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Relationship between systemic immune inflammation index and development of complete atrioventricular block in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

Fatma Esin[1], Saban Esen[2], Semih Aktürk[1], Ömer Pekersen[1], Tuncay Kiris[1*] and Mustafa Karaca[1]

Abstract

Background The systemic immune-inflammation index (SII), based on white blood cell, neutrophil, and platelet counts, is a proposed marker of systemic inflammation and immune activation. This study aimed to explore the relationship between SII and complete atrioventricular block (CAVB) development in STEMI patients undergoing primary PCI.

Methods We retrospectively analyzed data from 883 patients who underwent primary PCI for STEMI between January 2009 and December 2017. Patients were categorized into two groups based on CAVB development. SII levels were calculated from blood samples taken on admission.

Results Of the included patients, 48 (5.03%) developed CAVB. SII was higher in patients with CAVB compared to those without CAVB (1370 [1050–1779]x109/L vs. 771 [427–1462] x109/L, $p < 0.001$). Multivariate analysis showed a significant positive correlation between SII and the risk of CAVB development (OR:1.0003, 95%CI:1.0001–1.0005, $P = 0.044$). The cut-off value for the SII in the estimation of CAVB was 1117.7×10^9/L (area under the ROC curve [AUC]: 0.714, 95% CI = 0.657–0.770 with a sensitivity of 70.8% and specificity of 65.6%, $p < 0.001$).

Conclusion This study showed a significant link between high SII levels and CAVB development in STEMI patients undergoing PCI. Our findings suggest that SII may be a valuable, routinely available, and inexpensive marker for identifying patients at increased risk of CAVB.

Keywords Systemic immune inflammation index, Complete atrioventricular block, ST-elevation myocardial infarction, Primary percutaneous coronary intervention

*Correspondence:
Tuncay Kiris
drtkiris@hotmail.com
[1]Atatürk Training and Research Hospital, Department of Cardiology, Izmir Katip Çelebi University, Izmir, Turkey
[2]Department of Cardiology, Tunceli State Hospital, Tunceli, Turkey

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Introduction

Cardiovascular diseases (CVDs) continue to be the leading cause of mortality globally, with acute myocardial infarction (AMI) being a significant contributor to this burden. Among the various types of AMI, ST-elevation myocardial infarction (STEMI) is particularly severe, often requiring immediate intervention through primary percutaneous coronary intervention (PCI) as the preferred reperfusion strategy [1]. However, STEMI patients undergoing primary PCI are at risk of developing complications such as complete atrioventricular block (CAVB), which is associated with poor prognosis [2]. The overall incidence of high-grade AV block is reported to be 3–13% [2].

In recent years, the role of systemic inflammation in the pathogenesis of CVDs and AMI has gained attention [3]. Various indices have been developed to measure systemic inflammation, including the fibrinogen-to-albumin ratio and the systemic immune-inflammation index (SII) [4]. SII, calculated from peripheral lymphocyte, neutrophil, and platelet counts, has been shown to predict contrast-induced nephropathy in STEMI patients undergoing primary PCI [5]. Moreover, the effectiveness of SII in predicting the no-reflow phenomenon has been explored [6]. A recent study has shown that SII was an independent predictor of newly diagnosed reverse-dipper hypertensive patients [7]. There was a significant association between SII levels and hyperlipidemia in National Health and Nutrition Examination Survey (NHANES) adult participants [8]. It has been shown that the systemic immune inflammation index and system inflammation response index were both independently related to the presence of atrial fibrillation in patients with stroke [9].

In a previous study by Altunova et al., SII was associated with a high residual SYNTAX score in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention [10]. Emerging evidence suggests that dynamic fluctuations in biomarkers like SII could be valuable predictors of long-term adverse cardiovascular events in STEMI patients after undergoing PCI [11]. Despite these advances, the relationship between SII and the development of CAVB in STEMI patients undergoing primary PCI remains underexplored.

This study aimed to fill this gap by investigating the relationship between SII and the development of CAVB in patients with STEMI undergoing primary PCI.

Methods

Study design

This study is a retrospective, single-centre cohort study conducted at the Department of Cardiology, Katip Celebi University, Ataturk Education and Research Hospital. The study was approved by the Institutional Review Board and was conducted by the principles outlined in the Declaration of Helsinki.

The study population consisted of 883 consecutive patients admitted to our institution's cardiac catheterization laboratory with a diagnosis of ST-elevation myocardial infarction (STEMI) between January 2009 and December 2017. Patients were included if they met the following criteria: (1) diagnosed with STEMI based on clinical presentation, electrocardiographic changes, and elevated cardiac biomarkers; (2) underwent primary Percutaneous Coronary Intervention (PCI); and (3) had available pre-procedural complete blood count (CBC) data for calculation of the Systemic Immune Inflammation Index (SII). Patients with autoimmune diseases, hematologic disorders, or active infections were excluded from this study.

Data collection

Electronic medical records were retrospectively reviewed to collect relevant clinical and laboratory data. Demographic characteristics, medical history, medication use, and procedural details were recorded. Laboratory parameters, including complete blood count, were obtained from the hospital's laboratory database.

Calculation of systemic immune inflammation index (SII)

Systemic Immune Inflammation Index (SII) was calculated using the formula: SII = Platelet count × (Neutrophil count / Lymphocyte count). The platelet, neutrophil, and lymphocyte counts were obtained from the pre-procedural complete blood count.

Outcome assessment

The primary outcome of this study was the development of a CAVB, occurring either before cardiac catheterization or before hospital discharge. CAVB was defined as a complete absence of atrioventricular conduction resulting in a ventricular rate that was independent of the atrial rate, confirmed by continuous electrocardiographic monitoring and evaluated by a cardiologist. The patients were divided into two groups according to whether CAVB developed or not; CAVB (+) ($n=48$) or CAVB (-) ($n=835$). Considering the CAVB rates, the study needed to recruit 771 participants to have 80% power with a 5% type 1 error level.

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the study population. Continuous variables were presented as mean ± standard deviation or median with interquartile range depending on their distribution, while categorical variables were presented as frequencies and percentages. The normality of the data was assessed using the Shapiro-Wilk test. A correlation

Table 1 Baseline characteristics of the study population

Variables	CAVB (-) (n = 835)	CAVB (+) (n = 48)	*p*-value
Age	59.1 ± 12.7	70.7 ± 10.7	< 0.001
Male, n (%)	687 (82)	30 (63)	0.001
Diabetes mellitus, n (%)	209 (25)	16 (33)	0.199
Hypertension, n (%)	335 (40)	22 (46)	0.433
Previous CAD, n (%)	172 (21)	9 (19)	0.758
Previous CHF, n (%)	37 (4)	3 (6)	0.556
Chronic kidney disease, n (%)	50 (6)	9 (19)	< 0.001
Previous stroke, n (%)	46 (6)	3 (6)	0.827
Hyperlipidemia, n (%)	112 (13)	6 (13)	0.857
Multivessel disease, n (%)	419 (51)	31 (65)	0.219
Smoking, n (%)	431 (52)	18 (38)	0.057
Inotrope usage, n (%)	55 (7)	17 (35)	< 0.001
Killip class > 2, n (%)	102 (12)	23 (48)	< 0.001
IABP usage, n (%)	55 (7)	17 (3575)	< 0.001
Thrombus aspiration device, n (%)	140 (17)	20 (42)	< 0.001
GpIIB3A inhibitors, n (%)	293 (35)	22 (46)	0.131
Final TIMI-3 flow n (%)	745 (89)	36 (75)	0.003
Infarct related artery, n (%)			< 0.001
LMCA, n (%)	9 (1)	2 (4)	
LAD, n (%)	374 (45)	9 (19)	
CX, n (%)	92 (11)	3 (6)	
RCA, n (%)	275 (33)	32 (67)	
Others n (%)	59 (7)	1 (2)	
Medical treatment at discharge, n (%)	90 (51)	19 (66)	0.159
Aspirin n (%)	738 (97)	26 (90)	0.016
Clopidogrel, n (%)	523 (69)	22 (73)	0.600
Prasuqrel, n (%)	64 (8)	0 (0)	0.097
Tigacrelor, n (%)	151 (20)	5 (17)	0.661
Beta blockers, n (%)	670 (88)	18 (60)	< 0.001
ACE/ARB, n (%)	627 (83)	18 (64)	0.048
Statin n (%)	708 (93)	26 (90)	0.726
Outcomes			
In-hospital mortality, n (%)	75 (9)	22 (46)	< 0.001
Long-term mortality, n (%)	164 (20)	13 (27)	0.210

Abbreviations: CAD: coronary artery disease, CHF: chronic heart failure, CX: Circumflex artery, LAD: Left anterior descending artery, RCA: right coronary artery, IABP: intra-aortic baloon pump; ACE-I/ARB: angiotensin-converting enzyme inhibitors/ angiotensin receptor blocker, TIMI: Thrombolysis in myocardial infarction

analysis between SII and other variables was conducted using the Pearson correlation test. The association between SII and the development of CAVB was assessed using logistic regression analysis, adjusting for potential confounding variables such as age, gender, and comorbidities. The predictive values of neutrophil to lymphocyte ratio (NLR), platelet, and SII were estimated by the areas under the receiver operating characteristic curve (ROC). All statistical analyses were conducted using SPSS 26 (SPSS Inc., Chicago, IL, USA). A two-sided p-value < 0.05 was considered statistically significant.

Table 2 Laboratory findings of the patients before matching

Variables	CAVB (-) (*n* = 835)	CAVB (+) (*n* = 48)	*p*-value
WBC count (×10^3/μL)	11.8 ± 3.8	13.1 ± 4.2	0.019
Hemoglobin (g/dl)	14.1 ± 1.9	12.4 ± 1.9	< 0.001
eGFR* (mL/min/1.73m^2)	90 (73–108)	67 (37–82)	< 0.001
Platelet count (×10^3/μL)	267 ± 77	313 ± 110	< 0.001
Neutrophil (×10^3/μL)	8.1 ± 3.6	10.1 ± 3.7	< 0.001
Lymphocyte (×10^3/μL)	2.7 ± 1.6	2.1 ± 0.8	< 0.001
Total cholesterol (mg/dL)	184 ± 48	166 ± 46	0.050
LDL-C (mg/dL)	114.5 ± 37.9	102.8 ± 36.3	0.110
HDL-C (mg/dL)	37.1 ± 11.7	37.5 ± 15.9	0.852
Trigliseride * (mg/dL)	141 (102–195)	115 (92–182)	0.168
LVEF *	46.3 ± 10.0	42.8 ± 9.2	0.021
SII* (x10^9/L)	771 (427–1462)	1370 (1050–1779)	< 0.001

Abbreviations: WBC; white blood cell, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, SII; systemic immune-inflammatory index, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol

* Comparison was made using the Mann-Whitney *U* test at $p < 0.05$, and these values were described by a median with an interquartile range (25th and 75th percentile)

Results

Baseline characteristics

A total of 883 STEMI patients were included in the study. 15 patients developed CAVB before PCI or at admission, and 33 patients developed CAVB after PCI or before hospital discharge. The baseline demographic and clinical characteristics of the patients are presented in Table 1. CAVB was more common in patients who were female and older. The histories of hypertension, diabetes mellitus, hyperlipidemia, and previous coronary artery disease (CAD) were similar between groups (Table 1). Chronic kidney disease was more frequent in CAVB patients compared with those without (19% vs. 6%, $p < 0.001$).

The culprit lesion was the right coronary artery in most CAVB patients (67% vs. 33%, $p < 0.001$). Inotrope and intra-aortic balloon pump usage were more common in CAVB patients than in those without (Table 1). CAVB patients had a higher Killip class than those without CAVB (48% vs. 12%, $p < 0.001$).

The laboratory findings are presented in Table 2. WBC and neutrophil counts were higher in CAVB patients (13.1 ± 4.2 vs. 11.8 ± 3.8, $p = 0.019$; 10.1 ± 3.7 vs. 8.1 ± 3.6, $p < 0.001$, respectively). Lymphocyte count was lower in patients with CAVB compared to those without (2.1 ± 0.8 vs. 2.7 ± 1.6, $p < 0.001$). The patients with CAVB had lower LVEF than patients without CAVB (42.8 ± 9.2% vs. 46.3 ± 10.0%, $p = 0.021$). SII was higher in CAVB patients (1370 [1050–1779]x10^9/L vs. 771 [427–1462] x10^9/L, $p < 0.001$, Table 2). The correlations of SII with other variables were presented in Table 3.

Table 3 The correlations of SII with other variables

Variables	r	*p*-value
Age (years)	0.172	< 0.001
LVEF (%)	-0.175	< 0.001
Killip class	0.189	< 0.001
Final TIMI flow	-0.104	0.002
Total cholesterol (mg/dl)	-0.103	0.004
LDL-C (mg/dl)	-0.078	0.034
HDL-C (mg/dl)	0.011	0.754
Trigliseride (mg/dl)	-0.100	0.006
Haemoglobin (mg/dl)	-0.270	< 0.001
eGFR	-0.124	< 0.001

Abbreviations: LDL: low-density lipoprotein cholesterol; HDL-C: HDL-C;high-density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, TIMI: Thrombolysis in myocardial infarction

Association between SII and CAVB

Logistic regression analysis was used to assess the association between SII and the development of CAVB, adjusting for potential confounding variables such as age, sex, comorbidities, and procedural characteristics. After adjusting for these variables, SII was found to be an independent predictor of the risk of developing CAVB (OR:1.0003, 95%CI:1.0001–1.0005, $P=0.044$, Fig. 1).

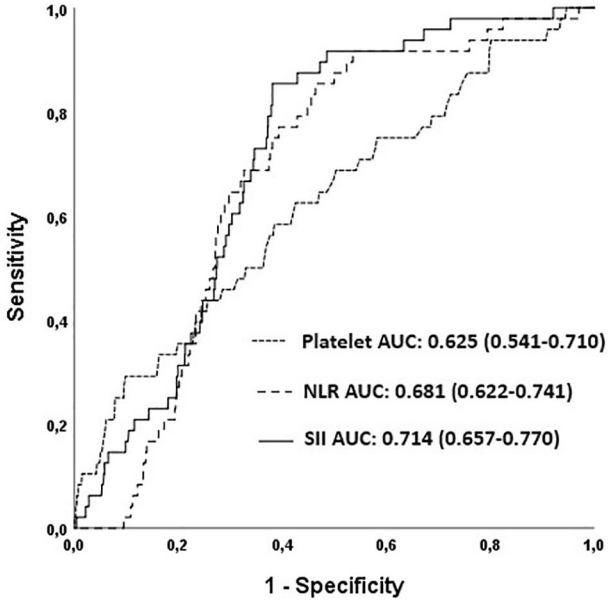

Fig. 2 Receiver operating characteristic (ROC) curves for the neutrophil-to-lymphocyte ratio (NLR), platelet, and systemic immune-inflammation index (SII) for predicting complete atrioventricular block (CAVB)

ROC analysis (Fig. 2) revealed that SII > 1117.7×10^9/L

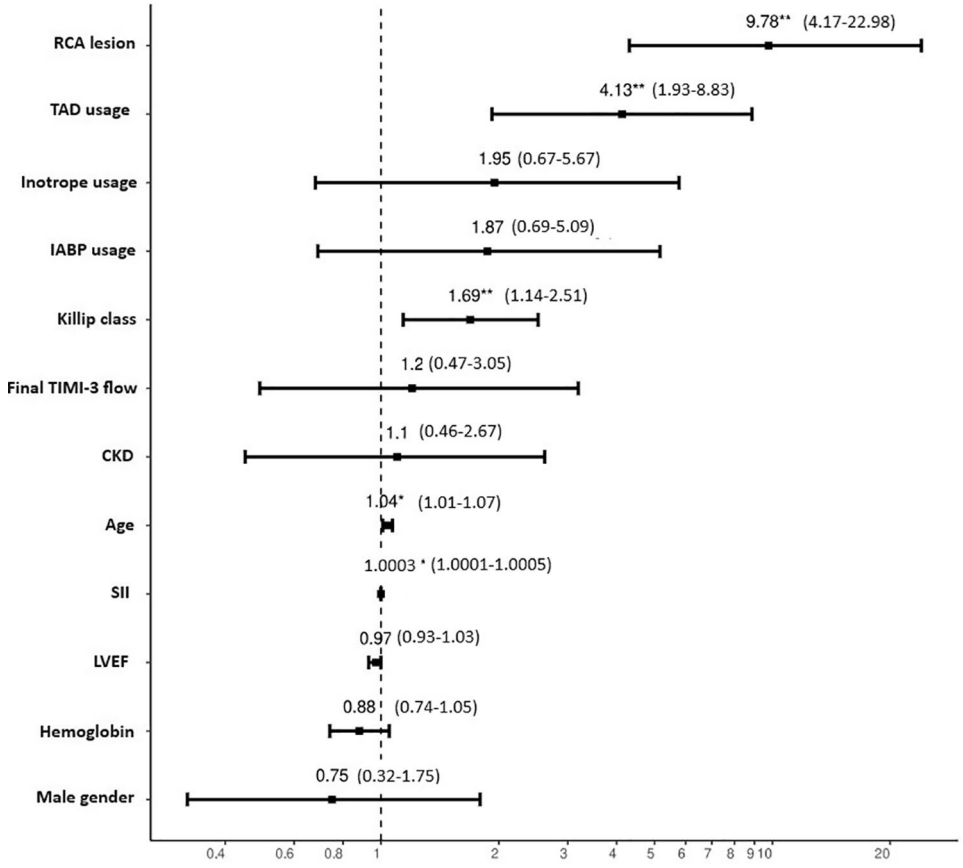

Fig. 1 The predictors of the development of complete atrioventricular block (CAVB)

was predictive with a sensitivity of 70.8% and specificity of 65.6% (area under the ROC curve [AUC]: 0.714, 95% CI=0.657–0.770, $p<0.001$, Fig. 2) for predicting CAVB. The value of SII in predicting CAVB was better than neutrophil to lymphocyte ratio (NLR) alone (AUC:0.714 vs. 0.681, z=2.001, p-value for the difference=0.045) and PLT alone (AUC:0.714 vs. 0.625, z=2.290, p-value for the difference=0.022, Fig. 2).

The patients with CAVB had a higher in-hospital mortality rate (46% vs. 9%, $p<0.001$). However, the long-term mortality rate was not different between groups (27.1% vs. 19.6%, $p=0.210$).

Discussion

To the best of our knowledge, this is the first study to investigate the association of SII with CAVB in STEMI patients who underwent PCI. Our findings showed a significant association between higher SII levels and an increased risk of CAVB development in this patient population.

The SII is a composite index calculated using the counts of peripheral lymphocytes, neutrophils, and platelets. It is considered a novel marker for inflammation and immune response. In other words, it is a numerical representation of certain components of the immune and inflammatory systems in the body [12]. There may be a connection between some factors represented by SII and the development of CAVB. This connection could involve the influence of gap junctions and the immune-inflammatory system on atrioventricular conduction [13–16]. However, the underlying mechanism linking SII and CAVB development remains unclear. Inflammatory cells and IL-6, a pro-inflammatory cytokine, can damage the conduction system, culminating in the development of CAVB [17, 18]. This suggests that the association between SII and CAVB development may be mediated, at least in part, by IL-6. IL-6 can affect the electrical activity of cardiac muscle cells by altering the function of ion channels, which can lead to abnormalities in cardiac conduction and ultimately contribute to the development of CAVB. A recent study showed that IL-6 potently inhibited connexins (specifically Cx40 and Cx43), which are proteins that form gap junctions, facilitating communication between adjacent cells, in cultured cardiomyocytes and macrophages [19, 20]. The inhibitory effect of IL-6 on connexins was reversed when cells were preincubated with a monoclonal anti-IL-6 antibody [19]. This suggests that the antibody could neutralise or block the effects of IL-6 on connexins. In guinea pigs, the injection of IL-6 was associated with a slowing of AV conduction, as indicated by the prolongation of the PR interval and PR-segment [20, 21]. Additionally, there was an increased susceptibility to drug-associated severe bradyarrhythmia, including complete AV dissociation and asystole [21]. Therefore, there have been recent studies confirming the important role of excess IL-6 in the development of CAVB, and there is a suggestion that IL-6 antagonists like Anakinra could be a potential therapeutic option. However, it is important to consider the potential roles of other inflammatory cytokines, oxidative stress, and autoimmune responses. Tumour necrosis factor alpha (TNF-α) and CRP as inflammatory markers have also been shown to be associated with CAVB development [19, 22]. Therefore, the relationship between SII and CAVB development may also be regulated by inflammatory mediators other than IL-6.

Oxidative stress, which results from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defence system, has been implicated in the pathogenesis of various cardiovascular diseases, including atherosclerosis, and hypertension [23, 24]. Also, it has been shown that oxidative stress and autoimmune responses may also play a role in the development of CAVB. A study by Lazzerini et al. found that patients with rheumatoid arthritis, a systemic inflammatory disease, had a higher risk of developing arrhythmic risk compared to the general population [25].

It is important to consider the potential impact of age on the development of CAVB. In previous studies, age was found to be an independent predictor of CAVB in STEMI patients [26, 27]. Similar to the results of these studies, age was independently associated with the development of AV block in these patients in our study. It has been shown that the responsible lesion in most patients with AV block was RCA [26, 27]. In our study, the culprit lesion was found to be RCA in these patients. Also, it was independently related to the development of CAVB. The Killip class was found to be a predictor of CAVB in acute coronary syndrome patients in a study published by Santos et al. [28]. We showed that a higher Killip class was associated with a higher risk of CAVB in STEMI patients treated with PCI. Although female gender was an independent predictor of the development of CAVB in previous studies [27, 28], it was not significant in multivariate analysis in our study.

The presence of CAVB was associated with in-hospital mortality in the acute coronary syndrome setting [29]. Different results have been reported in the related literature regarding the impact of CAVB on long-term mortality in the setting of ACS [26–28]. Kawamura et al. showed that CAVB in nonanterior STEMI was associated with long-term mortality [29]. In another study, it was not an independent predictor of mortality in ACS patients [28]. CAVB patients had a higher rate of in-hospital mortality, however long-term mortality rate was not different between groups in the presented study.

It is worth noting that our study has several limitations. It is a single-centre, retrospective study with a relatively

small sample size, which may limit the generalizability of our findings. The retrospective nature of our study may have introduced selection bias, and the small sample size may have limited our ability to detect smaller effect sizes. We did not assess other inflammatory markers, such as TNF-α and IL-6, which may also be associated with CAVB development. Additionally, we cannot rule out the presence of unmeasured confounders, which could have influenced the development of CAVB. The results of this study should be considered as hypothesis generating. Therefore, future research may address these issues to gain a more comprehensive understanding of the relationship between SII and the development of CAVB in these patients.

Conclusion

Our study suggested that a higher SII level was associated with an increased risk of developing CAVB in patients with STEMI undergoing primary PCI. In cases where atrioventricular block is exacerbated or triggered by systemic inflammation, it might be beneficial to promptly and specifically manage the inflammatory process. This implies that controlling inflammation could potentially alleviate or improve the conduction disturbance seen in severe atrioventricular blocks. This could involve using anti-inflammatory medications or treating the underlying cause of systemic inflammation.

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Author contributions
All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by [TK, SE, FE, SA]. The primary draft of the manuscript was written by [FE], [TK], and [OP]. Writing-review and editing of the final version of the manuscript were carried out by [TK], [FE], [OP], and [SE]. [MK] adds critical points to the study. All authors read and approved the final manuscript.

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Data availability
The data supporting this study's findings are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study followed the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Izmir Katip Çelebi University, Atatürk Training, and Research Hospital (2023/0473). Due to the study's retrospective nature, the need for informed consent was waived by the Medical Ethics Committee of Izmir Katip Çelebi University, Atatürk Training, and Research Hospital.

Consent for publication
Not applicable.

Competing interests
The author(s) declared no potential conflicts of interest concerning this article's research, authorship, and publication.

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