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Systemic immune-inflammation index predicts mortality in infective endocarditis

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Abstract

Objectives: The aim of our study was to evaluate the usefulness of systemic immune-inflammation index (SII) at admission in predicting in-hospital mortality in patients with infective endocarditis.

Methods: 133 definite IE patients (≥ 18 years) according to modified Duke criteria, treated in our tertiary care hospital between December 2009 and May 2019, were retrospectively analysed. Symptoms, comorbidities, predisposing valvular diseases, prosthetic valve, device, history of injectable drug use, blood culture results, echocardiography findings, and complications were collected. We calculated the SII as follows: $SII = \text{platelet count} \times \text{neutrophil count} / \text{lymphocyte count}$ at admission.

Results: The median age of the patients was 56 (40–66) years. Prosthetic valve disease was the most frequent predisposing valve lesion. Staphylococcus species were the most common microorganisms. The most frequent complication was in-hospital mortality (22%) followed by renal failure. Older population, syncope, increased inflammatory markers, high systolic pulmonary artery pressure (PAPs), heart failure, renal failure, and septic shock were associated with high mortality. However age, syncope, hypocalcemia, not going to surgery, and SII were independent predictors of in-hospital mortality. According to receiver operating characteristic curve analysis, the optimal SII cut-off value for predicting mortality was 2314 (area under the curve 0.641; $P = 0.019$).

Conclusion: We demonstrated that high SII levels are independently associated with in-hospital mortality. The SII may be a promising prognostic predictor for patients with infective endocarditis.

Keywords: Infective endocarditis, Mortality, Systemic immune-inflammation index, Clinical characteristics, Inflammatory markers

1. Introduction

Infective endocarditis (IE) is defined as an infection of a native or prosthetic cardiac valve, endocardial surface, or cardiac device [1,2]. Despite the improvements in the diagnosis and treatment of IE, mortality and morbidity remain high [3,4]. The aim of the present study was to

evaluate the usefulness of the systemic immune-inflammation index (SII) at admission in predicting in-hospital mortality in patients with IE. The increase of prosthetic valves or intracardiac devices, elderly patients with coexisting medical conditions, [4–6] has changed the spectrum of IE. Although rheumatic heart disease (RHD) still remains the key risk factor for IE in low-income

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countries, it has declined sharply and degenerative valvular lesions have become the most frequent valvular abnormalities in developed countries. Years ago, streptococci were the main causative microorganisms of IE. However, recent studies have shown a significant increase in frequency of *Staphylococcus aureus*. So new consensus guidelines have modified the approach to antibiotic therapy and prophylaxis [7,8].

Risk stratification in IE may help us to determine timing of surgery, prevention of complications and mortality that need more aggressive treatment. For this purpose, several biomarkers such as the neutrophil–lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR), have been evaluated for several types of disease. Recently, an indicator that is known as SII, that integrates three types of inflammatory cells (SII = platelet count \times neutrophil count/lymphocyte count), has been shown to be promising [9,10]. SII, which is positively correlated with neutrophil, platelet counts and inversely correlated with lymphocyte count, was first developed by Hu et al. in 2014 [11]. Later, several studies also evaluated its prognostic values in various tumors, such as renal cell cancer, lung cancer, prostate cancer and in vasculitis [12–14]. Thus, the aim of our study was to evaluate the role of SII at admission in predicting in-hospital mortality and characterize the factors that trigger unfavorable outcomes in IE.

2. Materials and methods

133 definite IE patients (≥ 18 years) according to modified Duke criteria, treated in our tertiary care hospital between December 2009 and May 2019, were retrospectively analysed. The local ethics committee approved the study protocol. Patients with inflammatory diseases, autoimmune disease involving systemic lupus erythematosus, cancer, leukemia or any other blood system diseases were excluded. Retrospective evaluation of the patients was performed using electronic medical records. We excluded cancer and other blood system diseases by evaluating patients' history, blood test results on admission and electronic medical records. Symptoms, comorbidities including diabetes, hypertension, congestive heart failure, chronic kidney disease, predisposing valvular diseases, prosthetic valve, device, history of injectable drug use, blood culture results, echocardiography findings, and complications were collected.

Blood was collected from at least 3 separate venous sites for blood cultures in all participants at

Abbreviations

CHD	congenital heart disease
CRP	C-reactive protein
IE	infective endocarditis
MSCNS	Methicillin sensitive coagulase negative staphylococci
MRCNS	Methicillin resistant coagulase negative staphylococci
NLR	neutrophil–lymphocyte ratio
PAPs	systolic pulmonary artery pressure
PLR	platelet lymphocyte ratio
RHD	rheumatic heart disease
SII	systemic immune-inflammation index
TTE	transthoracic echocardiography
TEE	transoesophageal echocardiography

1-hour intervals starting at admission to the hospital. Extra samples were drawn to examine various specific antibodies. Any valves and structures extracted during surgery were examined and sent for culture. Based on either the American Heart Association guidelines or the European Society of Cardiology guidelines, empiric antibiotic treatment was given [7,8]. According to blood culture results, patients were switched over to suitable antibiotics.

All hematologic and biochemical data were obtained. Routine laboratory investigations such as complete blood count, C-reactive protein (CRP) level and serum chemistry were periodically recorded. Renal failure was identified if creatinine increased > 0.5 mg/dL or 25% by using the most common definition [15]. We calculated the SII as follows: SII = platelet count \times neutrophil count/lymphocyte count at admission. PLR and NLR were directly calculated from complete blood count results.

Each participant underwent an echocardiographic examination by Vivid 5 (GE, Horten, Norway) or Epic 7 (Philips). The echocardiograms were analysed from the records by an experienced cardiologist blinded to the participants' results. Nearly all patients underwent transesophageal echocardiography (TEE) to determine suspected prosthetic valve endocarditis, cardiac mechanical complications, or high clinical suspicion of IE despite normal transthoracic echocardiographic findings. Measurements of the vegetation length were performed in various planes, and the maximum length was selected. Other than sinus rhythm were also found from the records.

The main indications for surgery were severe heart failure, prevention of peripheral embolism and uncontrolled infection. Outcomes were defined as in-hospital mortality, within 3 months mortality, renal failure, rhythm disturbances, cerebrovascular

attack, transient ischemic attack, heart failure and septic shock.

2.1. Statistical analysis

Statistical analysis was made using the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 21.0. released 2012, IBM Corp., Armonk, New York, USA). Fitness to normal distribution was analyzed with the Kolmogorov Simirnov test. Data was expressed as “mean \pm standard deviation (SD)” for normal distribution, “median (25th-75th percentiles)” for abnormal distribution and “n (%)” for categorical variables. The effects of different variables on clinical outcomes were calculated by univariate analysis for each. The variables for which the unadjusted P value was <0.05 in univariate regression analysis were identified as potential risk markers and included in the multivariate regression model. A p-value <0.05 was considered statistically significant. Chi-square or Fischer exact tests were used to analyze categorical variables. Mann-Whitney U test was used for comparing quantitative variables with abnormal distribution while Student t-test was used for comparing the means between two groups with normal distribution. ROC analysis was conducted to determine the optimal SII value to indicate mortality in terms of both sensitivity and specificity.

3. Results

A total of 133 patients with diagnosis of definite IE were retrospectively assessed for ten years period. Demographic, clinical findings, echocardiographic and microbiological data are shown in [Table 1](#). Ninety one (68,4%) males and 42 (31.6%) females were in this study, with the median age of 56 (40–66) years. The most common symptoms were high fever (61.7%), dyspnea (55.6%) and weakness (41.4%). Thirty one patients had a history of hypertension while five patients had a history of injectable drug usage. Three patients were on dialysis and 9 patients had pacemaker. Fifteen patients' rhythm was atrial fibrillation during hospitalization. Total median length of hospitalization was 35 (20,5–47) days.

Affected sites were mitral valve in 72 (54.1%), aortic valve in 56 (42.1%), tricuspid valve in 6 (4,5%) and intracardiac device in 7 (5.3%) patients. In our study vegetation size was $10,4 \pm 5,06$ mm for aortic valve, 9 (6–13) mm for mitral valve. Prosthetic valve disease was the most frequent predisposing valve lesion followed by degenerative valvular

diseases, RHDs, mitral valve prolapse and bicuspid aorta. The predominantly complications were perforation in 23 (17,3%) and abscess in 16 (12,0%) patients.

Staphylococcus species were the most common microorganisms. Of these, coagulase-negative staphylococci were the most common causative pathogen (23,3%). The following microorganisms were also isolated: *Staphylococcus aureus* (9,8%), *Streptococcus* (8,3%), *Enterococcus faecalis* (5,3%). The culture negative rate was 50,4%. This numerically high culture negative rate can be explained by high rate of antimicrobial usage in another hospital prior to referral and inability to access archive results.

Surgical therapy was performed in 96 patients (72.2%). The median time interval from hospitalization to surgery was 17 (9,2–30) days. The most frequent complication was in-hospital mortality (22%). Acute renal failure occurred in 12% and heart failure in 6% patients as a complication. Patients were divided into 2 groups according to the presence of mortality ([Table 1](#)). In-hospital mortality occurred in 30 patients. Several factors were associated with in-hospital mortality, including older population, syncope, increased inflammatory markers, high systolic pulmonary artery pressure (PAPs), heart failure, renal failure, and septic shock.

In our study, the median value of SII was 1103 (679–1865), while 1063 (639–1620) in mortal group and 1471 (841–2576) in survivors. SII and CRP values were not different in terms of native and prosthetic valve and also valve type. On univariate logistic regression analysis, age, syncope, hypocalcemia, septic shock, renal failure, heart failure, high WBC, neutrophil, monocyte, CRP, urea, creatinine, PAPs, NLR, and SII were associated with high mortality. Whereas, having surgery due to IE was associated with lower mortality. In the multivariate model, age [odds ratio (OR) 1.072, 95% CI 1.011–1.136; $p = 0.020$], syncope (OR 24,843, 95% CI 3,207–192,431; $p = 0.002$), hypocalcemia (OR 0.268, 95% CI 0,083–0,862; $p = 0.027$), not having surgery (OR 0,123, 95% CI 0,030–0,507; $p = 0.004$), and SII (OR 16,886, 95% CI 1,777–160,490; $p = 0.014$) remained independent predictors of in-hospital mortality ([Table 2](#)). In the ROC curve analysis, using a cut point of 2314, the area under the curve (AUC) for the systemic immune inflammation index was 0.641 (95% CI, 0.524–0.757; $P = 0.019$) ([Fig. 1](#)). SII had 33% sensitivity and 91% specificity in its association with in-hospital mortality. Besides SII, details of NLR, PLR sensitivity and specificity were shown in [Fig. 2](#) comparatively.

Table 1. Baseline characteristics and outcomes of the study patients.

	All patients	Patients without In-hospital mortality (n = 103)	Patients with In-hospital mortality (n = 30)	p
Age	56 (40–66)	53 (40–62)	66 (52–72)	0,001
Gender (Female)	31,6 (42)	33,0 (34)	26,7 (8)	0,511
Hospitalisation time	35 (20,5–47)	40 (25–47)	24 (10–42)	0,003
Comorbidities				
IV drug user	3,8 (5)	2,9 (3)	6,7 (2)	0,315
DM	15,0 (20)	13,6 (14)	20,0 (6)	0,275
CHF	13,5 (8)	12,6 (13)	16,7 (5)	0,38
AF	11,3 (15)	9,7 (10)	16,7 (5)	0,226
Cardiac device	9,0 (12)	9,7 (10)	6,7 (2)	0,463
Dialysis	2,3 (3)	1,9 (2)	3,3 (1)	0,539
Symptoms				
Syncope	7,5 (10)	3,9 (4)	20,0 (6)	0,009
Fever	61,7 (82)	63,1 (65)	56,7 (17)	0,523
CVA-TIA	12,0 (16)	11,7 (12)	13,3 (4)	0,509
Laboratory variables				
Hgb	10,6 ± 2	10,84 ± 2,08	10,09 ± 1,88	0,079
WBC	10,1 (7,7–13,9)	9,8 (7,5–12,4)	13,8 (8,4–17,7)	0,007
Neu	7,7 (5,2–10,5)	7 (5–9,5)	10,5 (6,6–13,5)	0,002
Lymphocyte	1,6 (1,1–2)	1,6 (1,3–2,2)	1,4 (1–1,7)	0,064
Monocyte	0,77 ± 0,32	0,74 ± 0,3	0,89 ± 0,38	0,022
Platelet	246 ± 97	252 ± 95,5	228 ± 101,7	0,228
MPV	9,5 ± 1,5	9,5 ± 1,5	9,9 ± 1,9	0,25
CRP	67 (31–119)	52 (27–108)	109,5 (48,8–180)	0,012
RDW	15,3 ± 2,4	15,2 ± 2,6	16 ± 2	0,095
Urea	20 (13–30)	17 (12–27)	32 (21–41)	<0,001
Creatinin	0,95 (0,71–1,2)	0,93 (0,7–1,18)	1,11 (0,8–1,6)	0,026
Calcium	8,5 ± 0,7	8,6 ± 0,6	8,2 ± 0,77	0,002
NLR	4,8 (2,8–7)	4,55 (2,73–6,18)	7,49 (3,63–12,88))	0,002
PLR	149,7 (104–204)	146,9 (103,4–203,2)	150,3 (109,8–205)	0,561
SII	1103 (679–1865)	1063 (639–1620)	1471 (841–2576)	0,019
Native valve	61,7 (82)	64,1 (66)	53,3 (16)	0,287
Prosthetic material	38,3 (51)	35,9 (37)	46,7 (14)	
PAPs	40 (30–50)	40 (25–45)	45 (32–60)	0,018
EF	60 (50–60)	60 (55–60)	50 (45–60)	0,016
TEE				
Aortic vegetation	42,1 (56)	43,9 (43)	50,0 (13)	0,577
Mitral vegetation	54,1 (72)	59,2 (58)	53,8 (14)	0,624
Tricuspid vegetation	4,5 (6)	5,1 (5)	3,8 (1)	0,631
Pulmonary vegetation	0,8 (1)	1,0 (1)	0 (0)	0,79
Device vegetation	5,3 (7)	5,1 (5)	7,7 (2)	0,453
Abscess	12,0 (16)	12,2 (12)	15,4 (4)	0,443
Fistula	3,8 (5)	3,1 (3)	7,7 (2)	0,281
Psoedoaneurysm	4,5 (6)	5,1 (5)	3,8 (1)	0,631
Dehiscence	5,3 (7)	4,1 (4)	11,5 (3)	0,159
Veg. size				
Aortic	10,4 ± 5,06	11,06 ± 5,72	13,4 ± 6,75	0,187
Mitral	9 (6–13)	10,5 (5,5–16)	12 (8,5–14)	0,651
Blood culture results				
Coa negative staph.	23,3 (31)	21,4 (22)	30 (9)	
MRCNS	15,0 (20)	11,7 (12)	26,7 (8)	
MSCNS	8,3 (11)	9,7 (10)	3,3 (1)	
Staph. aureus	9,8 (13)	7,7 (8)	16,6 (5)	
MRSA	2,3 (3)	1,9 (2)	3,3 (1)	0,131
MSSA	7,5 (10)	5,8 (6)	13,3 (4)	
Streptococcus	8,3(11)	8,8 (9)	6,6 (2)	
Entr faecalis	5,3 (7)	6,9 (7)	0	
Gram negative	4,8 (6)	4 (4)	6,6 (2)	
Brucella	0,8 (1)	1,0 (1)	0	
Candida	0,8 (1)	0	3,3 (1)	

(continued on next page)

Table 1 (continued)

	All patients	Patients without In-hospital mortality (n = 103)	Patients with In-hospital mortality (n = 30)	p
Surgery	72,2 (96)	78,6 (81)	50,0 (15)	0,002
Complication				
Heart failure	6,0 (8)	2,9 (3)	16,7 (5)	0,015
Renal failure	12,0 (16)	7,8 (8)	26,7 (8)	0,01
CVA-TIA	4,5 (6)	3,9 (4)	6,7 (2)	0,408
Peripheral embolus	2,3 (3)	1,9 (2)	3,3 (1)	0,539
Septic shock	4,5 (6)	1,0 (1)	16,7 (5)	0,002

AF: atrial fibrillation; DM: diabetes mellitus; CHD; congenital heart disease; CHF:congestive heart failure; CRP: C-reactive protein; CVA:cerebrovascular attack; EF: ejection fraction; MRCNS: methicillin resistant coagulase negative stap. ; MSCNS: methicillin sensitive coagulase negative stap. ; MRSA: methicillin resistant stap. aureus; MSSA: methicillin sensitive stap. aureus ; NLR: neutrophil lymphocyte ratio; PAPs: pulmonary artery sistolic pressure; PLR: platelet lymphocyte ratio; RDW: red cell distribution width; SII:systemic immun-inflammation ratio; TEE: transesophageal echocardiography; TIA: transient ischemic attack; WBC: white blood cell

Table 2. Significant predictors of in-hospital outcomes in univariable and multivariable regression analysis.

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% C.I. (Lower-Upper)	p	Odds ratio	95% C.I. (Lower-Upper)	p
Age	1,048	1,016–1,083	0,004	1,072	1,011–1,136	0,02
Syncope	6,187	1,618–23,664	0,008	24,843	3,207–192,431	0,002
WBC	1,096	1,020–1,177	0,012			
Neutrophil	1,116	1,032–1,206	0,006			
Monocyte	3,982	1,148–13,196	0,029			
CRP	1,008	1,002–1,014	0,01			
Urea	1,048	1,021–1,077	0,001			
Creatinin	1,521	1,064–2,174	0,021			
Calcium	0,362	0,186–0,703	0,003	0,268	0,083–0,862	0,027
PAPs	1,031	1,007–1,057	0,013			
EF	0,966	0,933–1,000	0,047			
Surgery	0,272	0,115–0,640	0,003	0,123	0,030–0,507	0,004
Heart failure	6,667	1,492–29,787	0,013			
Renal failure	4,318	1,460–12,769	0,008			
Septic shock	20,4	2,281–182,485	0,007			
NLR	1,136	1,043–1,238	0,003			
SII	4,65	1,709–12,651	0,003	16,886	1,777–160,490	0,014

NLR: neutrophil–lymphocyte ratio; PAPs: systolic pulmonary artery pressure; SII: systemic immune-inflammation index

To evaluate associations between SII and clinical outcome, patients were divided into two groups according to SII cut-off value (<2314 vs. >2314%). The properties of these subgroups were compared, as shown in Table 3. In-hospital mortality was more common in patients with increased SII (Fig. 3).

4. Discussion

In our study, we investigated different variables in IE patients affecting mortality. We found that age, syncope, hypocalcemia, renal failure, heart failure, septic shock, high WBC, neutrophil, monocyte, CRP, urea, creatinine, PAPs, NLR, and SII, were associated with high in-hospital mortality. Our study exclusively focused on SII on the effect of mortality in IE patients. High SII at admission, older age, syncope, hypocalcemia, not going to surgery were independent

predictors for in-hospital mortality in patients with IE. Among those factors, SII and syncope had the highest odds ratio for fatal outcome.

The median age of our patients was 58 (43–66) similarly to reports of developed countries [16,17]. In our study cohort 30 (22%) patients died during hospital stay. Coagulase negative staphylococci were the most common pathogen and prosthetic valve disease were the most frequent predisposing valve lesion. Staphylococci of invasive procedure origin replaced streptococci of dental origin in the last era, probably because of the reduction in the incidence of RHD [18]. The reported in-hospital mortality of patients with IE varies from 12% to 30% [18–20] similarly to our results. %61,7 patients had native valve endocarditis. The most common valvular complication was perforation (17,3%).

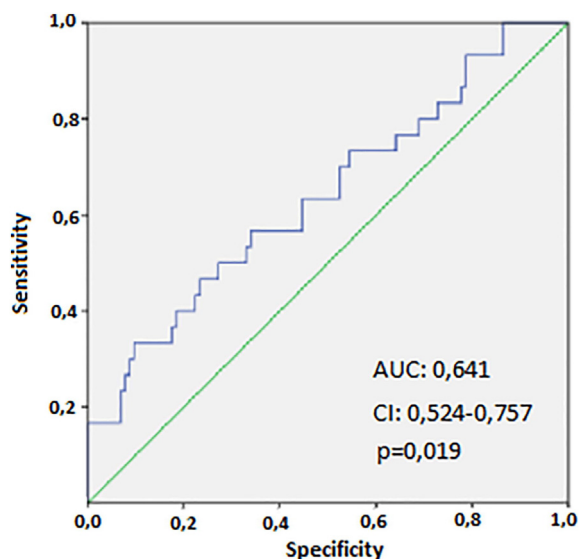


Fig. 1. The receiver-operating characteristic curve of systemic immune-inflammation index (SII) for predicting in-hospital mortality in patients with infective endocarditis.

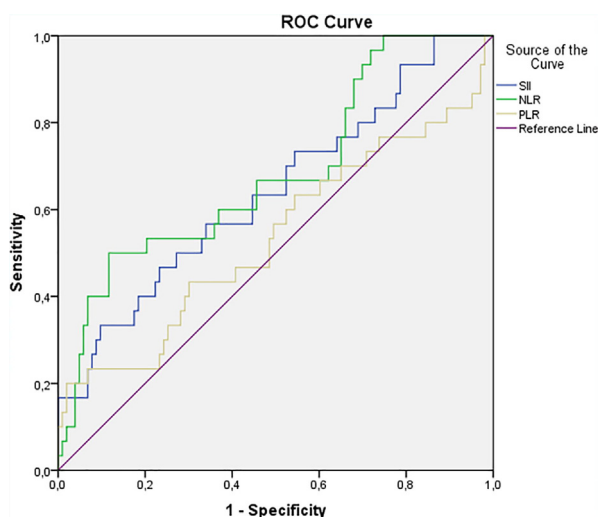


Fig. 2. The receiver-operating characteristic curve of SII, NLR and PLR for predicting in-hospital mortality in patients with infective endocarditis.

Table 3. Comparison of outcomes according to SII values.

SII cut off: 2314	Low SII (n = 113)	High SII (n = 20)	p
Heart failure	5,3 (6)	10,0 (2)	0,345
Renal failure	9,7 (11)	25,0 (5)	0,067
CVA-TIA	4,4 (5)	5,0 (1)	0,632
Intracerebral hemorrhage	2,7 (3)	0	0,611
Arrhythmia	5,3 (6)	10,0 (2)	0,345
Septic shock	3,5 (4)	10,0 (2)	0,222
In-hospital mortality	17,7 (20)	50,0 (10)	0,003

Surgical therapy was performed in 96 patients (72.2%) after a median time of 17 days from hospital admission. The most common indication for surgery was heart failure followed by prediction of peripheral embolism and uncontrolled infection. In our study surgery was associated with lower in hospital mortality in patients with surgical indication in agreement with the studies of Moreira et al. and Leone et al. [17,21].

In recent years various inflammatory markers have been investigated in IE. Turak et al. retrospectively analyzed 121 patients with IE and hypothesized that increased NLR is associated with unfavorable in-hospital outcome [22]. Recent evidence suggests that the NLR provides a higher predictive value than the stand-alone leukocyte differential; because it can reflect more about disease severity than either of the former leukocyte subgroups [23,24]. Bozbay et al. [25] also investigated the role of NLR in IE and found an independent association between NLR and in-hospital mortality. In a study by Guray et al., increased RDW was an independent predictor of mortality [26]. PLR levels were found significantly higher and independently associated with in-hospital mortality in IE patients by a study of Zencir et al [27]. In another study, including 155 IE patients; age, syncope, heart failure, perforation, septic shock, renal failure, high RDW were associated with high mortality [28].

The primary mechanism responsible for neutrophilia is that stem cells boost neutrophil generation by the effects of growth factors [29]. In contrast, lymphocytopenia is caused by redistribution of lymphocytes to lymphatic organs, increased catecholamine and cortisol levels, and apoptosis [30]. Platelets release numerous inflammatory mediators and play a pivotal role in inflammation. The presence of increased platelets promotes inflammation, which in turn triggers a cascade of events resulting in the release of neutrophils, monocytes and lymphocytes to the vessel wall. Lymphocytes play an important role in immune surveillance and immune defense. Increased platelet and decreased lymphocyte levels in the circulation have been reported to be associated with the poor prognosis in cardiovascular disease [31]. However, although some authors in the field of oncology suggest that another prognostic biomarker, known as SII, is superior to NLR, no data are available in cardiac patients.

According to a study of Nie et al., SII was an independent prognostic factor for poor prognosis and correlated with decreased survival in patients with epithelial ovarian cancer [32]. Guo et al. found that, higher SII may be associated with tumor angiogenesis, invasion, and metastasis, thus leading to

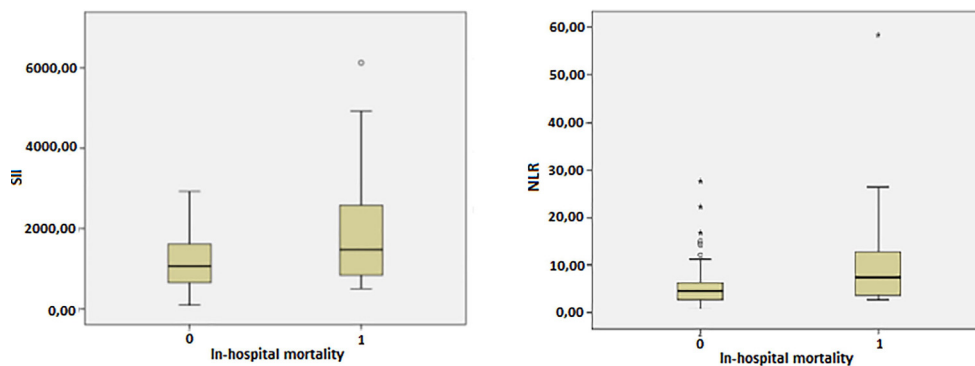


Fig. 3. Comparison of systemic immune-inflammation index and neutrophil lymphocyte ratio values in survivors and non-survivors.

poor survival in patients with lung cancer and also showed better prognostic ability than the NLR and PLR [33].

In a meta-analysis of Zhang et al., which enrolled 24 published articles with 9,626 cases found that gastrointestinal cancer patients with a high SII value had a poor prognosis [34].

Therefore, an elevated SII is correlated with poor survival in cancer patients according to recent studies. SII prognoses have already been reported in, colorectal cancer, prostate cancer, pancreatic cancer, hepatocellular carcinoma, and gastric cancer [11,35,36]. Given these results, we wanted to investigate SII, a marker that has not been studied in the field of cardiology, in infective endocarditis patients.

The cutoff value for SII in our study was higher than the other studies with cancer patients which it predicted mortality. Numerically high value can be explained by the inclusion of infected patients. In a study of Guo et al., the optimal cutoff values for the prediction of survival were 419.6 for the SII in lung cancer patients [33]. Kim et al., calculated the optimal cut-off of SII at diagnosis using AUROC (area 0.696, 95% confidence interval (CI) 0.612, 0.781), and found that 1,573.56 of SII was a strongest value for poor outcome [14].

The main limitations of our study are its retrospective design and small sample size. In this study, we focused on the assessment of the relation between inflammatory levels especially SII on admission and in-hospital mortality. Being a first study about SII in cardiology field, these results that we have obtained need to be confirmed further in large-scale studies.

5. Conclusion

Our study is the first to conduct research on SII in the field of cardiology. We demonstrated that high SII levels are independently associated with in-hospital mortality. Besides that age, hypocalcemia,

syncope, not going to surgery were independently associated with high mortality. The SII, which can be easily measured, is a simple, available, and inexpensive parameter that allows us to identify high-risk IE patients for mortality.

Conflict of interests

The authors state that they have no conflicts of interest.

Author contributions

Conception and design of the study: Hicaz Zencirkiran Agus, Serkan Kahraman, Ali Kemal Kalkan, Mehmet Erturk.

Data collection: Hicaz Zencirkiran Agus, Ceren Yildirim, Cagdas Arslan.

Analysis: Serkan Kahraman.

Processing: Mustafa Yildiz.

Literature review and writing: Hicaz Zencirkiran Agus.

Final review: Hicaz Zencirkiran Agus, Serkan Kahraman, Mustafa Yildiz.

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