median (IQR)	12th month, median (IQR)	Friedman Test p-value	Wilcoxon analysis p-value
AST (U/L)	21 (17-28)	21 (17-29)	20 (17-26.5)	20 (16-23)	0.081	
ALT (U/L)	21.5 (16-48)	22 (16-44.5)	19 (14-26.2)	18 (14.7-22)	<0.001	
				Baseline vs	3rd month	0.443
					6th month	0.004
					12th month	<0.001
				3rd month vs	6th month	0.002
					12th month	<0.001
				6th month vs	12th month	0.005
Prevalence of abnormal ALT (n, %)	27 (26.5)	27 (26.5)	11 (10.8)	6 (5.9)	<0.001	
				Baseline vs	3rd month	0.346
					6th month	0.008
					12th month	<0.001
				3rd month vs	6th month	<0.001
					12th month	<0.001
				6th month vs	12th month	0.059
Detectable HBV DNA (n, %)	39 (38.2)	13 (12.7)	11 (10.8)	3 (2.9)	<0.001	
				Baseline vs	3rd month	<0.001
					6th month	<0.001
					12th month	<0.001
				3rd month vs	6th month	0.317
					12th month	0.002
				6th month vs	12th month	0.005

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AASLD: American Association for the Study of Liver Diseases, IQR: Interquartile range

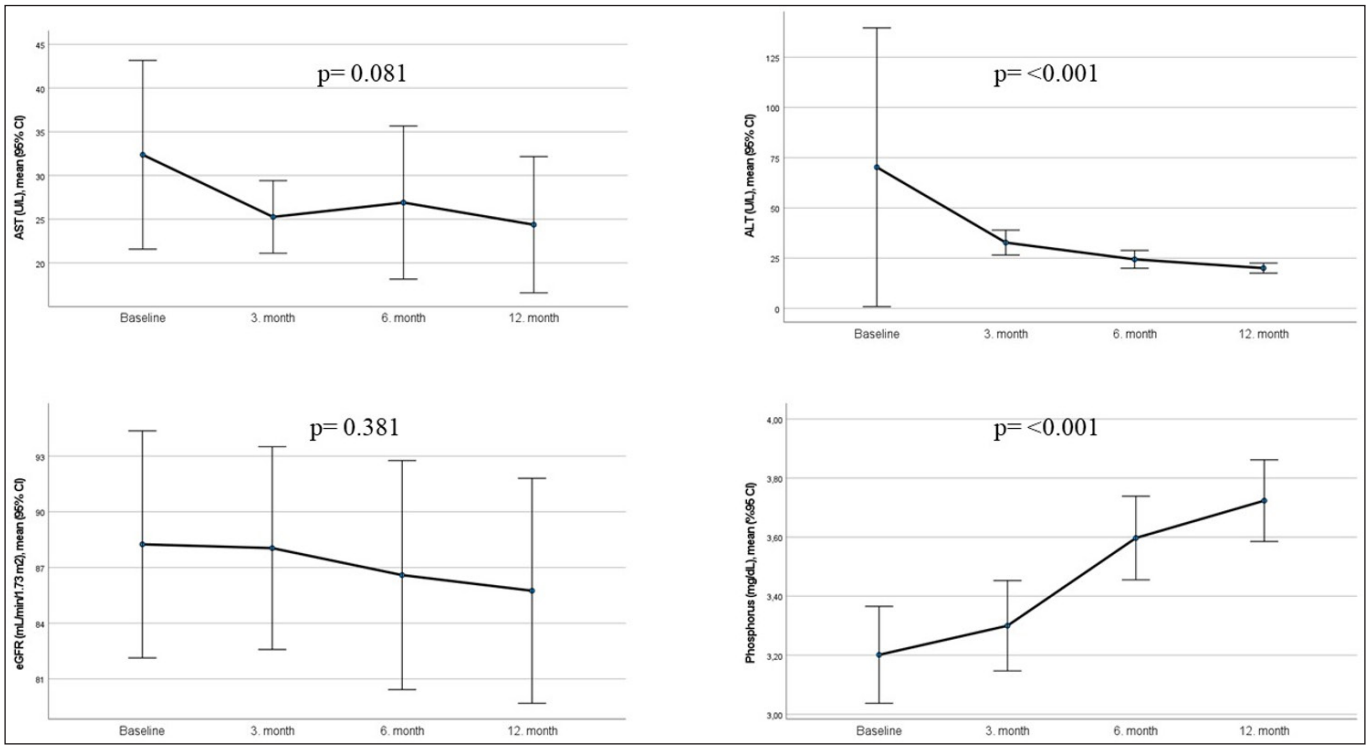

Figure 2. The changes in AST, ALT, eGFR, and phosphorus levels over time

When eGFR and phosphorus data obtained from all four follow-up periods within 12 months after switching to TAF treatment were examined, while the eGFR level did not change statistically significantly during the follow-up period (p=0.381), the phosphorus level changed statistically significantly (p-value<0.001). After starting TAF treatment, the phosphorus level increased statistically significantly (**Table 3**).

DISCUSSION

The best predictor of HBV infection treatment response is the course of HBV DNA. Achieving undetectable HBV DNA directly correlates with positive clinical outcomes.[12] In our study, the rate of detectable HBV DNA in CHB patients at 12 months was 2.9%. A high virological response was achieved in 97.1% of patients. This effective antiviral treatment can be explained by the longer plasma half-life of TAF and its more effective concentration in hepatocytes.[12]

The EASL (European Association for the Study of the Liver) 2017 clinical practice guideline on managing hepatitis B virus infection identified ALT normalization as another endpoint of long-term suppression of viral replication in treating HBV infection.[13] In our study, consistent with the literature, it was observed that median ALT values decreased significantly with the initiation of TAF. Abnormal ALT rates, according to AASLD criteria, also decreased significantly. However, it has been stated in the literature that ALT normalization may be affected by various factors such as being overweight, having low albumin, being young, and having a high cholesterol level.[12,14]

Tenofovir disoproxil fumarate has adverse effects on renal function and bone mineral density. It is known that there is a decrease in bone density and kidney function with TDF. In addition to risk factors such as age and baseline renal function, urinary excretion of low molecular weight proteins, phosphate, uric

Table 3. Change in the eGFR and phosphorus levels

Factors (n)	Baseline, mean± SD	3rd month, mean± SD	6th month, mean± SD	12th month, mean± SD	ANOVA Test p-value	p-value*
eGFR (mL/min/1.73 m²)	88.25±24.5	88±21.9	86.6±24.7	85.8±24.3	0.381	
Phosphorus (mg/dl)	3.2±0.67	3.3±0.63	3.6±0.58	3.7±0.6	<0.001	
				Baseline vs	3rd month	0.194
					6th month	<0.001
					12th month	<0.001
				3rd month vs	6th month	<0.001
					12th month	<0.001
				6th month vs	12th month	0.215

eGFR: glomerular filtration rate, *: Adjustment for multiple comparisons: Bonferroni.

acid, and glucose increases with TDF. In extensive studies, the use of TDF has been identified as one of the main risk factors associated with chronic kidney disease. Hyperphosphaturia secondary to tubular dysfunction can lead to progressive bone loss. Bone loss due to changes in phosphate metabolism can be rapidly resolved by TDF discontinuing.[15] The information provided suggests that there are studies in the literature demonstrating no significant association between the use of TDF and a higher degree of kidney damage in patients with HBV compared to other nucleoside and nucleotide reverse transcriptase inhibitors. Specifically, it has been shown that TDF is not associated with a worsening of kidney function during short or medium-term follow-up periods in patients without significant renal failure.[16,17] In our study, we observed no significant change in GFR values during the follow-up period, and we attribute this to the fact that the initial and follow-up GFR levels in the patients of our study were nearly normal overall. Furthermore, our study is consistent with the literature in showing a significant increase in phosphate levels at 3, 6, and 12 months after the initiation of tenofovir alafenamide (TAF) treatment.[18,19]

Limitations

Our study had some limitations. The most important limitation of this study is that it is a retrospective study. Additionally, our study included a small number of patients. Since there were deficiencies in the necessary follow-up of patients for osteoporosis/osteopenia, sufficient information could not be obtained about the effects of TAF on bone tissue. Another limitation of our study was that data regarding the measurements of the patients' lipid profiles during the follow-up period were missing. For this reason, the changes in the patients' lipid profiles over time could not be investigated. There was no significant change in GFR level in our study. We think longer-term follow-up data is needed for the change in GFR to be meaningful.

CONCLUSION

In our study, a significant improvement in detectable HBV DNA, ALT level, and phosphorus level was observed in both naïve and treatment-experienced patients with the initiation of TAF. In addition, a positive but not statistically significant change was observed in AST and GFR. TAF, whose reliability in terms of bone and kidney is supported by various studies, is a promising treatment option for side effects that may occur in patients using TDF.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date: 28.11.2023, Decision No: 953).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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Diagnostic performance of whole blood viscosity indices in predicting the presence and severity of coronary artery disease

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ABSTRACT

Aims: Growing evidence suggests that blood viscosity plays a crucial role in both the development and acceleration of atherosclerosis. In this study, aimed to investigate the diagnostic performance of the mean platelet volume-age-total protein-hematocrit (MAPH) score, a new index for blood viscosity, in predicting the presence and severity of CAD in patients with suspected coronary artery disease (CAD).

Methods: We retrospectively evaluated 431 patients who underwent coronary angiography. SYNTAX score (SS) were divided into 3 groups; low group (<22), intermediate group (22-32) and, high group (≥32). Low (LSR) and and high (HSR) shear rates were derived using values of total protein and hematocrit. The MAPH score was calculated based on the threshold values of mean platelet volume, age, total protein, and hematocrit for predicting CAD.

Results: The median LSR (60.7 vs. 43.1, p<0.001), mean HSR (17.3±1.3 vs. 16.2±1.2, p<0.001), and mean MAPH score (2.7±0.8 vs. 1.6±0.5, p<0.001) were higher in the CAD group compared to the non-CAD group. These indices of blood viscosity were found to be higher in the intermediate-high SS group compared to the low SS group. The threshold value of MAPH score for predicting CAD was >2 (sensitivity=78.2%, specificity=70.0%). It also had a graduated threshold value (>3, sensitivity=71.1%, specificity=62.5%) in distinguishing intermediate-high SS than low SS groups. In predicting both the presence and severity of CAD, the MAPH score exhibited superior diagnostic performance relative to the levels of LSR and HSR.

Conclusion: In patients with suspected CAD, a gradual increase in the MAPH score demonstrated significant diagnostic performance in distinguishing both the presence and severity of CAD. In these patients, the MAPH score may serve as a potential screening tool and can be utilized for risk stratification.

Keywords: Blood viscosity, coronary artery disease, MAPH score, microcirculation, SYNTAX score

INTRODUCTION

Coronary artery disease (CAD) arises from intricate and prolonged atherosclerotic processes influenced by both environmental and genetic factors.[1] The onset and advancement of atherosclerosis are significantly influenced by traditional risk factors including hypertension, smoking, diabetes, obesity, inactive lifestyle, and age, as well as critical factors like lipid oxidation, leukocyte activation, platelet aggregation, and endothelial cell activation.[2,3] These risk factors involved in atherosclerosis can affect blood viscosity, which may lead to erythrocyte deformation.[4] Previous studies have demonstrated that any changes in hemorheological factors might have a pivotal role in the progression of atherosclerotic processes.[5,6]

Early atherosclerotic changes in coronary arteries are closely associated with variations in wall shear stress (WSS).[7] Plaque formation typically begins in areas of low WSS, and as the plaque develops, it changes the surrounding WSS landscape.[8] An experimental study on rabbits has demonstrated that arterial blockages lead to elevated levels of hematocrit (HCT) and total plasma protein (TP), which in turn influence the characteristics of blood flow and thereby impact WSS.[9] Blood viscosity, a determinant of shear stress, can be calculated using a validated equation based on HCT and TP levels for both low (LSR) and and high (HSR) shear rates.[6] On the other hand, advancing age and elevated mean platelet volume (MPV), crucial risk factors for atherosclerosis and CAD,[10,11] may influence both WSS and blood viscosity.[12,13] Therefore, a scoring system that incorporates these risk factors could exhibit superior diagnostic performance in predicting CAD.

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It has been shown that the MAPH score, calculated using MPV, age, TP, and HCT, is a significant blood viscosity indicator in predicting the coronary slow-flow phenomenon (CSFP) and thrombus burden in patients undergoing coronary angiography (CAG).[14-16] However, we have not encountered any previous study that demonstrates its association with the presence and extent of CAD. We hypothesized that the MAPH score, which includes potential risk factors for CAD, could serve as a simple and readily accessible tool for predicting CAD before undergoing CAG. Hence, this study aimed to investigate the diagnostic performance of the MAPH score in predicting the presence and severity of CAD in patients undergoing CAG with a suspicion of CAD.

METHODS

Ethics

The study protocol received approval from the Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.09.2022, Decision No: 146/03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study was conducted on patients who underwent CAG between January 2018 and January 2022 in the Cardiology Department of Dışkapı Yıldırım Beyazıt Training and Research Hospital. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Previous studies have reported a prevalence of CAD ranging from 30% to 52% in patients undergoing CAG due to suspected CAD.17,18 Accordingly, assuming a 45% prevalence of CAD in patients undergoing CAG, the necessary sample size was determined to be at least 281 patients with a 5% margin of error and 90% power.

Study Population

During the study period, 3456 patients over the age of 18 who underwent CAG following ischemia detected by myocardial perfusion scintigraphy were retrospectively evaluated. Exclusion criteria for patients included any autoimmune or systemic inflammatory diseases, peripheral artery disease, glucocorticoid therapy within the past 3 months, malignancies or hematological disease, thyroid disease, advanced/end-stage liver or renal failure, history of acute coronary syndrome or revascularization (such as prior percutaneous coronary intervention or coronary artery bypass grafting). After applying the exclusion criteria, 431 patients were included in the study.

Patient demographics and lab results were documented from their medical records. Traditional risk factors for CAD assessed included smoking, hypertension (identified by a systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg and/or ongoing anti-hypertensive treatment), and diabetes mellitus (identified by fasting blood glucose ≥126 or glucose ≥200 mg/dl during a 2-hour oral glucose tolerance test or ongoing anti-diabetic treatment).

Laboratory Measurements

The complete blood count values of all of the patients were measured one day before the myocardial perfusion scintigraphy. A Beckman Coulter LH 780 device (Mervue, Galway, Ireland) and Hitachi Modular P800 autoanalyzer (Roche Diagnostics Corp., Indianapolis, IN, USA) were used to evaluate patients' venous blood samples. Levels of hemoglobin (photometrically), platelet count (impedance method), C-reactive protein (CRP) (immunoturbidimetric method), albumin (bromocresol green method), triglycerides and total cholesterol (enzymatic colorimetry), and high-density lipoprotein cholesterol (HDL-C) (homogeneous enzymatic colorimetry) were determined. The Friedewald formula was used to determine low-density lipoprotein cholesterol (LDL-C).[19]

The values for LSR and HSR were determined using hematocrit and total protein values, employing the method previously established and verified.[20] The threshold values for MPV, age, TP, and HCT in predicting CAD were determined by employing the Youden index in ROC Curve analysis. Levels above the threshold value for each parameter were assigned a score of 1 point, and the MAPH score was thus evaluated on a scale from 0 to 4.[15]

Coronary Angiography

CAG was carried out employing traditional Judkins methods. CAD was identified as coronary stenosis involving a narrowing of ≥50% in the lumen diameter, as determined by quantitative CAG. Individuals whose vessel diameter was under 1.5 mm and/or who exhibited less than 50% narrowing were categorized as part of the control group. The SYNTAX Score (SS) was computed for lesions with a stenosis of ≥50% diameter in vessels larger than 1.5 mm (www.syntaxscore.com).[21] SS values were categorized into three groups: <22 (low), 22-32 (intermediate), and ≥32 (high).[22]

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium) software. Categorical data were represented in terms of frequency and percentage. Group-wise comparisons were made utilizing the Chi-square test (with post-hoc cell-wise analysis) and the Fisher's Exact test. The normal distribution of numerical variables was assessed using the Kolmogorov-Smirnov test. Data exhibiting a normal

distribution were presented as mean±standard deviation, and comparisons between groups were made using the Student's T-test or ANOVA test (post-hoc: Bonferroni test). Non-normally distributed data were displayed as median (interquartile range (IQR): 25-75 percentiles) and comparisons between groups were conducted using the Mann-Whitney U test or Kruskal-Wallis test (post-hoc: Dunn's test). Stepwise multivariable logistic regression analysis was used to evaluate independent predictors of the presence and severity of CAD. The evaluation of diagnostic performance was conducted through ROC analysis, and the cut-off values were determined using the Youden index method. Value of p <0.05 were considered statistically significant.

RESULTS

A total of 431 patients were analyzed in the study, including 239 males and 192 females with the mean age of 57.4±10.3 years. CAD was detected in 58.7% (n=253) of patients (median SS: 15, IQR=8-23), with 186 patients having low SS, 40 patients intermediate SS, and 27 patients high SS. The demographic and laboratory findings are shown in Table 1. The ratios of smoking and hypertension were higher in the CAD group compared to the non-CAD group, while the ratio of diabetes mellitus was comparable between the groups. The counts of neutrophil and monocyte, and the levels of MPV, HCT, LDL-C, CRP and total protein were higher in the CAD group compared to the non-CAD group, while the levels of HDL-C and albumin were lower. The median LSR (60.7 vs. 43.1, p<0.001) and mean HSR (17.3±1.3 vs. 16.2±1.2, p<0.001) were higher in the CAD group compared to the non-CAD group. Other laboratory parameters did not differ significantly in the CAD and non-CAD groups (Table 1).

Table 1. Demographic and laboratory findings associated with the presence of coronary artery disease

Variables	All population n=431	CAD		p
		No n=178	Yes n=253	
Age, years	57.4±10.3	55.2±10.7	58.9±9.6	<0.001*
Male gender, n (%)	239 (55.5)	94 (52.8)	145 (57.3)	0.377
BMI, kg/m²	27.9±6.0	27.6±5.8	28.1±6.2	0.398
Smoking, n (%)	214 (49.7)	70 (39.3)	144 (56.9)	<0.001*
Hypertension, n (%)	295 (68.4)	93 (52.2)	202 (79.8)	<0.001*
Diabetes mellitus, n (%)	158 (36.7)	58 (32.6)	100 (39.5)	0.141
Drugs, n (%)				
Beta-blockers	182 (42.2)	62 (34.8)	120 (47.4)	0.009*
ACE/ARB inhibitors	196 (45.5)	73 (41.0)	123 (48.6)	0.118
Calcium canal blockers	83 (19.3)	28 (15.7)	55 (21.7)	0.119
Diuretics	97 (22.5)	34 (19.1)	63 (24.9)	0.156
Antidiabetic agents	157 (36.4)	58 (32.6)	99 (39.1)	0.164
Multivessel disease, n (%)	113 (26.2)	0	113 (44.7)	-
SYTANX score	6 (0-17)	0	15 (8-23)	-
Laboratory findings				
Hemoglobin, g/dl	13.2±1.6	13.3±1.4	13.1±1.7	0.348
Neutrophil count, $\times10^9$/L	4.8±1.4	4.3±1.2	5.2±1.4	<0.001*
Lymphocyte count, $\times10^9$/L	2.2±0.7	2.2±0.6	2.1±0.7	0.177
Monocyte count, $\times10^9$/L	0.7±0.2	0.6±0.1	0.7±0.2	<0.001*
Platelet count, $\times10^9$/L	245.7±68.5	243.8±71	247.1±66.9	0.630
Mean platelet volume, fL	8.3±1.0	8.0±1.1	8.4±0.9	<0.001*
Hematocrit, %	41.1±5.1	39.0±5.4	42.5±4.4	<0.001*
HDL-C, mg/dl	45.2±11.1	47.9±11.2	43.4±10.6	<0.001*
LDL-C, mg/dl	123.7±35.3	118.5±32.4	135.4±37.5	<0.001*
Triglycerides, mg/dl	128 (94-195)	124 (91-185)	131 (96-203)	0.811
Creatinine, mg/dl	0.8 (0.7-1.0)	0.7 (0.6-0.9)	0.8 (0.6-1.1)	0.315
Albumin, g/dl	4.1±0.4	4.2±0.4	4.1±0.5	0.027*
CRP, mg/dl	0.5 (0.2-0.8)	0.4 (0.2-0.7)	0.6 (0.4-0.9)	0.035*
Total protein	72.3±6.9	70.0±5.7	73.9±7.2	<0.001*
WBV at LSR	52.6 (36.6-74.6)	43.1 (24.9-58.8)	60.7 (44.6-82.3)	<0.001*
WBV at HSR	16.9±1.4	16.2±1.2	17.3±1.3	<0.001*
MAPH score	2.3±0.7	1.6±0.5	2.7±0.8	<0.001*

Numerical variables were shown as mean±standard deviation or median (IQR). Categorical variables were shown as numbers (%). * P <0.05 shows statistical significance. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HSR, high shear rate; LSR, low shear rate; WBV, whole blood viscosity.

Table 2 displays the potential risk factors found to be associated with CAD. Among these potential risk factors, three different multivariable logistic regression models were created for independent predictors of CAD. In the Multivariable Model I and Model II regression analyses, HCT and total protein levels, which are components of LSR and HSR, were not included due to multicollinearity. Based on this, increased age, hypertension, smoking, higher monocyte levels, and elevated LDL-C levels were determined as shared independent predictors of CAD in both Model I and Model II. LSR in Model I (OR=1.03, p<0.001) and HSR in Model II (OR=1.92, p<0.001) were established as other independent predictors of CAD (Table 2).

For predicting CAD risk, the established optimal cutoff values are as follows: age over 47 years (AUC=0.588, sensitivity=91.3%, and specificity=25.8%), HCT above 42.2% (AUC=0.698, sensitivity=59.0%, and specificity=73.6%), MPV over 8.3 fL (AUC=0.622, sensitivity=58.1%, and specificity=65.2%), and TP above 72.2 g/L (AUC=0.669, sensitivity=60.5%, and specificity=68.5%). Based on the set threshold values, the MAPH score was computed and incorporated into Model III. However, its components (MPV, age, TP, HCT) were excluded from Model III due to the multicollinearity associated with the MAPH score. The Model III regression analysis indicated that hypertension, smoking, elevated monocyte and LDL-C levels, along with the MAPH score, are independent risk factors for CAD. Accordingly, it was determined that each one-unit increase in the MAPH score independently increased the likelihood of CAD by 2.83 folds (OR=2.83, p<0.001). The threshold value of the MAPH score for predicting CAD was determined to be >2 (AUC=0.792, sensitivity=78.2%, and specificity=70.0%). On the other hand, in predicting CAD, the MAPH score exhibited superior diagnostic performance relative to the levels of LSR and HSR (Figure 1A). Furthermore, Model III demonstrated greater variance explanation for CAD and a higher AUC value than both Model II and Model I (For Nagelkerke R2 → Model I: 0.45, Model II: 0.46, and Model III: 0.58 in Table 2; For AUC → Model I: 0.47, Model II: 0.48, and Model III: 0.58 in Figure 1B).

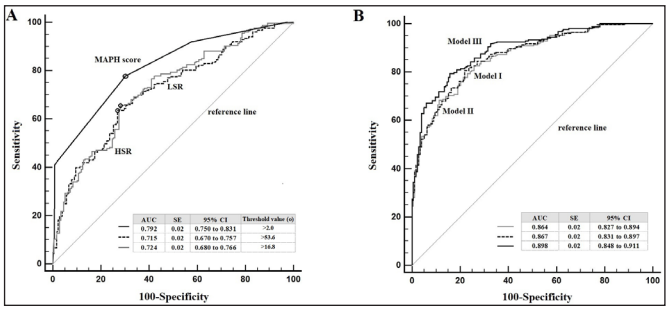

Figure 1. Diagnostic performance assessment of blood viscosity indices (A) and multivariable regression models (B) in predicting presence of CAD

Table 2. Multivariable regression models including whole blood viscosity indices to predict coronary artery disease

Variables	Univariable Regression			Multivariable Model I			Multivariable Model II			Multivariable Model III		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Age	1.04	1.02-1.06	<0.001*	1.03	1.01-1.07	0.003*	1.04	1.01-1.07	0.004*		not included	
Smoking	2.04	1.38-3.01	<0.001*	2.51	1.43-4.41	0.001*	1.81	1.11-2.98	0.018*	2.10	1.29-3.13	<0.001*
Hypertension	3.62	2.37-5.54	<0.001*	2.40	1.46-3.94	0.001*	2.95	1.80-4.82	<0.001*	3.45	2.10-5.68	<0.001*
Neutrophil count	1.28	1.05-1.56	<0.001*	-	-	-	-	-	-	-	-	-
Monocyte count	1.77	1.54-2.02	<0.001*	1.84	1.69-2.19	<0.001*	1.86	1.63-2.25	<0.001*	1.84	1.60-2.34	<0.001*
Hematocrit	1.16	1.11-1.21	<0.001*		not included			not included			not included	
Mean platelet volume	1.46	1.19-1.79	<0.001*	1.54	1.20-1.98	0.001*	1.57	1.22-2.01	<0.001*		not included	
HDL-C	0.96	0.95-0.98	<0.001*	-	-	-	-	-	-	-	-	-
LDL-C	1.02	1.01-1.03	<0.001*	1.03	1.01-1.05	<0.001*	1.92	1.55-2.38	<0.001*	1.03	1.01-1.05	<0.001*
Albumin	0.86	0.79-0.95	0.027*	-	-	-	-	-	-	-	-	-
CRP	1.07	1.01-1.12	0.035*	-	-	-	-	-	-	-	-	-
Total protein	1.10	1.06-1.13	<0.001*		not included			not included			not included	
WBV at LSR	1.03	1.02-1.04	<0.001*	1.03	1.02-1.04	<0.001*		not included			not included	
WBV at HSR	1.95	1.64-2.33	<0.001*		not included		1.92	1.55- 2.38	<0.001*		not included	
MAPH score	3.13	2.43-4.01	<0.001*		not included			not included		2.83	2.16-3.71	<0.001*
				Nagelkerke R^2=0.45			Nagelkerke R^2=0.46			Nagelkerke R^2=0.58		

In multivariable regression models, the effects of drugs were adjusted. * P <0.05 shows statistical significance.
Abbreviations: see Table 1, CI, confidence intervals; OR, odds ratio

The meaningful potential risk factors for CAD identified above also exhibited significant differences between the low SS group and the non-CAD group (Table 3). The ratio of multivessel disease, mean neutrophil level, mean MPV level, mean HCT, mean LDL-C level, and mean TP level were higher in mid-high SS groups compared to low SS group. In terms of blood viscosity indices, LSR, HSR, and the MAPH score were higher in the mid-high SS group compared to the low SS group (Table 3). Independently of other risk factors, it was determined that each one-unit increase in the MAPH score increased the likelihood of low SS by 2.98 folds compared to the non-CAD group, and the likelihood of mid-high SS by 1.78 folds compared to the low SS group (Table 4). The MAPH score exhibited superior diagnostic performance than LSR and HSR in predicting low SS (with the non-CAD group as reference) (Figure 2A) and mid-high SS (with the low SS group as reference) (Figure 2B).

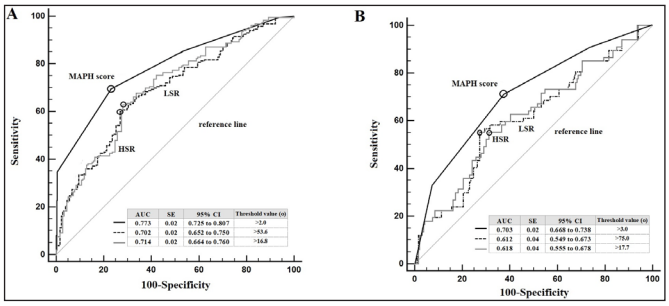

Figure 2. Diagnostic performance assessment of blood viscosity indices in predicting severity of CAD. A: Low SYNTAX score vs. non-CAD group. B: Intermediate -high SYNTAX score vs. low SYNTAX score

Table 3. Demographic and laboratory findings associated with the severity of coronary artery disease

Variables	CAD			p
	No n=178	Low SS n=186	Intermediate -High SS n=67	
Age, years	55.2±10.7[bc]	58.4±9.8[a]	60.2±9.3[a]	0.001*
Male gender, n (%)	94 (52.8)	100 (53.8)	45 (67.2)	0.108
BMI, kg/m²	27.6±5.8	28.2±6.0	28.5±6.5	0.459
Smoking, n (%)	70 (39.3)[bc]	107 (57.5)[a]	37 (55.2)[a]	0.002*
Hypertension, n (%)	93 (52.2)[bc]	149 (80.1)[a]	53 (79.1)[a]	<0.001*
Diabetes mellitus, n (%)	58 (32.6)	78 (41.9)	22 (32.8)	0.152
Drugs, n (%)				
Beta-blockers	62 (34.8)	85 (45.7)[a]	35 (52.2)[a]	0.007*
ACE/ARB inhibitors	73 (41.0)	92 (49.5)	31 (46.3)	0.264
Calcium canal blockers	28 (15.7)	40 (21.5)	15 (22.4)	0.293
Diuretics	34 (19.1)	46 (24.7)	17 (24.5)	0.370
Antidiabetic agents	58 (32.6)	77 (41.4)	22 (32.8)	0.188
Multivessel disease, n (%)	0	58 (31.2)[c]	55 (82.1)[b]	0.001*
SYTANX score	0	10.5 (7-16)[c]	29 (25-34)[b]	<0.001*
Laboratory findings				
Hemoglobin, g/dl	13.3±1.4	13.1±1.7	13±1.7	0.601
Neutrophil, $\times10^9$/L	4.3±1.2[bc]	4.9±1.5[ac]	5.4±1.4[ab]	<0.001*
Lymphocyte, $\times10^9$/L	2.2±0.6	2.1 (1.7-2.7)	2.0 (1.6-2.5)	0.252
Monocyte, $\times10^9$/L	0.6±0.1[bc]	0.7±0.2[a]	0.7±0.2[a]	<0.001*
Platelet count, $\times10^9$/L	243.8±71	247.6±66.6	245.6±68	0.873
Mean platelet volume, fL	8.0±1.1[bc]	8.3±0.9[ac]	8.6±0.8[ab]	<0.001*
Hematocrit, %	39.0±5.4[bc]	42.2±4.5[ac]	43.8±3.9[ab]	<0.001*
HDL-C, mg/dl	47.9±11.2[bc]	43.1±10[a]	43.8±12.2[a]	<0.001*
LDL-C, mg/dl	118.5±32.4[bc]	130.8±32.6[ac]	143.4±39.2[ab]	<0.001*
Triglycerides, mg/dl	124 (91-185)	132 (99-203)	115 (88-235)	0.939
Creatinine, mg/dl	0.7 (0.6-0.9)	0.8 (0.6-1.0)	0.8 (0.6-1.1)	0.548
Albumin, g/dl	4.2±0.4[bc]	4.1±0.5[a]	4.0±0.7[a]	0.034*
CRP, mg/dl	0.4 (0.2-0.7)[ab]	0.6 (0.2-0.9)[a]	0.7 (0.4-1.0)[a]	0.041*
Total protein	70.0±5.7[bc]	73.2±6.9[ac]	75.8±7.5[ab]	<0.001*
WBV at LSR	43.1 (24.9-58.8)[bc]	59.2 (42.5-79.6)[ac]	75.8 (50.5-88.9)[ab]	<0.001*
WBV at HSR	16.2±1.2[bc]	17.2±1.3[ac]	17.7±1.3[ab]	<0.001*
MAPH score	1.6±0.5[bc]	2.2±0.7[ac]	3.0±0.8[ab]	<0.001*

Numerical variables were shown as mean±standard deviation or median (IQR). Categorical variables were shown as numbers (%).
* P <0.05 shows statistical significance. Post-hoc analyzes were expressed as follows: a: P <0.05 vs. non-CAD group, b: P <0.05 vs. low SS group, c: P <0.05 vs. mid-hihg SS group.
Abbreviations: see Table 1

Table 4. Independent predictors of the presence and severity of CAD

Variables	Univariable Regression			Multivariable Regression		
	OR	95% CI	p	OR	95% CI	p
Low SS (ref: non-CAD)						
Smoking	2.10	1.38-3.18	0.001*			
Hypertension	3.68	2.31-5.86	<0.001*	2.08	1.16-3.71	0.014*
Neutrophil count	1.67	1.41-1.98	<0.001*	-	-	-
Monocyte count	1.81	1.65-2.10	<0.001*	1.78	1.62-2.04	<0.001*
HDL-C	0.96	0.94-0.98	<0.001*			
LDL-C	1.08	1.03-1.13	<0.001*	1.10	1.03-1.17	0.006*
Albumin	0.82	0.75-0.90	0.031*	-	-	-
CRP	1.05	1.01-1.10	0.045*	-	-	-
MAPH score	2.78	2.15-3.59	<0.001*	2.98	2.18-4.06	<0.001*
					Nagelkerke R2=0.50	
Mid-high SS (ref: low SS)						
Multivessel disease	10.12	5.04-20.31	<0.001*	11.78	5.68-24.40	<0.001*
Neutrophil count	1.13	1.04-1.24	0.023*	1.18	1.07-1.32	0.042*
LDL-C	1.08	1.02-1.15	0.015*	1.07	1.01-1.14	0.035*
MAPH score	1.59	1.16-2.17	0.004*	1.85	1.30-2.65	0.008*
					Nagelkerke R2=0.34	

In multivariable regression models, the effects of drugs were adjusted. * P <0.05 shows statistical significance.
Abbreviations: see Table 1, CI, confidence intervals; OR, odds ratio

DISCUSSION

To the best of our knowledge, this is the first study evaluating the MAPH score, a novel indicator of blood viscosity, for predicting CAD in patients with suspected CAD. The main findings of our study were as follows: 1) Higher MAPH scores were significantly associated with the presence and severity of CAD, 2) In predicting CAD, the MAPH score exhibited a superior diagnostic performance compared to LSR and HSR, 3) The gradual increase in MAPH scores demonstrated significant diagnostic performance in distinguishing the severity of CAD.

The SS is crucial for assessing the severity and extent of CAD, particularly for making revascularization decisions.[23] Despite this, it's noted that a considerable number of patients suspected of having CAD may exhibit normal coronary arteries when assessed via CAG, posing risks of unnecessary radiation exposure and financial burdens.[24,25] Therefore, there is an escalating interest in the use of cost-effective and easily accessible biomarkers for classifying patients with suspected CAD in clinical settings, aiming to streamline patient management and mitigate unwarranted diagnostic interventions.

The main cause of CAD, atherosclerosis, is known to have a prolonged incubation period, and its resultant diseases frequently manifest acutely, usually leading to a poor prognosis.[2] The pathophysiological mechanism of atherosclerosis is a multifaceted and complex process. It begins with the activation of the endothelium, which is then followed by a series of events including the accumulation of lipids, fibrous elements, and calcification, leading to vessel narrowing and the activation of inflammatory pathways.[26] Growing evidence suggests that blood viscosity is a critical factor in these processes. Blood viscosity, which represents the intrinsic resistance to blood flow within vessels, correlates directly with endothelial shear stress, influenced by the diameter of the vessel via the secretion of endothelial vasoactive factors.[27] Increased blood viscosity alters the WSS landscape, leading to a response in endothelial cells. Under normal physiological conditions, endothelial cells respond to normal shear stress by producing endothelial nitric oxide synthase (eNOS), encouraging the expression of genes that protect against atherosclerosis, and reducing endothelin-1 (ET-1) messenger ribonucleic acid (mRNA). However, in conditions of low shear stress, these cells increase the absorption of oxidized LDL-C and enhance the levels of several adhesion molecules such as ICAM-1, VCAM-1 and inflammatory cytokine such as tumor necrosis factor-alpha (TNF-α), while reducing the expression of eNOS and protein.[28,29] As a result, the rheological characteristics of blood alter, resulting in endothelial injury and inflammation, and this is accompanied by an increase in blood viscosity.[30]

Consistent with the aforementioned mechanisms, increased blood viscosity leads to a decrease in WSS, potentially exacerbating the severity of endothelial dysfunction.[31] This also suggests that blood viscosity might be a key player in the initiation of atherosclerotic plaque formation in areas with low WSS, in the acceleration of atherosclerosis, and in the increased probability of rupture.[32] In the current study, patients with CAD having higher levels of LSR and HSR is

consistent both with these mechanisms and with previous studies.[33-35] In a previous study, both LSR and HSR were found to be increased in patients with CAD compared to the control group. Also, it has been reported that LSR demonstrated a sensitivity of 82% and a specificity of 78% in predicting CAD, while HSR exhibited a sensitivity of 83% and a specificity of 77%.[33] In another study, it was found that both HSR and LSR were significantly higher in the group with severe coronary artery stenosis compared to the group with non-significant coronary artery stenosis. Furthermore, it has been reported that in predicting significant coronary artery stenosis, the LSR exhibited a sensitivity of 58.4% and a specificity of 62.1%, while the HSR showed a sensitivity of 61.5% and a specificity of 70.4%.[35] However, it is known that blood rheology is affected by coronary risk factors such as advanced age, hypertension, and smoking.[30] Additionally, increased MPV levels, which are associated with atherothrombotic disorders such as atherosclerosis,[36] may also have a potential impact on blood rheology.[37,38] On the other hand, it has been reported that antihypertensive drugs such as beta-blockers and angiotensin-converting enzyme inhibitors, or diabetic agents, can also affect blood viscosity.[39-41] Independent of these potential factors, both Model I and Model II regression analyses showed that LSR and HSR are independent predictors of CAD. Nonetheless, both LSR and HSR showed low sensitivity in forecasting the presence and severity of CAD. A previous study demonstrated that the sensitivities of LSR and HSR in distinguishing patients with significant coronary artery stenosis from those without were 58.4% and 61.5%, respectively.[35] Therefore, an improved blood viscosity index might exhibit better diagnostic performance in distinguishing both CAD and its severity.

Recently, the MAPH score, incorporating age and MPV parameters in addition to the components of LSR and HSR, has been introduced as a new index for blood viscosity.[15] It has been associated with a high thrombus burden in patients with both ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction.[14,15] In a study involving 260 patients who underwent primary percutaneous coronary intervention and had TIMI 0 flow, it was reported that the MAPH score predicted the presence of TIMI coronary flow after stent implantation with 78% specificity and 45% sensitivity.[42] In addition to these cohorts as a consequence of atherosclerosis, the predictive role of the MAPH score has also been investigated in patients with CSFP, which is a distinct angiographic clinical entity characterized by delayed coronary opacification in the absence of significant obstructive CAD. In the mentioned study, it was demonstrated that the MAPH score exhibited a sensitivity of 43% and a specificity of 86% in differentiating between CSFP and normal coronary flow.[16] Increasing evidence indicates that patients with CSFP are prone to atherosclerosis and obstructive CAD.[43,44] Consistent with these findings, the MAPH score was identified as a significant indicator in distinguishing both the presence and the severity of CAD, exhibiting better diagnostic performance than LSR and HSR. Moreover, the regression model incorporating the MAPH score explained a higher variance of CAD compared to the regression models that included the LSR and HSR indices. Furthermore, it also exhibited a graduated threshold value with a sensitivity of 71.1% and a specificity of 62.5% in differentiating patients with intermediate-high SS.

Limitations

Although this study is the first to evaluate the relationship between the MAPH score and CAD, it possesses certain limitations. Besides being single-centered and retrospective, the study evaluated the severity of luminal stenosis in coronary arteries solely through visual coronary angiograms. Additional information such as the luminal area, plaque burden, and characteristics related to the quantitative evaluation of atherosclerosis was not included in the study. Finaly, the MAPH score is a new biomarker, and each of its components requires cut-off points. Widespread adoption of the MAPH score necessitates multi-center, prospective studies involving a large number of participants.

CONCLUSION

In patients with suspected CAD, the MAPH score, a new indicator of blood viscosity, is associated with the presence and severity of CAD. A gradual increase in the MAPH score demonstrates significant diagnostic performance in distinguishing patients with high-risk CAD. In patients suspected of CAD, the MAPH score may serve as a potential screening tool and can be utilized for risk stratification.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.09.2022, Decision No: 146/03).

Informed Consent

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

Referee Evaluation Process
Externally peer-reviewed.

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

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

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

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Original Article

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The assessment of serum uric acid-to-HDL cholesterol ratio as a new predictor of mortality in ST-elevation myocardial infarction: a cross-sectional study

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ABSTRACT

Aims: The objective of this study was to evaluate the predictive efficacy of the Uric Acid-to-High Density Lipoprotein Cholesterol Ratio (UHR) as a novel inflammatory and metabolic marker for mortality in patients with ST-segment Elevation Myocardial Infarction (STEMI).

Methods: This retrospective, single-center, cross-sectional, observational study enrolled 1361 patients diagnosed with STEMI undergoing primary percutaneous coronary intervention (PPCI) from March 2021, to January 2022. The participants were categorized into two groups: those experiencing in-hospital mortality (n=100) and those without in-hospital mortality (n=1265).

Results: In-hospital mortality occurred in 100 patients (7.3%). UHR was notably higher in the mortality group compared to the non-mortality group (23.6±14.9% vs. 15.3±6.9%, p<0.001). Logistic regression analysis identified several independent determinants of in-hospital mortality among STEMI patients, including age (odds ratio [OR]=1.050, p<0.001), the presence of DM (OR=2.077, p=0.016), serum glucose (OR=1.004, p=0.002), hemoglobin (OR=0.855, p=0.020), White blood cell count (OR=1.064, p=0.025), UHR (OR=1.683, p<0.001), and SYNTAX score (OR=1.099, p<0.001). Receiver operating characteristic curve analysis revealed that UHR>13.9% determined in-hospital mortality in STEMI patients who underwent PPCI with 81.1% sensitivity and 49.2% specificity (AUC=0.668, p=0.001)

Conclusion: The UHR exhibited a significant and independent positive correlation with in-hospital mortality among STEMI patients undergoing PPCI.

Keywords: Uric acid, HDL-C, uric acid-to-high density lipoprotein cholesterol ratio, STEMI, SYNTAX score, in-hospital mortality

INTRODUCTION

Despite the advancements in coronary reperfusion strategies, ST-segment elevation myocardial infarction (STEMI) remains the leading cause of death worldwide.[1,2] This critical cardiovascular event necessitates prompt intervention due to its time-sensitive nature. STEMI is characterized by the combination of chest pain or equivalent symptoms and the presence of ST-segment elevation on the electrocardiogram (ECG) or newly confirmed left bundle branch block and elevated cardiac troponin levels.[3] Recognizing the urgency, primary percutaneous coronary intervention (PPCI) has become the main treatment strategy of choice for patients with STEMI.[4,5]

Research has increasingly highlighted the combined impact of elevated uric acid (UA) levels and low high-density lipoprotein cholesterol (HDL-C) on the cardiovascular system, revealing synergistic deleterious effects.[6-9] Recognizing the need for a comprehensive biomarker that captures the interplay between these two factors, the UA-to-HDL-C ratio (UHR) emerged. Developed from two inflammatory parameters, UHR has garnered attention as a novel biomarker of metabolic dysfunction and has been extensively investigated for various comorbid conditions.[10-14] Its unique profile positions UHR as a promising inflammatory and metabolic biomarker, demonstrating potential in predicting cardiac outcomes.[12,15]

Despite extensive investigations into the impact of numerous risk factors on mortality in patients with STEMI, a leading global cause of death, the efficacy of UHR, a novel proinflammatory marker, in predicting mortality within this patient cohort remains an understudied aspect in the existing literature. Thus, the present study aims to address this gap by evaluating the predictive capacity of UHR in assessing mortality risk among individuals with STEMI undergoing PPCI.

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METHODS

Ethics

The study protocol received approval from the Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 20.07.2023, Decision No: 2720). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Population Sample

The retrospective, single-center, cross-sectional, observational study included a sample of 1365 patients. These individuals were hospitalized between March 2021 and January 2022 due to STEMI and underwent PPCI. The study was conducted at the Adana City Training and Research Hospital Coronary Intensive Care Unit.

The hospitalization files of the patients were meticulously reviewed in a retrospective fashion. Comprehensive patient information, including demographic and clinical characteristics such as age, gender, hypertension (HTN), diabetes mellitus (DM), current smoking status, history of coronary artery disease (CAD), and history of cerebrovascular event/transient ischemic attack (CVE/TIA), was obtained from the National Chronic Disease and Drug Use Information System (accessible at https://medeczane.sgk.gov.tr/doktor/login.jsp).

The study inclusion criteria comprised individuals aged between 18 and 85 who presented to the hospital with STEMI within 12 hours of the onset of related symptoms and underwent PPCI. Exclusion criteria included chronic obstructive pulmonary disease (COPD), estimated glomerular filtration rate <30 ml/min/1.73 m² or chronic renal failure requiring hemodialysis, liver transplantation or decompensated cirrhosis, history of moderate-to-severe heart valve disease (insufficiency or stenosis), secondary hyperlipidemia, gout, systemic infection, thyroid disease history, active cancer, and current use of immunosuppressive or steroid therapy for any reason (Figure 1).

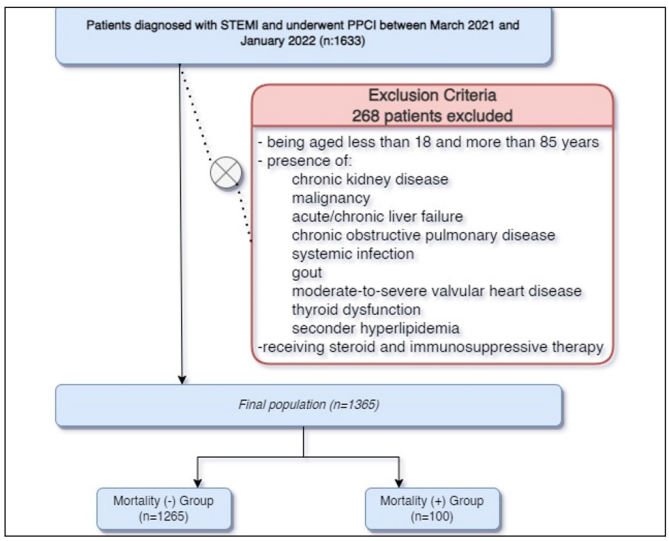

Figure 1. Flowchart of study inclusion and exclusion criteria

Data Collection and Definitions

ST-segment elevation myocardial infarction was diagnosed based on the presence of new ST-elevation at the J point in two consecutive leads on routine ECG, adhering to specific criteria: ≥0.25 mV in men <40 years old, ≥0.2 mV in men ≥40 years old, ≥0.15 mV in leads V2-V3 in women, and/or ≥0.1 mV in other leads. The diagnosis also considered the presence of a new left bundle branch block or prolonged chest pain lasting ≥30 minutes, under current clinical guidelines for positive cardiac markers.[3]

All patients received acetylsalicylic acid along with loading and maintenance doses of purinergic receptor type Y subtype 12 (P2Y12) inhibitors, adhering to the current treatment guidelines.[3] The initiation of beta-blocker and angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) treatment was contingent upon the absence of contraindications, as determined during coronary angiography conducted during hospitalization.

Routine blood samples were collected from all patients at the emergency triage unit, serving as the initial medical point of contact before PPCI. These samples underwent laboratory analyses using an automated chemistry analyzer (Roche Diagnostic Modular Systems, Tokyo, Japan). The laboratory parameters, including plasma glucose, serum creatinine, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, triglyceride (TG), UA, complete blood count, electrolytes, brain natriuretic peptide (BNP), high-sensitive troponin I (hs-TnI), and high-sensitivity C-reactive protein (Hs-Crp), were obtained for each patient through the hospital information system. The UHR was calculated by dividing UA by HDL-C.

Coronary Angiography, Percutaneous Coronary Intervention, and SYNTAX Score

Angiographic imaging of the left and right coronary systems was conducted in multiple orthogonal projections using the Judkins technique, administered from the femoral route for all patients. Coronary intervention procedures were performed using 6 French (Fr) or 7 Fr guiding catheters. All patients received intracoronary administration of 100 U/kg unfractionated heparin. Decision-making during the procedure, including intracoronary nitrate administration, pre-dilatation before stent implantation, selection of stent size and type, implantation technique, and post-dilatation, was at the discretion of the operator. Epicardial coronary arteries with at least 70% luminal stenosis were deemed indicative of critical coronary lesions. Further analysis was conducted on coronary lesions with at least 50% diameter and a lumen diameter exceeding 1.5 mm. The SYNTAX (Synergy Between Percutaneous Coronary Intervention (PCI) With Taxus and Coronary Artery Bypass Surgery (CABG)) scores were independently calculated by two cardiologists, blinded to patient survival data. The calculations were performed using www.syntaxscore.com (version 2.10) as described previously.[16]

The study group was categorized into two distinct groups: patients who experienced in-hospital mortality (mortality (+) group, n=100) and those who did not experience in-hospital mortality (mortality (-) group, n=1265).

Statistical Analysis

The statistical analyses for the collected data were conducted using the SPSS 22.0 (Statistical Product and Service Solutions for Windows, Version 22.0, IBM Corp., Armonk, NY, U.S., 2013) software package. Homogeneously distributed variables were presented as mean±standard deviation and compared using the independent sample t-test. Non-normally distributed variables were expressed as median and interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical variables were presented as frequency and percentage and compared using Pearson's chi-squared test or Fisher's exact test. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each independent variable.

Multivariable binary logistic regression models were employed to identify independent predictors of in-hospital mortality. Variables exhibiting significant probability (p) values in the univariable analysis underwent further analysis within the scope of the multivariable analysis. Internal correlation analysis (multicollinearity) was conducted by testing whether variance inflation factor <3, condition index <15, and variance proportions <0.6 were achieved using numerical expressions for all parameters.

The results of both univariable and multivariable regression analyses were presented as OR with 95% CI values. Receiver operating characteristics (ROC) curve analysis was utilized to determine the optimal cut-off values of UHR in predicting in-hospital mortality. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

Clinical, Demographic, and Procedural Characteristics of the Study Group

The study included 1365 patients, with a mean age of 60.9±12.2 years, of whom 955 (70.0%) were male. In-hospital mortality occurred in 100 (7.3%) patients. The mortality (+) group was significantly older, with a higher proportion of patients with DM. Various biomarkers and laboratory values at admission, including blood glucose, UA, creatinine, hs-Crp, BNP, hs-TnI levels, as well as platelet and white blood cell counts, were significantly higher in the mortality (+) group. TC, LDL-C, and hemoglobin values were significantly higher in the mortality (-) group. No significant difference was observed between the groups regarding the rate of ST-elevation MI type, implanted stent type, associated lesion, and whether pre-dilatation or post-dilatation was performed. However, the mortality (-) group exhibited significantly higher total stent length and SYNTAX score, while the stent diameter was significantly narrower. Table 1 displays the distribution of demographic, clinical, and laboratory characteristics by the mortality groups, while Table 2 illustrates the distribution of angiographic and procedural characteristics by the mortality groups.

Table 1. Demographic and clinical characteristics

Variables	All (n=1365)	Alive (n=1265)	Deceased (n=100)	p*
Age (years)	60.9±12.2	60.3±11.9	68.9±13.1	<0.001
Male gender (n [%])	955 (70.0)	892 (70.5)	63 (63.0)	0.115
CVE/TIA (n [%])	60 (4.4)	54 (4.3)	6 (6.0)	0.416
Hypertension (n [%])	648 (47.5)	592 (46.8)	56 (56.0)	0.076
DM (n [%])	307 (22.5)	260 (20.6)	47 (47.0)	<0.001
Previus CAD (n [%])	106 (7.8)	101 (8.0)	5 (5.0)	0.283
Current smokers (n [%])	427 (31.3)	387 (30.6)	40 (40.0)	0.052
Laboratory parameters				
Glucose (mg/dl)	138 (110-200)	136 (109-193)	184 (136-324)	<0.001
Sodium (mmol/L)	134.6±6.2	134.7±6.2	134.2±6.2	0.508
Potassium (mEq/L)	4.2±1.3	4.2±1.3	4.4±0.8	0.247
TC (mg/dl)	188.2±48.6	189.6±48.1	167.9±51.5	<0.001
LDL-C (mg/dl)	126.7±42.7	167.9±51.5	127.7±42.1	0.003
HDL-C (mg/dl)	38.4±11.4	38.5±11.2	37.4±14.0	0.470
TG (mg/dl)	126 (79-199)	129 (82-201)	90 (66-138)	0.001
UA (mg/dl)	5.5±1.7	5.4±1.6	7.2±3.0	<0.001
Creatinine (mg/dl)	0.9±0.6	0.9±0.6	1.4±1.0	<0.001
Hemoglobin (g/dl)	13.4±2.0	13.5±1.9	12.3±2.5	<0.001
Platelet count (10^3/ul)	263.1±83.8	261.3±76.8	285.5±143.2	0.009
WBC (10^3/ul)	12.2±4.3	11.9±4.0	15.0±6.7	<0.001
Hs-Crp (mg/L)	0.5 (0.2-1.2)	0.4 (0.2-1.0)	1.1 (0.2-4.6)	0.007
BNP (pg/ml)	95 (32-271)	80 (29-231)	677 (162-2879)	<0.001
hs-TnI (ng/ml)	2.5 (0.4-12.0)	2.4 (0.4-10.9)	5.9 (0.7-28.7)	0.001
UHR (%)	15.7±7.8	15.3±6.9	23.6±14.9	<0.001

Values are n (%), median (interquartile range [IQR]), or mean± standard deviation. P value was calculated using an independent samples t-test or the Mann-Whitney U-test for continuous variables and a chi-squared test or the Fisher's exact test for categorical variables, as appropriate. Abbreviations: BNP, brain natriuretic peptide; CAD, coronary artery disease; CVE/ TIA, cerebrovascular event/ transient ischemic attack; DM, Diabetes mellitus; HDL-C, High-density lipoprotein cholesterol; hs-TnI, high-sensitive troponin I; Hs-Crp, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; UA, uric acid; TG, triglycerides; UHR, uric acid to High-density lipoprotein cholesterol ratio; WBC, White blood cell count. *p value <0.05 was considered significant.

Table 2. Angiographic and procedural features

Variable	All (n=1365)	Alive (n=1265)	Deceased (n = 100)	p*
Culprit vessel, (n [%])				0.190
LMCA	6 (0.4)	5 (0.4)	1 (1.0)	
LAD	648 (47.5)	592 (46.8)	56 (56.0)	
LCx	441 (32.3)	417 (33.0)	24 (24.0)	
RCA	270 (19.8)	251 (19.8)	19 (19.0)	
ST elevation type				0.059
Anterior MI (n [%])	654 (47.9)	597 (47.2)	57 (57.0)	
Inferior MI (n [%])	711 (52.1)	668 (52.8)	43 (43.0)	
Type of stent				0.053
DES (n [%])	852 (62.4)	799 (63.2)	53 (53.0)	
BMS (n [%])	513 (37.6)	466 (36.8)	47 (47.0)	
Stent length (mm)	28.5±16.2	28.2±16.2	32.2±16.1	0.018
Stent diameter (mm)	2.9±0.4	2.9±0.4	2.8±0.3	0.028
Pre-dilatation (n [%])	1206 (88.4)	1112 (87.4)	94 (94.0)	0.067
Post-dilatation (n [%])	1186 (86.9)	1096 (86.6)	90 (90.0)	0.338
SYNTAX Score	14.8±8.2	14.2±7.7	22.9±10.1	<0.001

Values are n (%), mean± standard deviation. P value was calculated using an independent samples t-test and chi-squared test or the Fisher's exact test for categorical variables, as appropriate. Abbreviations: BMS, bare-metal stent; DES, drug-eluting stent; LMCA, left main coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; MI, Myocardial Infarction; RCA, right coronary artery; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; *p<0.05 was considered significant.

The Relationship between UHR and In-hospital Mortality

The serum UA level was significantly higher in the mortality (+) group compared to the mortality (-) group (5.4±1.6 vs. 7.2±3.0, p<0.001). Conversely, there was no significant difference between the two groups in terms of HDL-C level (38.5±11.2 vs. 37.4±14.0, p=0.470). However, UHR exhibited a significant increase in the mortality (+) group compared to the mortality (-) group (23.6±14.9% vs. 15.3±6.9%, p<0.001), indicating a substantial positive correlation between UHR and mortality among STEMI patients.

Regression and Sensitivity Analyses

Logistic regression analysis identified several independent determinants of in-hospital mortality in STEMI patients who underwent PPCI. The determinants included age (OR=1.050, 95% CI 1.027-1.173, p<0.001), the presence of DM (OR=2.077, 95% CI 1.147-3.758, p=0.016), serum glucose (OR=1.004, 95% CI 1.001-1.006, p=0.002), hemoglobin (OR=0.855, 95% CI 0.749-0.975, p=0.020), WBC (OR=1.064, 95% CI 1.008-1.123, p=0.025), UHR (OR=1.683, 95% CI 1.261-2.246, p<0.001), and SYNTAX score (OR=1.099, 95% CI 1.069-1.130, p<0.001) (Table 3). Additionally, based on the Youden index, ROC analysis revealed that a UHR>13.9% determined in-hospital mortality in STEMI patients who underwent PPCI with 81.1% sensitivity and 49.2% specificity (AUC=0.668, 95% CI 0.566-0.771, p=0.001) (Figure 2).

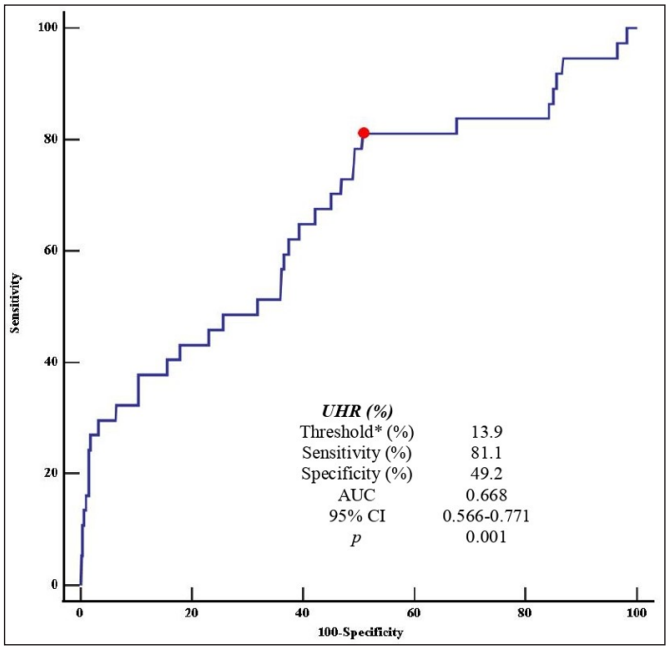

Figure 2. Receiver operating characteristic curve analysis of UHR for determining in-hospital mortality. *The cut-off was determined by the Youden Index. Abbreviations: AUC, Area under the curve; CI, Confidence Interval; UHR: uric acid-to-High-density lipoprotein cholesterol ratio.

Table 3. Univariable and multivariable analyses of predictors of in-hospital mortality on logistic regression analysis

Variable	Univariable			Multivariable+		
	OR	95% CI	p*	OR	95% CI	p*
Age (years)	1.058	1.040-1.076	<0.001	1.050	1.027-1.173	<0.001
DM (n [%])	3.428	2.262-5.195	<0.001	2.077	1.1.47-3.758	0.016
Glucose (mg/dl)	1.005	1.003-1.006	<0.001	1.004	1.001-1.006	0.002
TC (mg/dl)	0.992	0.988-0.996	<0.001			
TG (mg/dl)	0.998	0.996-1.000	0.088			
Creatinine (mg/dl)	1.667	1.367-2.034	<0.001			
Hemoglobin (g/dl)	0.719	0.649-0.796	<0.001	0.855	0.749-0.975	0.020
Platelet count (10^3/ul)	1.002	1.000-1.004	0.020			
WBC (10^3/ul)	1.122	1.080-1.166	<0.001	1.064	1.008-1.123	0.025
Hs-Crp (mg/L)	1.004	0.995-1.012	0.388			
BNP (pg/ml)	0.999	0.998-1.001	0.004			
hs-TnI (ng/ml)	1.015	1.008-1.023	<0.001			
UHR (%)	1.697	1.389-2.073	<0.001	1.683	1.261-2.246	<0.001
Stent diameter (mm)	0.542	0.313-0.939	0.029			
Stent length (mm)	1.013	1.002-1.024	0.020			
SYNTAX score	1.116	1.091-1.143	<0.001	1.099	1.069-1.130	<0.001

Abbreviations: BNP, brain natriuretic peptide; DM, Diabetes mellitus; Hs-Crp, high-sensitivity C- reactive protein; hs-TnI, high-sensitive troponin I; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; TC, total cholesterol; TG, triglycerides; UHR, uric acid to High-density lipoprotein cholesterol ratio; WBC, White blood cell count. +Model performance parameters: Hosmer-Lemeshow test p=0.532; Omnibus tests of model coefficients p<0.001; Nagelkareke R square=0.364, -2 log-likelihood=479.9; *p value<0.05 was considered significant.

DISCUSSION

The primary findings of this study can be summarized as follows: 1) In-hospital mortality occurred in 100 (7.3%) patients; 2) The mortality (+) group exhibited a significantly higher mean age and a greater prevalence of DM; 3) Age, the presence of DM, serum glucose, hemoglobin, WBC, UHR, and SYNTAX score emerged as independent predictors of mortality in patients with STEMI.

ST-segment elevation myocardial infarction stands as a predominant global cause of mortality. Numerous studies conducted across European countries have scrutinized in-hospital mortality rates among patients with STEMI. Notably, the Euro Heart Survey of Acute Coronary Syndromes and GRACE (Global Registry of Acute Coronary Events) registry[17] reported a 7.0% mortality rate, the Swiss national registry AMIS Plus (Acute Myocardial Infarction and Unstable Angina in Switzerland)[18] documented a 7.6% mortality rate, the RO-STEMI registry (ROmanian ST-Elevation Myocardial Infarction registry)[19] reported a 7.1% mortality rate, and MINAP (Myocardial Infarction National Audit Project)[20] recorded a 10.6% mortality rate. Consistent with these findings, the in-hospital mortality rate among STEMI patients in this study was determined to be 7.3%. A recent meta-analysis highlighted higher in-hospital mortality rates for STEMI in low- and middle-income countries compared to high-income countries.[21] Consequently, while the in-hospital mortality data presented in this study, which focuses on STEMI patients, may not cover the entire country, it might offer insights into the observed trends in European countries, particularly those with geographical and political affiliations to Turkiye.

Increased UA levels have been proposed as a risk factor for the development of DM and hypertension, while also serving as an independent biomarker for vascular complications and mortality.[22,23] In our study, the mortality (+) group showed significantly lower levels of TC, LDL-C, and TG, along with higher UA levels, compared to the mortality (-) group. Additionally, although not statistically significant, the mortality (+) group also exhibited lower levels of HDL-C compared to the mortality (-) group. Consistent with our study findings, elevated LDL-C and TG levels, along with low HDL-C levels, are widely recognized as risk factors for acute myocardial infarction (AMI). However, intriguingly, there exists a concept known as the 'lipid paradox' in AMI patients. Some studies suggest that low LDL-C and TG levels are associated with significantly higher in-hospital mortality rates in AMI patients.[24,25] Conversely, another study has demonstrated that low HDL-C levels are linked to significantly higher mortality rates among STEMI patients.[26] The findings from our study align with and contribute to the existing body of evidence surrounding this lipid paradox.

The combination of UA and HDL-C, represented by the UHR, has been proposed as a novel and more sensitive marker for various metabolic and inflammatory states. Previous studies have indicated that reduced levels of serum HDL-C and hyperuricemia might collectively worsen cardiovascular health by fostering insulin resistance and causing oxidative harm to endothelial cells.[27] For instance, Hu et al.[28] found that elevated serum UA levels alter how HDL-C affects carotid atherosclerosis. While a correlation between hyperuricemia and reduced HDL-C levels exists in cardiometabolic conditions, the impact of the interplay between UA and HDL-C on STEMI patients remains insufficiently explored. On the other hand, our study's results highlight the UHR as a reliable predictor of mortality in STEMI patients. In addition, one study reported elevated UHR values in patients with coronary fistula compared to control subjects.[29] Another study found that high UHR levels were associated with poor collateral circulation in patients with chronic total occlusion.[30] Similarly, UHR levels were reported to increase significantly in patients with hemodynamically significant coronary lesions.[31] Beyond coronary conditions, UHR has demonstrated associations with various non-coronary comorbidities. Studies have found significant correlations between UHR and adverse outcomes, including waist circumference, non-alcoholic fatty liver, body mass index, TG, fasting glucose, and glycated hemoglobin levels.[10,12] Taken together, the ease of obtaining a parameter such as UHR and its potential for predicting in-hospital mortality in individuals undergoing PPCI for STEMI highlight its clinical utility and the importance of its inclusion in risk assessment protocols.

Despite its initial development as a marker for the complexity of coronary lesions, the SYNTAX score has been extensively investigated for its implications for various complications and morbidities among patients with STEMI.[32-34] In alignment with existing literature, our study's findings affirm that a high SYNTAX score stands as an independent risk factor for in-hospital cardiovascular mortality in AMI patients.[35,36] Furthermore, parameters such as advanced age, high BNP levels, and an increased length of the implanted stent were also identified as contributors to poor outcomes, consistent with previous literature.[37-42] Moreover, anemia stands out as a prevalent and well-established factor contributing to short-term or in-hospital mortality among STEMI patients.[43] This association likely mirrors the link between anemia, comorbidities, and major adverse cardiovascular events. Similarly, our study reveals that higher hemoglobin levels are correlated with reduced in-hospital mortality. Additionally, impaired glucose regulation and uncontrolled DM emerge as significant predictors of mortality in STEMI cases.[44] Plausible mechanisms contributing to this observation among individuals with DM include advanced age, often accompanied by conditions such as dyslipidemia and elevated body mass index, endothelial dysfunction, and ultimately an increased prevalence of atherosclerosis. Our findings further emphasize an independent association between DM, elevated serum glucose levels, and in-hospital mortality in STEMI patients.

Limitations

Nevertheless, it's essential to acknowledge the primary limitation of our study, namely its retrospective, single-center design, which may introduce patient selection bias. Additionally, the determination of all-cause in-hospital mortality as the study's outcome poses another limitation. While our study successfully illustrates the association between UHR and short-term mortality in STEMI patients, we acknowledge the absence of comparative analysis between UHR and other inflammatory markers, as well as the lack of medium-to-long-term outcomes assessment in STEMI. Given the diverse causes of in-hospital mortality in the STEMI patient group, further investigations focusing on each etiological cause are warranted.

CONCLUSION

The UHR exhibited a significant positive correlation with in-hospital mortality in patients with STEMI undergoing PPCI. Serving as a novel biomarker, UHR, comprising serum UA and HDL-C, both easily and rapidly measurable through basic biochemical tests, holds promise for contributing to the prognostic classification of this patient group from the initial medical contact onward.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 20.07.2023, Decision No: 2720).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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

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

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Original Article

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Comparison of clinical and functional outcomes of patients who underwent plate osteosynthesis and intramedullary nailing for forearm fractures

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ABSTRACT

Aims: The aim of this study was to compare the functional and radiographic results of patients with forearm diaphyseal fractures after intramedullary nailing (IMN) and plate and screw osteosynthesis.

Methods: A total of 58 patients, including 31 patients operated on with the plate osteosynthesis method and 27 patients operated on with the IMN method for forearm diaphyseal fractures between 2017 and 2022, were retrospectively analyzed. The mean age was 35.9±14.5 years in the plate group and 33±13.1 years in the IMN group. The mean follow-up period was 157±83 days in the IMN group and 220±97 days in the plate group. Evaluation criteria for functional outcomes were forearm pronation; supination range of motion; the Disabilities of the Arm, Shoulder, and Hand (DASH) score; and the Grace-Eversmann score.

Results: The mean union time was 66.7 days in the plate group and 54.4 days in the IMN group (p=0.039). The mean length of hospitalization was 3.9±3.44 days in the plate group and 2.93±1.49 days in the IMN group. The mean supination range was 72.5±9.9 degrees in the plate group and 72.2±11.8 degrees in the IMN group. The mean pronation range was 81.2±11.7 degrees in the plate group and 80.3±15.5 degrees in the IMN group. The mean follow-up period was 157±83 days in the IMN group and 220±97 days in the plate group (p=0.011). According to the Association for Osteosynthesis/Orthopedic Trauma Association (AO/OTA) classification, 30 cases were classified as type A, 21 cases as type B, and 7 cases as type C. According to the Grace-Eversmann classification, 2 cases in the plate group were classified as unacceptable, 2 were classified as acceptable, 10 were classified as good, and 16 were classified as excellent, while 2 cases in the IMN group were classified as unacceptable, 4 were classified as acceptable, 5 were classified as good, and 16 were classified as excellent. The mean DASH score was 14.74±10.49 in the plate group and 15.11±12.7 in the IMN group.

Conclusion: With the advantages of minimal incision, less soft tissue damage, and no evacuation of the fracture hematoma, the union time and follow-up periods were found to be shorter in the IMN group. Thanks to the bearing force of intracanal intramedullary nails, patients were able to move earlier and satisfactory functional outcomes were obtained.

Keywords: Forearm fracture, intramedullary nailing, plate osteosynthesis, ulna fracture, radius fracture

INTRODUCTION

Forearm fractures occur as a result of falls, traffic accidents, sports activities, and occupational accidents and are common in young adults. The kinematics between the proximal and distal radioulnar joints are critical for load transfer throughout the upper limb.[1] Due to the functional and anatomical structure of the forearm bones, diaphyseal forearm fractures are considered as intraarticular fractures.[2,3] Formerly, these fractures were treated with nonsurgical methods such as casts. However, surgical interventions are performed to restore axial and rotational stability lost due to reasons such as nonunion, shortening, or false union.[4,5] Plate osteosynthesis is the most common treatment method for adult diaphyseal fractures.[6-8] Although this method provides adequate fixation, excellent union rates, and functional outcomes, it has some disadvantages. Among these are large surgical incisions, soft tissue stripping, periosteal stripping, skin irritation due to implants, delayed union due to fracture hematoma evacuation, and cosmetic problems.[6-8]

Intramedullary nailing surgeries using older models of intramedullary nails are not a preferred treatment method for forearm fractures due to high nonunion rates and insufficient stability. However, more recent locking intramedullary nails do provide adequate stabilization and rotation, which has made IMN a more frequently

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used method.[9-11] The locking and compression abilities of the more recent intramedullary nails help achieve high union rates, less soft tissue dissection, less bleeding, and better cosmetic appearance.[12,13] We suggest that IMN using new-generation intramedullary nails is not only an alternative to plate osteosynthesis, but also a better option for fixation in the treatment of forearm fractures.

The aim of this study was to retrospectively review patients who underwent plate osteosynthesis and IMN for forearm diaphyseal fractures and to compare their radiographic and functional outcomes and patient satisfaction. Our hypothesis was that IMN treatment, which has been used more frequently recently, is more feasible and more satisfactory in terms of outcomes than plate osteosynthesis.

METHODS

Ethics

Institutional approval was obtained for the study. Ethical approval was obtained from the Clinical Researches Ethics Committee of Gazi Yaşargil Training and Research Hospital where all imaging and patient procedures were performed in a single center (Date: 21.07.2023, Decision No: 466). The study had no financial incentives. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

A total of 58 patients, including 31 patients operated on with the plate osteosynthesis method and 27 patients operated on with the IMN method for forearm diaphyseal fractures between 2017 and 2022, were retrospectively analyzed. Forty-eight of the patients were male and 10 were female. Of the patients, 22 underwent operation for the right arm and 36 for the left arm. In plate group 16 patients had fractures as a result of falls, 9 as a result of traffic accidents, 3 as a result of assault, 1 as a result of gunshot injury, and 2 as a result of occupational accidents. In IMN group 14 patients had fractures as a result of falls, 8 as a result of traffic accidents, 1 as a result of assault, 1 as a result of gunshot injury, and 3 as a result of occupational accidents. Posteroanterior (PA) and lateral forearm radiographs of the patients, which were taken at the time of admission, postoperatively, and every 15 days until union and every 3 months after union, were evaluated. Fractures were classified according to the Association for Osteosynthesis/Orthopedic Trauma Association (AO/OTA) classification.[14] Ten of the fractures were opened. According to the Gustilo-Anderson classification,[15] 6 patients had type 1, 2 patients had type 2, and 2 patients had type 3 fractures. Absence of pain at the fracture line and cortical trabeculation and callus formation in at least 3 cortices evident by radiographs were considered as signifying union. Absence of union after 6 months was considered as nonunion. Patients were evaluated for shortening, rotational deformity, and malunion. For functional evaluation, forearm supination pronation angles were measured after union and Disabilities of the Arm, Shoulder, and Hand (DASH)[16] and Grace-Eversmann[17] scores were calculated. Time of union, presence and type of complications, open fractures, length of hospitalization, and etiologies were recorded. Complications encountered were radial nerve injury in 2 cases, radial and median nerve injury in 1 case, ulnar nerve injury in 1 case, median nerve neuropraxia in 1 case, and malunion of 10 degrees in 1 case.

Patients under 18 years of age, patients with open epiphyses, patients with pathological fractures, patients with Galeazzi and Monteggia fracture dislocation, patients with head trauma, and patients who did not attend regular follow-up appointments were excluded from the study. Two patients were excluded from the study because they died due to multiple trauma, while 5 patients in the plate group and 2 patients in the IMN group were excluded because they did not attend regular follow-ups.

Surgical Technique

All patients received a long arm splint until surgery. Surgeries were performed in the supine position using a radiolucent hand surgery table and a pneumatic tourniquet with 250 mmHg pressure. C-arm fluoroscopy was utilized to assess fracture reduction. The operations were performed by 4 different surgeons. All patients were operated on under general anesthesia or axillary block. All patients received 1 g of intravenous cefazolin 30 minutes before the operation. Patients with open fractures were operated on early to allow irrigation and debridement simultaneously with bone fixation on admission.

The surgical procedure was performed through separate incisions for patients who underwent plate osteosynthesis. Patients in the plate group were operated on with 3.5-mm limited-contact dynamic compression plates (TST Rakor Tıbbi Aletler Sanayi ve Ticaret Limited Şirketi, İstanbul, Turkiye). The volar Henry approach was used for middle and distal 1/3 fractures and the Thompson approach was used for proximal fractures. Operations for ulnar fractures involved an incision to the subcutaneous ulnar border. Only the area where the plate was to be placed was prepared subperiosteally. Soft tissue connections were retained whenever possible. Blood, clots, and soft tissues were removed from the fracture line, the fracture was reduced, and plates were placed. At least 3 screws (6 cortices) were placed distal and proximal to the fracture line. More screws were used

for osteoporotic and comminuted fractures. At the end of the surgery, the tourniquet was removed, the incisions were closed after controlling bleeding, and the operation was terminated.

In the IMN reduction group, patients were operated on using a single type of intramedullary nail (TST Rakor Tıbbi Aletler Sanayi ve Ticaret Limited Şirketi, İstanbul, Turkiye). The nails and plates used were made of titanium alloy.

The radius nail was solid and oval. Its 3-cm proximal part had a parabolic shape with a 10-degree angle towards the front. It was applied without carving. It provided three-point contact stability in the fracture line and had a distal 15-degree angled static locking hole. This angle prevented the locking screw from moving towards the joint. Preoperative radiographs were evaluated in order to determine the appropriate sizes of nails. Nail length was calculated by subtracting 2-3 cm from the distance between the radial styloid and the radial neck. Nail thickness was calculated as the narrowest point of the bone according to the PA radiograph. Although there were different diameter options for nails, the same nails were used for both right and left limbs. The operation was initiated through a 2-cm incision over the Lister tubercle. The second compartment was opened. An awl was used to drill the radius by excising the extensor carpi radialis longus and brevis tendons laterally. The entry point was advanced into the intramedullary space with a curved awl. A radius nail of appropriate length and diameter was advanced into the canal with rotational movements using a holder. When the nail tip reached the fracture line, it was advanced in the intramedullary direction after closed reduction. In cases where closed reduction was not successful, the fracture was reduced through a miniature open incision. After fluoroscopic evaluation, the distal locking screw was locked.

The 4-cm proximal part of the ulnar nail was tubular and its distal part was solid. Different locking options were available for both the distal and proximal part. The same nails are used for both right and left limbs. The proximal part was a standard 6 mm, but there were different length options for the distal part. Titanium allows for bending and twisting due to its elastic structure. Measurements for ulnar procedures were made similarly to those for radial procedures. The length of the ulnar nail was calculated by subtracting 2 cm from the distance between the ulnar styloid process and the olecranon. The operation was initiated through an incision of 2-3 cm at 90 degrees of flexion from the tip of the olecranon. The incision was advanced towards the canal using a straight awl. The K wire was inserted into the intramedullary canal and a 3-cm partial zone was opened with a cannulated drill. A nail of appropriate length and diameter was then advanced into the canal. When the fracture line was reached, the fracture was reduced without an incision or using a mini-incision and the nail was advanced distally. Proximal static or dynamic locking was performed. Distal locking was performed depending on the surgeon's preference. Patients were discharged 2-4 days after surgery according to pain control in the early postoperative period. The plate group was followed with a long arm splint for 3 weeks. All patients in the plate group had their splints removed and were allowed to perform passive movements of the wrist and elbow in the 3rd week. The IMN group did not receive splints postoperatively and were allowed to move their limbs on postoperative day 1.

Statistical Analysis

Statistical analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software package program (NCSS LCC, Kaysville, UT, USA). The data were analyzed using descriptive statistical methods (mean, standard deviation, median, and interquartile range). The distribution of the variables was examined with the Shapiro-Wilk normality test. The independent t-test was used in the comparisons of paired groups of normally distributed variables, while the Mann-Whitney U test was used in comparisons of paired groups of variables that did not show normal distribution. The chi-square test was used in the comparison of qualitative data. Values of $p<0.05$ were considered statistically significant.

RESULTS

Of the 58 patients, 48 (83%) were male and 10 (17%) were female. The mean age was 35.9±14.5 years in the plate group and 33±13.1 years in the IMN group. The mean length of hospitalization was 3.9±3.4 days in the plate group and 2.9±1.4 days in the IMN group (p=0.525). Ten of the patients (17%) had open fractures (Table 1). The mean pronation range was 81.2±11.7 degrees in the plate group and 80.3±15.5 degrees in the IMN group (p=0.799) (Table 1).

Table 1. Evaluation of parameters between groups

	Plate group n=31		IMN group n=27		p
Age Mean±SD	35.9±14.5		33±13.1		0.426*
Sex					0.249+
Male	24	77.4%	24	88.9%	
Female	7	22.6%	3	11.1%	
Laterality					0.501+
Right	13	41.9%	9	33.3%	
Left	18	58.1%	18	66.7%	
Follow-up period (days) Mean±SD	220.6±97.5		157.7±83		0.011*
Supination Mean±SD	72.58±9.9		72.22±11.8		0.901*
Pronation Mean±SD	81.2±11.7		80.3±15.5		0.799*
Hospitalization time (days)					0.525‡
Mean±SD	3.9±3.4		2.9±1.4		
Median (IQR)	3 (2-4)		2 (2-4)		

*: Independent t-test; ‡: Mann-Whitney U test; +: Chi-square test

The mean follow-up period was 157±83 days in the IMN group and 220±97 days in the plate group. Follow-up duration was significantly longer in the plate group than in the IMN group (p=0.011). (Table 2).

Table 2. Etiology of fractures

	Plate group n=31		IMN group n=27		p
Etiology					0.891+
Gunshot injury	1	3.3%	1	3.7%	
Assault	3	9.6%	1	3.7%	
Fall	16	51.6%	14	51.9%	
Occupational accident	2	6.5%	3	11.1%	
Traffic accident	9	29%	8	29.6%	

+: Chi-square test

Complications were observed in 3 patients in the plate group and 3 patients in the IMN group (p=0.858). The mean union time was 66.7±27.3 days in the plate group and 54.4±13.8 days in the IMN group, being significantly shorter in the IMN group (p=0.039) (Table 3). According to the Grace-Eversmann classification, 2 cases in the plate group were classified as unacceptable, 2 were classified as acceptable, 10 were classified as good, and 16 were classified as excellent, while 2 cases in the IMN group were classified as unacceptable, 4 were classified as acceptable, 5 were classified as good, and 16 were classified as excellent. (p=0.673) (Table 3). The mean DASH score was 14.74±10.49 in the plate group and 15.11±12.7 in the IMN group. There was no significant difference between the two groups in terms of DASH scores (p=0.755) (Table 3).

Table 3. Comparison of results between groups

	Plate group n=31		IMN group n=27		p
Fracture					0.199+
Double fracture of the forearm	12	38.7%	14	51.9%	
Radius shaft fracture	7	22.6%	8	29.6%	
Ulna fracture	8	25.8%	5	18.5%	
Ulna shaft fracture	4	12.9%	0	0.00%	
Union time (days) Mean±SD	66.7±27.3		54.4±13.8		0.039*
AO classification					0.798+
A	17	54.8%	13	48.2%	
B	10	32.3%	11	40.7%	
C	4	12.9%	3	11.1%	
Complications					0.858+
No	28	90.3%	24	88.9%	
Yes	3	9.7%	3	11.1%	
Type of complication					0.199+
Malunion of 10 degrees	1	33.3%	0	0.00%	
Median neuropraxia	1	33.3%	0	0.00%	
Radial injury	0	0.0%	2	66.7%	
Radial + median injury	0	0.0%	1	33.3%	
Ulnar nerve injury	1	33.3%	0	0.00%	
Open fracture					0.810+
No	26	83.9%	22	81.5%	
Yes	5	16.1%	5	18.5%	
Open fracture type					1+
Type 1	3	60.0%	3	60.0%	
Type 2	1	20.0%	1	20.0%	
Type 3	1	20.0%	1	20.0%	
Grace-Eversmann classification					0.673+
Unacceptable	2	6.4%	2	7.4%	
Acceptable	3	9.7%	4	14.8%	
Good	10	32.3%	5	18.5%	
Excellent	16	51.6%	16	59.3%	
DASH score					0.755‡
Mean±SD	14.7±10.4		15.1±12.7		
Median (IQR)	12 (7-20)		12 (8-18)		

*: Independent t-test; ‡Mann-Whitney U test; +: Chi-square test

DISCUSSION

In the current study, union time and follow-up duration were found to be shorter in patients who underwent IMN for forearm fractures compared to patients who underwent plate osteosynthesis. However, there was no significant difference between patients who underwent plate osteosynthesis and patients who underwent IMN in terms of functional outcomes and patient satisfaction. Good results were obtained in both groups (Figure 1, Figure 2).

In a study conducted by Polat et al.[18] with a group of 46 patients who underwent new-generation IMN and plate osteosynthesis for forearm fractures, the mean union time was 10.9 weeks in the IMN group and 13.2 weeks in the plate group, with union being faster among patients who underwent IMN. In their study including 100 patients, Savajiyani et al.[19] achieved adequate union in 88 cases using IMN and reported union times compatible with other studies in the literature. In a study by Özkaya et al.[12] union time was found to be 10 weeks in the IMN group and 14 weeks in the plate group. In their study, Kibar et al.[13] achieved a mean union time of 12.1 weeks in the IMN group and 12.2 weeks in the plate group. In the present study, the mean union time was 54 days in the IMN group and 66 days in the plate group, being significantly shorter in the IMN group. These results are consistent with the literature. The follow-up periods of IMN patients were shorter due to earlier union. As in cases of lower extremity fractures, we suggest that this difference occurs because nailing both allows micro-movement in the fracture and better retains normal anatomy.

In a study by Visna et al.[20] that included 115 fractures and 80 patients, no difference was found between the post-union DASH scores, Grace-Eversmann scores, and supination and pronation ranges of patients according to surgery method. Weckbach et al.[21] found a mean DASH score of 14 for forearm fractures treated with IMN. In a study conducted by Köse et al.[10] including patients who underwent IMN, the mean DASH score was 15, while 14 patients had excellent, 3 had good, and 1 had an acceptable Grace-Eversmann classification. Lee et al.[22] found no significant difference between the DASH scores, Grace-Eversmann scores, and supination and

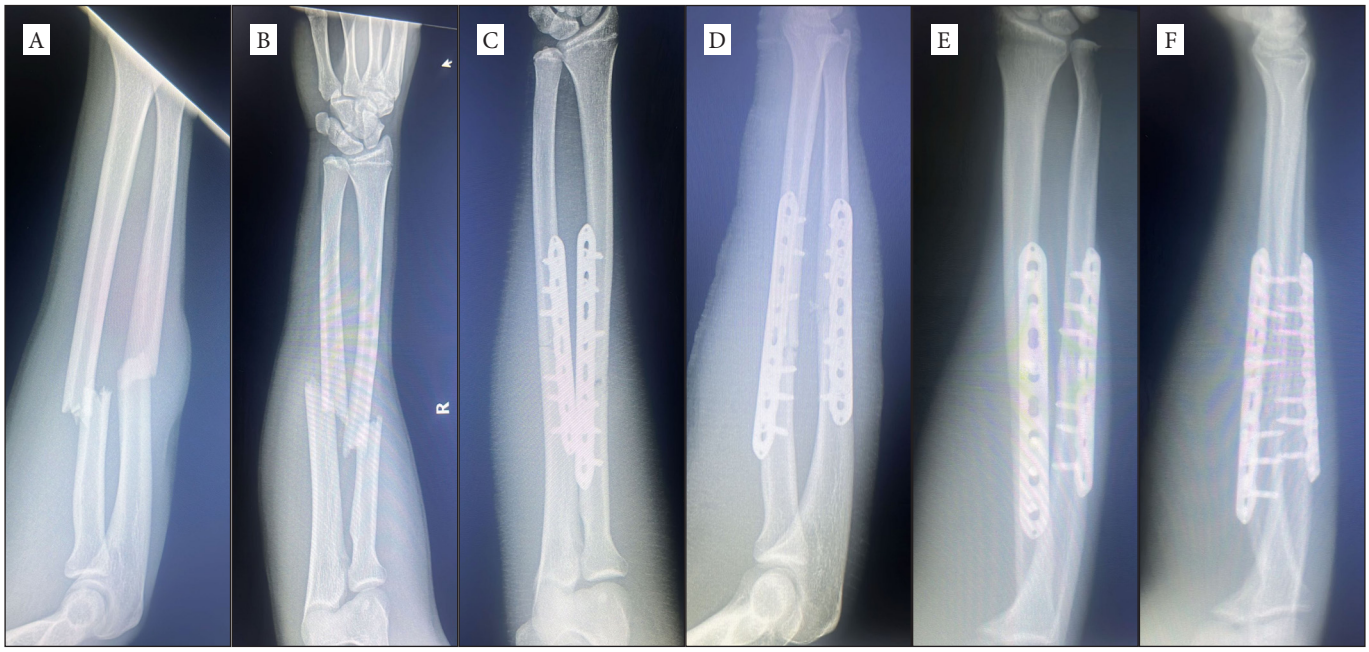

Figure 1. Preoperative posterior-anterior and lateral radiographs of a 34-year-old male patient who underwent plate osteosynthesis due to right diaphyseal forearm fracture (A, B); postoperative posterior-anterior and lateral radiographs at 2 weeks (C, D); postoperative posterior-anterior and lateral radiographs at 12 months (E, F).

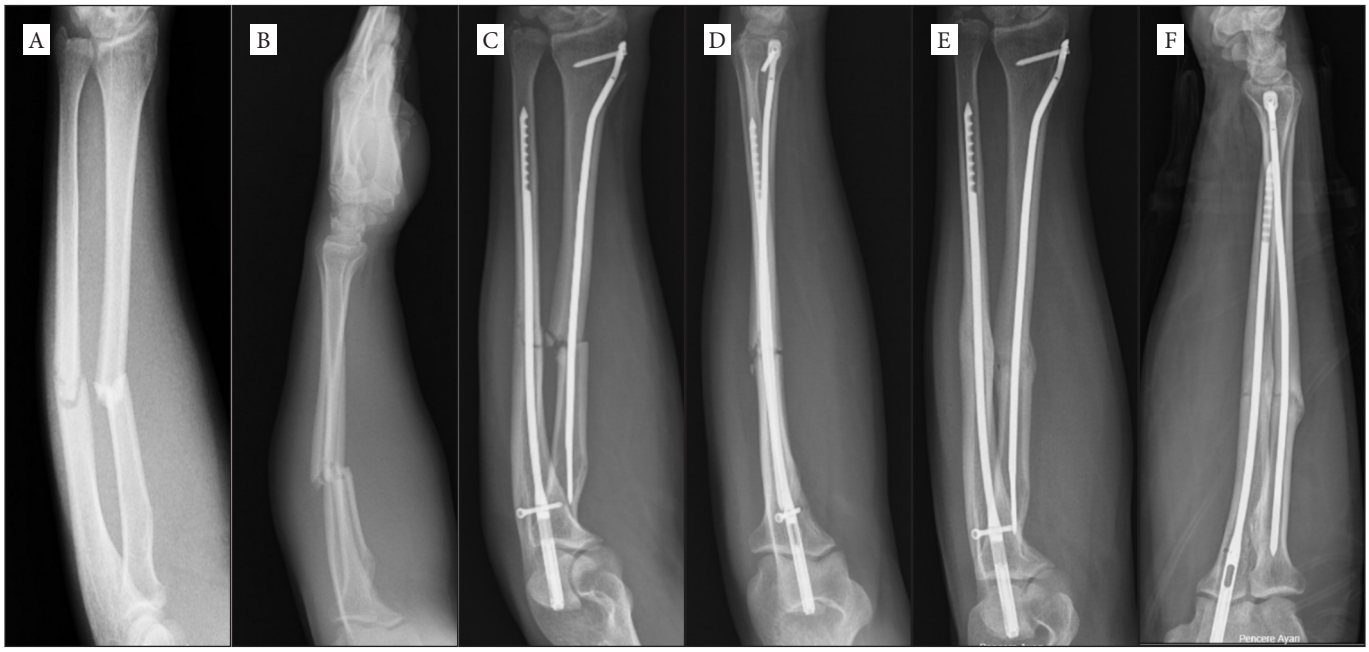

Figure 2. Preoperative posterior-anterior and lateral radiographs of a 34-year-old male patient who underwent IMN due to right diaphyseal forearm fracture (A, B); postoperative posterior-anterior and lateral radiographs at 2 weeks (C, D); postoperative posterior-anterior and lateral radiographs at 12 months (E, F).

pronation ranges of patients in the plate group and the IMN group. In the present study, no difference was found between functional scores according to surgery method. It was found that new-generation IMN achieved functional outcomes comparable to plate osteosynthesis.

In their study comparing fracture types and open and closed fractures, Polat et al.[18] classified 9 cases as type A, 9 cases as type B, and 3 cases as type C in the IMN group and 11 cases as type A, 9 cases as type B, and 5 cases as type C in the plate group according to the AO/OTA classification, and they found no significant differences between the groups in terms of union time. In the study by Lee et al.[22] 16 cases were classified as type A and 19 as type B in the IMN group while 14 cases were classified as type A and 18 as type B in the plate group, and no significant difference was found between the groups in terms of union time and operation time. Both of these studies reported no significant difference between open and closed fractures in terms of union time. The present study also found no difference between classifications and open and closed fracture types in terms of union time, and union times were compatible with those of other studies in the literature.

Elastic titanium nails were used in this study. Radius instability was the most common problem of old-generation nails. By establishing three-point contact and distal locking, new-generation nails provide better rotational stability and radial bow. Distal locking allows compression up to 7 mm. Both dynamic and static locking provide adequate stabilization in the ulna and allow for earlier postoperative motion compared to plate osteosynthesis.[10,11,23] The proximal locking of new-generation intramedullary nails reduces the risk of nerve damage in radius nailing.[24] In their study, Lee et al.[22] did not find any difference between the functional and clinical outcomes of patients who underwent plate osteosynthesis and IMN, although their radial bow restoration and the location of the maximum radial bow significantly differed. That study guided us to emphasize the use of IMN instead of plate osteosynthesis. In addition, since implant discomfort in patients treated with IMN is very low compared to patients who undergo plate osteosynthesis, requests for implant removal have decreased among these patients and most patients have not undergone reoperation. Despite the many advantages of IMN, its main disadvantage is excessive exposure to radiation due to excessive use of scopes during surgery.

Limitations

The main limitations of this study are its retrospective design and the small number of patients included. In addition, since the study was retrospective, the patient distribution was not homogeneous. Patients who did not attend regular postoperative follow-up had to be excluded from the study. The fact that the operations were performed by different surgeons is another limitation. In addition, forearm fractures could not be evaluated separately as radius, ulna, and forearm double fractures due to the small number of patients. Other limitations include the lack of standardization of follow-up periods and the unequal numbers of screws used for the patients.

CONCLUSION

With the advantages of a minimal incision, less soft tissue damage, and no evacuation of the fracture hematoma, the union time and follow-up periods were found to be shorter in the IMN group. Thanks to the bearing force of intracanal intramedullary nails, patients were able to move earlier and satisfactory functional outcomes were obtained. We suggest that IMN should be the treatment of choice rather than merely an alternative to plate osteosynthesis due to better union times, good functional outcomes, good cosmetic results, and fewer implant-related problems.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of University of Health Sciences Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 21.07.2023, Decision No: 466).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Obesity among adolescent students in private and public schools investigation of awareness: a cross-sectional study

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ABSTRACT

Aims: The aim of this study was to examine the obesity awareness of adolescent students in private and public schools.

Methods: The research is a quantitative study. The research group for the study consisted of 1393 private and public school students between the ages of 10 and 13 in Kırıkkale province. The first stage included a personal information form including questions about gender, age, BMI, socio-economic status, physical activity for half an hour or more per week, and daily food distribution. In the second stage, the Obesity Awareness Scale developed by Allen (2011) and adapted into Turkish by Kafkas and Özen (2014) was used. The scale consists of 3 sub-dimensions and 20 questions.

Results: It was observed that there was a significant difference in the anthropometric characteristics, obesity awareness, nutrition and physical activity, BMI, daily food distribution, and socio-economic status groupings of private and public school children. It was seen that there was a significant difference in all other variables and sub-dimensions except body weight, BMI, and obesity total between girls and boys; there was a significant difference in all other variables except anthropometric characteristics of girls in private and public schools; and there was a significant difference in all other variables except the age variable of boys in private and public schools.

Conclusion: The anthropometric characteristics, obesity awareness, nutrition and physical activity, BMI, daily food distribution, and socio-economic status of female and male students in private and public schools were significantly different from each other. In private school students, the highest correlation was found between obesity total and socio-economic status, while the lowest correlation was found between obesity total and the physical activity dimension. In public school students, the highest correlation was found between the obesity dimension and BMI, and the lowest correlation was found between the physical activity dimension and socio-economic status.

Keywords: Obesity, obesity awareness, adolescent, private and public school, students

INTRODUCTION

Obesity is a growing public health concern affecting all age groups, characterized by abnormal or excess fat accumulation with detrimental effects on health.[1-4] It significantly increases the risk of chronic conditions such as diabetes, heart disease, and joint pain.[5-7] Recognizing its prevalence and associated comorbidities underscores the importance of raising awareness and promoting preventative measures.[8-10] Early detection and intervention are crucial in mitigating the risk of obesity-related health complications, emphasizing the need for effective preventive health policies.[11-14] The World Health Organization (WHO) states that the number of people suffering from obesity worldwide is more than 500 million.[15,16] The prevalence of obesity in Turkiye is increasing day by day and was reported to be 21.1% in 2019.[17,18] In Turkiye, 19.9% of the population aged 15 years and over are classified as obese, while 33.7% are recorded as overweight.[19,20] Early awareness-raising in society and especially among adolescents plays a critical role in combating common diseases such as obesity.[21,22] Most children and young people spend too much time at home watching television, using tablets, spending time with game consoles, and spending too much time in front of the computer without participating in social activities.[23] In addition, individuals who adopt a physically sedentary lifestyle increase the risk of obesity due to improper eating habits.[24,25] For these reasons, it is of great importance for individuals to raise awareness about obesity, to raise awareness about the diseases that cause obesity, and to increase obesityawareness.[26]

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Given the enormous burden obesity imposes on both individuals and society, there is an urgent need to deepen our understanding of the factors that influence obesity awareness, particularly among the adolescent population. Adolescence represents a crucial stage in the development of lifelong habits and attitudes towards health and is a critical juncture for targeted interventions. Therefore, this study will contribute to the literature by examining the obesity awareness levels of adolescent students in both private and public schools. Obesity, which is an important risk factor in human life from an early age, is one of the factors that directly affect the quality of life. In order to prevent and treat obesity, increasing obesity awareness and transferring healthy lifestyle habits to individuals is the most fundamental step. The aim of this study is to examine the obesity awareness of adolescent students in private and public schools.

METHODS

Ethics

This study was carried out with the permission of Kırıkkale University Social and Human Sciences Researches Ethics Committe (Date: 18.10.2023, Decision No: 2023/207445). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Research Model

The research is a quantitative study. The research was conducted based on the descriptive survey model. The survey model refers to the type of research in which factors such as the opinions, attitudes, abilities, interests, and skills of the individuals participating in the research are determined.[27]

Research Group

The research group for this study consists of 1393 private and public school students between the ages of 10 and 13 in Kırıkkale province. Participation was completely voluntary. All participants participated in the study with an informed consent form. Participants who did not want to participate in the study left without completing the form before continuing the study.

Data Collection

The data collection process consisted of two stages: The first stage consisted of a personal information form including questions about gender, age, BMI, socio-economic status, physical activity for half an hour or more per week, and daily food distribution. In the second stage, the Obesity Awareness Scale developed by Allen[28] and adapted into Turkish by Kafkas and Özen[29] was used. The Obesity Awareness Scale is a measurement tool with three subscales and a total of 20 items. The first subscale (obesity awareness) consists of 8 items; the second subscale (nutritional awareness) consists of 7 items; and the third subscale (physical activity awareness) consists of 5 items. An increase in score indicates an increase in obesity awareness.

Statistical Analysis

Cronbach's alpha was analyzed to determine the reliability of the study. The "Kolmogorov-Smirnov" test was used to determine whether the data were normally distributed. Statistical information on the anthropometric characteristics of the children studying in private and public schools, sub-dimension scores of the Obesity Awareness Scale, BMI, daily meal distributions, and socioeconomic status groupings was determined and entered into the SPSS program. The data obtained were analyzed in the IBM SPSS 25.0 program. The mean and standard deviation descriptive statistics of all the data were calculated. An independent sample t-test was applied to analyze the differences between groups, and Cohen's effect size was also analyzed between groups. The Obesity Awareness Scale's Cronbach's alpha was determined to be 0.786.

RESULTS

When the descriptive data on children in private and public schools were examined, the highest percentages of the participants in the age variable were in the 12 age group with 37.8%, 61.5% of the male students and 38.5% of the female students, 58.1% of the participants were public school students and 41.9% were private school students, 9.5% of the participants were overweight, 20.9% were overweight, and 39.8% were normal weight according to BMI data. According to the data on physical activity for half an hour or more per week, 19.5% did nothing, 51.6% did physical activity 1-2 days per week, 17.9% did physical activity 3-4 days per week, and 10.9% did physical activity 5-6 days per week. It was observed that 6.5% of the participants had 2 meals, 52.8% had 3 meals, 36.2% had 4 meals, and 4.5% had 5 meals daily (**Table 1**).

When the statistical data on anthropometric characteristics of children in private and public schools, sub-dimensions of the obesity awareness scale, BMI, frequency of physical activity for half an hour or more per week, daily food distribution, and socio-economic status groupings were examined according to the private and public school variables, it was seen that there was a significant difference in all variables. While BMI had the lowest effect size, the highest effect size was observed in the physical activity dimension (**Table 2**).

Table 1. Descriptive data of children in private school and state school

Demographics characteristic	n	%
Total number of participants	1393	100
Age		
10 years	169	12.1
11 years	459	33
12 years	526	37.8
13 years	229	17.2
Gender		
Boys	857	61.5
Girls	536	38.5
School type		
Private school	583	41.9
State school	810	58.1
BMI		
Overweight	133	9.5
At risk for overweight	291	20.9
Normal weight	555	39.8
Underweight	414	29.7
Socioeconomic status groupings		
High	421	30.2
Medium	834	59.9
Low	138	9.9
Half an hour or more per week physical activity		
Nothing	272	19.5
1-2 days	719	51.6
3-4 days	250	17.9
5-6 days	152	10.9
Daily meal distributions		
Two meals	91	6.5
Three meals	735	52.8
Four meals	504	36.2
Five meals	63	4.5

BMI: Body mass index.

Table 2. T-test results and effect sizes of students in private and public schools according to the sub-dimensions of the obesity awareness scale

Variables	Private School (n=583)	State School (n=810)	Total (n=1393)	p	Cohen's d
Anthropometric					
Age (yrs)	12.3±1.0	12.0±0.9	12.9±0.9	0.001*	0.31
Height (cm)	153.7±9.7	152.0±9.4	152.7±9.6	0.001*	0.18
Body mass (kg)	50.4±13.2	47.7±11.9	48.9±12.8	0.001*	0.22
BMI (kg/m²)	21.2±4.9	20.5±4.3	20.8±4.6	0.001*	0.15
Obesity awareness and sub dimension scores					
Obesity	29.2±4.5	28.4±5.2	28.7±4.9	0.001*	0.16
Nutrition	19.5±3.3	18.9±3.6	19.1±3.5	0.001*	0.17
Physical activity	16.7±3.0	15.3±3.4	16.5±3.2	0.001*	0.43
Obesity total	65.3±9.2	63.5±10.7	64.3±10.1	0.001*	0.18
Half an hour or more per week physical activity					
Nothing	101	171	272	0.001*	
1-2 days	316	403	719	0.001*	
3-4 days	107	143	250	0.001*	
5-6 days	59	93	152	0.001*	
BMI					
Weak	151	263	414	0.001*	
Normal weight	243	312	555	0.001*	
Overweight	103	188	291	0.001*	
Very overweight	86	47	133	0.001*	
Daily meal distributions					
Two meals	38	53	91	0.001*	
Three meals	313	422	735	0.001*	
Four meals	207	297	504	0.001*	
Five meals	25	38	63	0.001*	
Socioeconomic status groupings					
High	51	87	138	0.001*	
Medium	335	499	834	0.001*	
Low	197	224	421	0.001*	

BMI: body mass index; *p<0.001

According to the gender variable, when the statistical data on the anthropometric characteristics of girls and boys, age and height, obesity awareness scale sub-dimensions, BMI, daily food distribution, and socio-economic status groupings were examined, it was seen that there was a significant difference in the sub-dimensions of all of these variables. When the effect sizes between genders were examined, it was seen that the effect size was the smallest in body weight, while the effect size was the highest in the physical activity sub-dimension (Table 3).

When the data of female students in private and public schools were examined, it was seen that there was no significant difference in the anthropometric characteristics of female students in private and public schools, and when the statistical data related to the sub-dimensions of the obesity awareness scale, BMI, frequency of physical activity for half an hour or more per week, daily food distribution, and socio-economic status groupings were examined, it was seen that there was a significant difference in the sub-dimensions of all of these variables. When the effect sizes of the scores of female students in private and public schools were analyzed, the lowest effect size was seen in height scores, while the highest effect size was seen in the physical activity sub-dimension. When the data of male students in private and public schools were examined, it was seen that there was no significant difference in the age variable among the anthropometric characteristics, and when the statistical data related to the sub-dimensions of the obesity awareness scale, BMI, frequency of physical activity for half an hour or more per week, daily food distribution, and socio-economic status groupings were examined, it was seen that there was a significant difference in the sub-dimensions of all of these variables. When the effect sizes of the scores of male students in private and public schools were analyzed, the lowest effect size was found in the physical activity sub-dimension, and the highest effect size was found in body weight (Table 4).

Table 3. T-test results and effect sizes of male and female students in private and public schools according to the sub-dimensions of the obesity awareness scale

Variables	Girls (n=536)	Boys (n=857)	Total (n=1393)	p	Cohen's d
Anthropometric					
Age (yrs)	12.0±0.9	12.2±0.9	12.1±0.9	0.001*	0.22
Height (cm)	151.4±9.2	153.6±9.7	152.7±9.5	0.001*	0.24
Body mass (kg)	48.1±12.3	49.3±12.7	48.8±12.6	0.061	0.01
BMI (kg/m²)	20.9±4.4	20.8±4.7	20.8±4.6	0.836	0.02
Obesity Awareness and sub dimension scores					
Obesity	27.8±4.8	29.7±4.9	28.7±4.9	0.001*	0.40
Nutrition	18.2±3.4	19.3±3.6	19.1±3.5	0.001*	0.32
Physical activity	14.5±3.2	16.6±3.2	16.5±3.2	0.001*	0.66
Obesity Total	64.5±9.9	64.1±10.3	64.3±10.1	0.579	0.04
Half an hour or more per week Physical activity					
Nothing	104	168	272	0.001*	
1-2 days	289	430	719	0.001*	
3-4 days	92	158	250	0.001*	
5-6 days	51	101	152	0.001*	
BMI					
Weak	154	260	414	0.001*	
Normal Weight	215	340	555	0.001*	
Overweight	128	163	291	0.001*	
Very overweight	39	94	133	0.001*	
Daily meal distributions					
Two meals	36	55	91	0.001*	
Three meals	276	459	735	0.001*	
Four meals	197	307	504	0.001*	
Five meals	27	36	63	0.001*	
Socioeconomic status groupings					
High	55	83	138	0.001*	
Medium	320	514	834	0.001*	
Low	161	260	421	0.001*	

BMI: body mass index; *p<0.001

Table 4. T-test results and effect sizes of girls in private and public schools and boys in private and public schools according to the sub-dimensions of the obesity awareness scale

n=1393	Private school girls (n=223)	State school girls (n=313)	p	Cohen's d	Private school boys (n=360)	State school boys (n=497)	p	Cohen's d
Anthropometric								
Age (yrs)	11.9±0.9	12.0±0.9	0.278	0.11	12.4±0.9	12.0±0.9	0.153	0,44
Height (cm)	151±8.6	151±9.6	0.966	0.01	155.2±10.6	152.2±9.3	0.001*	0,30
Body mass (kg)	47.1±12.8	48.7±12.4	0.146	0.13	52.5±13.5	47.1± 11	0.001*	0,56
BMI (kg/m²)	20.4±4.3	21.1±4.5	0.072	0.16	21.7±5.2	20.1±4.1	0.001*	0,34
Obesity awareness and sub dimension scores								
Obesity	28.3±4.2	30.5±5.2	0.001*	0.47	29.1±4.7	28.3±5.2	0.001*	0,16
Nutrition	19.6±3.0	18.9±3.7	0.001*	0.21	19.4±3.4	18.8±3.7	0.001*	0,17
Physical activity	18.8±2.9	16.3±3.4	0.001*	0.80	16.6±3.1	16.3±3.3	0.001*	0,09
Obesity Total	65.6±8.4	63.6±10	0.001*	0.33	65.1±9.6	63.4±10	0.001*	0,24
Half an hour or more per week Physical activity								
Nothing	40	64	0.001*		61	107	0.001*	
1-2 day	127	162	0.001*		189	241	0.001*	
3-4 day	38	54	0.001*		69	89	0.001*	
5-6 day	18	33	0.001*		41	60	0.001*	
BMI								
Weak	71	83	0.001*		80	180	0.001*	
Normal weight	89	126	0.001*		154	186	0.001*	
Overweight	55	73	0.001*		48	115	0.001*	
Very overweight	8	31	0.001*		78	16	0.001*	
Daily meal distributions								
Two meals	14	22	0.001*		24	31	0.001*	
Three meals	112	164	0.001*		201	258	0.001*	
Four meals	84	113	0.001*		123	184	0.001*	
Five meals	13	14	0.001*		12	24	0.001*	
Socioeconomic status groupings								
High	22	33	0.001*		29	54	0.001*	
Medium	128	192	0.001*		207	307	0.001*	
Low	73	88	0.001*		124	136	0.001*	

When the correlation data of the private and public school students in Table 5 are analyzed, it is seen that the low correlationis between the physical activity dimension and socio-economic status, and the lowest correlation is between obesity status and the physical activity dimension in private and public schools. When the correlation data of the private school students were analyzed, it was seen that the low correlation was between obesity total and socio-economic status, and the lowest correlation was between obesity total and physical activity dimension. When the correlation data of the public school students were analyzed, it was seen that the low correlation was between the obesity dimension and BMI, and the lowest correlation was between the physical activity dimension and socio-economic status. In summary, it can be said that BMI is highly correlated with obesity, and obesity is also highly correlated with socio-economic status (Table 5).

Table 5. Data on the correlation results of BMI with socio-economic status, physical activity, and nutrition status of students in private and public schools

Variable	r	r^2	p value
Obesity Total- Socioeconomic status	0.091**	0.008	0.01
Private and State School			
Obesity Total -BMI	0.071**	0.005	0.01
Obesity dimension-BMI	0.059*	0.003	0.05
Obesitydimension-Socioeconomic status	0.079**	0.006	0.01
Obesity dimension-Physical activity dimension	0.058*	0.003	0.05
Nutrition dimension- BMI	0.079**	0.006	0.01
Nutrition dimension-Socioeconomic status	0.064*	0.004	0.05
Physical activity dimension-Socioeconomic	0.100**	0.01	0.01
Physical activity dimension- Physical activity	0.062*	0.004	0.05
Private School			
Obesity Total- Socioeconomic status	0.128**	0.016	0.01
Obesity Total - Physical activity	0.091*	0.008	0.05
Obesity dimension- Socioeconomic status	0.125**	0.016	0.05
Nutrition dimension-Socioeconomic status	0.121**	0.015	0.05
State School			
Obesity Total -BMI	0.131**	0.017	0.01
Obesity dimension-BMI	0.219**	0.047	0.01
Nutrition dimension- BMI	0.172**	0.03	0.01
Physical activity dimension-Socioeconomic	0.123**	0.015	0.01

**, Correlation is significant at the 0.01 level (2-tailed); *, Correlation is significant at the 0.05 level (2-tailed); BMI: body mass index

DISCUSSION

The aim of this study was to investigate obesity among adolescent students in private and public schools. Awareness of the participants. When the results of the research were examined, it was determined that the highest participation rate was in the 12 age group and the lowest participation rate was in the 10 age group. According to gender, male students had the highest participation rate. It was determined that the participation of public school students was higher than that of private school students. According to BMI results, it was determined that the rate of students with normal weight was higher than that of those with overweight, overweight, and underweight. According to the socio-economic status grouping, the highest value was found to be 59.9% of students with medium economic status. It was observed that the highest frequency of doing physical activity for half an hour or more per week was 1-2 days. In the daily meal distribution rates, it was concluded that those who ate three meals had the highest value.

Anthropometric measurements performed between students in private and public schools showed that there were significant differences between age, height, body weight, and BMI values. In addition, it was determined that there was a significant difference between the obesity awareness scale and its sub-dimensions: the frequency of physical activity performed for half an hour or more per week, daily meal distributions, and socio-economic status. According to Yüksel and Akıl's[30] study, while the physical activity levels of young people were low, their awareness of obesity was high, but their eating habits were found to be negative. Their study showed that adolescents have high awareness of obesity, but they behave negatively in terms of nutrition. In a study conducted by Vançelik et al.[31] it was found that doing regular sports significantly affected the nutritional habit score, a large proportion of university students (87.4%) skipped meals, and students frequently skipped breakfast. Ermiş et al.[32] reported that socio-demographic characteristics and healthy lifestyle habits were related to nutritional habits. These studies are in parallel with our study. Lytle[33] showed that physical activity and nutrition-oriented course programs temporarily create changes in weight or eating habits. The study reveals that curricula based on physical activity and nutrition have a short-term effect on eating habits or weight.

It was determined that there was a significant difference between boys and girls in the anthropometric characteristics of age and height, sub-dimensions of the obesity awareness scale, BMI, daily food distribution, and socio-economic status. When the effect sizes between genders were analyzed, it was observed that the lowest effect size was in body weight and the highest effect size was in the physical activity sub-dimension of the obesity awareness scale. In the study conducted by Uyar et al.[34] it was determined that the majority of students with underweight or normal weight were in public schools, while overweight and obese students were private

school students. It was determined that students in the underweight and normal categories had high rates of taking nutrition to school, while overweight and obese students were more likely to eat from the school canteen and take nutrition with them.

It is observed that children who both receive nutrition and are fed from the school canteen or cafeteria are in the overweight and obese category. This shows that the number of meals increased. It can be said that children with increased number of meals and shorter meal intervals are exposed to weight gain. In different studies conducted by Alasmari et al.,[35] Özkan et al.,[36] Yıldırım et al.,[37] Aslan and Gündoğdu,[38] it was concluded that there was no significant difference between genders in obesity awareness levels. Al-Zandee and Ünlü[39] and Coşkun and Karagöz[40] determined that boys are more active than girls in physical activity levels between genders and that boys perform physical activity at higher rates.[46,47] In our study, it was observed that there was a difference in obesity awareness and physical activity level between genders.

There was no significant difference in the anthropometric characteristics of female students between private and public schools, but there was a significant difference in obesity awareness, BMI, frequency of physical activity of half an hour or more per week, daily food distribution, socio-economic status groupings, and sub-dimensions. In female students, the effect size was lowest in height scores and highest in the physical activity sub-dimension. Among the anthropometric characteristics of male students, there was no significant difference in the age variable, but there was a significant difference in height, body weight, obesity awareness, BMI, physical activity frequency of half an hour or more per week, daily food distribution, socio-economic status groupings, and sub-dimensions. Alphan, Keskin, and Tatlı[41] found that both male and female students in private schools were at least 3 cm taller than both male and female students in public schools. In our study, it was observed that there was no significant difference between female students in private and public schools according to the height variable. In our study, it was seen that there was a difference in the height variable for male students. In male students, the lowest effect size was found in the physical activity sub-dimension and the highest effect size was found in body weight.

In the correlation data of total students between private and public schools, the highest correlation was found between the physical activity dimension and socio-economic status, and the lowest correlation was found between obesity status and the physical activity dimension. In the correlation data of the students in private schools, the highest correlation was between obesity total and socio-economic status, and the lowest correlation was between obesity total and physical activity dimension. When the correlation data of the public school students were analyzed, it was seen that the highest correlation was between the obesity dimension and BMI, and the lowest correlation was between the physical activity dimension and socio-economic status. In the study conducted by Yıldırım et al.,[37] it was determined that the obesity awareness of individuals with high physical activity levels was also high. In the study conducted by Bereket and Atay[42] and Marwaha et al.,[43] it was determined that those with high socio-economic levels had high obesity problems. Salmon et al.,[44] and Chhatwal et al.[45] found that children with high socio-economic status were more likely to be obese than poor children.

CONCLUSION

As a result, it is seen as a result of the studies that students who study in private schools and have a high socio-economic status have a high probability of obesity. We can say that the probability of obesity is low in favor of students studying in public schools or students with lower socio-economic status. Good economic opportunities create more comfort in students who have the opportunity to study in private schools, and instead of taking food to school, they benefit from the cafeteria at school, feed from the school canteen, take more calories during the day, consume packaged products, and increase the frequency of nutrition from 3 meals to more than 3 meals. The full-day nature of private schools also keeps students tied to school all day and limits their mobility. Students who eat more than they should and move less than they should will increase their weight and BMI. Public school children should be prevented from getting less nutrition than they need due to a lack of resources. In this case, regardless of the circumstances, it is the responsibility of families, educators, health scientists, and the whole society to educate our children correctly, raise their awareness against obesity, and raise awareness of healthy living. Building a healthy society means raising good generations, preparing a good future, creating good economic conditions, and preparing a prosperous life for everyone. It is thought that our future generations should be raised with this awareness.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was carried out with the permission of Kırıkkale University Social and Human Sciences Researches Ethics Committe (Date: 18.10.2023, Decision No: 2023/207445).

Informed Consent
Participation was completely voluntary. All participants participated in the study with an informed consent form. Participants who did not want to participate in the study left without completing the form before continuing the study.

Referee Evaluation Process
Externally peer-reviewed.

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

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

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

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Original Article

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Outcomes of fetal non-cardiac thoracic abnormalities: a single center experience

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ABSTRACT

Aims: This study planned to evaluate fetal non-cardiac thoracic anomalies, which are less common than other organ systems, in terms of diagnosis, incidence, therapy and prognosis.

Methods: The data of 66 cases who were evaluated in a perinatology department between January 2021 and July 2023 with diagnosis of fetal non-cardiac thoracic abnormalities were analyzed retrospectively.

Results: A total of 66 cases were in our study with a mean maternal age of 28.61±4.9 years and a median gestational week of first assessment at our center of 24 weeks (15-38 weeks). The most common non-cardiac thoracic malformation was congenital diaphragmatic hernia (30 cases, 45.4%), followed by congenital pulmonary airway malformation (CPAM) (17 cases, 25.7%). Termination of pregnancy was performed in 4 cases (6.06%). While genetic testing was carried out in a total of 9 cases (13.9%), no chromosomal abnormality was found in any of these cases. In utero interventional procedure was performed in 5 cases (7.57%) and success was achieved in 3 cases. Ten (58.8%) cases with CPAM lesions were resolved during the late antenatal or postnatal period with expectant management. Surgery was performed in 2 (11.8%) of 17 cases with CPAM.

Conclusion: Deliveries of the FNTA cases should be planned in tertiary centers where necessary intervention and care can be provided. A multi-disciplinary team could demonstrate a crucial role in assuring that the pregnant woman and fetus obtain appropriate treatment and are managed during the antenatal and postnatal periods. US plays a crucial role in the diagnosis and management of FNTA cases during the prenatal period rather than fetal MRI and other diagnostic tools. More than half of the CPAM lesions regressed spontaneously with expectant management.

Keywords: Congenital thoracic malformations, prenatal ultrasound, postnatal treatment

INTRODUCTION

Fetal non-cardiac thoracic abnormalities (FNTA) are reported to occur in 1/10000-1/35000 pregnancies that originate from lung parenchyma, airways or vascular structures. These abnormalities develop as a consequence of diverse embryologic abnormalities. However, because of the similar physiopathologic mechanisms, these anomalies might potentially have a devastating effect on normal fetal development and perinatal outcomes.[1]

FNTA are increasingly being detected using prenatal ultrasound nowadays.[2] FNTA take a place in a wide range from asymptomatic and small-sized pathologies to covering most of the thorax, accompanied by other anomalies and requiring urgent intervention. Intrauterine recognition of thoracic anomalies and knowing their possible complications play a decisive role in pregnancy follow-up strategy, delivery method and perinatal care.[3]

The main method of examination is ultrasonography (USG). Magnetic resonance imaging (MRI) can be considered in addition to USG in cases where USG is not sufficient. USG appearances of some pathologies are very similar and prenatal definitive diagnosis is often not possible. Especially, MRI is used as an auxiliary method in cases where diagnosis is difficult and in calculating lung volüme comes into play.[4] The most important predictor of perinatal survival in a fetus with a lung mass is the presence or absence of fetal hydrops. The mortality rate can reach%90 in the presence of hydrops.[5]

The most common thoracic anomalies in fetuses are congenital diaphragmatic hernia (CDH), congenital pulmonary airway malformation (CPAM) and hydrothorax. Congenital bronchogenic cysts, esophageal duplication cysts, bronchial atresia, and arteriovenous malformations are rare anomalies.[6,7]

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In this study, FNTA cases of our maternal-fetal medicine unit were classified according to their origin and presented based on USG findings.

METHODS

Ethics

The study was carried out with the permission of Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 11.10.2023, Decision No: 462). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study was conducted by evaluating a total of 66 cases referred from the external center or diagnosed for the first time with the diagnosis of prenatal FNTA between January 2021 and July 2023 in the Perinatology Department of Çam and Sakura City Hospital. Our hospital serves as a tertiary reference center of the region.

Fetal USG examination and prenatal diagnosis were made by maternal-fetal medicine specialists using ultrasonic equipment with the option of color and pulsed Doppler USG. After the diagnosis of the fetal anomaly, all cases were re-evaluated and discussed by the multidisciplinary perinatal team, which consists of medical specialists involved in perinatal care, including maternal-fetal medicine specialists, obstetricians, neonatologists, paediatric surgeons, paediatric intensive care specialists, and clinical geneticists. Following this, information was given to parents about the significance of the diagnosis, whether surgical or non-surgical treatment modalities would be required after birth, the expected short and long-term prognosis of the cases, and the option of termination of pregnancy.

All examinations were performed using ultrasonic equipment with the option of color and pulsed Doppler with Arietta 850 USG (Hitachi, Japan). The confirmation of diagnosis was assessed by postnatal follow-up in the first months of life, and/or by autopsy in cases of termination of pregnancy.

Maternal age, gestational week at diagnosis, the presence of consanguineous marriage, the diagnosis before referral to our clinic, the presence of chromosomal anomalies, and prenatal and postnatal treatment procedures were recorded in detail.

Statistical Analysis

IBM SPSS Statistics for Windows, Version 26.0 (Chicago, IL, USA) was used for statistical analysis of the data. Our analysis was confined to descriptive statistical methods and encompassed the utilization of mean±standard deviation, or median (minimum-maximum), and percentage distributions to delineate the demographic and clinical features of the participants. A p-value less than 0.05 was considered statistically significant.

RESULTS

A total of 1124 pregnant women with a major fetal abnormality were assessed in our center during the study period. The total number of fetuses diagnosed with FNTA or whose FNTA diagnosis was confirmed before referral was 66 (5.87%) in our center during this period of more than 2 years. The antenatal prevalence of FNTA in our study cohort was 5.87%. The median gestational age at first evaluation at our center was 24 weeks (minimum 15 weeks, maximum 38 weeks) and the mean maternal age was 28.61±4.9 years.

Table 1 shows prenatal and postnatal diagnostic lesions and types of malformations of cases in our study. As can be seen in Table 1, seven different types of FNTA were detected prenatally. These are CDH (n=30, 45.4%), CPAM (n=17, 25.7%), esophageal atresia (n=6, 9%), idiopathic hydrothorax (n=5, 7.5%), bronchopulmonary sequestration (n=5, 7.5%), congenital bronchogenic cysts (n=1, 1.5%), Cantrell pentalogy (n=1, 1.5%), and congenital high airway obstruction syndrome (CHAOS) (n=1, 1.5%). Postnatal information of 39 patients (59%) who were followed up and delivered in our hospital out of a total of 66 cases was obtained. Information about the remaining 23 cases that were not delivered in our hospital could not be obtained.

Table 1. Types of fetal noncardiac thoracic malformations

	Prenatal diagnosis	Postnatal diagnosis
Congenital diaphragmatic hernia, n (%)	30 (45.4%)	18
Congenital pulmonary airway malformation, n (%)	17 (25.7%)	7
Esophageal atresia, n (%)	6 (9%)	6
Idiopathic hydrothorax, n (%)	5 (7.5%)	2
Bronchopulmonary sequestration, n (%)	5 (7.5%)	5
Congenital bronchogenic cysts, n (%)	1 (1.5%)	1
Cantrell pentalogy, n (%)	1 (1.5%)	-
Congenital high airway obstruction syndrome, n (%)	1 (1.5%)	-
Total	66	39

Demographic and clinical characteristics of the cases are shown in Table 2. Chromosomal analysis was performed in 9 of the cases (13.64%); of which 6 fetuses had a CDH, and three had idiopathic hydrothorax. However, no chromosomal abnormality was found in any of these cases. Parents opted for termination of pregnancy (TOP) in 10 cases; of which, 4 fetuses had a CDH, 2 had CPAM, one had esophageal atresia, one had pulmonary sequestration, one had Cantrell pentalogy, and one had

CHAOS. Termination of pregnancy was performed in a total of 4 cases with fetal hydrops; of which two fetuses had CPAM, one had CDH, and one had Cantrell pentalogy. Two patients who opted for pregnancy termination but did not choose this option (one fetus had CDH, and one had CHAOS) experienced spontaneous intrauterine fetal demise. In total, intrauterine fetal death was observed in 4 cases (6.06%) during the follow-up visits in the intrauterine period; of which, two fetuses had CPAM, one fetus had CDH, and one had CHAOS. Three cases received intrauterine treatment during the follow-up period. Neonatal death was observed in 8 cases (12.12%).

Table 2. Demographic and clinical characteristics of the cases

Maternal age, years (mean±std.)	28.61±4.9
Gravida, median (min-max)	2 (1-11)
Gestational week at diagnosis, median (min-max)	24 (15-38)
Chromosomal analysis, n (%)	9 (13.64%)
Diaphragmatic hernia, n	6
Idiopathic hydrothorax, n	3
Intrauterine treatment, n (%)	5 (7.57%)
Termination of pregnancy, n (%)	4 (6.06%)
Congenital pulmonary airway malformation, n	2
Diaphragmatic hernia, n	1
Cantrell pentalogy, n	1
Intrauterin fetal death, n (%)	4 (6.06%)
Congenital pulmonary airway malformation, n	2
Diaphragmatic hernia, n	1
Congenital high airway obstruction syndrome, n	1
Neonatal death, n (%)	8 (12.12%)

In our study, we did not feel the need for MRI in any of the cases. Pleuroamniotic shunt procedure was performed in 5 of the total cases diagnosed as hydrothorax in the prenatal period and they were followed up. Of these 5 cases, the procedure was successful in 3 cases and the shunt remained until birth in these patients. At the end of the pregnancy, healthy fetuses were born without any further problems. However, in the remaining 2 cases, the shunt was found to be dislocated in the USG examination performed on the 7th day after the procedure and the shunt was removed. Because of the failure of this procedure, hydrothorax reoccurred in these cases. Prenatally, no procedure was performed for diagnoses other than hydrothorax in cases with FNTA.

Five (29.4%) of 17 cases with CPAM were resolved late antenatally with expectant management. These patients were subsequently excluded from follow-up. Also, 5 cases with CPAM were lost to follow-up. Seven of 17 cases with CPAM were delivered at our center. Of this, 5 cases with CPAM were resolved during the postnatal period with expectant management. In total, 10 (58.8%) cases with CPAM lesions were resolved during the late antenatal or postnatal period with expectant management. Surgery was performed in 2 (11.8%) of 17 cases with CPAM.

As mentioned above, of the 66 fetuses with a prenatal diagnosis of FNTA, 39 were delivered in our center. The prenatal FNTA diagnosis of all of the cases was confirmed after birth. Congenital diaphragma hernia cases were confirmed by X-ray radiography. Esophageal atresia cases were confirmed by orogastric tube. All CPAM and bronchopulmonary sequestration cases were confirmed by computerized tomography.

Postnatally, surgery was performed in 18 cases with a diagnosis of CDH, in 2 cases with a diagnosis of CPAM, in 6 cases with a diagnosis of esophageal atresia, and in 5 cases with bronchopulmonary sequestration.

DISCUSSION

For lung maturity of the fetus, sufficient thoracic space, intrapulmonary fluid and diaphragm innervation are necessary. Most of the masses in the fetal thorax can be detected by USG examination as early as the 16th week of pregnancy. All thoracic masses should be considered potentially life-threatening, because the pressure on developing lungs may cause pulmonary hypoplasia. Development of hydrops in a fetus with lung mass is an indicator of poor prognosis, regardless of the type of mass. After accurate prenatal diagnosis, planning in utero interventional procedures, delivery, and immediate postnatal surgery is very important for FNTA.[8,9]

As USG technology continues to improve, the diagnosis of fetal thoracic lesions increases. Much still needs to be learned about the in-utero natural history and pathophysiology of these fetal thoracic lesions. These lesions may affect the development of the pulmonary parenchyma, causing lung hypoplasia. Large lesions may obstruct venous return, causing hydrops fetalis.[10]

Accurate prenatal diagnosis of a chest mass is important because the natural history, treatment, and prognosis vary depending on the etiology. The USG is a noninvasive, inexpensive, and widely available modality to assess fetal anatomic structures. Thus, the USG examination is routinely used to screen for fetal anomalies and can provide real-time studies without ionizing radiation. Most USG scans are diagnostic for these abnormalities.[11-13] In recent years, with the ultrafast sequences technology evolution, MRI has been considered a beneficial diagnostic procedure complementary to the USG. Recio Rodríguez et al.[14] reported that fetal MRI can provide further information useful in predicting prognosis and in neonatal management of FNTA. However, as there seemed to be that prenatal management and prediction according to the lesion size was more cost-effective than

prediction according to the suspected final histology, MRI did not show any further benefit regarding diagnosis and prognosis compared to the USG.[15] Based on this knowledge, we did not perform an MRI in any of the cases to confirm the diagnosis, management, and prognostication.

In the literature, the most common FNTA is CDH, which accounts for approximately 40% of cases.[16] CPAM is the second most common congenital lung lesion and accounts for 25% of FNTA cases.[17] In our study, likewise in other studies, the most common fetal chest masses were CDH (45.4%), and CPAM (25.7%). Also, similar to the literature, the prevalence of esophageal atresia, bronchopulmonary sequestration (BPS), and idiopathic hydrothorax is relatively rare than CDH and CPAM.[6,7,10,18]

Most CPAM cases can be managed with maternal support, planned termed delivery, and postnatal resection. However, once these lesions have been identified, they must be followed carefully because the lesion may involute in utero or increase in size. With progressive increasing size, there may be associated fetal hydrops, which are believed to be indicative of impending fetal demise.[18] In our study, the CPAM lesion regressed with expectant management in 29.4% of the cases during the antenatal period and in also 29.4 of the cases during the postnatal period. Postnatal surgery was required in 14.3% (n= 2) of our cases whose postnatal information was accessed. In their study, Kaya et al.[19] included 37 cases (71.2%) diagnosed with CPAM and 15 cases (28.8%) with bronchopulmonary sequestration. The presence of bronchopulmonary malformation was demonstrated radiologically in 23 cases (59%) in the neonatal period, and 18 of the cases (78.3%) with CPAM and bronchopulmonary sequestration were operated on in the first year of life. When the cases were analyzed separately, 14 cases with bronchopulmonary sequestration and 4 cases with CPAM (10.8%) were operated in their first year. Similarly, Atalay et al.[15] revealed that 64.7% of congenital pulmonary malformation cases resolved spontaneously. Thus, we consider that CPAM cases demonstrated favorable outcomes with appropriate management.

In utero therapies for FNTA are variable but there are no large randomized trials to compare risks and benefits. Fetal endoscopic tracheal occlusion therapy for diaphragmatic hernia, radiofrequency thermal ablation for CPAM and thoracoamniotic shunting for hydrothorax are current intrauterine treatment approaches.[20-22] In our clinic, only thoracoamniotic shunting procedure was performed for only 5 patients with a diagnosis of hydrothorax among these treatment approaches. After this shunt procedure, healthy fetuses were born in these 3 patients without the need for any other prenatal or postnatal surgery. In the remaining 2 patients, the shunt procedure failed and these patients refused to have the shunt reinserted, and the fetuses died during follow-up. Unfortunately, the Fetal endoscopic tracheal occlusion therapy and Laser procedure could not be performed in our clinic due to the lack of an experienced specialist and the lack of necessary equipment for these procedures.

Limitation

The main limitation of this study is the retrospective design of this research and the absence of long-term postnatal outcomes. Also, the inability to confirm the diagnosis of the cases with autopsy who experienced pregnancy termination or intrauterine fetal demise is the other crucial limitation of our study.

CONCLUSION

Although the incidence of thoracic anomalies, which we see less frequently than other organ systems has not changed much over the years, treatment approaches and postpartum prognosis have improved over the years. Deliveries of the FNTA cases should be planned in tertiary centers where necessary intervention and care can be provided. A multi-disciplinary team could demonstrate a crucial role in assuring that the pregnant woman and fetus obtain appropriate treatment and are managed during the antenatal and postnatal periods. US plays a crucial role in the diagnosis and management of FNTA cases during the prenatal period rather than fetal MRI and other diagnostic tools. More than half of the CPAM lesions regressed spontaneously with expectant management.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 11.10.2023, Decision No: 462).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Review

MEDICINE PALLIATIVE CARE

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The diagnosis and treatment of idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease (ILD) of unknown cause. The prognosis of IPF is poor, respiratory failure is the most common cause of mortality. Velcro rales are typical on respiratory system examination. Clubbing is seen in 30-60% of IPF cases. There is no laboratory test specific to IPF. Usual interstitial pneumonia (UIP) pattern is seen in IPF. UIP features in high-resolution computed tomography (HRCT); peripheral subpleural bibasilar reticular opacities, honeycombing, traction bronchiectasis and interseptal thickening. It shows craniocaudal localization. Diagnosis of IPF; It is diagnosed by the combination of HRCT findings and clinical findings. Antifibrotic drugs (Pirfenidone and Nintedanib) slow down the progression of IPF and reduce the number of annual attacks and reduce the frequency of hospitalization.

Keywords: Idiopathic pulmonary fibrosis, usual interstitial pneumonia, antifibrotic drugs

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease (ILD) of unknown cause. It leads to rapid and progressive alterations in lung function. IPF has a poor prognosis, with an average life expectancy of 3-5 years from diagnosis if left untreated. The mortality rate is higher than that of many malignancies.

IPF is uncommon in people under 50 years of age. Both prevalence and incidence rise with increasing age, with presentation commonly occurring in the sixth and seventh decades.[1]

The prevalence and incidence rates of IPF are increasing worldwide. it is more common in men.[2]

IPF is still a rare disease with a recent global incidence of 0.09–1.30 and a prevalence of 0.33-4.51 per 10,000 of the population.[3]

PATHOGENESIS AND GENETIC PREDISPOSITION

It is well recognized that the combination of environmental and genetic risk factors leads to the development of IPF. The alveolar epithelium is predominantly impacted by repetitive microdamages. An abnormal healing process begins after epithelial damage. Accumulation of myofibroblast, fibroblast, and collagen is brought on by an imbalance between fibrotic and anti-fibrotic mediators. Following that, fibrosis, honeycomb cysts, and tissue degeneration happen.[4]

While there have been reports of familial cases, the majority of IPF cases are sporadic.

Familial IPF is defined as IPF in at least two of the primary biological family members. Familial IPF; It is seen at a rate of 0.5-2.2%.[5]

It is autosomal dominant and is observed at earlier ages.

Short telomere syndromes, Hermansky-Pudlak syndrome, and familial pulmonary fibrosis (FPF) all typically manifest earlier than IPF. While some genetic variants have been identified in people with sporadic IPF, none are well-established.

Telomere shortening, decreased mucociliary clearance due to MUC5B, surfactant protein changes and TOLLIP mutation are genetic changes detected in IPF.

POTENTIAL RISK FACTORS

There are some risk factors that cause the development of the IPF. These factors are male gender, age, smoking history over 20 pack/year, environmental and occupational factors, chronic micro-aspirations because of gastroesophageal reflux and viral factors.[6]

The study in the USA identified some occupations associated with the IPF. These professions agriculture,

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animal husbandry, hairdressing, bird breeding, stone cutting and polishing are occupations that are exposed to metal dust and vegetable dust.[6]

CLINICAL MANIFESTATIONS

The most common IPF symptoms are nonproductive cough and exertional dyspnea. Generally, the first symptom is a dry cough. Cough is a symptom that reduces quality of life and is difficult to manage. It is more prevalent, particularly among nonsmokers and those with severe disease. Fever, weight loss, and muscle and joint pain are uncommon.

It is important to ask detailed questions about the patient's past smoking, family history,hobbies, exposure to the environment and their job, and drug usage during their anamnesis. It is important to do a systemic examination, particularly in cases with signs or symptoms of rheumatic disease (Table 1).[7]

Table 1. Questions for patient with suspected idiopathic pulmonary fibrosis (IPF)[7]

Tobacco use
• Do you smoke tobacco now or have you in the past? If yes, how many packs per day and how many years?
Symptoms of rheumatic disease/sarcoidosis
• Do you have joint pain or inflammation, digital ulcers, dry eyes, dry mouth, fatigue, fever, hair loss, muscle weakness or pain, photosensitivity, Raynaud phenomenon, skin changes such as thickening or telangiectasia? • Any new rash, particularly around tattoos or scars? • Any palpitations or fainting episodes? • Any parotid swelling?
Exposures associated with hypersensitivity pneumonitis
• Do you have pets or birds at home? How about livestock? • Any exposure to humidifiers, hot tubs, sauna, Jacuzzi, feather bedding, wind instruments, barns? • Any water damage at home or at work? • What are your hobbies? Do they involve exposure to dusts, feathers, fur, mold, fumes, or chemicals?
Occupational causes of ILD
• What types of work have you had? Any exposure to animals, stables or barns, mushroom growing, brewery, winery, asbestos, silica, plastics, epoxy, metalworking, spray painting, sandblasting?
Medication and radiation-induced lung toxicity
• What medications do you take? Have you ever taken nitrofurantoin, amiodarone, chemotherapy, or biologic agents? Have you had radiation therapy? If so to what part of the body?
Family history
• Do you have any family history of lung disease, particularly ILD or lung fibrosis? Any history of premature graying, cirrhosis, aplastic anemia, other bone marrow diseases?

Adapted from Reference 7, IPF: idiopathic pulmonary fibrosis; ILD interstitial lung disease.

On physical examination, bibasilar crackles are usually audible. However in rare cases, they may be absent or only heard unilaterally in the early stages of the disease. Due to traction bronchiectasis, patients with more advanced illness may experience end-inspiratory "squeaks".

Clubbing is practiced at a rate of 30-60% in IPF.

In our country, the rate of clubbing was determined to be 36.4% in a study.[8]

Hypoxemic patients may develop right heart failure and pulmonary hypertension. Examination signs such as jugular vein distention, pretibial edema, and hepatomegaly are observed in these instances.

LABORATORY

As there are no specific laboratory tests for the diagnosis of IPF, the purpose of laboratory testing in patients who have just been diagnosed with ILD is to determine which processes to rule out or identify as part of the differential diagnosis.

Serologic investigations may be useful in identifying subclinical rheumatic disease in patients undergoing an initial evaluation for possible IPF.

Antinuclear antibodies, anticyclic citrullinated peptide antibodies, and rheumatoid factor tests are usually obtained. Certain experts obtain the nonspecific measures of inflammation, such as erythrocyte sedimentation rate and creactive protein (CRP).

Additional tests, like creatine kinase, aldolase, Sjögren's antibodies (anti-SS-A, anti-SS-B), scleroderma antibodies (anti-topoisomerase [SCL-70], anti-PM-1), and other myositis panel antibodies (e.g., anti-Jo-1, anti-PL7, anti-melanoma differentiation associated gene 5 [MDA-5]), may be useful in some cases with suggestive symptoms or signs.[9]

Some biomarkers that are believed to be useful in forecasting the disease's prognosis have been developed recently. These biomarkers include antigens such as endothelin-1, matrix metalloproteinases like MMP-7 and MMP-1, surfactant proteins A and D, and KL-6. It hasn't been used on a regular basis yet.

PULMONARY FUNCTION TESTS

While pulmonary function tests (PFT) are normal in the early stages, restrictive disorder develops later. Total lung capacity, functional residual capacity, and residual volume all decrease, resulting in impaired compliance. The FEV1/FVC ratio (Tiffenau ratio) remains constant as forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) decrease. When an airway disease is present, both restrictive and obstructive patterns can be seen.

Diffusion capacity (DLCO) has decreased as an indicator of gas exchange disorder, and it is the first parameter to deteriorate. While the DLCO/VA ratio remains constant, the decrease in DLCO is a significant finding that differentiates it from obstructive diseases.

During cardiopulmonary exercise testing, the alveolar-arterial oxygen gradient ($P(A\text{-}a)O_2$) rises while arterial oxygen pressure and saturation fall. The six-minute walk test (6MWT) is a noninvasive, easily applied test that assesses patients' functional exercise capacity. In patients with IPF, the distance walked and desaturation measured during the 6MWT are strong predictors of mortality.

CHEST IMAGING

Chest Radiography

The most common finding in IPF is an increase in reticular markings, though this is a nonspecific finding that is also associated with other ILDs and heart failure.

High-resolution Computed Tomography

All patients suspected of having IPF should have an HRCT. The "Usual interstitial pneumonia (UIP) pattern" is seen in the IPF. That is distinguished by peripheral, basilar-predominant opacities associated with honeycombing and traction bronchiectasis-bronchiolectasis on HRCT. It shows craniocaudal location (**Figure 1**).

Both definite UIP and probable UIP patterns on HRCT show histopathologic confirmation of UIP greater than 80 percent of the time.[7]

The 2022 Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis ATS/ERS/JRS/ALAT Adult Clinical Practice Guidelines.[10]

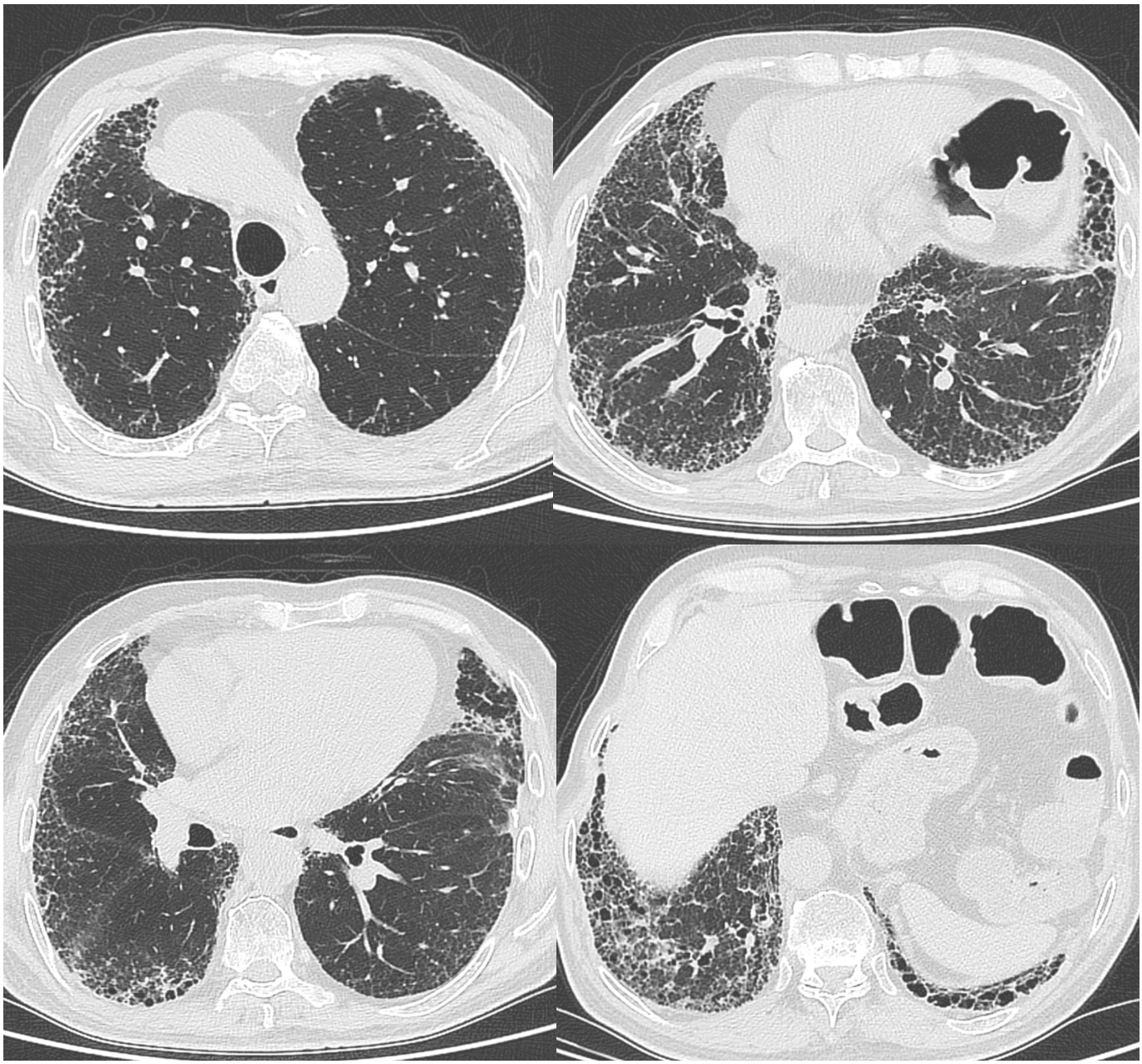


Figure 1. Usual interstitial pneumonia (UIP) pattern at High-resolution computed tomography (HRCT)

Review HRCT model categories. The 2018 guideline considered merging UIP diagnoses with probable UIP, but it was ultimately decided to keep the four categories with minor changes. (Table 2)

HISTOPATHOLOGY

Histopathological diagnosis of IPF; patchy interstitial fibrosis, which causes roof damage in the lung, is diagnosed with the appearance of UIP consisting of honeycomb and fibroblastic focus. The main feature of fibrosis is that it is histologically heterogeneous. The pathological diagnostic criteria in the 2018 IPF guideline9 are summarized in Table 3.

DIAGNOSIS

A characteristic presentation (such as the gradual onset of dyspnea in a patient over 60,) combined with characteristics of usual interstitial pneumonia (UIP) or probable UIP on high-resolution computed tomography (HRCT) can often lead to the diagnosis of IPF without the need for a biopsy.

Diagnosis of IPF; It is diagnosed by the combination of HRCT findings and histopathological findings (Figure 2)

Other known causes of radiographic UIP must be clinically excluded, including environmental exposures (e.g., asbestos, causes of hypersensitivity pneumonitis), medications, and rheumatic disease

To reach histopathological diagnosis, diagnostic methods such as Bronchoalveolar Lavage (BAL), transbronchial biopsy, transthoracic biopsy, transbronchial cryobiopsy, endobronchial ultrasonographyguided fine needle aspiration, video-guided thoracoscopic surgery (VATS), and surgical biopsy are preferred. Bronchoalveolar lavage (BAL) has a limited role in the evaluation of patients with an HRCT that suggests IPF and it is used to differantiate other causes (such as sarcoidosis, hypersensitivity pneumonitis)

Surgical lung biopsies should ideally be obtained from multiple lobes of the lung and from areas of varying severity. When inflated, lung biopsy samples should be larger than 4 cm in the greatest dimension and 3 to 5 cm deep from the pleural surface.[7]

Transbronchial cryobiopsy (TBCB), when performed in centers with multidisciplinary experience in the diagnosis and treatment of ILD, is a suitable substitute for surgical lung biopsy.

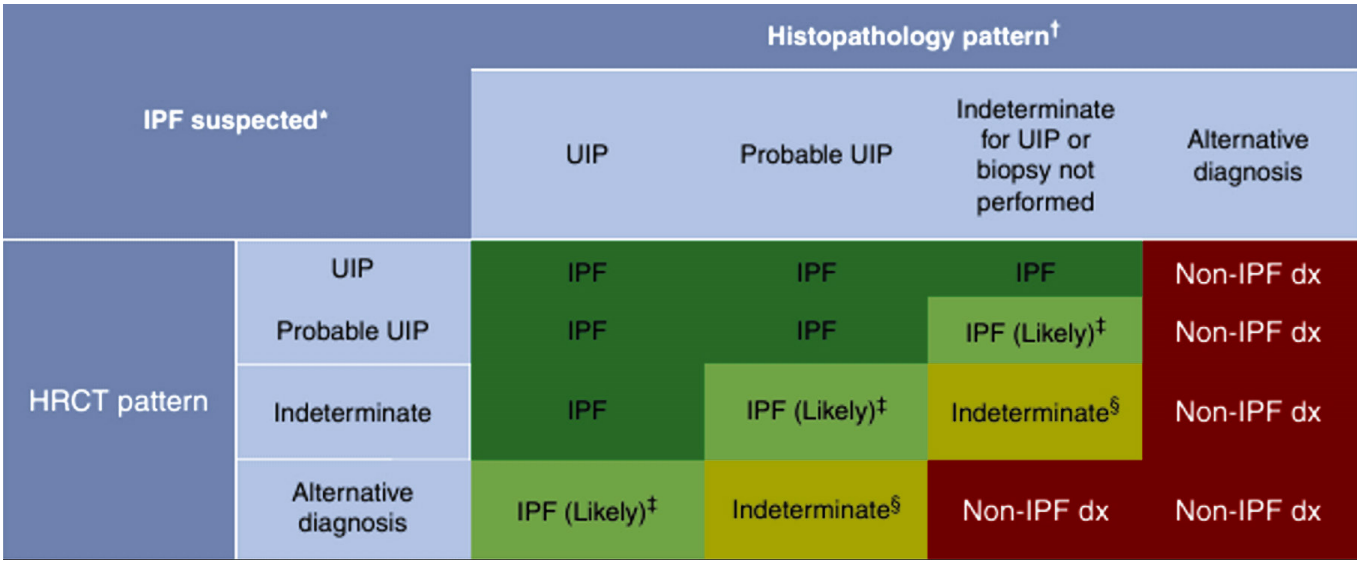
Table 2. High-resolution computed tomography patterns in idiopathic pulmonary fibrosis[10]

	UIP	Probable UIP	Indeterminate UIP	Alternative Diagnosis
Confidence level	90%	70-89%	51-69%	<50%
Distribution	• Basal and subpleural dominance • Heterogeneous distribution • Diffuse distribution • It is possible to be asymmetrica	• Basal and subpleural dominance • Heterogeneous distribution	• Diffuse distribution without subpleural predominance • Indeterminate reticulation, • slight groundglass or distortion (Early UIP)	• Peribronchovascular prednominance and sub-plaveral prevention (NSIP) • Perilymphatic (sarcoidosis) • Upper and middle zone involvement (fibrotic HP, CTD-ILD, sarcoidosis) • Sub-plveral prevention (NSIP or smoking-associated ILD)
HRCT view	• Honeycomb and/or peripheral traction bronchiectasis or bronchiolectasis • Presence of irregular thickening of the interlobular septa • Generally reticular pattern superimpose, slightly ground-glass • There may be pulmonary ossification	• Peripheral traction bronchiectasis or bronchiectasis with reticular pattern • Possible to have moderate frosted glass • Absence of subpleural involvement	• Pulmonary fibrosis distribution (if not suggestive of any specific etiology)	Lung findings • Cysts (LAM, LCH, LIP, DIP) • Mosaic attenuation, three density hulgus (HP) • Common ground-glass (HP, cigarette-related illicit drug toxicity, fibrotic acute attack) • Diffuse nodules (sarcoidosis) • Centrilobular nodules (HP or non-associated disease) • Consolidation (OP) Mediastinal findings • Pleural plaque (asbestosis) • Dilated esophagus (CTD)

NSIP: Nonspecific Interstitial Lung Disease, HP: Hypersensitivity Pneumonia, LAM: Lymphangia Leio Myomatosis, LCH: Langerhans Cell Histiocytosis, LIP: Lymphocytic Interstitial Pneumonia, OP: Organized Pneumonia, ILD: Interstitial Lung Disease, UIP: Usual Interstitial Pneumonia, CTD: Connective Tissue Diseases

Table 3. Histopathological diagnostic criteria[9]

UIP	Probable UIP	Indefinite UIP	Alternative diagnoses
• Condense fibrosis causing structural damage • Subpleural and/or para-septal dominant distribution of fibrosis • Heterogeneous involvement of the parenchyma with fibrosis • Fibroblast foci • Absence of alternative diagnostic findings	• Some of the features of the UIP pattern are present but not sufficient to diagnose UIP and there are no alternative diagnostic findings or • Only honeycombing	• Fibrosis with/without structural damage • Non-UIP pattern or features of UIP due to secondary causes • Some of the features of the UIP pattern are present and there are findings suggesting an alternative diagnosi	• Other histological patterns of idiopathic interstitial pneumonias in all biopsies • Histological findings pointing to other diseases (such as HP, PLHH, sarcoidosis, LAM



*"Clinically suspected of having IPF" is defined as unexplained patterns of bilateral pulmonary fibrosis on chest radiography or chest computed tomography, bibasilar inspiratory crackles,and age >60 years. Middle-aged adults (40 and 60year old) can rarely present with other wise similar clinical features, especially in patients with features suggesting familial pulmonary fibrosis.
‡IPF is the likely diagnosis when any of the following features are present:

1) Moderateto severe traction bronchiectasis and/or bronchiolectasis (defined as mild traction bronchiectasis and/or bronchiolectasis in four or more lobes, including the lingula as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man >50 years old or in a woman >60 years old,
2) Extensive (30%) reticulation on HRCT and age >70 year
3) İncreased neutrophils and/or absence of lymphocytosis in BAL fluid, and
4) Multidisciplinary discussion produces a confident diagnosis of IPF

§Indeterminate for IPF
1)without an adequate biopsy remains indeterminate and
2)with an adequate biopsy maybe reclassified to a more specific diagnosis after multidisciplinary discussion and/or additionalc onsultation.
Adapted from Reference 10, dx=diagnosis;UIP=usual interstitial pneumonia.

Figure 2. Idiopathic pulmonary fibrosis (IPF) diagnosis on the basis of high-resolution computed tomography (HRCT) and biopsy patterns10

The transbronchial cryobiopsy method was highlighted among the diagnostic methods in the Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis ATS/ERS/JRS/ALAT Clinical Practice Guidelines in Adults published in 2022.[10] Transbronchial cryobiopsy was found to have a lower risk of pneumothorax and bleeding than surgical lung biopsy.

DIFFERENTIAL DIAGNOSIS

Other diseases with radiographic and histopathologic features of typical interstitial pneumonia (UIP) are included in the differential diagnosis of IPF. Such as rheumatic diseases, chronic hypersensitivity pneumonitis, asbestosis, and certain drug-induced lung diseases.

Pleuropulmonary elastosis, pulmonary Langerhans' cell histiocytosis, combined pulmonary fibrosis and emphysema, and other idiopathic interstitial pneumonias are also included in the differential diagnosis of IPF. The interpretation of lung biopsy results in interstitial pneumonitis is discussed separately.

TREATMENT

There is no cure for IPF, but two antifibrotic drugs, nintedanib and pirfenidone, appear to slow disease progression and decrease the frequency of acute exacerbations. The use of anti-fibrotic drugs that prevent fibrosis in the lung parenchyma has been the most significant advancement in the treatment of IPF in recent years. The only definitive treatment is lung transplantation. New drug studies are still ongoing.

In our country, both drugs are within the scope of reimbursement, and patients who are diagnosed with IPF by lung biopsy or HRCT, in mild-to-moderate stages, with DLCO≥30%, FVC≥50%, are started. Anti-fibrotic drug selection should be made considering the patient's comorbid diseases, drugs used and contraindicated conditions.

One of the most important effects of pirfenidone is to alter the pleiotropic TGF-β pathway. Pirfenidone is used at a dose of 2400-2403 mg/day in the world and in our country. In our country, the drug is available as 200-400-600 mg tablets. The drug is started at a low dose (200 mg tablet 4x1), weekly hemogram and biochemistry values are checked and if the patient can tolerate it, the dose is increased and continued at the maximum dose (200 mg tablet 4x3 or 600 mgr 4x1) from the 15th day.

Skin rash, photosensitivity, and gastrointestinal (GI) side effects (nausea, vomiting, dyspepsia, loss of appetite, and diarrhea) are the most frequent side effects. All patients should be advised to wear sun protective clothing and sunscreen with at least a 50 factor in order to prevent skin side effects. It should be recommended to take drugs with meals and use proton pump inhibitors to prevent and reduce GI system side effects.

Nintedanib plays a role in the treatment of IPF by inhibiting multiple receptor tyrosine kinases (TKIs), including platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGFR).

There is only one form of nintedanib. 2x150 mg daily is started. Depending on the side effects seen in the patient, the nintedanib dose can be reduced by 2x100 mg. It should be used with caution in patients on anticoagulant therapy or with coronary artery disease.

The most common side effects are related to the gastrointestinal tract and the most common side effect is diarrhea. Antidiarrheal drugs added to the treatment of patients with diarrhea.

Hemogram and biochemistry values of patients using anti-fibrotic should be checked weekly in the first month of treatment, and then every three months.

There is no clear information on the treatment's duration. Patients should be evaluated every 3-6 months.

Supportive Therapy

Smokers should be referred to smoking cessation clinics, and psychosocial support should be provided as needed. Patients with respiratory failure should receive oxygen therapy support. Following a diagnosis, physicians should refer all patients to pulmonary rehabilitation centers. COVID-19, and seasonal influenza vaccination should be administered to patients on an annual basis and pneumococcal vaccine should be given. The treatment of comorbid diseases should be regulated. Patients at high risk of mortality should be referred for transplantation at the time of diagnosis, unless there are contraindications.

PROGNOSIS

The prognosis for IPF is poor. It is known that 20-30% of patients survive within five years of diagnosis, with an average life expectancy of two to five years.[1] The mortality rate has been reported at 13.36/100.000.[11] Respiratory failure is the most common cause of death.

CONCLUSION

IPF is a rare disease. Antifibrotic treatments, which have recently been used to slow the progression of the disease, have raised awareness. The disease's prognosis is altered by early diagnosis and treatment. New medical treatment options in IPF will increase diagnosis and awareness.

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Informed Consent

Written informed consent was obtained from all participants who participated in this ....study (If study retrospective: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

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Kilic C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

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