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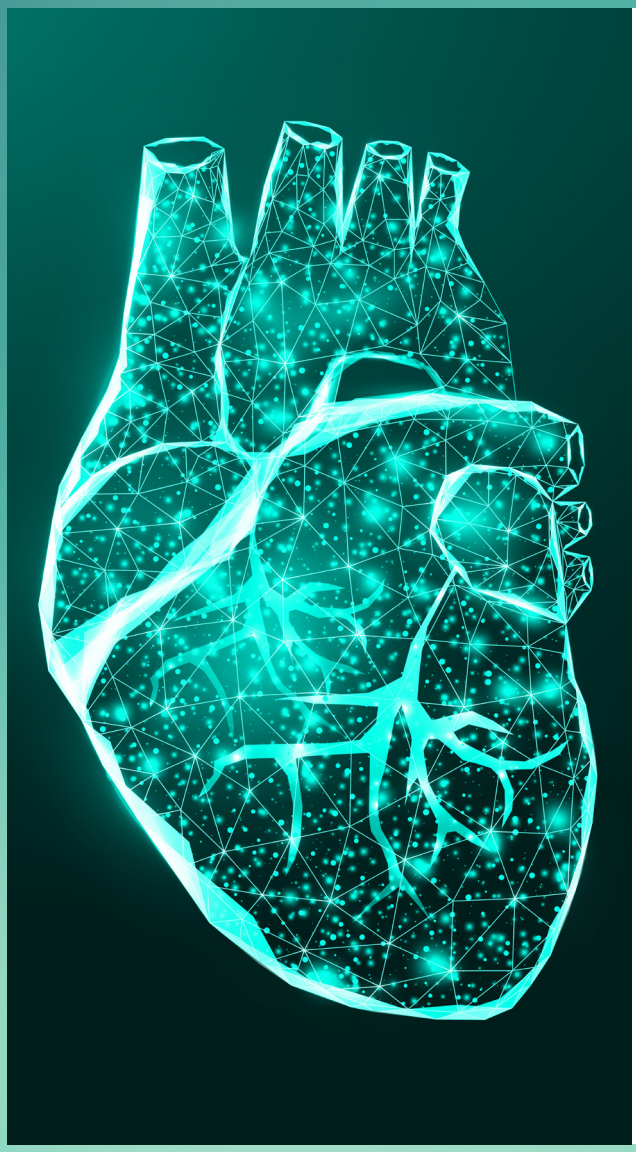

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RESEARCH ARTICLE

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Assessment of Coronary Artery Calcium Score among Asymptomatic Individuals at Intermediate Risk of Developing Coronary Artery Disease

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Abstract

Background and Aim: The present study was designed to estimate the coronary artery calcium score (CACS) and its association with the incidence of major adverse cardiovascular events (MACE) in asymptomatic patients who are at the risk of coronary artery disease (CAD).

Materials and Methods: In this prospective cross-sectional observational study, 108 consecutive patients were enrolled. The patients at intermediate risk of cardiovascular disease, atypical chest pain, and a positive family history of CAD were included. Demographic details and clinical data including lipid profile, systolic blood pressure, electrocardiography, 2D echocardiography, and routine blood investigations were reported. CACS was derived from computed tomography using a 256-slice scanner with a rotation time of 270 milliseconds. MACE was recorded at 1-year follow-up.

Results: The mean age was 54.55 ± 7.7 years with male predominance (62%). CACS categories 0, 1-99, 100-399, 400-999, and more than 1000 constituted 43.5%, 28.7%, 17.6%, 9.3%, 0.9%, respectively. The correlation between the groups of positive and negative CACS and presence or absence of standard risk factors was found to be statistically significant in diabetes mellitus ($P = 0.001$), hypertension ($P = 0.001$), and history of CAD in the family ($P = 0.029$). Although the association between smokers and calcium was statistically insignificant, it had clinical significance ($P = 0.212$). Out of 108 patients, MACE was observed in 16 (14.81%) patients with positive CACS at 1-year follow-up.

Conclusion: CACS measurement is often regarded as the primary non-invasive approach for risk stratification, MACE estimation, and promptly identifying high-risk asymptomatic individuals.

Keywords: Coronary artery calcium score, cardiovascular events, coronary calcification, risk stratification

INTRODUCTION

One of the leading causes of death worldwide is atherosclerotic heart disease. In recent years, non-fatal acute myocardial infarction (MI) or sudden death has been experienced by at least 25% of patients without prior symptoms.[1] Thus, the identification of asymptomatic individuals at intermediate risk who may experience future cardiovascular events is fundamental for primary preventive strategies of atherosclerotic cardiovascular disease.

Traditionally, a medical risk model, for instance the Framingham risk score, has been used to stratify (low, intermediate, or high) risk of coronary events in individuals without prior symptoms of coronary artery disease (CAD) and thus determine the aggressiveness of management.[2] However, there are some limitations. For instance, potential overestimation in a low-risk population or underestimation in a high-risk one.[3] The assessment of coronary artery calcium score (CACS) by computed tomography (CT) in asymptomatic

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patients is an alternate strategy to improve risk prediction over the Framingham risk score.[4]

Coronary calcifications are usually expressed as "Agatston score" and in numerous studies, CACS has been demonstrated to be an excellent prognosticator of cardiac incidents.[4-6] Cardiac calcification and atherosclerotic disease clinical manifestation is associated with an Agatston score >400 and is undoubtedly a strong indicator of increased risk for future cardiovascular problems.[7,8] However, the widespread use of CACS has not occurred due to cost and radiation exposure.[9] Moreover, there is a lack of literature on risk stratification using CACS among asymptomatic individuals from India. Thus, the present study aimed to estimate CACS and its association with the incidence of major adverse cardiovascular events (MACE) in asymptomatic individuals at intermediate risk of CAD.

MATERIALS AND METHODS

Study design and setting

A cross-sectional prospective observational study was carried out at a tertiary care center in India between 1st April 2017 and 31st March 2018. A total of 180 asymptomatic patients (aged ≥40 years) with a family history of premature cardiovascular disease, atypical chest pain, and an intermediate risk level (absolute 10-year cardiovascular risk score between 10 and 20) were included. The study excluded patients with poor technical quality CT images, chronic renal disease, and uncontrolled tachycardia.

Methodology

Demographic details and clinical characteristics were recorded. Data of type 2 diabetes mellitus, systemic arterial hypertension, dyslipidemia, smoking, and family history of premature CAD were collected using a standardized questionnaire. Patients at intermediate risk were estimated using the Framingham risk score. After clinical assessment, patients underwent electrocardiography, 2D echocardiography, routine blood investigations, and CACS measurements for diagnostic evaluation.

CT scan was performed on a 256-slice scanner with a rotation time of 270 milliseconds per rotation. The effective radiation dosage in this investigation was between 1 and 1.2 mSv using the 256-slice Philips Brilliance iCT system with Essence Technology by Philips. A CT scan without contrast was performed to score calcium, encompassing the region between the diaphragm and the tracheal bifurcation. The following specifications were used: 120 KVp, 300 mA, 0.270 s rotation time, 3 mm slice thickness with 3 mm intervals, and 80 mm coverage per gantry rotation. Each area and vessel's calcium scores were computed offline using dedicated software on a commercially available workstation. Calcium scores were divided into the following categories:[10]

- CACS of 0
- CACS between 1 and 99
- CACS between 100 and 399
- CACS between 400 and 999
- CACS of 1000 or higher

The patients were regularly monitored for a period of one year, and the occurrence of MACE, which includes coronary revascularization, cardiac mortality, and nonfatal MI, was recorded and analyzed.

Statistical analysis

Descriptive analysis involved calculating the mean and standard deviation for normally distributed quantitative variables, determining the median and interquartile range for non-normally distributed quantitative variables, and examining the frequency and proportion for categorical variables. For statistical analysis, IBM SPSS (Chicago, IL, USA; version 22) was used. A *P*-value less than 0.05 was statistically significant when examining the association between categorical variables and non-normally distributed variables using the Mann-Whitney U test/Kruskal-Wallis test. The correlation between two quantitative variables was evaluated using Pearson/Spearman rank correlation coefficient. Cross tabulation was used to analyze the association between two categorical variables, and the chi-square test/Fisher's exact test was used to assess the statistical significance of the difference between the proportions.

Ethical statement

This research was authorized by the Institutional Human Ethics Committee of Ramesh Hospitals, Vijayawada, Andhra Pradesh India on 3 May 2019 (number: ECR/81/INST/AP/2013/RR/2016).

All participants were provided with comprehensive information regarding the study objectives, the possibility of risk and benefits, and the fact that participation is voluntary. Informed written consent was then obtained from each participant. Throughout the study, strict confidentiality measures were implemented to safeguard the privacy and confidentiality of the participants.

RESULTS

The study included 108 patients. The average age of the study population was 54.55 ± 7.7 years, and males (62%) were predominant over females (38.0%). Demographic details with descriptive analysis of risk factors and CACS groups are portrayed in Table 1.

Positive CACS existed in 50.8% diabetic patients, 31.1% hypertensive, 23% smokers, 68.9% of individuals who had a family history of CAD, 72.1% males, and 27.9% females. Table 2 represents the descriptive analysis of risk factors associated with a positive calcium score. The mean age of patients with positive and negative calcium scores was found to be 56.69 ± 7.3 years and 51.06 ± 5.9 years, respectively. Table 3 displays the descriptive analysis of the mean age for individuals with positive and negative calcium scores in the study population.

The occurrence of MACE among the study population is illustrated in Table 4. Among the 108 patients, 4 (3.70%) underwent CABG and 12 (11.11%) underwent PCI. Table 5 illustrates the descriptive analysis of the event occurrence among different CACS groups among the study participants. There were no reported events in the group with a calcium score of zero. In the CACS group with 1-99 Agatston units (AU), the event rate was 9.68%. For the group with 100-399 AU, the event rate was 26.31%. In the group with 400-999 AU, the event rate was 70%, while in the group with over 1000 AU, the event rate was 100%. Calcium score and the risk of events were found to be directly proportional.

Table 1: Demographic data, risk factors and CACS groups (*n*=108)

Parameters	*n* (%)
Age groups (years)	
40-50	34 (31.5%)
51-60	52 (48.1%)
>61	22 (20.4%)
Gender	
Males	67 (62.0%)
Females	41 (38.0%)
Risk Factors	
Hypertensive	59 (54.6%)
Non-hypertensive	49 (45.4%)
Diabetic	40 (37.0%)
Non-diabetic	68 (63.0%)
Positive F/H/O pre-matured CAD	65 (60.2%)
Negative F/H/O pre-matured CAD	43 (39.8%)
Smokers	21 (19.4%)
Non-smokers	87 (80.6%)
CACS groups	
0	47 (43.5%)
1-99	31 (28.7%)
100-399	19 (17.6%)
400-999	10 (9.3%)
>1000	1 (0.9%)

F/H/O: Family history of, CAD: Coronary artery disease, CACS: Coronary artery calcium score

DISCUSSION

In the present study, CACS and its association with MACE among non-symptomatic patients at transitional risk of CAD were assessed, where in total 108 consecutive patients were included. Analysis of the calcium score based on gender revealed a higher prevalence of calcification in coronary arteries among males compared with females. Similar findings were observed in previous studies.[11,12] In total, 61 patients (56.5%) had a positive CACS. Additionally, this study evaluated the common risk factors that put patients at risk for CAD, where hypertension (54.6%) was most prevalent, followed by diabetes mellitus type-2 (37%), smoking (19.40%), and a family history of premature CAD (60.2%).

Among patients with diabetes, 50.8% had a positive CACS, while 19.1% had a negative CACS. The association between these two groups was statistically significant (chi-square = 11.418, P = 0.001). The existence of any degree of coronary artery calcification in individuals with type 2 diabetes was found to indicate a greater risk of all-cause mortality compared with non-diabetic individuals. This result was consistent with a former study by Raggi et al., [13] who observed that the survival rate of diabetic patients without any signs of coronary calcification is the same as that of non-diabetic people with a calcium score of zero throughout the five-year follow-up period. Based on these findings, it could be inferred that the evaluation of coronary calcium could be valuable in enhancing the stratification of short-term risk among patients with diabetes. Previously, in a meta-analysis, it was reported that people with a CACS <10 were 6.8 times less likely to experience cardiovascular events and a CACS of more than 10 has been allied to elevated mortality and cardiovascular events, demonstrating high sensitivity but low specificity.[14] Hypertensive patients with positive and negative CACS constituted 31.1% and 85.1%, respectively, and statistical analysis revealed a significant association between the groups (chi-square = 31.184, P = 0.001). Sung et al.[15] and colleagues found comparable outcomes in which hypertension was positively correlated with calcification of the coronary arteries. Smokers who had positive or negative CACS were present in percentages of 23% and 14.9%, respectively, and there was no statistically significant relationship between the groups (chi-square = 1.100, P = 0.212) but clinically there was a significant relationship between smokers and coronary calcium. In contrast, a study conducted by McEvoy et al.[16] reported that higher CACS was associated with increased hazard of all-cause mortality among both smokers as well as non-smokers, compared to CACS = 0. Among the patients with a family history of CAD, 68.9% had a positive CACS, whereas 48.9% had a negative CACS. The statistical analysis indicated a significant association between these two groups (chi-square= 4.394, P = 0.029). Otaki et al.[17] reported that a positive family history of CAD was associated with the presence of obstructive

Table 2: Descriptive evaluation of risk factors with positive calcium score (*n*=108)

Risk factor	CACS category n (%)		Chi-square	*P*-value
	Positive CACS	Negative CACS		
Diabetes mellitus				
Diabetic	31 (50.8%)	9 (19.1%)	11.418	0.001
Non-diabetic	30 (49.2%)	38 (80.9%)		
Hypertension				
Hypertensive	19 (31.1%)	40 (85.1%)	31.184	0.001
Non-hypertensive	42 (68.9%)	7 (14.9%)		
Smoking				
Smokers	14 (23.0%)	7 (14.9%)	1.100	0.212
Non-smokers	47 (77.0%)	40 (85.1%)		
F/H/O CAD				
Positive	42 (68.9%)	23 (48.9%)	4.394	0.029
Negative	19 (31.1%)	24 (51.1%)		
Gender				
Males	44 (72.1%)	23 (48.9%)	6.064	0.012
Females	17 (27.9%)	24 (51.1%)		

F/H/O: Family history of, CAD: Coronary artery disease, CACS: Coronary artery calcium score

Table 3: Descriptive evaluation of mean age of positive and negative calcium scores in the study population (*n*=108)

The CACS category	N	Minimum age	Maximum age	Mean	*P*-value
Positive	61	40	70	56.69±7.352	t = 4.2700 df = 106 <0.001
Negative	47	40	62	51.06±5.998	

CACS: Coronary artery calcium score, SD: Standard deviation

Table 4: Major cardiovascular events occurring among the study population

Parameters	*n* (%)			
Overall MACE	16 (14.81)			
Cardiac death	0			
Non-fatal myocardial infarction	0			
Coronary revascularization	16 (14.81)			
PCI	12 (11.11)			
CABG	4 (3.70)			
Timing of development of MACE				
Within 1 month	0			
Between 1 and 3 months	3 (2.78)			
Between 3 and 6 months	7 (6.48)			
Between 6 months and 1 year	6 (5.55)			
Telephonic follow-up after enrollment into study	**Stable angina**	**Unstable angina**	**Non-fatal MI**	**Death**
0-1 months	0	0	0	0
1-3 months	0	3	0	0
3-6 months	0	7	0	0
6-12 months	1	4	1	0

MACE: Major adverse coronary events, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass graft, MI: Myocardial infarction

Table 5: Descriptive evaluation of event occurrence in different CACS groups among the study population (*n*=108)

Positive CACS	Frequency	Event occurrence
1-99	3	9.68%
100-399	5	26.31%
400-999	7	70%
>1000	1	100%

CACS: Coronary artery calcium score

CAD. The mean age of individuals in the group with a positive calcium score was 56.69 ± 7.3 years, while among the negative calcium score group, the mean age was 51.06 ± 5.9 years (t = 4.2700, $P < 0.001$), reinforcing the observation that coronary artery calcification increases with age.[18]

No MACE was reported in patients under CACS = 0 category whereas only 9.68% of patients with a CACS of 1 AU or higher but less than 100 AU suffered MACE, even though a CACS of 1 AU or higher was linked to an increased risk of MACE. In cases where the CACS was below 100 AU, the need for CABG or PCI was infrequent. A CACS of 100 AU or greater significantly enhanced the need for PCI. CABG was necessary when the CACS exceeded 565 AU. In this research, identification of a particularly vulnerable group was made possible by the addition of a new stratum for people whose CACS was greater than 1000 AU; this group had a 100% MACE rate. Although further research is required to validate this statement, as in our study only one patient had CACS >1000 AU. Our results were consistent with those of Al-Mallah et al.,[19] who found that a CACS of 400 AU or above improved cardiac event prediction beyond the information provided by clinical data.

Study limitations

There are some drawbacks in this research. Primarily, since this study was conducted at a tertiary care center with multidisciplinary care, the generalizability of the findings to the wider population may be limited. Subsequently, this study had a smaller sample size and short follow-up duration to evaluate the MACE. There was variation in the effective radiation dose for this procedure. Moreover, elevated calcium levels could occasionally be accompanied by subsequent diagnostic tests for cardiac disorders, which might or might not yield clinically valuable results and may be accompanied by adverse outcomes. Further evidence is required for using CACS as the primary non-invasive test in risk stratification.

CONCLUSION

The present study concluded that in non-symptomatic individuals with a moderate risk of developing CAD, the CACS assessment might be thought of as the non-invasive approach of first choice for risk stratification, early identification of high-risk asymptomatic people, and estimating the risk of MACE.

Ethics

Ethics Committee Approval: This research was authorized by the Institutional Human Ethics Committee of Ramesh Hospitals, Vijayawada, Andhra Pradesh India on 3 May 2019 (number: ECR/81/INST/AP/2013/RR/2016).

Informed Consent: Informed written consent was then obtained from each participant.

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RESEARCH ARTICLE

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Convenient Novel Method for Diagnosing Diastolic Dysfunction: Electrocardiographic Diastolic Index

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Abstract

Background and Aim: Left ventricular diastolic dysfunction (LVDD) is the primary pathophysiology in patients with preserved ejection heart failure. Hypertension (HT) results in myocardial structural changes and accelerates the progression to LVDD. Electrocardiographic diastolic index (EDI) calculated from electrocardiogram parameters can provide information about the correlation between hypertrophy of the left ventricle and LVDD. We investigated the predictor of EDI in detecting LVDD in patients followed up with HT.

Materials and Methods: This study included 202 consecutive patients with HT between January 2022 and March 2022. The patients were classified without and with LVDD. The EDI is created as (V5-R amplitude + V1-S amplitude x aVL-R amplitude/PWL-I amplitude). The prediction value of the EDI for LVDD was evaluated by curve analysis of the receiver operating curve. Multivariate and univariate logistic regression analyzes were used to evaluate the free predictors of LVDD. Two multivariate models were used (model I: EDI as a continuous variable and model II: EDI as a categorical variable).

Results: The patients were classified into two groups by showing LVDD. The average age of the study population was 50 ± 14 years, and 57.4% of the patients were female. The patient EDI value was 8.5 ± 7.3. The EDI value of the first group was remarkably lower than that of the second group. When the limit value of EDI is greater than 7.4 mV, it predicts LVDD with 63.6% sensitivity and 79.8% specificity. In univariate logistic regression analysis, the presence of LVDD was associated with EDI. Two different multivariate regression models were constructed to evaluate EDI as both a continuous variable and a categorical variable. EDI was determined as an independent predictor of LVDD in both models.

Conclusion: The EDI is an essential assessment tool in predicting DD in patients who are followed up with HT because it is a cheap, accessible, and easy-to-use formula.

Keywords: Diastolic dysfunction, electrocardiographic diastolic index, hypertension

INTRODUCTION

Diastolic dysfunction (DD) is a relaxation defect of the left ventricular myocardium.[1] It can show a broad clinical course, simple impaired myocardial relaxation to end-stage heart failure (HF).[2] In recent years, it has emerged as an essential factor in the pathogenesis of HF.[3] Left ventricular diastolic dysfunction (LVDD) is the primary pathophysiology in patients with HF with preserved ejection fraction (HFpEF).[4] Recent studies have shown that increased myofilament sensitivity to calcium plays a role in DD, but more molecular and clinical studies are needed.[5]

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Hypertension (HT) is one of the most common chronic diseases in developed countries. Higher blood pressure complications result in myocardial structural changes and accelerate the progression to HF.[6] DD is commonly observed in patients with dysregulated blood pressure.[7] In summary, high blood pressure causes myocardial structural changes and these changes cause DD and subsequently HFpEF. For this reason, DD can be considered an intermediate clinical stage in the progression to HF. Early diagnostic methods can detect the development of DD and slow the progression to HF.

Many patients with DD are asymptomatic before clinical symptoms of HF.[3] Consequently, cost-effective diagnostic methods come to the fore in diagnosing DD. It has been shown that transthoracic echocardiography (TTE) can detect DD in the early stage of HT before the development of left ventricular hypertrophy (LVH).[7] Tissue Doppler examination, which can be performed in TTE, provides information about the left ventricle's early and late relaxation functions and the presence of DD.

Electrocardiogram (ECG) can give information about the relationship between LVH and the presence of DD.[8] The Sokolow-Lyon voltage criterion is used as an ECG parameter to predict HT and related LVH, and DD.[9] However, the relationship between electrocardiographic diastolic index (EDI) and DD has been investigated in recent years.[10] Various studies on the relationship between ECG and DD are under scope because it is both easily accessible and cost-effective in predicting DD.

In this study, we investigated the predictor of EDI in detecting DD in patients followed up with HT.

MATERIALS AND METHODS

The single-center retrospective observational study included 202 consecutive patients with HT who applied to the cardiology policlinic between January 2022 and March 2022. Baseline clinical characteristics and clinical information were recorded. Patients with lower left ventricular ejection fraction (LVEF) than 55%, congenital heart disease, infiltrative cardiomyopathy, coronary artery disease, chronic kidney disease, previous thromboembolic event, presence of valve diseases, bundle branch blocks, atrial fibrillation, bradyarrhythmia, tachyarrhythmia, and missing data in the hospital recording system were excluded from the study. The patients were divided into groups with and without DD by TTE parameters. Baseline characteristics, TTE and ECG findings, and EDI was compared between the two groups.

This study was approved by the University of Health Sciences Turkey, Ankara City Hospital Ethics Committee (number: E1-22-2587, date: 20.04.2022). HT was defined as resting blood pressure above 140/90 mmHg at least twice or current use of antihypertensive medication.

TTE was performed using a Philips EPIQ7 (Philips Healthcare) ultrasound device. LVEF was calculated by the modified Simpson method.[11] E wave, A wave, tissue Doppler annular velocities, and left atrial diameter were recorded with TTE by the American Society of Echocardiography (ASE) guidelines.[12] According to the recommendations of the ASE, segmental wall movements of the left ventricle were evaluated from the apical four-chamber, three-chamber, and two-chamber windows in the left lateral decubitus position. The left ventricular end-diastolic and end-systolic diameters was measured in M mode on parasternal long-axis images. The lateral E-value was determined by tissue Doppler examination.

Standard 12-lead ECG (filter 40 Hz, 25 mm/s, 10 mm/mV) was recorded in all patients. ECGs were scanned at 300 dpi, and all images were magnified 5x. The P wave amplitude in the lead I (PWLI) was measured from the peak of the P wave to the isoelectric line of the TP interval (Figure 1). The amplitude of the R wave in aVL and the Sokolow-Lyon voltage (sum of the amplitudes of the S wave in V1 and the R wave in V5) were calculated (Figure 1). The EDI is expressed as [aVL R amplitude × (V1S amplitude + V5R amplitude)/PWLI amplitude].[10] The EDI values of the patients were calculated by two experienced cardiologists who were unaware of the patients' TTE parameters.

Statistical analysis

The data were analyzed using the SPSS 22.0 Statistical Package Program for Windows (SPSS; IBM, Armonk, New York, USA). A Kolmogorov-Smirnov test was used to assess the normality of distribution. Continuous variables were presented as mean ± standard deviation (normal distribution) or median ± interquartile ranges (without normal distribution) and categorical variables as the number of patients and percentages.

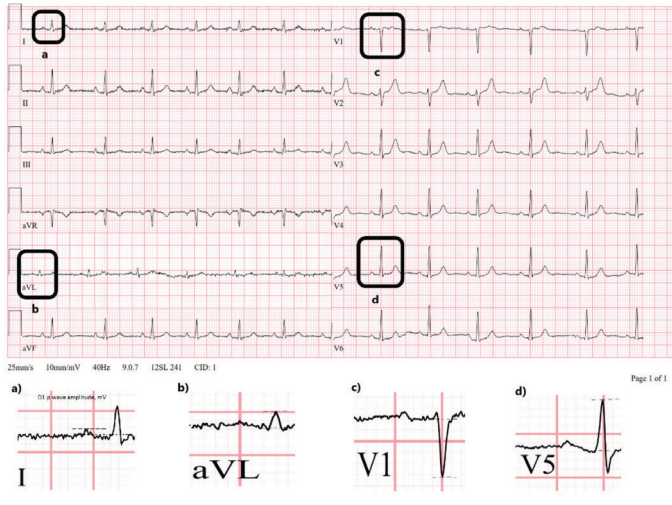

Figure 1: Electrocardiographic parameters of the EDI formula [aVL R amplitude × (V1S amplitude + V5R amplitude)/ P wave amplitude in the lead I amplitude]

A comparison between groups was made with the Student's t-test for normally distributed variables and a Mann-Whitney U test for the variables without a normal distribution. Categorical data from both groups were compared using the χ^2 or Fisher's exact test.

The prediction value of the EDI for LVDD was evaluated by receiver operating curve (ROC) curve analysis and area under the curve (AUC) values. The cutoff value was calculated according to the Youden index. A *P* value lower than 0.05 (using a two-sided test) was considered significant.

Univariate and multivariate logistic regression analyses were used to evaluate the independent predictors of LVDD. Variables displaying $P < 0.05$ in the univariate analysis were used in a multivariate logistic regression analysis. Two multivariate models were used (model I: EDI as a continuous variable and model II: EDI as a categorical variable).

RESULTS

Two hundred two patients followed with a diagnosis of HT were included in the study. Basal characteristics are given in Table 1. The patients were divided into two groups according to the presence of LVDD (105 patients without LVDD, group 1; 97 patients with LVDD, group 2).

The mean age of the study population was 50 ± 14 years, and 57.4% of the patients were female. Patients in group 2 had a higher age ($P = 0.19$), more frequent diabetes diagnosis ($P = 0.023$), and a higher body mass index (BMI) value ($P = 0.005$) compared to group 1. Left ventricular end-diastolic and end-systolic diameter measurements were similar between the two groups. Interventricular septum thickness (IVST) and posterior wall thickness (PWT) were found to be significantly higher in group 2 (respectively; $P < 0.01$, $P = 0.02$). Higher LVEF ($P = 0.032$) and larger left atrial diameter ($P = 0.031$) was found in group 2. Lower E wave (peak early filling velocity during atrial

Table 1: Baseline clinical characteristics, echocardiographic, and electrocardiographic findings of all patients

	All populations (*n*=202)	LVDD (-) (*n*=105)	LVDD (+) (*n*=97)	*P*-value
Age, years	50±14	47±14	53±13	0.019
Male, n (%)	86 (42.6)	35 (33.3)	51 (52.6)	0.007
Female, n (%)	116 (57.4)	70 (66.7)	46 (47.4)	0.007
Diabetes mellitus, n (%)	33 (16.3)	11 (10.5)	22 (22.7)	0.023
Smoking, n (%)	93 (46)	44 (41.9)	49 (50.5)	0.259
BMI, kg/m^2	30±10	28.5±11	32±9	0.005
Echocardiography parameters				
LVEDD, mm	46±3	46±3	46±3	0.124
LVESD, mm	29±4	28±3	29±4	0.051
IVST, mm	1.0±0.2	1.0±0.1	1.1±0.2	<0.001
PWT, mm	1.0±0.1	1.0±0.10	1.0±0.11	0.002
LVEF, %	61±5	62±5	60±3.5	0.032
LA, mm	35±3	35±4	36±4	0.031
E, cm/sn	70 ± 10	80 ± 10	70 ± 10	<0.001
A, cm/sn	60 ± 20	60 ± 10	80 ± 30	<0.001
E/A ratio	1.2±0.5	1.4±0.3	0.9±0.5	<0.001
E' Lateral, cm/sn	10±4	12±2	8±2	<0.001
Electrocardiography parameters				
D1 P wave amplitude, mV	0.1±0.06	0.1±0.04	0.1±0.05	0.181
aVL R amplitude, mV	0.4±0.3	0.3±0.3	0.5±0.3	<0.001
V1S amplitude, mV	0.7±0.3	0.7±0.4	0.7±0.5	0.043
V5R amplitude, mV	1.0±0.6	1.0±0.5	1.1±0.7	0.093
V1S amplitude + V5R amplitude, mV	1.7±0.7	1.7±0.7	2.0±0.9	0.005
EDI	8.5±7.3	5.2±3.7	10.6±8.5	<0.005

Data are presented as mean ± standard deviation for normal distribution or median ± interquartile range for not-distribution normality or n (%).

BMI: Body mass index, LVEDD: Left ventricular end-diastolic dimension, LVESD: Left ventricular end-systolic dimension, IVST: Interventricular septum thickness, PWT: Posterior wall thickness, LVEF: Left ventricular ejection fraction, LA: Left atrial, EDI: Electrocardiographic diastolic index

systole), higher A wave (late peak filling velocity during atrial systole), decreased E/A ratio, and decreased lateral E' wave were observed in group 2 ($P < 0.001$ for all parameters). While there was no significant difference between PWLI and V5R amplitude in both groups, aVR amplitude was higher in group 2 than in group 1 ($P < 0.001$). When V1S and V1S + V5R amplitudes were compared, it was observed that patients in group 2 were significantly higher than those in group 1 (respectively; $P = 0.043$, $P = 0.005$). The EDI value of the patients included in the study was 8.5 ± 7.3. The EDI value in group 2 was significantly higher than that in group 1 ($P < 0.005$).

ROC analysis was performed to test the optimal cut-off value reliability of EDI in group 2. The AUC of EDI in predicting LVDD was found to be 0.773 [95% confidence interval (CI):0.708 - 0.839; $P < 0.001$] (Figure 2). When the cutoff value of the EDI is greater than 7.4 mV, it predicts LVDD with 63.6% sensitivity and 79.8% specificity.

First, the factors affecting the presence of LVDD were examined by univariate logistic regression analysis. In univariate logistic regression analysis, the presence of LVDD was associated with EDI (OR:1,248, 95% CI:1,159-1,345, $P < 0.001$), age [OR:1,025, 95% CI:1,005-1.047), $P = 0.016$], presence of diabetes [OR:2,507, 95% CI:1,144-5,495, $P = 0.022$] and BMI [OR:1,060, 95% CI:1,015-1.106, $P = 0.009$] (Table 2).

Multivariate logistic analysis was used to investigate the effect of significant parameters in univariate logistic regression analysis for predicting the presence of LVDD. Two different models were constructed to evaluate EDI as both a continuous variable and a categorical variable. EDI was determined as an independent predictor of LVDD in both models (Table 3).

DISCUSSION

Our study is an investigation presenting an ECG index to predict DD in patients with HT. This study shows that the EDI formula is a simple and easily applicable tool for DD estimation.

ECG is easier to reach than an echocardiography device. Therefore, more patients can be scanned for DD using the ECG index. According to ECG findings, it can be referred to an advanced center in terms of definitive diagnosis at an earlier stage. In this way, worsening can be prevented by applying the necessary medications in the earlier period.

A higher EDI value was found in patients with LVDD than in those without LVDD. In our study, IVST, and PWT were significantly higher in the LVDD patient group. However, a larger left atrial diameter was found in patients with LVDD. aVL R amplitude was found to be higher in patients with LVDD. A higher EDI value predicted LVDD, and the optimal cutoff value was calculated at 7.4 mV. These results show that changes in cardiac diastolic parameters can be detected in the 12-lead

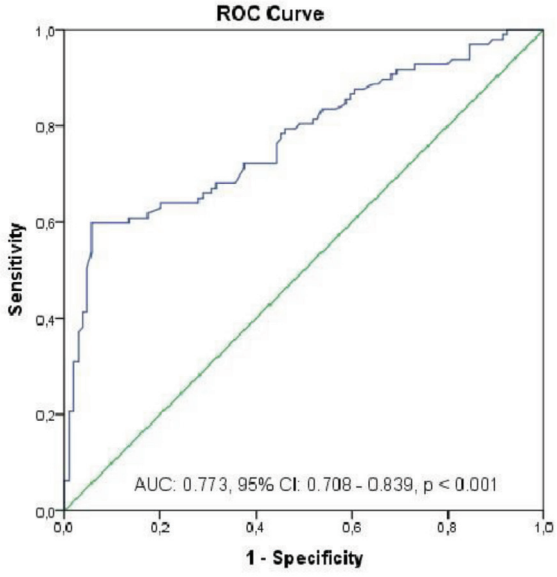

Figure 2: A receiver operating curve (ROC) analysis showed that the optimal cut-off value of the electrocardiographic diastolic index to predict diastolic dysfunction was 7.4 mV with 63.6% sensitivity and 79.8% specificity [area under the curve (AUC) 0.773; 95% confidence interval (CI) 0.708-0.839; $P < 0.001$].

Table 2: Univariate logistic regression analysis for left ventricular diastolic dysfunction

	Odds ratio (95% CI)	*P*-value
EDI	1,248 (1,159-1,345)	<0.001
Age	1,025 (1,005-1,047)	0.016
DM	2,507 (1,144-5,495)	0.022
BMI	1,060 (1,015-1,106)	0.009

CI: Confidence interval, EDI: Electrocardiographic diastolic index, DM: Diabetes mellitus, BMI: Body mass index

Table 3: Multivariate logistic regression analysis for left ventricular diastolic dysfunction

	Odds ratio (95% CI)	*P*-value
Model 1		
EDI	1,253 (1,161-1,352)	<0.001
Age	1,015 (0.986-1,044)	0.322
DM	2,666 (1,071-6,638)	0.035
BMI	1,025 (0.968-1,086)	0.395
Model 2		
EDI >7.4	7,262 (3,771-13,985)	<0.001
Age	1,012 (0.986-1,040)	0.369
DM	2,263 (0.986-1,040)	0.078
BMI	1,033 (0.987-1,091)	0.247

CI: Confidence interval, EDI: Electrocardiographic diastolic index, DM: Diabetes mellitus, BMI: Body mass index

surface ECG in the patient population without coronary artery disease followed by HT.

In conditions of pressure overload owing to systemic HT, the left ventricle undergoes extensive growth, leading to LVH. LVH is seen as an increased voltage on ECG. The excess myocardial collagen present in hypertensive LVH is suggested to result from several alterations. These changes lead to DD and subsequently to HFpEF.[13]

Atrial dilatation reflects atrial remodeling due to HT.[14] ECG changes related to atrial dilatation, such as broad P wave and prolongation of the PR interval, can be observed on surface ECGs.[15] A previous study has shown that the initial P wave in lead V1 was associated with atrial dilatation, confirmed by cardiac magnetic resonance examination.[16] P wave amplitude in D1 constitutes an essential component of EDI to evaluate the relationship between left atrial dilatation and DD.[10] Left ventricular filling restriction and decreased LV function are ventricular structural changes caused by HT.[14,17] These changes can result in increased LVH markers in the ECG.[18] LVH appears to be both a cause and a result of DD in HT patients without coronary artery disease. The Sokolow-Lyon voltage criteria are commonly used in ECG for detecting LVH.[19] Using R amplitude in aVL, a component of the Cornell and Sokolow-Lyon voltage criteria, in the EDI calculation is intended to increase the DD estimation.[10] The research also confirmed the relationship between LVH and DD.[10]

Krepp et al.[8] evaluated the relationship between patients' ECG, TTE, and diastolic functions. They divided the patients into two groups diagnosed with and without DD in TTE. In this study, isovolumetric relaxation time, deceleration time, and the left atrial volume index were also calculated in TTE. ECG examination, Cornell criterion, and Sokolow-Lyon voltage criteria were calculated. In our study, evaluating the components of both criteria in a single formula in the electrocardiographic examination increased the index predictiveness.

Another study divided patients into three equal groups according to their EDI.[10] Baseline features, ECG, and TTE findings were compared in these patient groups. The mean age of the patient population was 62.8 ± 8.9 years, and the female sex ratio was 24.5%. In our study, the mean age was 50 ± 14 years, and the female sex ratio (57.4%) was higher. Our study divided the patients into two groups according to their TTE findings. The relationship between DD and EDI was examined. Hayıroğlu et al.[10] found that the optimal threshold value of EDI was determined as 8.53 mV with a sensitivity of 70% and a specificity of 70%. In our study, this value was determined as 7.4 mV with sensitivity of 63.6% and specificity of 79.8%.

In this study, the EDI value was significantly higher in patients with LVDD, suggesting that ECG can be used as a critical diagnostic parameter in predicting DD.

Study limitations

There are several limitations to our study. First, it is a retrospective and single-center trial. Therefore, it has limited value in terms of generalizability. As this is a retrospective study, the etiology of HFpEF (such as amyloidosis) is not identified as an underlying factor. Using TTE as an imaging modality involves subjective evaluation elements. In addition, TTE measurements can be affected by variables such as respiration and heart rate. However, ECG measurements have limitations in terms of standardization because computerized measurement techniques are not used. More patients are needed to classify DD and to determine its relationship with ECG findings more clearly.

CONCLUSION

EDI is an essential assessment tool in predicting DD in patients who are followed up with HT because it is a cheap, accessible, and easy-to-use formula.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Ankara City Hospital Ethics Committee (number: E1-22-2587, date: 20.04.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.O.Ö., C.Ç., Concept: M.O.Ö., Design: M.O.Ö., O.M., Data Collection or Processing: M.O.Ö., Ö.Ç.K., Analysis or Interpretation: Ö.Ç.K., C.Ç., Literature Search: M.O.Ö., O.M., Writing: M.O.Ö., C.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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RESEARCH ARTICLE

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Int J Cardiovasc Acad 2023;9(2):36-41

The Prognostic Value of the Systemic Immune-inflammation Index in ST-segment Elevation Myocardial Infarction Patients and Its Correlation with Syntax II Score and TIMI Risk Score

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Abstract

Background and Aim: The systemic immune-inflammation index (SII) has been identified as a novel prognostic marker in various illnesses. We investigated the relationship between SII and mortality in patients undergoing primary percutaneous coronary intervention (pPCI). In addition, we planned to examine how SII correlated with SYNTAX II and thrombolysis in myocardial infarction (TIMI) risk scores in this population.

Materials and Methods: This retrospective observational study included patients with ST-segment elevation myocardial infarction who underwent pPCI. The endpoint was 1 year all-cause mortality. SII [(neutrophil x platelet)/lymphocyte] was calculated from admission blood samples. Besides clinical and laboratory findings, SII, Syntax II and TIMI risk scores were compared between survivors and non-survivors. The correlation between SII and Syntax II and TIMI risk scores was also evaluated.

Results: The study included 334 patients (82.3% male). In the 1 year follow-up, 18 patients (5.4%) died. The SII, Syntax II, and TIMI risk scores were significantly higher in non-survivors than in survivors [mean (standard deviation: SD), 2423 (2005) vs 1686 (998), $P = 0.005$; median (interquartile range) 43 (35-53) vs 30 (25-37), $P < 0.001$; and 4 (2-5) vs 2 (1-3), $P = 0.005$, respectively]. Furthermore, the Syntax II score, TIMI risk score, and SII was independent predictors of 1 year all-cause mortality. SII showed a significant correlation with Syntax II and TIMI risk scores ($R^2 = 0.28$, $P = 0.001$ and $R^2 = 0.37$, $P < 0.001$, respectively).

Conclusion: SII might provide additional prognostic data alongside Syntax II and TIMI risk scores in patients undergoing pPCI.

Keywords: Systemic immune-inflammation index, STEMI, PCI, Syntax II score, TIMI risk score

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide.[1] Around 18 million people die from ischemic heart disease (IHD) yearly, and atherosclerosis is a key contributing factor.[2,3] In the context of IHD, ST-segment elevation myocardial infarction (STEMI) is more common than non-ST-segment elevation myocardial infarction.[2] The primary cause of STEMI is the rupture of the coronary atherosclerotic plaque with subsequent thrombus development.[4]

According to studies, immunological and inflammatory responses play a significant role in all stages of STEMI development, including the progression of atherosclerosis,

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plaque rupture, and intraluminal thrombosis.[4-6] As part of the immune system, white blood cells, platelets, neutrophils, and lymphocytes play various roles in atherosclerosis and acute coronary syndrome.[7,8] Increased platelet counts indicate a prothrombotic state and harmful inflammatory activity.[7] Neutrophils can accelerate tissue damage by activating cytotoxicity, while lymphocytes regulate the inflammatory response and have a protective effect.[7,8]

The systemic immune-inflammation index (SII) was developed using neutrophil, platelet, and lymphocyte counts to evaluate the inflammatory and immunological states.[9] SII is considered an accurate prognostic indicator in many conditions, including cancer and CVDs.[9-11] However, limited scientific publications are available investigating SII association with long-term prognosis in patients with STEMI. Our objective was to investigate the relationship between SII and 1 year all-cause mortality in patients undergoing primary percutaneous coronary intervention (pPCI). We also planned to look at how SII correlated with conventional scoring systems, the Syntax II score, and the thrombolysis in myocardial infarction (TIMI) risk score in this population.

MATERIALS AND METHODS

Patients with STEMI undergoing pPCI between September 01, 2019 and June 30, 2021 were included retrospectively in this observational study. Patients with severe valvular heart disease, cardiogenic shock, active infection, history of coronary revascularization, oncological illness, and liver or kidney disorders were excluded. In addition, patients whose follow-up data could not be retrieved or who had incomplete data were not included. The study endpoint was 1 year all-cause mortality. The study was performed according to the 2008 revision of the Declaration of Helsinki. Kafkas University Ethics Committee approved the study (decision no: 80576354-050-99/260, date: 24.02.2023).

STEMI was diagnosed based on a recently accepted definition.[12] The hospital database was used to obtain the patients' demographics, comorbidities, admission laboratory results, and angiographic views. The formula used to determine SII was (neutrophil count x platelet count)/lymphocyte count.

Hypertension was described as a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg in two measurements or antihypertensive medication. Smokers were defined as patients who had smoked continuously for at least six months in the previous year.

Patients with fasting glucose levels of ≥126 mg/dL or postmeal glucose levels of ≥200 mg/dL or using antidiabetic drugs were diagnosed with diabetes mellitus. Patients with dyslipidemia were identified as those whose serum low-density lipoprotein cholesterol was ≥140 mg/dL, triglyceride levels were ≥150 mg/dL, or high-density lipoprotein cholesterol was less than 40 mg/dL. The estimated glomerular filtration rate (eGFR) was determined using the Cockcroft-Gault formula. We used the modified Simpson technique to quantify the left ventricular ejection fraction (LVEF).[13]

Coronary artery angiography (CAG) was conducted through the femoral artery using the Seldinger technique. Before CAG, patients received 300 mg of acetylsalicylic acid, a loading dose of P2Y12 inhibitors, and 70-100 U/kg of infractionated heparin. Two experienced cardiologists blinded to the data thoroughly examined the angiographic views of the patients. Lesions in coronary arteries with stenosis of ≥50% and ≥1.5 mm in diameter were recorded using the online Syntax Score calculator (https://syntaxscore.org/calculator/start.htm, accessed in March-April 2023). An online calculator was used to obtain the Syntax II score[14] (https://syntaxscore.org/calculator/start.htm, accessed in March-April 2023). Variables for the Syntax II score were age, gender, chronic obstructive pulmonary disease, peripheral arterial disease, creatinine clearance, and LVEF. The TIMI risk score for STEMI was calculated using an online calculator (https://www.mdcalc.com/calc/99/timi-risk-score-stemi, accessed in March-April 2023).

Clinical follow-up information was acquired using the hospital and pharmacy databases or by calling patients or their relatives on the phone. Death certificates from the governmental database were used to confirm the death.

Statistical Analysis

SPSS software, version 21.0, was used for the statistical analysis. The normality test was maintained by using the Kolmogorov-Smirnov test. Continuous variables that showed a normal distribution were represented as mean [standard deviation (SD)] and those that did not show a normal distribution were expressed as median [interquartile range (IQR)]. Categorical data were represented as numbers (percentages) and analyzed using Pearson chi-square or Fisher's exact tests. The independent Student's t-test or Mann-Whitney U test was used to analyze continuous variables. Univariate regression analysis was performed for variables that differed significantly across the groups. A multivariate logistic regression analysis, including age, eGFR, Syntax II score, TIMI risk score, and SII, was used to describe the independent predictors of mortality. Data are displayed as odd ratios [95% confidence intervals (CI)]. Receiver operating characteristic (ROC) curve analysis was also used to indicate the performance of SII for predicting mortality. Pearson correlation analysis was performed to show the correlation between SII and Syntax II and TIMI risk scores. A *P*-value of 0.05 was used as the statistical significance threshold.

RESULTS

Our study included 334 patients (82.3% male). Table 1 represents the demographic characteristics and laboratory findings. The mean age of the patients was 56.6 ± 11 years. A total of 18 patients (5.4%) died during the 1-year follow-up period.

Non-survivors were older than survivors [age, years mean, standart deviation (SD), 62.8 (10.8) vs 56.2 (11), P =0.013]. Creatinine levels were significantly higher, whereas hemoglobin levels were significantly lower in non-survivors than in survivors [median (IQR), 1.04 (0.86-1.6) vs 0.89 (0.77-1), P = 0.019 and 12.4 (11.25-14.1) vs 13.9 (13-15), P = 0.015, respectively]. In non-survivors, eGFR was also significantly lower [mean (SD) 69 (28) vs 86 (23), P = 0.003]. Furthermore, non-survivors had significantly higher SII, TIMI risk score, and Syntax II score [mean (SD), median (IQR), 2423 (2005) vs 1686 (998), P = 0.005;43 (35-53) vs 30 (25-37), P < 0.001; and 4 (2-5) vs 2 (1-3)], P = 0.005, respectively]. In univariate analysis, age, eGFR, Syntax II score, TIMI risk score, and SII were associated with mortality [odds ratio (OR) (95% CI), 1.054 (1.010-1.100), P = 0.015; 0.968 (0.946-0.989), P = 0.003; 1.089 (1.048-1.132), P < 0.001; 1.325 (1.069-1.642), P = 0.009; and 1.030 (1.028-1.062), P = 0.011, respectively]. According to multivariate analysis, the Syntax II score, TIMI risk score, and SII were independent predictors of mortality [OR (95% CI), 1.084 (1.031-1.139), P = 0.002; 1.068 (1.014-1.361), P = 0.012; and 1.016 (1.008-1.068), P = 0.048, respectively] (Table 2). The results of univariate and multivariate analyzes are presented in Table 2. In ROC curve analysis (Figure 1), a cutoff value of 1820 for SII predicted mortality with a sensitivity of 61% and specificity of 63% [area under the curve (AUC) was 0.628; P = 0.047)], AUC for TIMI risk and Syntax II scores was 0.689 (P = 0.007) and 0.826 (P < 0.001), respectively. In the Pearson correlation test,

Table 1: Demographic and laboratory findings

	Total (n=334)	Survivors (n=316)	Non-survivors (n=18)	P-value
Male, n (%)	275 (82.3)	262 (82.9)	13 (72.2)	0.247
Age (years), mean (SD)	56.6 (11)	56.2 (11)	62.8 (10.8)	0.013
SBP (mmHg), median (IQR)	135 (120-1447)	135 (120-148)	131 (90-139)	0.316
DBP (mmHg), median (IQR)	80 (70-90)	80 (70-90)	76 (56-90)	0.278
Heart rate, median (IQR)	80 (70-88)	80 (70-88)	81 (65-98)	0.588
SII, mean (SD)	1725 (1084)	1686 (998)	2423 (2005)	0.005
Syntax II score, median (IQR)	31 (25-39)	30 (25-37)	43 (35-53)	<0.001
TIMI risk score, median (IQR)	2 (1-4)	2 (1-3)	4 (2-5)	0.005
Laboratory				
Hemoglobin (g/dL) median (IQR)	13.9 (13-15.1)	13.9 (13-15)	12.4 (11.25-14.1)	0.015
WBC ($\times10^3$/µL), median (IQR)	12.83 (11.18-14.59)	12.8 (11.2-14.35)	13 (10.22-17.57)	0.762
Neutrophil ($\times10^3$/µL), median (IQR)	10.2 (8-12)	10 (8-11.7)	12.05 (8.8-14.7)	0.066
Lymphocyte($\times10^3$/µL), median (IQR)	1.8 (1.29-2.5)	1.8 (1.3-2.5)	1.35 (1.07-2.17)	0.078
Platelet ($\times10^3$/µL), median (IQR)	260 (222-298)	260 (222-298)	227 (214-297)	0.988
Troponin I (ng/mL) median (IQR)	2.66 (0.81-5.78)	2.4 (0.75-5.6)	3.83 (2.25-8.13)	0.091
CK-MB (ng/mL) median (IQR)	35 (25-47)	35 (25-46)	42.5 (29.2-61.7)	0.181
Creatinine (mg/dL) median (IQR)	0.9 (0.78-1.03)	0.89 (0.77-1)	1.04 (0.86-1.6)	0.019
eGFR, mean (SD)	85 (23)	86 (23)	69 (28)	0.003
Glucose (mg/dL), mediyan (IQR)	129 (108-172)	129 (108-172)	138 (100-293)	0.477
Comorbities				
Hypertension, n (%)	153 (45.8)	144 (45.6)	9 (50)	0.714
Diabetes, n (%)	77 (23.1)	70 (22.2)	7 (38.9)	0.101
Smoking, n (%)	190 (56.9)	180 (57)	10 (55.6)	0.907
COPD, n (%)	19 (5.7)	17 (5.4)	2 (11.1)	0.307
PAD, n (%)	51 (15.3)	46 (14.6)	5 (27.8)	0.168
Dyslipidemia, n (%)	138 (41.3)	134 (42.4)	4 (22.2)	0.091

CK-MB: Creatine kinase-MB, COPD: Chronic obstructive pulmonary disease, DBP: Diastolic blood pressure, eGFR: Estimated glomerular filtration rate, IQR: Interquartile range, SBP: Systolic blood pressure, SII: Systemic immune-inflammation index, SD: Standard deviation, PAD: Peripheral artery disease, TIMI: Thrombolysis in myocardial infarction, WBC: White blood cell count

SII was significantly correlated with the TIMI risk score and the Syntax II score ($R^2 = 0.37$, $P < 0.001$ and $R^2 = 0.28$, $P = 0.001$, respectively) (Figure 2).

DISCUSSION

The main findings of our study are that; 1) age, eGFR, Syntax II score, TIMI risk score, and SII were significantly associated with 1 year all-cause mortality in patients undergoing pPCI, 2) the Syntax II score, TIMI risk score, and SII were independent predictors of mortality, and 3) SII, albeit weakly, showed a positive correlation with the TIMI risk score and Syntax II score.

Despite technological and therapeutic advances, mortality remains high in patients with STEMI.[1,2] In this sense, the investigation of factors related to clinical outcomes is critical in terms of preventing mortality. Age showed a positive association with mortality in our study. Similarly, previous reports have established that age is associated with both short- and long-term mortality after pPCI.[15,16] Coronary artery characteristics also play a critical role in the prognosis of CVD. Several scoring systems have been established previously in this respect.[14,17] Syntax II and TIMI risk scores are the most studied.[18] In agreement with the literature, our study demonstrated that Syntax II and TIMI risk scores were associated with mortality and were independent predictors of mortality. The Syntax II score calculated from clinical and angiographic variables, accurately predicted 1-year mortality in patients with STEMI.[19] Besides, early reports showed that the TIMI risk score also predicts in-hospital and 1-year death in this population.[20,21] Inflammation plays a key role in all stages of STEMI, including the formation, evolution, and dissection of the plaque and thrombus.[4-6,22,23] SII has recently been proposed as a possible marker based on inflammatory cells associated with poorer outcomes in several disorders, including CVD.[9-11,24] In patients with CVD, the elevation of standard inflammatory markers, e.g., white blood cell count or C-reactive protein, was not only observed, but also associated with atherosclerotic plaque instability and mortality due to CAD.[25,26] Nevertheless, these counts are susceptible to various factors, such as dehydration and fluid overload.[27] SII appears to be more stable and better predicts adverse cardiovascular outcomes than the standard blood counts.[28] Many studies have investigated the relationship between SII and adverse outcomes in CVD. Erdogan et al.[29] showed a significant association between SII and CAD severity. Dey et al.[10] found a relationship between SII and poor postoperative results following off-pump coronary artery bypass surgery. Agus et al.[30] reported that patients with infective endocarditis had an independent relationship between SII and in-hospital mortality. According to Yang et al.,[9] SII was an independent predictor of unfavorable outcomes in patients with STEMI, non-STEMI, and stable angina pectoris. The latter included a heterogeneous coronary artery disease group, but our study included a homogeneous group (only STEMI). A recent report by Saylik and Akbulut[24] showed the role of SII in predicting major adverse cardiovascular events in 843 patients undergoing pPCI. This study included a larger population with a more extended follow-up period. However, it differed in methodology from our study. Furthermore, they did not study the correlation of SII with traditional risk scores. Overall, similar to these publications,

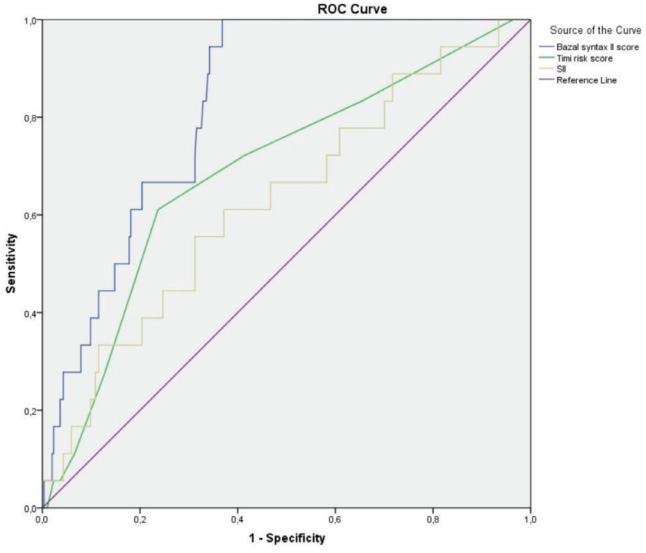

Figure 1: The receiver operating characteristic (ROC) curve for predicting 1 year all-cause mortality using the systemic immune-inflammation index (SII). The area under the curve is 0.628 (cut-off value: 1820, sensitivity: 61%, specificity: 63%).

Table 2: Univariate and multivariate regression analyzes for predicting 1 year all-cause mortality

	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Age	1.054 (1.010-1.100)	0.015	1.001 (0.946-1.059)	0.972
eGFR	0.968 (0.946-0.989)	0.003	0.996 (0.969-1.023)	0.749
Syntax II score	1.089 (1.048-1.132)	<0.001	1.084 (1.031-1.139)	0.002
TIMI risk score	1.325 (1.069-1.642)	0.009	1.068 (1.014-1.361)	0.012
SII	1.030 (1.028-1.062)	0.011	1.016 (1.008-1.068)	0.048

CI: Confidence interval, eGFR: Estimated glomerular filtration rate, OR: Odds ratio, SII: Systemic immune-inflammation index, TIMI: Thrombolysis in myocardial infarction

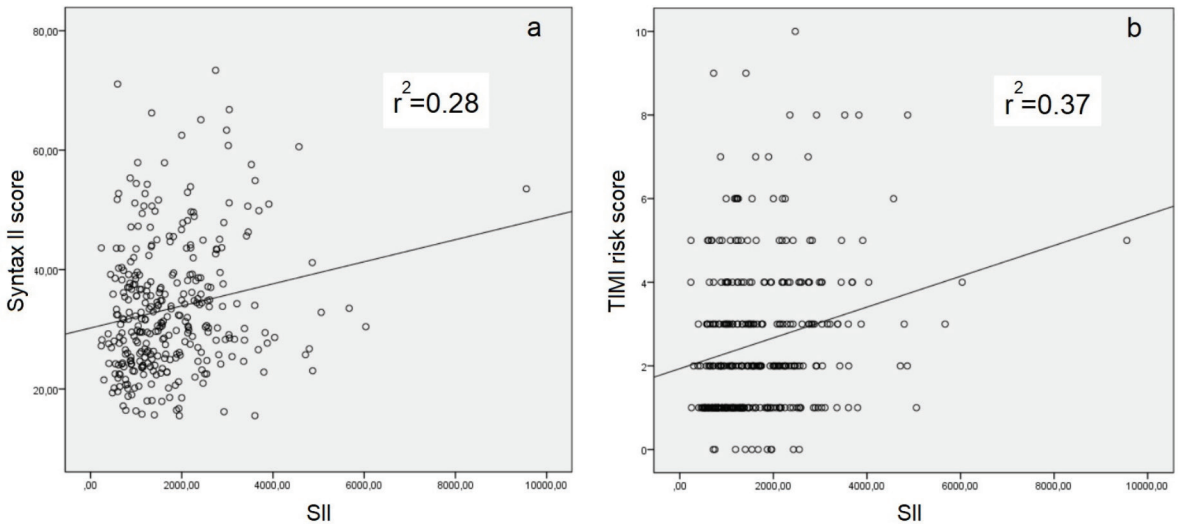

Figure 2: Correlation graphics between the systemic immune-inflammation index (SII) and Syntax II score (**a**) and TIMI risk score (**b**)

our study revealed a relationship between SII and 1 year all-cause mortality. Moreover, we demonstrated a 1 year predictive value of SII in a particular patient group (STEMI). Furthermore, we showed a positive correlation between SII and TIMI risk and Syntax II scores.

Consequently, predicting adverse outcomes early in risky STEMI patients who undergo pPCI is crucial for prioritized treatment. In this context, SII may play an essential prognostic role in risk stratification for these patients, alongside the Syntax II score and TIMI risk score.

Study limitations

Our study has main limitations were the relatively small size of the study population and the single-center and retrospective design. In addition, our endpoint was all-cause mortality, and we could not provide the exact cause of death. Large randomized controlled studies are needed to confirm the predictive value of SII in STEMI patients receiving p-PCI.

CONCLUSION

Our study found a positive correlation between SII and Syntax II and TIMI risk scores in patients undergoing pPCI. SII and Syntax II and TIMI risk scores were associated with 1 year all-cause mortality. Thus, SII, as an easily calculable marker, might provide additional prognostic data alongside Syntax II and TIMI risk scores in patients undergoing pPCI.

Ethics

Ethics Committee Approval: Kafkas University Ethics Committee approved the study (decision no: 80576354-050-99/260, date: 24.02.2023).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K., İ.A., Y.K., İ.R., Concept: M.K., Design: T.O., Data Collection or Processing: B.A., Analysis or Interpretation: C.D., İ.R., Literature Search: A.A., Writing: T.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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RESEARCH ARTICLE

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Evaluation of Right Ventricular Global Longitudinal Strain in COVID-19 Patients After Intensive Care Unit Discharge

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Abstract

Background and Aim: Using two-dimensional speckle tracking echocardiography (2D-STE), the ventricular functions of hospitalized coronavirus disease-2019 (COVID-19) patients were assessed. However, there is limited information about cardiac functions in the first year after recovery from the intensive care unit (ICU). This research aims to assess the right ventricular functions of COVID-19 patients and their changes within the first year after ICU discharge using 2D-STE.

Materials and Methods: The study was conducted prospectively. The study included 68 consecutive patients and 70 control patients. Echocardiography was performed in the ICU and the first year after discharge from the hospital. Right ventricular global longitudinal strain (RVGLS) was measured using the 2D-STE method.

Results: The mean age of the study group was 48.67±8.10 and 37 (54.4%) patients were males. There were no substantial differences across the groups, including age, gender, body mass index, heart rate, diabetes, dyslipidemia, and smoking ($P > 0.05$). A substantially significant positive correlation was detected between right ventricular dimension (RAD) ($r = 0.644$, $P < 0.001$), right ventricular diastolic dimension (RVDD) ($r = 0.573$, $P < 0.001$), ferritin ($r = 0.454$, $P < 0.001$), D-dimer ($r = 0.305$, $P = 0.011$) values and RVGLS in the in-hospital and after-discharge first-year groups. The RVGLS values of the control, in-hospital, and after-discharge first-year groups were -20.36±3.06, -16.98±3.78, and -17.58±6.45, indicating a statistically significant difference across the groups ($P < 0.001$). Tricuspid annular plane systolic excursion was higher in the control group ($P < 0.05$).

Conclusion: RVGLS was found to be depressed during the in-hospital period and showed no improvement in the 1 year post discharge.

Keywords: Echocardiography, strain, right ventricle, speckle-tracking, COVID-19

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INTRODUCTION

Coronavirus disease-2019 (COVID-19), which has turned into a widespread epidemic worldwide, first affects the respiratory system.[1] Although we know that it directly affects the heart, it usually causes cardiac impairment secondary to the involvement of other organs.[2] Recent investigations have revealed that the cardiac involvement may result in pericarditis, myocarditis, cardiac tamponade, and myocardial infarction.[3] The most common cause of in-hospital mortality in COVID-19 patients is ventricular dysfunction.[4]

The right ventricle (RV) is more likely to be damaged than the left ventricle (LV) due to rising RV afterload because COVID-19 primarily affects the lungs.[5] In previous research, individuals with acute respiratory distress syndrome (ARDS) and respiratory failure were found to have RV dysfunction.[6] Standard echocardiographic measures may not be able to detect subclinical RV abnormalities, which makes diagnosis and risk categorization difficult. The most objective and sensitive examination of RV systolic dysfunction is provided by two-dimensional speckle tracking echocardiography (2D-STE).[7] Thus, right ventricular global longitudinal strain (RVGLS) has been examined for predicting mortality in hospitalized patients. In COVID-19 patients, evaluation of RV function with 2D-STE in the first year after intensive care unit (ICU) discharge has not been published.

This study aims to investigate whether improving RV functions or not by measuring RVGLS with 2D-STE at the end of the first year after discharge from the ICU.

MATERIALS AND METHODS

The selection of participants

The study was conducted prospectively. The RVGLS values of 68 consecutive patients who met the inclusion criteria from COVID patients admitted to the critical care unit between December 2020 and December 2021 were recorded, and RVGLS values were reanalyzed after a 1 year follow-up between December 2021 and December 2022. The study included 70 healthy volunteers as a control group. Clinical conditions affecting RV strain such as structural heart disease, hypertension, chronic liver or kidney disease, pulmonary embolism, malignancy, history of asthma and pulmonary hypertension, obstructive pulmonary disease, and previous COVID were excluded from the study. Additionally, patients who had COVID of within the first year after discharge and who died were not included in the study.

Study protocol

Demographic characteristics, echocardiographic measurements, and blood samples of patients with COVID-19 hospitalized in intensive care were obtained from medical records. Complete blood cell analysis, C-reactive protein (CRP), ferritin, hs-TnT, D-dimer, and echocardiography were performed for all patients in the first year after discharge. Blood samples were examined from the control group while echocardiography was performed on the same day. All patients underwent bedside transthoracic echocardiographic tests using the Philips EPIQ 7C device (Andover, Massachusetts). The size of the right atrium and RV was assessed using a 4-chamber apical view. On M-mode imaging, tricuspid annular plane systolic excursion (TAPSE) was measured as the systolic displacement of the tricuspid lateral annulus. Using PW tissue Doppler imaging, the RV myocardial performance index (RVMPI) was measured. (RV end-diastolic area RV end-systolic area)/end-diastolic area 100% was used to determine RV fractional area change (RVFAC). Pulmonary artery systolic pressure (sPAP) was measured using the peak velocity of the tricuspid regurgitation jet and the size and collapsibility of the inferior vena cava to calculate right atrial pressure.[8] In line with recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging[9], 2D-STE was applied to assess longitudinal systolic strain (Figure 1). Images were obtained in the four (4C)-chamber views at 70-100 frames per second from the end of expiration and were evaluated blindly by two independent specialists.

Ethical statement

This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital (no: 133, date: 22.07.2022). It adhered to the Declaration of Helsinki's ethical guidelines for human experimentation (2013).

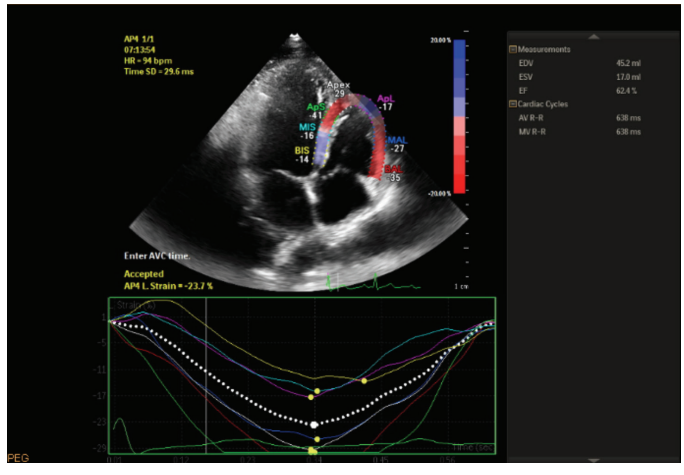

Figure 1: Measurement of right ventricular global longitudinal strain

Statistical analysis

IBM SPSS 24.0 version analyzed the data. Student's t-test or One-Way analysis of variance was used for normally distributed data and Mann-Whitney U or Kruskal-Wallis tests was used for non-normally distributed data. The chi-square or Fisher's exact test was used to compare categorical variables reported as frequency (%). The correlation between RVGLS and right ventricular dimension (RAD), RVDD, TAPSE, sPAP, D-dimer, CRP, and ferritin levels was determined using Pearson or Spearman correlation analysis. A $P < 0.05$ signified statistical validity.

RESULTS

A total of 138 individuals, 68 of whom recovered from COVID-19 and 70 controls, were enrolled in the study. The average age of the study group was 48.67 ± 8.10 and 37 (54.4%) patients were male. There were no substantial differences across the groups, including age, gender, BMI, HR, diabetes, dyslipidemia, and smoking ($P > 0.05$, Table 1).

The WBC, CRP, D-dimer, and ferritin levels were higher in the study group than in the controls ($P < 0.001$). In the study group, 7 (10.3%) patients had ARDS, and 6 (8.8%) patients were administered immune-modulators. High-flow oxygen was given to 9 (13.2%) patients. Non-invasive mechanical ventilation and IMV were performed on 16 (23.5%) and 7 (10.3%) patients, respectively. In the echocardiographic parameters, RAD, RVSD, RVDD, RVMPI, RVGLS, and sPAP were higher in the in-hospital and after-discharge first-year groups ($P < 0.05$, Table 2). E/A ratio was lower and LV ejection fraction was higher in the control group ($P > 0.05$).

The RVGLS values of the control, in-hospital, and after-discharge first-year groups were -20.36 ± 3.06, -16.98 ± 3.78, and -17.58 ± 6.45, indicating a statistically significant difference across the

Table 1: Clinical characteristics and laboratory parameters of patients

Parameters	The control group *n = 70*	The study group *n = 68*	*P*-value
Age (years)	47.24±8.45	48.67±8.10	0.311
Gender, male, n (%)	33 (47.1)	37 (54.4)	0.393
BMI (kg/m^2)	23.67±4.24	24.31±4.54	0.396
HR (beats/min)	86.0±8.75	89.2±13.23	0.092
Diabetes mellitus, n (%)	15 (21.4)	19 (27.9)	0.375
Dyslipidemia, n (%)	6 (8.6)	8 (11.8)	0.534
Smoking, n (%)	19 (27.1)	16 (23.5)	0.626
Laboratory findings			
Hemoglobin (g/dL)	13.67±2.03	13.09±2.40	0.124
WBC (10^3/µl)	8.26±0.77	11.93±4.23	<0.001
Lymphocytes (10^3/µl)	2.84±0.78	2.79±1.48	0.238
Neutrophil (10^3/µl)	6.02±7.89	6.35±1.48	0.094
Increased troponin, n (%)	-	22 (32.4)	-
Glucose (mg/dL)	88.45±8.56	92.29±23.28	0.199
CRP (mg/L)	0.3 (0.08)	2.1 (2.51)	<0.001
D-dimer (ng/mL)	238.5 (20.0)	810 (260.2)	<0.001
Ferritin (mL/ng)	181.5 (35.5)	495.5 (31.2)	<0.001
ALT (U/L)	21.54±8.33	21.89±8.63	0.807
AST (U/L)	23.68±5.22	24.51±9.61	0.529
Treatment			
Immune modulator, n (%)	-	6 (8.8)	-
Highflow, n (%)	-	9 (13.2)	-
NIMV, n (%)	-	16 (23.5)	-
IMV, n (%)	-	7 (10.3)	-
ARDS, n (%)	-	7 (10.3)	-

Data are expressed as appropriate as mean ± standard deviation and median (interquartile range). BMI: Body mass index, HR: Heart rate, WBC: White blood cell, CRP: C-reactive protein, ALT: Alanine transaminase, AST: Aspartate transaminase, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation, ARDS: Acute respiratory distress syndrome

groups ($P < 0.001$). RVFAC was not significant across the groups ($P > 0.05$). TAPSE was higher in the control group ($P < 0.05$). There were no significant differences between the in-hospital and after-discharge first years in terms of echocardiographic parameters ($P > 0.05$). However, sPAP was statistically different between the in-hospital and after-discharge first-year groups ($P = 0.031$). On the other hand, RVSD and RVMPI were statistically significant between the in-hospital and control groups ($P = 0.044$, $P = 0.048$). There was an association between RVGLS and RAD, RVDD, TAPSE, sPAP, D-dimer, CRP, and ferritin levels. A positive correlation was detected between RAD ($r = 0.644$, $P < 0.001$), RVDD ($r = 0.573$, $P < 0.001$), ferritin ($r = 0.454$, $P < 0.001$), D-dimer ($r = 0.305$, $P = 0.011$) values and the in-hospital group. Likewise, a negative correlation was detected between TAPSE ($r = -0.511$, $P < 0.001$), CRP ($r = -0.315$, $P = 0.009$) and the in-hospital group (Table 3).

In addition, a positive correlation was determined between RAD ($r = 0.409$, $P = 0.001$), RVDD ($r = 0.268$, $P = 0.027$), Ferritin ($r = 0.495$, $P < 0.001$), D-dimer ($r = 0.388$, $P = 0.001$) and after-discharge first-year group.

DISCUSSION

This study evaluated right ventricular functions with 2D-STE in the first year in ICU discharge. After one year of follow-up, no statistically significant RV improvement was observed in RAD, RVSD, RVDD, TAPSE, and RVGLS parameters ($P > 0.05$). On the contrary, the sPAP value increased even more ($P = 0.031$).

Viral infections provoke an intense inflammatory reaction in the body. CRP, ferritin, and D-dimer were indicators of the systemic inflammation of COVID-19. CRP was found to be high in 75-90% of patients with severe COVID-19 involvement.[10] A value greater than 10 indicates the widespread involvement. In Chinese studies by Guan et al.[11], 46% of individuals had raised D-dimer values (>0.5 mg/L). Huang et al.[12] discovered that COVID-19 hospitalized in the ICU had a greater D-dimer level than those who did not receive ICU care. Another acute phase reactant is serum ferritin.[13] In Zhou et al.[14] retrospective research, blood ferritin levels were significantly higher in non-survivors than in survivors. Mahmoud-Elsayed et al.[15] reported that inflammation parameters predicted RV dysfunction independently of left ventricular dysfunction in patients with

Table 2: Comparison of right ventricular echocardiographic parameters between the groups

	The control group (A) *n = 70*	The study group (In-hospital) (B) *n = 68*	The study group (After discharge first year) (C) *n = 68*	P (A-B)	P (B-C)	P (A-C)
RAD (mm)	3.59±0.45	3.81±0.72	3.70±0.67	0.041	0.305	0.022
RVSD (mm)	2.77±0.50	2.96±0.73	2.92±0.57	0.048	0.461	0.166
RVDD (mm)	3.75±0.59	4.01±0.74	3.81±0.55	0.019	0.072	0.049
RVFAC (%)	53.18±8.91	51.69±8.92	52.76±9.15	0.083	0.287	0.605
RVMPI	0.47±0.07	0.50±0.10	0.49±0.07	0.044	0.395	0.130
RVGLS (%)	-20.36±3.06	-16.98±3.78	-17.58±6.45	<0.001	0.453	<0.001
TAPSE (mm)	2.20±0.14	2.08±0.30	2.10±0.30	0.007	0.692	0.014
sPAP (mmHg)	17.20±4.53	26.60±7.11	24.70±3.20	<0.001	0.031	<0.001
E/A ratio	1.5±0.52	1.7±0.91	1.6±0.58	0.168	0.387	0.423
LVEF (%)	65.1±3.9	64.2±7.7	64.6±5.5	0.412	0.197	0.384

Values are mean ± standard deviation, n (%), or median (interquartile range). RAD: Right atrium dimension, RVSD: Right ventricular systolic dimension, RVDD: Right ventricular diastolic dimension, RVFAC: Right ventricular fractional area change, RVMPI: Right ventricular myocard performance index, RVGLS: Right ventricular global longitudinal strain, TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary artery pressure, LVEF: Left ventricular ejection fraction

Table 3: Correlation of right ventricular global longitudinal strain with parameters

		RAD	RVDD	TAPSE	sPAP	CRP	Ferritin	D-dimer
RVGLS In-hospital	*r*	0.644	0.573	-0.511	-0.200	-0.315	0.454	0.305
	P	**<0.001**	**<0.001**	**<0.001**	0.101	**0.009**	**<0.001**	**0.011**
RVGLS After discharge	*r*	0.409	0.268	-0.229	0.160	-0.081	0.495	0.388
	P	**0.001**	**0.027**	0.060	0.193	0.514	**<0.001**	**0.001**
RVGLS Controls	*r*	-0.403	-0.026	0.059	0.331	-0.011	0.072	-0.306
	P	**0.001**	0.830	0.628	**0.005**	0.929	0.556	**0.010**

RVGLS: Right ventricular global longitudinal strain, RAD: Right atrium dimension, RVDD: Right ventricular diastolic dimension, TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary artery pressure, CRP: C-reactive protein

COVID-pneumonia. Although these parameters were associated with mortality in many meta-analysis studies, the values were mostly associated with the severity of the disease in our study.[16] Qeadan et al.[17] obtained results similar to the outcomes of our study.

Right ventricular dysfunction has been reported in echocardiography of COVID-19 patients.[18] In a large-scale study of 69 countries, Dweck et al.[19] noted that a quarter of all patients had right ventricular dysfunction, with the vast majority of these patients exhibiting severe symptoms. The RV dilates due to an increase in afterload. This increases RAD, RVSD, and RVDD. In a meta-analysis, Corica et al.[20] reported that 1 in 5 patients had increased right ventricular diameters. The vast majority of them consisted of ICU patients. In accordance with earlier research and Chotalia et al.'s[21] findings, the patient's right ventricular diameters and sPAP values were found to be increased in our study.

TAPSE, RVFAC, and RVMPI are conventional measures of the right ventricular ejection fraction. According to Baycan et al.[22] research, there was no difference in RVFAC and RVMPI between the control and study groups. Li et al.[23] found lower TAPSE and RVFAC values lower and higher RVMPI in COVID patients compared with the control group. Günay et al.[24] found lower RVFAC values in recovery patients. Catena et al.[25] reported that there was no difference in right ventricular conventional parameters between the in-hospital and post-discharge groups. The same results were obtained in our study ($P > 0.05$).

Unlike conventional methods, RVGLS is an independent predictor of COVID involvement and is a superior method because it is measured independently of angle.[26] Using the RVGLS measure, Turan et al.[27] revealed right ventricular impairment following recovery in asymptomatic and mildly symptomatic individuals. Carluccio et al.[28] demonstrated that this method provides prognostic information for right ventricular failure in patients with preserved TAPSE and RVMPI measurements. Ozer et al.[29] reported that TAPSE and RVFAC values were normal in the echocardiography performed at the 3rd month after discharge from the ICU, and only deterioration in RVGLS values. In our study, although RVGLS values were lower than those in the control group, no improvement was found in RVGLS values in the first year in discharge. In addition, a correlation has been found between RVGLS and inflammatory markers.[30] In this trial, a positive correlation was found between RVGLS measurement, which is a sensitive indicator of right ventricular subclinical involvement, and CRP, D-dimer, and ferritin. Increased CRP, D-dimer and ferritin levels at the hospital admission and to recovery were related to RVGLS impairment, supporting this conclusion.

Study limitations

Our study population was small. Previously, detailed echocardiography measurements of the patients were not available in the records. Due to technical limitations, 3D-STE and cardiac MRI were not performed on the patients.

CONCLUSION

In this study, the results showed that impaired RVGLS values did not improve at the first year of follow-up. The long-term effects of COVID-19 infection on right ventricular function are unknown, so prospective studies with longer follow-ups are required.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital (no: 133, date: 22.07.2022).

Informed Consent: Prospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G., A.A., A.Ak., R.K., M.A.I., M.Z.K., Concept: S.G., A.A., T.G., F.K., M.Ç., M.Z.K., Design: S.G., A.Ak., R.K., B.A., M.Z.K., Data Collection or Processing: S.G., T.G., M.Z.K., Analysis or Interpretation: S.G., A.A., M.A.I., M.Ç., M.Z.K., Literature Search: S.G., A.Ak., F.K., B.A., M.Z.K., Writing: S.G., M.A.I., M.Z.K.

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CASE REPORT

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Causation or Coincidence? A Case of Coexisting Spontaneous Coronary Artery Dissection and Coronary Thrombosis in a Patient with Kounis Syndrome

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Abstract

Kounis syndrome (KS) is a hypersensitive coronary disorder leading to acute coronary syndrome triggered by drugs, food, and environmental factors. Herein, we report a 39-year-old patient who was admitted to our clinic due to type 2 KS after oral diclofenac use. Interestingly, spontaneous coronary artery dissection was detected simultaneously on coronary angiography. Up to now, no case has been defined including the combination of these two different conditions.

Keywords: Allergic myocardial infarction, Kounis syndrome, diclofenac potassium, spontaneous coronary artery dissection

INTRODUCTION

Kounis syndrome (KS) is defined as the appearance of acute coronary syndrome symptoms because of activation of mast cells and other inflammatory cells in cases of allergy, hypersensitivity, anaphylaxis or anaphylactic reactions.[1] Various mediators released from mast cells after contact with an allergen may start thrombotic processes by causing spasm in coronary arteries and erosion or rupture of atherosclerotic plaques. KS can be induced by drugs, food, environmental exposures, and other conditions.

The spontaneous coronary artery dissection (SCAD) is also a rare condition with an incidence of 1-4%.[2,3] It may also result in acute coronary syndrome because of disturbance in coronary flow. SCAD has been described commonly in women aged between 47 and 53 years. In this report, we present the case of a patient who had simultaneous type 2 KS and SCAD.

CASE REPORT

A 39-years old male patient who had a history of widespread itching and rashes after oral diclofenac potassium intake for headache came to the emergency department with chest pain. He did not have any known disease and said that he had rashes on his body after taking a medicine 5 years ago. He could not remember his name. On his examination, he had a red-looking face, urticaria-like rashes, and his respiratory rate was increased. Blood pressure was 105/70 mmHg, oxygen saturation 96%, and fever measured 37.2 °C. Electrocardiography revealed sinus rhythm and minimal ST-segment depressions in V1-V3 derivations. Considering an allergic reaction, methylprednisolone and pheniramine were administered intravenously. Considering that KS was possible due to the persistence of severe chest pain, coronary angiography was performed. Coronary angiography showed normal LMCA and LAD artery, total occluded osteal Cx with

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thrombosis, and type 1 SCAD was observed in the mid region of right coronary artery (RCA) (Figure 1A). Three hundred mg acetylsalicylic acid and 600 mg clopidogrel were administered and intravenous 7500 IU heparin was administered to the patient. When the Cx lesion was crossed with a floppy wire, TIMI-3 flow was obtained (Figure 1B). Then, a heavy thrombus burden extending from the Cx osteal to the LMCA was observed and the patient's pain was significantly decreased after coronary flow was established. Considering the high no-reflow risk due to severe thrombus burden, thrombolytic therapy (tPA) was planned to be applied to the patient who was hemodynamically stable. Low dose (25 mg tPA), slow infusion (24 h) tPA were given. Control angiography was performed after 24 h. It was observed that the thrombus in the Cx osteal region completely disappeared (Figure 1C). Since the RCA mid-region SCAD remained unchanged angiographically thrombolysis in myocardial infarction (TIMI) with TIMI-3 flow and the patient was clinically stable, it was decided that he should be followed up medically. The patient was discharged with acetylsalicylic acid, clopidogrel, metoprolol, perindopril, and atorvastatin therapy. After 2 months of follow-up, myocardial perfusion scintigraphy was performed and no ischemia was observed in the RCA area. When the patient was seen at the 6th month of follow-up, he had no complaints. Written consent was obtained from the patient for this case report.

DISCUSSION

KS is defined as the appearance of the acute coronary syndrome symptoms because of activation of mast cells and other inflammatory cells in cases of allergy, hypersensitivity, anaphylaxis or anaphylactic reactions.[1] KS may occur due to various environmental exposures and medications.[4] After contact with the allergen, mast cells are activated and from these cells local and systemic release of biogenic amines such as histamine; neutral proteases such as chimase, tryptase, cathepsin-D; arachidonic acid derivatives and platelet activating factor such as leukotrienes, thromboxane. Histamine causes coronary vasoconstriction, increases tissue factor synthesis, and activates platelets. Proteases, on the other hand, cause plaque wear and tear activating matrix metalloproteinases. Angiotensin-II increase causes vasoconstriction. Thromboxane and thrombocyte activating factor both cause vasoconstriction and activate thrombocytes.[5,6]

Three types of KS have been identified. Type 1; Patients with normal or near-normal coronary arteries without risk factors for coronary artery disease have coronary vasospasm caused by allergic mediators. Type 2; It is the group with an undiagnosed disease, even if there is no history of acute coronary syndrome, with a lesion that causes obstruction in the vein after erosion or rupture of the coronary plaque. Type 3 is the group defined by the presence of eosinophils and mast cells in the extracted thrombus material in some cases who developed stent thrombosis after drug-eluting stent implantation.[5,6]

Previously, KS due to diclofenac have been published in the literature.[7] We wanted to share the treatment management of SCAD occurring in a different coronary artery associated with type 2 KS that developed following allergic findings after oral diclofenac potassium intake without previously known coronary artery disease and risk factors.

SCAD is defined as the separation of coronary artery layers from each other, regardless of trauma, iatrogenic cause, or

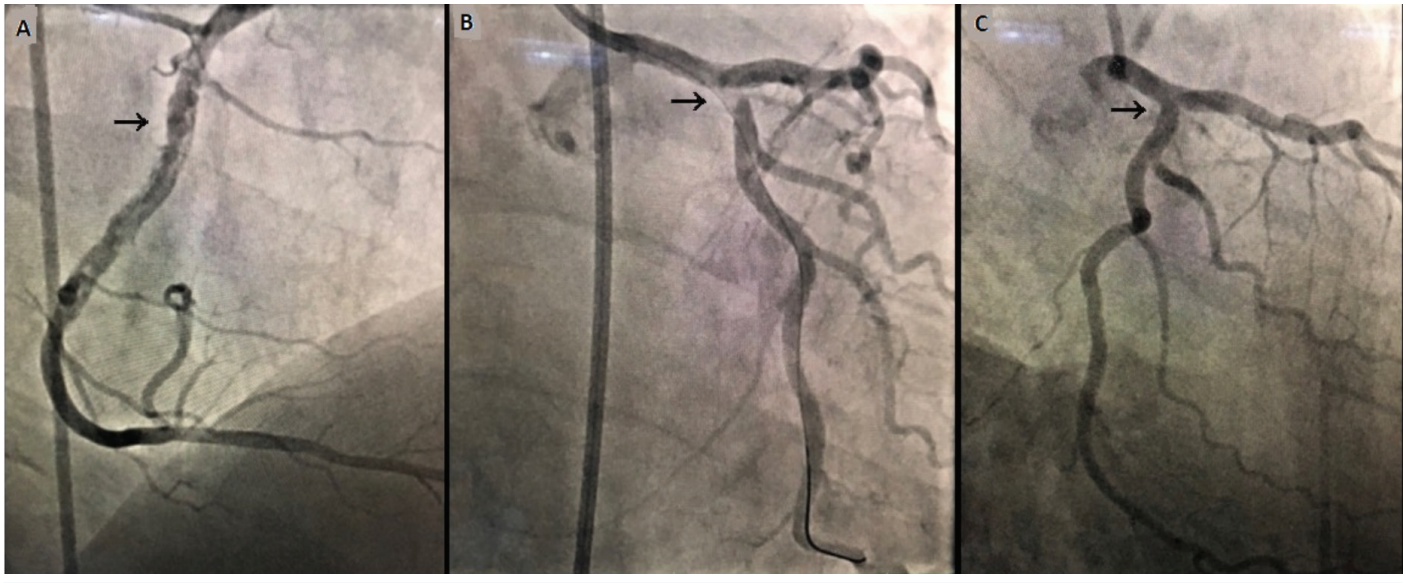

Figure 1. A) Simultaneous coronary dissection in the RCA, **B)** After wire crossing, a heavy thrombus burden was observed in the LAD and Cx osteal region, **C)** Resolution of the thrombus after t-PA infusion

atheromatous plaque rupture. The resulting false lumen can expand and spread, can block the flow within the true lumen, which may cause symptoms of myocardial ischemia. There can be many factors that increase hemodynamic stress and/or increase vessel wall fragility leading SCAD such as pregnancy or heavy sports like wrestling and heavy lifting.[8] On the other hand, the main pathophysiology in KS is coronary vasospasm. Coronary vasospasm increases shear stress on the coronary artery and may lead to dissection. Variant angina has been shown to be associated with SCAD.[9] SCAD cases caused by coronary artery spasm and vasoconstriction related to sympathomimetic drugs (cocaine, amphetamines) use have also been reported.[10] We found our case worth reporting because up to now, no cases have been reported including a combination of these two disorders. Whether it was a cause or co-incidence is not known in our case, but increased shear stress in the coronary artery due to vasospasm in KS might have led to SCAD.

In our patient, when the Cx lesion was crossed with a floppy guidewire, TIMI-3 flow was achieved in Cx. In the Cx osteal, a heavy thrombus burden extending to the LMCA was observed. The patient was hemodynamically stable and pain-free. Because of the high risk of no reflow and stent thrombosis after PCI for a lesion with a heavy thrombus burden in the Cx osteal region, we decided to apply tPA to the patient. Successfully treated cases with low dose, slow infusion thrombolytics have been reported in the literature.[11] The slow and ultraslow infusion of low-dose tPA was first described in the literature for the treatment of prosthetic valve thrombosis in the TROIA and PROMETEE Trials.[12,13] Following these papers, others have successfully used this regime for different clinical scenarios including coronary embolism. Moreover, Karakoyun et al.[14] and Yesin et al.[15] have reported the success of the low-dose t-PA regime in their large series. In fact, the general approach is to avoid thrombolytics specifically in patients with SCAD. However, the risk of propagation of intramural hematoma/complete obstruction of true lumen/vessel rupture is based on previous anecdotal reports where rapidly infused full dose thrombolytics were used. The novel regimen of ultraslow infusion of low-dose t-PA may be less risky in patients with SCAD, but this argument requires confirmation with robust data in the future. In this study, 25 mg tPA was administered to the patient as a slow infusion for 24 h. After 24 h, when we performed control angiography, it was observed that the thrombus in the Cx osteal region and LMCA completely disappeared. There was no progression in RCA dissection, and the appearance was the same as in the first angiography.

In SCAD treatment, conservative treatment is sufficient for most patients who are hemodynamically stable and do not have ongoing ischemia. The majority of conservatively managed SCADs have been found to regain normal coronary architecture, usually within 30 days. To prevent ongoing ischemia, stent implantation can be performed to cover the entire dissection in patients with unstable clinics.[3,16,17] We discharged our patient with dual antiaggregant and beta blocker therapies. In myocardial perfusion scintigraphy after 2 months, no ischemia was observed. The patient did not have any complaints. We decided that SCAD should be followed up medically, and the patient was examined again at the 6th month controls and did not have any complaints.

Negative results regarding the use of thrombolytics in SCAD have been reported due to the prolongation of the dissection or hematoma; therefore, it is generally not recommended. Thrombolytic therapies are not recommended in SCADs because they may cause progress in dissections.[3,16] However, in our case, we applied low-dose slow t-PA infusion successfully because the LMCA and Cx osteal thrombus burden was high, which might have caused no-reflow and cardiogenic shock after PCI. Although there was no negative result in our case, it should be kept in mind that thrombolytic treatments may cause worsening of the dissections.

CONCLUSION

In conclusion, KS is not a rare condition but it can often be overlooked due to cases that cannot be correctly identified. A complete and correct history should be taken before the physical examination. It should also be kept in mind that KS may develop in patients applying with-allergic symptoms, and coronary dissections may also accompany KS.

Ethics

Informed Consent: Written consent was obtained from the patient for this case report.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.B., U.A., Concept: F.B., U.A., Design: F.B., U.A., Data Collection or Processing: F.B., U.A., Analysis or Interpretation: F.B., U.A., Literature Search: F.B., U.A., Writing: F.B., U.A.

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