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The relation between apical thrombus formation and systemic immune-inflammation index in patients with acute anterior myocardial infarction

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Abstract

Left ventricular (LV) apical thrombus formation is a well described and clinically important complication of acute myocardial infarction (MI) with a substantial risk of thromboembolism. Alterations in the inflammatory status may contribute to this complication. The aim of this study was to evaluate the predictive role of the systemic immune-inflammation index (SII) in identifying high risk patients who will develop an apical thrombus formation during the acute phase of anterior transmural infarction. Consecutive 1753 patients (mean age: 61.5 ± 9.6 years; male: 63.8 %) with first acute anterior MI who underwent primary percutaneous coronary intervention were assessed. Patients were divided into 2 groups according to the presence of apical thrombus. SII was calculated using the following equation: neutrophil (N) × platelet (P) ÷ lymphocyte (L). LV apical thrombus was detected on transthoracic echocardiogram in 99 patients (5.6%). Patients with an apical thrombus had lower LV ejection fraction, prolonged time from symptoms to treatment, higher rate of post-percutaneous coronary intervention thrombolysis in myocardial infarction flow ≤1 and significantly higher mean high-sensitivity C-reactive protein, and SII values and lower lymphocyte than those without an apical thrombus. Admission SII level was found to be a significant predictor for early LV apical thrombus formation complicating a first-ever anterior MI. This simple calculated tool may be used to identify high-risk patients for LV thrombus and individualization of targeted therapy.

Abbreviations: ACS = acute coronary syndrome, CAD = coronary artery disease, hsCRP = high-sensitivity C-reactive protein, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous coronary intervention, SII = systemic immune-inflammation index, STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction.

Keywords: anterior myocardial infarction, apical thrombus, systemic immune-inflammation index

1. Introduction

Left ventricular (LV) apical thrombus formation is a well-described complication following acute anterior myocardial infarction (MI), being associated with a substantial risk of thromboembolism.[1] The development of apical thrombus is a complex process. In previous studies, some clinical and echocardiographic conditions, such as LV aneurysms, larger infarct size, anterior MI, low LV ejection fraction (LVEF), increased total ischemic time, apical akinesis or dyskinesis and low thrombolysis in myocardial infarction (TIMI) flow grade, have been well-described for apical thrombus formation.[2,3] Although the general predictors of thrombus development are recognized, it is not explicitly clear why ventricles with similar degrees of dysfunction seem to have different susceptibilities for the formation of apical thrombus. Because LV thrombus can be associated with the systemic embolic events, the characterization and elucidation of the underlying pathophysiology and identification of early predictors for apical thrombus formation is essential for risk stratification and decisions about effective management strategies.

The systemic immune-inflammation index (SII) has emerged as a new predictor of patients' inflammatory and immunothrombotic status, simultaneously.[4] Previously, increased SII level was shown to predict poor outcomes in cancer patients.[5] Additionally, the predictive value of this index on routine blood tests have been examined and suggested to be a powerful and independent prognostic factor of several cardiovascular diseases including heart failure, cardiomyopathies, coronary artery diseases (CADs) and acute coronary syndromes (ACSs).[6–8] The SII is calculated using the following equation: neutrophil (N) × platelet (P) ÷ lymphocyte (L).[4] The SII reflects 3 important immune response pathways: inflammation which is represented by neutrophilia, thrombosis which is represented by platelets, and stress response which is reflected by lymphocyte.[9,10] However, the relation between SII levels and apical thrombous formation has not yet been studied before. In this context, we aimed to investigate whether there is an association

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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between the SII level and LV thrombus formation in patients with first acute anterior MI who underwent primary percutaneous coronary intervention (PCI).

2. Material and Methods

2.1. Study population

A total of 1989 consecutive acute anterior MI patients within 12 hours of symptom onset who were admitted to our tertiary hospital between January 2017 and April 2021 were enrolled. Patients who had past medication history with warfarin or other oral anticoagulant drugs for chronic oral anticoagulation, active infection, malignancy or hematological disease, chronic inflammatory disease, severe renal dysfunction (serum creatinine levels ≥1.5 mg/dL) or hepatic failure, pregnancy, uncontrolled thyroid dysfunction, moderate-to-severe valvular disease, patients who were treated conservatively or with thrombolysis were excluded from the study. As the presence of apical aneurysm from the previous MI can affect the occurrence of apical thrombus, we enrolled only patients with a first episode of acute anterior MI. Thus, a total of 1753 patients were assessed after exclusion criteria. All data were retrospectively examined and prospectively analyzed. Baseline demographic and clinical features, medical history, transthoracic echocardiography and laboratory parameters, procedural characteristics and medications of the patients were obtained from hospital electronic database. The existence of classical cardiovascular risk factors, such as age, gender, diabetes mellitus, hypertension, dyslipidemia, and smoking were determined. The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by the institutional review board.

2.2. Laboratory parameters

Peripheral venous blood samples were obtained from a large antecubital vein and collected at baseline in dry tubes for biochemical tests and pre-cooled EDTA tubes for the hematological test. Complete blood counts were measured using an automated hematology analyzer XE-1200 (Sysmex, Kobe, Japan). Baseline SII level was calculated using the following equation:

$$\text{neutrophil} \quad (\text{N}) \times \text{platelet} \quad (\text{P}) \div \text{lymphocyte} \quad (\text{L}).$$

2.3. Echocardiography

All study patients underwent transthoracic echocardiography to evaluate LV functions, mechanical complications and the presence of apical thrombus during hospital stay using the same commercially available ultrasound equipments. Initial echocardiogram was performed within 48 to 96 hours following hospital admission. Patients were excluded if they did not have transthoracic echocardiogram within 48 to 96 hours of admission. The LVEF was calculated using modified Simpson method. A LV apical thrombus formation was described as an echodense mass adjacent to an akinetic or dyskinetic myocardial segment.

2.4. Coronary angiography and primary PCI procedure

Our hospital is a high volume tertiary cardiology center with the facility to perform PCI 24 hours, 7 days a week. All primary PCI procedures were performed in our hospital by expert operators according to the current practice guidelines and recorded in digital storage for quantitative analysis. All patients were treated with unfractionated heparin 100 U/kg, aspirin plus clopidogrel, prasugrel or ticagrelor before coronary intervention in the emergency department. The use of glycoprotein IIb/IIIa inhibitors and thrombus aspiration was left to the discretion of operators, based on the current practice. After stenting, all patients received dual antiplatelet treatment with acetylsalicylic acid and P2y12 inhibitors, and patients were advised to continue these medications for at least 12 months. Post-PCI anticoagulant treatment was deferred unless echocardiographic assessment showed LV apical thrombus formation. All the patients diagnosed with LV thrombus were treated with oral anticoagulant treatment for 3 to 6 months based on the current practice and followed up with serial echocardiography as clinically needed.

2.5. Definitions

Hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg and/or taking antihypertensive medications. Diabetes was defined as fasting blood glucose ≥126 mg/dL or using hypoglycemic agents. Family history of CAD was defined if a female first-degree relative developed CAD under the age of 65 or a male first-degree relative under 55. Patients were defined as smokers if they were active smoking or quit smoking within the last year. Anterior MI was diagnosed according to the criteria suggested by Fourth Universal Definition of Myocardial Infarction guideline; the presence of ST-segment elevation of at least 2.5 mm in men aged <40 years or 2 mm in men aged ≥40 years, and at least 1.5 mm in women at leads V2 to V3 and/or at least 1 mm at other leads in 2 adjacent chest leads.[11]

2.6. Statistical analysis

All statistical analyses were performed using the SPSS 22.0 Statistical Package Program for Windows (SPSS, Inc., IL). The continuous variables were presented as the mean values ± standard deviation and median with interquartile ranges and the categorical variables were expressed as frequency and percentage. Kolmogorov–Smirnov test was used for the evaluation of normality of distribution. The differences between the 2 groups were assessed by using Student t-test for normally distributed variables and Mann–Whitney U test for variables without normal distribution. The Chi-square test or Fisher exact test were used to compare categorical variables as appropriate. We used a univariate logistic proportional regression analysis to evaluate the association of each variable on the occurrence of apical thrombus. The receiver operating characteristic curve analysis was used to determine the best predictive SII level for apical thrombus formation. Youden index was used to establish the most appropriate cutoff value. Patients were divided into 2 quantiles according to the occurrence of apical thrombus and the optimal cutoff value of SII. Correlations were examined using Pearson correlation test. A P-value < .05 (using a 2-sided test) was considered significant.

3. Results

LV apical thrombus formation was detected on echocardiogram in 99 of the 1753 patients (5.6%). Baseline clinical characteristics, laboratory parameters, and angiographic findings of the patient groups with and without apical thrombus were demonstrated in Table 1. A total of 1119 patients (63.8%) were male, and the mean age of the study population was 61.5 ± 9.6 years old. As shown in Table 1, patients with apical thrombus showed prolonged time from symptoms to treatment, higher rate of post-PCI TIMI flow ≤1 and lower ejection fraction compared with those without apical thrombus. In addition, SII and high-sensitivity C-reactive protein (hsCRP) levels were higher and lymphocyte values were lower in patients with apical thrombus.

In receiver operating characteristic curve analysis, using a cutoff level of 579, the admission SII level predicted apical thrombus with a sensitivity of 75.8% and a specificity of 72.8% (area under the receiver operating characteristic curve: 0.74, 95% confidence interval: 0.70–0.79; P < .001) (Fig. 1).

Table 1

Baseline characteristics of patients according to the presence of early left ventricular apical thrombus formation.

	Total n = 1753	Thrombus (+) n = 99	Thrombus(–) n = 1654	*P* value
Age (yr)	61.5 ± 9.6	62.0 ± 9.2	61.5 ± 9.6	.614
Gender, male n (%)	1119 (63.8%)	67 (67.7 %)	1052 (63.6%)	.413
Diabetes, n (%)	705 (40.2 %)	38 (38.4 %)	667 (40.3 %)	.702
Hypertension, n (%)	694 (39.6 %)	45 (45.5 %)	649 (39.2 %)	.219
Smoking status, n (%)	660 (38.2 %)	49 (48.0 %)	611 (37.6 %)	**.036**
Dyslipidemia, n (%)	758 (45.8 %)	46 (46.5 %)	718 (44.2 %)	.902
Family history, n (%)	547 (31.2 %)	27 (27.3 %)	520 (31.4 %)	.385
LVEF (%)	34.2 ± 4.8	32.9 ± 3.9	34.3 ± 4.9	**.005**
Medical therapy				
Aspirin, n (%)	751 (42.9%)	43 (43.4 %)	708 (42.8 %)	.906
ß blocker, n (%)	855 (48.8%)	46 (46.5 %)	809 (48.9 %)	.636
Statin, n (%)	716 (40.8 %)	47 (47.5 %)	669 (40.4 %)	.167
ACE in h/ARB, n (%)	678 (38.7 %)	33 (33.3 %)	645 (39.0 %)	.261
Angiographic characteristics				
Use of GpIIb/IIIa inhibitor, n (%)	484 (27.6 %)	28 (28.3 %)	456 (27.6 %)	.877
Time from symptoms to treatment (h)	4.0 (3.0–5.0)	4.0 (4.0–6.0)	4.0 (3.0–4.0)	**.002**
BMS, n (%)	188 (10.7 %)	15 (15.2 %)	173 (10.5 %)	.143
Number of coronary arteries involved	1.8 ± 0.5	1.8 ± 0.4	1.8 ± 0.5	.446
TIMI flow ≤1	70 (4.0 %)	10 (10.1 %)	60 (3.6 %)	**.001**
Laboratory parameters				
Hemoglobin (g/dl)	13.8 ± 1.6	13.7 ± 1.6	13.8 ± 1.6	.787
WBC ($\times 10^3$ µL)	7.6 ± 1.6	7.9 ± 1.4	7.6 ± 1.6	.118
Neutrophil ($\times 10^3$ µL)	4.6 ± 1.2	4.9 ± 1.4	4.6 ± 1.2	.053
Lymphocyte ($\times 10^3$ µL)	2.2 (1.8–2.7)	2.0 (1.7–2.7)	2.2 (1.9–2.7)	**.010**
Monocyte ($\times 10^3$ µL)	0.5 (0.4–0.7)	0.5 (0.4–0.7)	0.5 (0.4–0.7)	.917
Platelet ($\times 10^3$ µL)	253 ± 73	264 ± 62	253 ± 74	.124
Creatinine (mg/dl)	0.9 (0.7–1.0)	0.9 (0.7–1.1)	0.9 (0.7–1.0)	.618
Total cholesterol (mg/dL)	177 ± 42	179 ± 45	176 ± 42	.481
Triglycerides (mg/dL)	133 (93–180)	145 (102–195)	133 (93–179)	.112
LDL-C (mg/dL)	109 ± 34	112 ± 38	109 ± 34	.411
HDL-C (mg/dl)	41 (34–48)	38 (32–48)	41 (34–48)	.067
CRP (mg/dl)	3.5 (1.8–6.9)	4.6 (2.8–7.6)	3.5 (1.8–6.9)	**.005**
SII	524 ± 188	656 ± 155	516 ± 187	**<.001**

Data are presented as mean ± SD or n (%).

Bolded values indicate statistical significance ($P < .05$).

ACE = angiotensin converting enzyme, ARB = angiotensin II receptor blocker, BMS = bare metal stent, CRP = C-reactive protein, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, SII = systemic immune-inflammation index, TIMI = thrombolysis in myocardial infarction, WBC = white blood cell.

The associations of possible risk factors with LV thrombus were evaluated in univariate logistic regression analysis. Univariate logistic regression analyze showed that the presence of TIMI flow ≤1, LVEF, time from symptoms to treatment, SII, hsCRP and lymphocyte levels were significantly associated with the occurrence of apical thrombus (for all, $P < .05$), (Table 2). In addition, correlation analysis revealed that there was a positive correlation of admission SII level with admission hsCRP level (r: 0.277, $P < .001$).

4. Discussion

In the present study, it was found that, among patients presenting with first acute anterior MI, patients with early LV thrombus had significantly higher SII levels. SII with a simple formula utilizing readily available laboratory parameters in routine daily practice was an important predictor of apical thrombus formation. SII was also positively correlated with admission serum hsCRP levels showing its strong relation with systemic inflammation. To our knowledge, current study is the first in the literature investigating the potential role of SII in development of apical thrombus in the setting of acute anterior MI

LV thrombus formation is a clinically significant complication of acute MI that impacts thromboembolic event risk and anticoagulant therapy.[12] Previous studies before the advent of primary PCI for the treatment of ST-segment elevation myocardial infarction (STEMI) have shown that the incidence of LV thrombus is 27 to 46% in patients with acute anterior MI. Since the introduction of widespread use of PCI and dual antiplatelet therapy, studies have reported a declining incidence of LV thrombus, ranging from 2 to 7% in large studies.[13,14] The incidence of LV thrombus was 5.6% in our study patients similar to those of previous studies.

Previous studies have demonstrated that some clinical, echocardiographic and laboratory parameters, such as anterior MI, large infarct size, prolonged door-balloon time, worse TIMI flow after primary PCI, decreased LVEF and increased CRP levels are associated with increased risk for LV thrombus formation in patients with acute MI.[13,15] Nevertheless, each of those parameters alone is not satisfactory to establish which patients with acute MI are liable to develop LV thrombus, and hence, development of additional predictors would be of notable benefit. Furthermore, since a LV thrombus can already be identified during hospitalization period following acute MI, identification of early predictors of LV thrombus is required.[16]

Recently, Hu et al[17,18] have advanced an easily accessible inflammation-based marker called the SII that brings together 3 inflammatory peripheral cell counts to consider patients' immune and inflammatory status together based on routine blood tests. It has been widely studied in different cancers and SII was shown to be a strong predictor of worse clinical outcomes in cancer patients and several other disease states.[19–23] Several studies demonstrated that higher SII was an important prognostic and predictive marker in various cardiovascular diseases such as: severity of CAD in patients with stable angina pectoris[7] aortic stenosis patients who underwent transcatheter

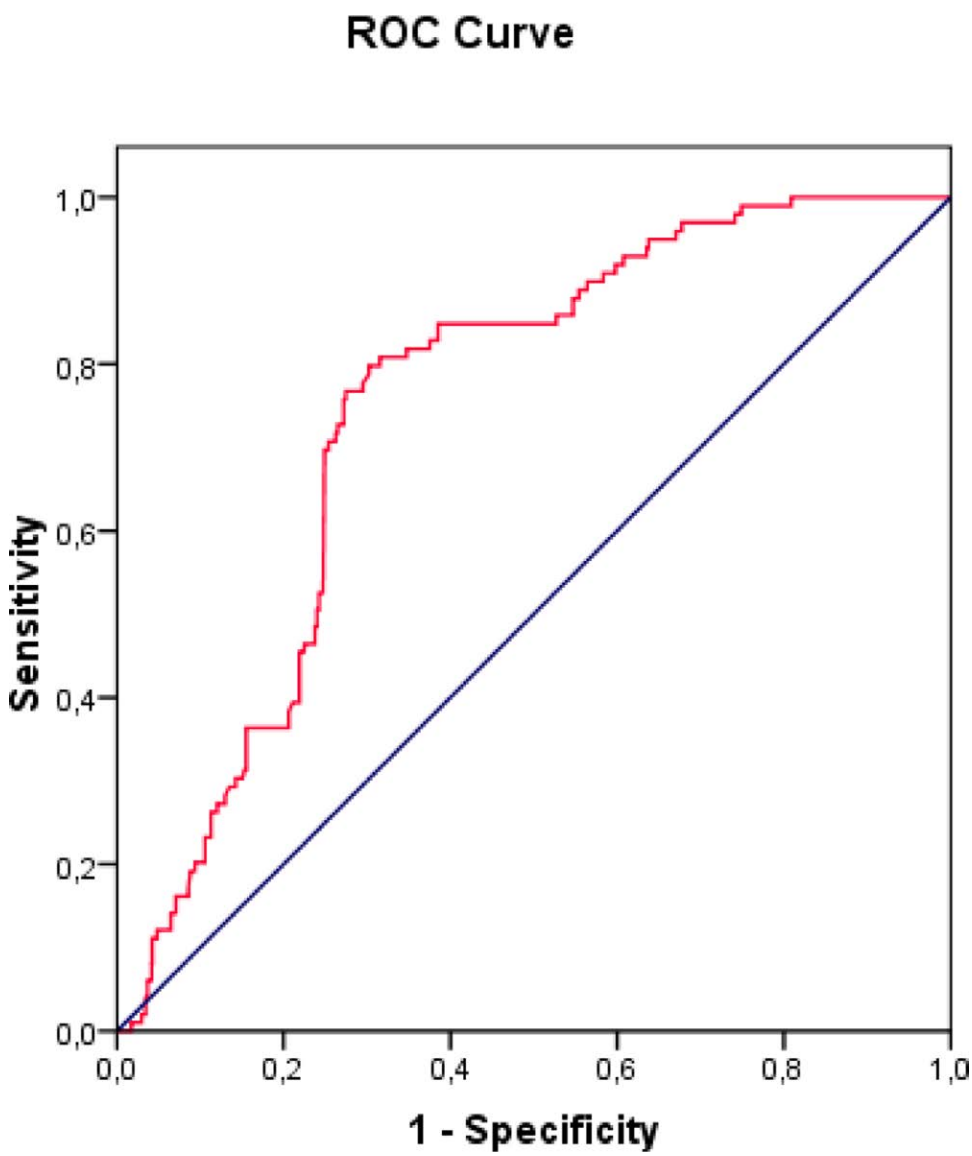

Figure 1. ROC curve analysis of SII levels to predict LV apical thrombus. LV = left ventricular, ROC = receiver operating curve, SII = systemic immune-inflammation index.

aortic valve implantation[24] and hypertrophic cardiomyopathy.[18] All these results demonstrate the importance of SII in inflammation which has an essential role in the development of cardiovascular events.

The pathogenesis of apical thrombus development is attributed to the combination of blood stasis, endothelial injury, and hypercoagulability, referred to as Virchow triad.[25] In the context of STEMI, regional akinesia/dyskinesia of necrotic myocardium contribute to blood stasis, whereas prolonged ischemia causes endothelial injury, triggers inflammatory changes and generates a hypercoagulable state with increased concentration of procoagulant factors.[26] Recent studies have also demonstrated that ACS is not only a hypoperfusion state but also related with increased level of pro-inflammatory molecules and inflammation.[27] Systemic inflammation and oxidative stress, which are mechanistically interrelated, cause calcium overload and reduce the amount of sodium channels ending up with electrical remodeling. Simultaneously, there is structural remodeling through proliferation of fibroblasts and apoptosis mechanism. The changes in ventricular tissue such as fibrosis, leukocyte infiltrates and oxidative damage may contribute to structural and electrical remodeling further, which may lead to apical thrombus development.[26] Previous studies have also demonstrated that high level of pro-inflammatory markers have been associated with thrombotic events[28] All these factors may contribute to the likely mechanism for increased apical thrombus formation in patients with higher SII values as an inflammatory marker.

Previously CRP, as a well-known and important inflammatory marker, was found to be significantly associated with apical thrombus formation.[15] In our study, SII had also a mild to moderate but significant positive correlation with serum CRP level, which supports its role in systemic inflammation. Whether the presence of a preexisting systemic inflammatory milieu culminates in LV thrombus or development of apical thrombus promotes inflammatory pathways remains unclear. Also, whether changes in blood elements could also play a role in apical thrombus formation is not apparent, but our study findings support this idea.

Recent studies have confirmed that inflammatory mediators can be beneficial to predict ACS patients' prognosis, but 1 or 2 component-based markers are possibly insufficient to predict the prognosis in ACS.[29,30] Therefore, one may hypothesize that, the SII level can better reflect the overall immune and inflammatory status of the body compared to utilizing any one of these

Table 2

Univariate logistic regression analysis for prediction of apical thrombus formation.

	Univariate analysis		
Variable	**HR**	**95 % CI**	***P* value**
Age	1.005	0.985–1.027	.614
Gender (male)	1.198	0.777–1.847	.413
Hypertension	1.290	0.858–1.940	.220
Dyslipidemia	0.366	0.683–1.541	.902
Smoking	0.988	0.424–2.299	.977
Diabetes mellitus	0.922	0.608–1.398	.702
Family history	0.818	0.519–1.288	.386
Use of GpIIb/IIIa inhibitor	1.036	0.660–1.626	.877
Time from symptoms to treatment	1.121	1.030–1.221	**.008**
BMS	1.529	0.863–2.707	.146
Number of coronary arteries involved	0.868	0.603–1.249	.445
TIMI flow ≤1	2.985	1.478–6.027	**.002**
LVEF	0.938	0.898–0.981	**.005**
Hemoglobin	0.984	0.873–1.109	.787
WBC	1.102	0.976–1.245	.118
Neutrophil count	1.176	0.997–1.365	.054
Monocyte count	0.554	0.218–1.407	.917
Lymphocyte count	0.690	0.509–0.937	**.010**
Platelet count	1.002	0.999–1.005	.124
Creatinine	1.522	0.808–2.867	.618
Urea	1.005	0.991–1.021	.474
eGFR	0.988	0.976–1.001	.077
Total cholesterol	1.002	0.997–1.006	.481
Triglycerides	1.001	0.998–1.004	.112
LDL	1.001	0.998–1.004	.442
HDL	1.002	0.997–1.008	.067
hsCRP	0.987	0.969–1.006	**.005**
SII >579	3.631	2.403–5.488	<**.001**

Bolded values indicate statistical significance ($P < .05$).

BMS = bare metal stent, CI = confidence interval, HDL = high-density lipoprotein, HR = hazard ratio, hsCRP = high-sensitivity C-reactive protein, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, SII = systemic immune-inflammation index, TIMI = thrombolysis in myocardial infarction, WBC = white blood cell.

markers in isolation. In recent years, many studies have demonstrated that high level of SII is related to poor outcomes in CAD and ACS. Esenboga et al[31] found that increased SII levels in patients undergoing primary PCI for acute STEMI may be a useful index to predict the non-reflow phenomenon. Also, Huang et al[6] showed that increased SII level predicts poor clinical outcomes for elderly patients after ACS.

Our findings supported the results of previous studies and extended the literatural knowledge as to the association of elevated SII levels and adverse cardiac outcomes related to CAD and ACS. SII level as a simple, widely available, and low cost marker seems to be a new marker of LV thrombus in patients with first acute anterior MI.

The present study has certain limitations such as its design in a retrospective, single center and observational fashion. Though hsCRP was assessed as an inflammatory marker, other inflammatory parameters such as tumor necrosis factor-α, monocyte chemoattractant protein and interleukin-6 were not simultaneously measured and compared with SII as they are not widely available in routine daily practice. SII level was assessed at only initial evaluation. Therefore, the impact of potential temporal changes in SII is unclear. In addition, we only evaluated early LV thrombus formation detected during hospital stay. Our study aimed to reflect the early incidence of LV thrombus formation, and it is therefore likely that thrombus could develop later post-MI. However, this is consistent with other previously published studies in literature and so is comparable. Another major limitation of this study is that we did not utilize contrast agents to better delineate the LV apex because these are not routinely used in our country. In addition, cardiac magnetic resonance imaging was not routinely performed in our study, this might have resulted in underestimation of apical thrombus. Finally, rather than a causal relation between SII and LV apical thrombus, we only demonstrated a likely association of SII and occurrence of early LV thrombus, so this study should be regarded as hypothesis generating. Since this is a retrospective study, we could not report the follow-up data in terms of ischemic events which would enhance the clinical value of the results. Further, large scale and prospective studies are needed to report the ischemic events, validate our results and clarify the predictive utility of SII more exactly.

5. Conclusion

In conclusion, SII can be easily and inexpensively calculated bedside with simple routine blood count analysis, for evaluation of inflammation. Our findings revealed a significant association between apical thrombus formation and SII. Accurate risk prediction for the occurrence of LV thrombus might help to identify high-risk patients and deciding on the most effective protective measures such as early and more frequent echocardiographic assessment and more careful consideration of anticoagulation in the setting of acute MI. However, our findings should be confirmed in well-designed randomized, prospective and large-scale studies involving other inflammatory markers and imaging techniques including cardiac magnetic resonance and contrast echocardiography to clarify the exact role of SII in apical thrombus formation.

Author contributions

Data curation: Bahar Tekin Tak.
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Project administration: Derya Tok.
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Writing – review & editing: Derya Tok.

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