Research Article / Araştırma Makalesi

The Association Between Systemic Immune Inflammation Index and Intermediate-Term Mortality in Patients with Acute Coronary Syndromes

Akut Koroner Sendromlu Hastalarda Sistemik İmmün İnflamasyon İndeksi ile Orta Dönem Mortalite Arasındaki İlişki

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Abstract

Background: ic immune inflammation has been investigated as a prognostic marker for different diseases. Considering the pivotal role of inflammation in the pathogenesis of acute coronary syndrome (ACS), it is paramount to predict the prognosis of patients with ACS. Therefore, we evaluated the association between inflammation measured by the systemic immune-inflammation index (SII) and middle-term mortality in patients with ACS.
Materials and Methods: This single-center, retrospective study was composed of 539 patients with ACS (139 unstable angina pectoris [USAP], 165 non-ST-elevation myocardial infarction [NSTEMI], and 235 ST-elevation myocardial infarction [STEMI]) aged over 18 years. Descriptive statistics and multivariate regressions were used to examine the association between clinical and laboratory parameter characteristics and 12-month mortality.
Results: The median age of the patients was 58 (50-67) and 73.1% of the patients were male. A total of 20 patients died in the next twelve months after ACS event. The median SII levels were highest in patients with STEMI [1301.96 (816.81-2174.53)] , followed by NSTEMI [955.50 (619.99-1576-06] and USAP [595.32 (437.52-918.27)] (p<0.001). The SII had moderate success for the prediction of the intermediate-term mortality (AUC: 0.653, 95% CI: 0.526-0.779, p=0.024). In multivariate analyses, every 100-unit increase in SII was associated with a two percent increase in the risk of intermediate mortality (OR: 1.020, 95% CI: 1.004-1.037, p=0.016).
Conclusions: We demonstrated that ACS patients with higher SII levels had a higher risk of mortality at twelve months, and higher SII levels were associated with a more severe underlying ACS etiology. If supported by prospective evidence, the SII index may guide clinicians in terms of both ACS severity and subsequent one-year survival rates.

Key Words: Acute coronary syndrome, Systemic immune-inflammation index, Mortality, Prognosis, Inflammation

Öz

Amaç: Sistemik immün inflamasyon farklı hastalıklar için prognostik bir belirteç olarak araştırılmıştır. Akut koroner sendrom (AKS) patogenezinde inflamatuar basıncın önemli rolü göz önüne alındığında, AKS'li hastaların prognozunu tahmin etmek çok önemlidir. Bu nedenle, AKS hastalarında sistemik immün-inflamasyon indeksi (SII) ile ölçülen inflamatuar basınç ile orta dönem mortalite arasındaki ilişkiyi değerlendirdik.
Materyal ve Metod: Bu tek merkezli, retrospektif çalışmaya 18 yaş üstü 539 AKS hastası (139 unstabil anjina pektoris [USAP], 165 ST elevasyonsuz miyokard enfarktüsü [NSTEMI] ve 235 ST elevasyonlu miyokard enfarktüsü [STEMI]) dahil edildi. Klinik ve laboratuvar parametre özellikleri ile 12 aylık mortalite arasındaki ilişkiyi incelemek için tanımlayıcı istatistikler ve çok değişkenli regresyonlar kullanıldı.
Bulgular: Hastaların ortanca yaşı 58 (50-67) idi ve hastaların %73,1'i erkekti. Toplam 20 hasta AKS olayından sonraki on iki ay içinde hayatını kaybetti. Ortanca SII düzeyleri STEMI (1301,96) hastalarında en yüksekti, bunu NSTEMI (955,50) ve USAP (595,32) izledi (p<0,001). SII, orta vadeli mortalitenin öngörülmesinde orta derecede başarılı olmuştur (AUC: 0,653, %95 GA: 0,526-0,779, p=0,024). Çok değişkenli analizlerde, SII'deki her 100 birimlik artış orta dönem mortalite riskinde yüzde iki artışla ilişkilendirilmiştir (OR: 1.020, %95 GA: 1.004-1.037, p=0.016).
Sonuç: Daha yüksek SII düzeylerine sahip AKS hastalarının on iki ayda daha yüksek mortalite riskine sahip olduğunu ve daha yüksek SII düzeylerinin altta yatan daha ciddi AKS etiyolojisi ile ilişkili olduğunu gösterdik. İleriye dönük kanıtlarla desteklenirse, SII indeksi hem AKS şiddeti hem de sonraki bir yıllık sağkalım oranları açısından klinisyenlere yol gösterebilir.

Anahtar Kelimeler: Akut koroner sendrom, Sistemik immün-inflamasyon indeksi, Mortalite, Prognoz, Inflamasyon

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Received / Geliş tarihi: 16.01.2024

Accepted / Kabul tarihi: 24.03.2024

DOI: 10.35440/hutfd.1420567

Introduction

Acute coronary syndrome (ACS), a broad term for unstable angina pectoris (USAP), acute non-ST segment elevation myocardial infarction (NSTEMI), and acute ST elevation myocardial infarction (STEMI), is a leading cause of morbidity and mortality (1, 2). The ACS is a symptomatic and fatal presentation of atherosclerotic cardiovascular disease and is responsible for over 30% of the deaths in adults over 35 years of age (3, 4). While previously regarded as a consequence of long-term cholesterol accumulation, recent evidence demonstrated that the atherosclerotic coronary disease is a dynamic process mainly perpetuated by the inflammation in the atheroma plaque after the accumulation of the lipid core (5, 6).

The pathopsysiologic process of ACS begins with the atheroma plaque rupture resulting the platelet aggregation and thrombus formation (7). This prothrombogenic process is accompanied by an uncontrolled high-level inflammation and recruitment of the inflammatory cells to the plaque rupture area to perpetuate the pro-thrombogenesis and inflammation (8). Considering the pivotal role of inflammation in the pathogenesis of ACS, non-invasive or minimal invasive quantification of this inflammation is paramount to predict the prognosis of patients with ACS.

Recently, Hu et al. developed the systemic immune-inflammation index (SII; neutrophil × platelet/lymphocyte), a new inflammatory index to assess immune and inflammatory status and to quantify the uncontrolled inflammatory pressure (9). The prognostic role of SII was demonstrated in several diseases, including cancer, cardiovascular disease (CVD), stent thrombosis, chronic kidney disease (CKD), and liver transplantation (10-13). Huang et al. showed that high SII predicted poor clinical outcomes for elderly patients after ACS (14). However, the association between SII levels and intermediate-term mortality was not previously reported. Therefore, in this study, we aimed to evaluate the relationship between inflammation measured by SII and middle-term (12 months) mortality in patients with ACS.

Materials and Methods

Study Design

The adult (18 years or older) patients who were hospitalized at Gazi Yasargil Research and Training Hospital with ACS between January 2020 to January 2021 were included in this retrospective study. Patients with USAP, NSTEMI, and STEMI within the classification of ACS were diagnosed according to the European Society of Cardiology (ESC) criteria (15). Patients with moderate or severe valvular heart disease, hypertrophic cardiomyopathy, pericardial disease, cardiac mortality during hospitalization, cardiogenic shock during hospitalization, and coronary by-pass grafting during hospitalization or incomplete follow-up were excluded from the study. After the exclusion of these patients with additional cardiac problem or short-term mortality, a total of 656 patients were retrieved for inclusion. After careful evaluation, 117 patients were excluded due to the following reasons: 34 patients with CKD (glomerular filtration rate below 60 ml/min); 23 patients with active infection at presentation; 21 patients with thyroid disease; 18 patients taking nephrotoxic drugs; 6 patients with hepatitis; 5 patients with a diagnosis of malignancy; 4 patients with SARS-COVID-19; 4 patients with autoimmune disease; and 2 patients with a history of kidney transplantation. In addition, all patients with After the exclusion of these 117 patients, 539 patients with ACS (139 USAP, 165 NSTEMI, and 235 STEMI) included in the study.

Data collection

The baseline demographics (age and gender), comorbidities, regularly used drugs for diabetes and hypertension were recorded. The following laboratory data were collected from the antecubital venous blood samples within the first day of admission: creatinine, albümin, uric acid, C-reactive protein, total cholesterol, high density lipoprotein, low density lipoprotein, troponin T, and complete blood count parameters. The SII levels were calculated with the following formula: SII index = (neutrophils x platelets)/lymphocytes.

Coronary Angiography

The coronary angiography (CAG) images of the patients were evaluated by two different cardiologists. The main vessels were identified as follows: left anterior descending artery (LAD), left main coronary artery (LMCA), left circumflex artery (LCx), and right coronary artery (RCA). Luminal narrowing of more than 70% in the LAD, LCx, and RCA and more than 50% in the LMCA were considered significant. All patients underwent complete revascularization via percutaneous coronary intervention in accordance with current guidelines and achieved TIMI 3 flow at the end of the procedure. Our primary outcome was intermediate-term mortality (12 months) after discharge (16). All patients were followed for at least twelve months from the ACS event or until the time of death for patients who died before twelve months.

Ethical approval

The present study followed the principles of the Declaration of Helsinki. The study protocol received official approval from the local ethics committee (Diyarbakır Gazi Yaşargil Training and Research Hospital Local Ethics Committee; date: 03.03.2023, number: 364).

Statistical Analyses

Categorical data were presented as frequency and percentage, while normally distributed continuous variables were reported as the mean ± standard deviation (SD) and non-normally distributed data as medians with interquartile ranges (IQRs). Categorical variables were compared using the chi-squared test or Fisher's exact test, as necessary. The comparison of medians across ACS types were conducted with Kruskal-Wallis test. Univariable logistic regression analysis was used to test the association between SII and intermediate-term mortality. To examine the association between SII and possible confounding factors, univariate and multivariate logistic regression analysis were performed. The correlation

risk was estimated by odds ratio (OR) and 95% confidence interval (95% CI). The IBM SPSS software package, version 25.0, was used for all statistical analyses in this study. A threshold of $p < 0.05$ was used to determine statistically significant results.

Results

A total of 539 ACS patients including were included in the study. The median age of the patients was 58 (IQR 50-67) and 73.1% of the patients were male. The hypertension and diabetes were present in the 30.6% and 23.7% of the patients, respectively. The STEMI was the most frequent ACS presentation (43.6%), followed by NSTEMI (30.6%). The 52.1% of the patients had stenosis in at least two coronary arteries in CAG and the LAD was the most frequently affected coronary artery (39.6%). The baseline characteristics of the study population is summarized in Table 1.

A total of 20 patients died in the next twelve months after ACS event. The patients were categorized according to the presence of intermediate-term mortality. The median age of the patients who died in the next 12 months after ACS events were significantly higher than patients who were alive at the 12 months after the ACS event (72 vs. 58, p=0.008). The other clinical and CAG parameters, including gender, diabetes and hypertension prevalance, type of ACS events, coronary involvement were similar between two groups (Table 2). For laboratory parameters; there was a trend towards higher median SII levels in patients with intermediate-term mortality (p=0.062), while the lipid profiles were similar across two groups (Table 2). Additionally, the median SII levels were highest in patients with STEMI [1301.96 (816.81-2174.53)] , followed by NSTEMI [955.50 (619.99-1576-06] and USAP [595.32 (437.52-918.27)] (Figure 1).

The multivariate analyses were conducted with the clinical and laboratory parameters with a p value of less than 0.10. The presence of hypertension (present vs. absent), haemoglobulin levels (continous), age (continous) and SII (continous) levels were used in the multivariate model. The SII values were divided by 100 in order to be used in multivariate analyses as a continuous parameter. In multivariate analyses, every 100-unit increase in SII was associated with a two percent increase in the risk of intermediate mortality (OR: 1.020, 95% CI: 1.004-1.037 p=0.016). Additionally, a one-year increase in age was associated with an 7.8% increase in the risk of mortality at twelve months (OR: 1.078, 95% CI: 1.032-1.125, p=0.001) and lower haemoglobin levels were associated with intermediate-term mortality (OR: 0.763, 95% CI: 0.599-0.971, p=0.028) (Table 3).

In addition to the regression analyses, ROC analyses were conducted to evaluate the predictive power of SII for intermediate-term mortality. The ROC analyses demonstrated a statistically significant predictive power for intermediate-term mortality (AUC: 0.653, 95% CI: 0.526-0.779, p=0.024) (Figure 2). The SII value of 1090 had 63.2% sensitivity and 56.6% specificity for intermediate-term mortality prediction.

Table 1. Demographic, clinical, and laboratory features of the participants

Baseline characteristics	
Age (years), median (IQR)	58 (50-67)
Male gender, n (%)	394 (73.1)
Diabets mellitus, n (%)	128 (23.7)
Hypertension, n (%)	165 (30.6)
Type of ACS	
STEMI	235 (43.6)
NSTEMI	165 (30.6)
UA	139 (25.8)
Infarct-related artery	
Left anterior descending artery, n (%)	213 (39.6)
Left circumflex artery, n (%)	141 (26.1)
Right coronary artery, n (%)	168 (31.2)
Left main coronary artery, n (%)	17 (3.1)
Vessel involved n (%)	
One-vessel, n (%)	103 (19.1)
Two-vessel, n (%)	189 (35.1)
Three-vessel, n (%)	247 (45.8)
Medications prior to PCI	
Aspirin, n (%)	120 (22.3)
ACEI/ARB, n (%)	143 (27.6)
Beta Blockers, n (%)	107 (19.9)
Calcium channel blocker, n (%)	60 (11.6)
Statin, n (%)	65 (12.1)
Nitrates, n (%)	2 (0.38)
Treatment	
PCI, n (%)	503 (93.3)
OMT, n (%)	21 (3.9)
CABG referral, n (%)	15 (2.8)

Abbreviations: CABG: coronary artery bypass grafting; HF: Heart Failure; IQR: interquartile range; NSTEMI: non-ST-elevation myocardial infarction; OMT: optimal medical therapy; PCI:percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction

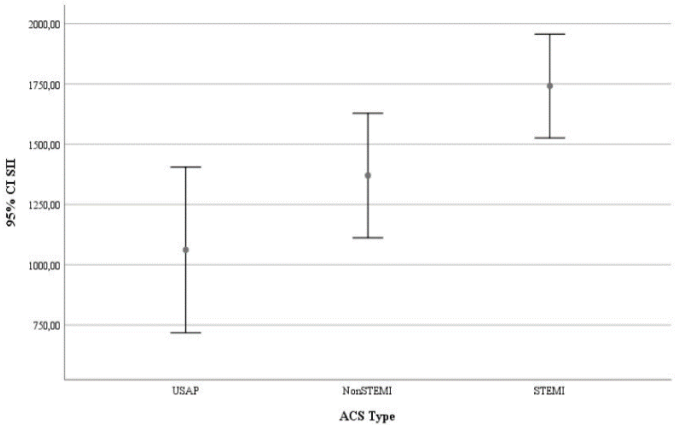

Figure 1. Comparison of systemic immune-inflammation index (SII) according to ACS type

Table 2. Comparison of the baseline characteristics and laboratory findings of the two groups

	Nonsurvivors (n=20)	Survivors (n=519)	p value
Age (years), median (IQR)	72 (65-77)	58 (50-66)	0.008
Male gender, n (%)	12 (60)	382 (73.6)	0.178
Diabetes mellitus, n (%)	2 (10)	126 (25.4)	0.119
Hypertension, n (%)	10 (50)	155 (31.2)	0.077
Type of ACS			0.246
STEMI	10 (50)	225 (43.4)	
NSTEMI	8 (40)	157 (30.3)	
UA	2 (10)	137 (26.4)	
Infarct-related artery			0.619
Left anterior descending artery, n (%)	8 (40)	204 (39.3)	
Left circumflex artery, n (%)	5 (25)	131 (25.3)	
Right coronary artery, n (%)	5 (25)	169 (32.6)	
Left main coronary artery, n (%)	2 (10)	15 (2.8)	
Number of vessels n (%)			0.533
One vessel, n (%)	2 (10)	101 (19.4)	
Two vessel, n (%)	7 (35)	182 (35.1)	
Three vessel, n (%)	11 (55)	236 (45.5)	
Laboratory findings			
Haemoglobin (g/dl), median (IQR)	12.30 (11.20-14.80)	14.2 (13.10-15.30)	0.014
White cell count (10^3/ml), median (IQR)	12.08 (8.48-15.31)	10.88 (9.04-13.21)	0.419
Neutrophil count (10^3/ml), median (IQR)	7.92 (6.12-13.06)	7.91 (5.84-10.22)	0.245
Lymphocyte count (10^3/ml), median (IQR)	1.73 (0.99-2.26)	2.09 (1.54-2.67)	0.016
Platelet count (10^3/ml), median (IQR)	263 (237-327)	262 (219-307)	0.612
Total cholesterol (mg/dl), median (IQR)	186.50 (154-219.50)	181 (155-217)	0.881
HDL-C (mg/dl), median (IQR)	36.70 (33.60-40.50)	40.10 (34.65-46.20)	0.200
LDL-C (mg/dl), median (IQR)	116 (80.25-135)	108.50 (85-135)	0.896
Triglycerides (mg/dl), median (IQR)	90 (65.25-139)	132 (91-204)	0.064
SII, median (IQR)	1305.28 (921.11)	951.56 (579.07-1686.05)	0.024

Abbreviations: HDL-C: high-density lipoprotein cholesterol; IQR: Inter Quantile Range; LDL-C: low-density lipoprotein cholesterol; SII: Systemic immune-inflammation index

Table 3. Univariate and multivariate logistic regression analysis for intermediate-term mortality

	Univariate analysis			Multivariate analysis		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
Age (continuous)	1.081	1.043-1.121	<0.001	1.078	1.032-1.125	0.001
Hypertension	2.294	0.955-5.513	0.063	2.012	0.742-5.456	0.170
Diabetes	2.847	0.661-12.271	0.160			
Male sex	0.547	0.223-1.337	0.186			
Haemoglobin	0.674	0.535-0.851	0.001	0.763	0.599-0.971	0.028
Triglyceride	0.998	0.992-1.003	0.438			
SII/100	1.014	1.002-1.025	0.018	1.020	1.004-1.037	0.016

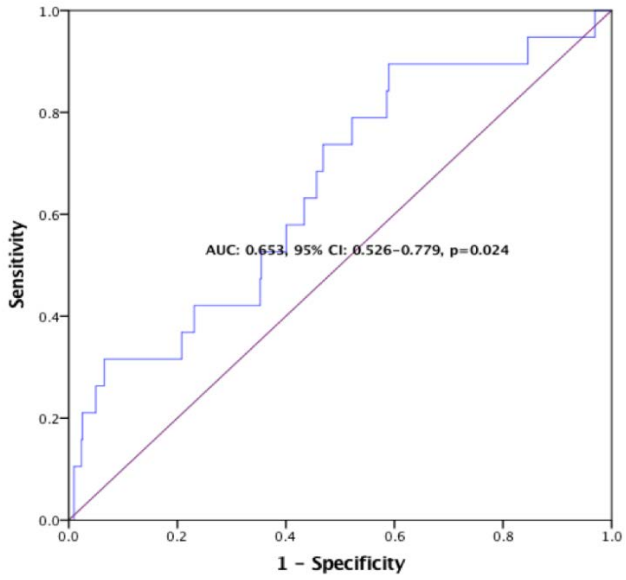

Figure 2. Receiver–operating characteristic curve for SII in the prediction of intermediate-term mortality

Discussion

In the present study, we observed a higher risk of intermediate-term mortality in patients with ACS with higher SII levels or older age. The SII levels had moderate success for intermediate term mortality prediction. Additionally, the median SII levels were increased with an increased severity of the ACS presentation (STEMI>NSTEMI>USAP). These results support the use of SII as an easily available biomarker to predict intermediate-term mortality after ACS events.

Recent studies have shown that atherosclerosis is not only a state of hypoperfusion but is also associated with a proinflammatory state (17, 18). The inflammation is associated with both plaque development and plaque destabilization, as well as the ischemic reperfusion injury in cardiac muscle in ACS (19). Recent clinical trials including the LoDoCo and CANTOS clinical trials reported benefits in cardiovascular morbidity with anti-inflammatory therapies, further supporting the importance of immune-inflammatory in atherosclerotic cardiovascular diseases including ACS (20, 21). In addition to being a treatment target, recent studies have

proven that inflammatory cells may be useful in predicting the prognosis of ACS patients (22-24). Toprak et al. demonstrated that ectodysplasin A is closely related to the presence and severity of CAD (25). Given that ACS inherently involves an inflammatory process, platelets and neutrophils have been shown to play a central role, although the using the levels of peripheral blood cells individually had limited power as a prognostic biomarker (26, 27). The SII index could be used to encounter to this limitation, with incorporation of the peripheral blood lymphocyte, neutrophil and platelets to the equation. The SII index was developed by Hu et al. in 2014 as a prognostic biomarker in patients with cancer(9), and was tested in diseases where inflammation plays a central role like ACS (28-30).

In recent years, several studies have shown that an association with increased SII levels and poor outcomes in cardiovascular disease. Özen et al. revealed that SII may be a valuable tool for predicting patient outcomes in HF and potentially guiding long-term patient management (31) Esenboğa et al. demonstrated that elevated SII levels could predict no-reflow phenomenon in patients undergoing primary intervention for STEMI with 79% sensitivity and 70% specificity (32). Yang et al. found that high SII levels were associated with poor clinical outcomes in coronary artery diseases (33). Dey et al. found a correlation between high SII and poor outcomes after elective off-pump coronary artery bypass graft operations (34). Huang et al. showed that high SII predicted poor clinical outcomes for elderly patients after ACS (14). However, the association of SII levels with intermediate-term mortality was not previously reported. If our observation will be confirmed in larger cohorts, ACS patients with higher levels of SII could be candidates for novel risk reducing therapies after ACS event.

In addition to the association with intermediate-term mortality and SII levels, we showed that as the severity of ACS progressed from USAP to STEMI, there was a gradual increase in the SII index, which was parallel to the increasing severity of inflammation. In particular, the neutrophil-lymphocyte ratio (NLR), another marker of inflammatory burden, also showed significant differences between ACS subtypes, with higher values observed in STEMI cases (35). In another study, C-Reactive Protein to Albumin Ratio (CAR) was found to be the most effective inflammatory parameter for identifying significant CAD (36).These findings are consistent with the pathophysiology of inflammation and the etiology of ACS and supports using of the compound inflammatory markers for prognosis and severity prediction in ACS. Our study indicates that anemia is independently associated with adverse clinical outcomes in patients presenting with ACS. There are multiple mechanisms exist for the association of anemia with poor clinical outcome in ACS. In the presence of anemia, the heart must maintain a high stroke volume and heart rate to maintain adequate systemic oxygen delivery, culminating in augmented myocardial oxygen consumption. However, in the presence of anemia, it has a negative effect of decreasing oxygen delivery to the blood vessels with coronary stenosis (37). This cascade of hemodynamic and ischemic challenges may underlie the exacerbated clinical deterioration observed in anemic ACS cohorts.

Limitations

The present study should be evaluated in light of limitations. First, the number of events (mortality at the twelve months) was relatively low compared to the size of the study population, diminishing the power of the analyses and preventing the conduction of additional subgroup analyses. While the all blood samples were retrieved within the first day after hospital admission, standardization regarding the timing of sample collection can not be assured. Furthermore, although all subjects underwent percutaneous revascularization in accordance with current guidelines, confounding due to time between the onset of the complaint and the first medical contact could not be excluded. Additionally, potential sources of bias or confounding that were not addressed in the study include differences in treatment modalities or comorbidities among participants. However, despite these limitations, we demonstrated a statistically significant association between the SII levels at presentation and the intermediate-term mortality in patients with ACS, first time in the literature.

Conclusion

We observed that ACS patients with higher SII levels had higher risk of mortality at twelve months and higher SII levels was associated with a more severe underlying ACS etiology. The SII index may guide clinicians in terms of both ACS severity and subsequent one-year survival rates. Therefore, a high SII index in ACS may aid in the follow-up of the patients with ACS. Prospective studies with larger patient cohorts are needed to validate these findings and assess the long-term prognostic value of SII in ACS patients.

Ethical Approval: This study was approved by the Ethics in Research Committee at Health Sciences University Gazi Yasargil Hospital (Reference number: 364 dated 03.03.2023).

Author Contributions:
Concept: S.A.
Literature Review: S.A., Ü.Ç.
Design : S.A., Ü.Ç.
Data acquisition: S.A., Ü.Ç.
Analysis and interpretation: S.A., Ü.Ç.
Writing manuscript: S.A., Ü.Ç.
Critical revision of manuscript: S.A.
Conflict of Interest: *The authors of this manuscript have no conflicts of interest to disclose.*
Financial Disclosure: *There is no funding to support this study.*

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