RESEARCH

EVALUATING THE SYSTEMIC IMMUNE-INFLAMMATION INDEX FOR ADVERSE OUTCOMES IN ELDERLY ACUTE CORONARY SYNDROME PATIENTS

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Abstract

Introduction: Acute coronary syndrome is a fatal clinical manifestation of coronary artery disease. A newly defined index—Systemic Immune–Inflammation Index—has recently been reported to have prognostic value in patients with cardiovascular disease. This investigation was aimed at evaluating the systemic immune-inflammation index predictive value for in-hospital and 1-year follow-up clinical outcomes in elderly patients with acute coronary syndrome.

Materials and method: We retrospectively enrolled 910 consecutive patients in the study. We divided the patients into two groups: young patients with acute coronary syndrome (Group 1) and elderly patients with acute coronary syndrome (Group 2). The patients were followed up on for one year. We compared the two groups' systemic immune-inflammation index results, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio.

Results: The neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index were significantly higher in Group 2. According to multivariate logistic regression analyses, systemic immune-inflammation index, and platelet-to-lymphocyte ratio ($p < 0.001$, and $p = 0.013$, respectively) emerged as independent predictors of in-hospital mortality in Group 2. Group 2 had significantly worse in-hospital mortality rates than those of Group 1. However, the groups' long-term outcomes were similar.

Conclusion: High systemic immune-inflammation index values were independently associated with an elevated risk of in-hospital mortality in Group 2. This investigation may be the first to demonstrate that this index is independently linked with in-hospital and long-term mortality in elderly acute coronary syndrome patients. It could be used as an easy, inexpensive, and practical predictor to identify high-risk elderly patients with acute coronary syndrome.

Keywords: Acute Coronary Syndrome; Inflammation; Aged.

INTRODUCTION

Cardiovascular disease is one of the most common causes of morbidity and mortality around the world and was responsible for approximately 17.7 million deaths in 2017 (1). Acute coronary syndrome (ACS) is an acute and lethal clinical manifestation of extensive coronary artery disease (CAD) that causes more than one-third of all deaths in developed nations annually (2). Advances in primary and secondary prevention have helped reduce disease incidence rates. However, compared to younger patients, elderly patients with ACS have a higher risk of death, complications, and decreased functional capacity (3).

Inflammation plays a key role in the formation and progression of atherosclerosis (4). Moreover, a correlation has been found between the inflammatory markers of this process and the high severity of and poor prognosis related to CAD. The vascular bed's inflammatory and immune cells, such as white blood cells and white blood cell subtypes (e.g., neutrophils, monocytes, and lymphocytes), reflect systematic inflammation severity and play an important role in AMI's mortality and morbidity (5). Therefore, in addition to the traditional risk factors, the distribution of cells in the complete blood count has begun to be evaluated among CAD's predictors in the interventional cardiology era.

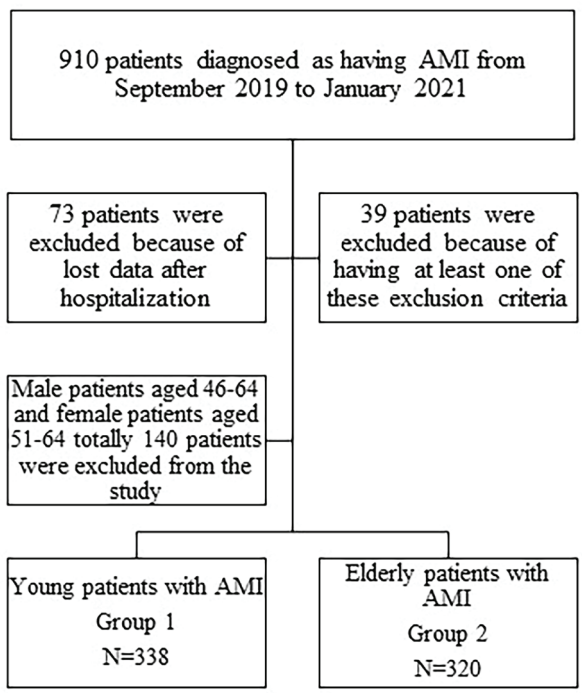
Recently, the Systemic Immune–Inflammatory Index (SII), derived from the distribution of blood cells, was developed. The SII is used to determine prognosis in various cardiovascular diseases and cancer types (6). It is based on platelet, neutrophil, and lymphocyte counts (7). Studies on cardiovascular diseases are a good predictor of in-hospital and long-term clinical outcomes in patients with chronic heart failure, CAD, and ACS (8,9). Nevertheless, the SII's prognostic role related to morbidity and mortality in elderly patients with ACS has not yet been evaluated. In our study, we examined the SII's prognostic value in young and elderly ACS patients during one year of follow-up.

MATERIALS AND METHOD

Study population

Between September 2019 and January 2021, we retrospectively enrolled 910 patients (aged 18–80 years) in our study. All patients were diagnosed with acute myocardial infarction (AMI) and underwent coronary artery angiography (CAG). We excluded 39 patients according to the exclusion criteria. We excluded 73 patients because some of their data were lost after hospitalization. We excluded male patients aged 46–64 years and female patients aged 51–64 years from the study. Finally, we included 658 patients in this study. We divided the patients into two groups: young patients with AMI (Group 1) and elderly patients with AMI (Group 2; Figure 1). We included male patients up to 45 years old and female patients up to 50 years old in the young AMI group. We included patients 65–80 years old in the elderly AMI group. We defined AMI according to

Figure 1. Study flow diagram



the diagnostic criteria of the European Society of Cardiology's non-ST-elevation myocardial infarction (NSTEMI) guidelines published in 2020 and the ST-elevation myocardial infarction (STEMI) guidelines published in 2017 (10,11).

We obtained the study population's demographic characteristics from their hospital records. The exclusion criteria were being aged under 18 years or over 80 years, experiencing changes in inflammatory or immune markers other than AMI (e.g., autoimmune diseases, sepsis, trauma, recent major surgery, and active malignancy), having a glomerular filtration rate of less than 30 ml/min, having severe hepatic failure, receiving thrombolytic therapy, and being pregnant. The local ethics committee approved the current study, and we conducted the research in compliance with the Declaration of Helsinki.

Blood sample test analysis

Fasting blood samples were obtained from the participants' peripheral veins. Their fasting glucose levels, cholesterol panels, and renal function tests were measured using a Roche Cobas 6000 analyzer. Blood samples were obtained for the calculation of SII values upon participants' admission to the hospital. Complete blood count parameters were measured using an auto hematology analyzer (BC 6800 Mindray Medical Electronics Co. Shenzhen, China). The participants' SII values were calculated according to the following formula at admission: SII = platelet count × neutrophil count ÷ lymphocyte count. Platelet–lymphocyte ratios (PLR) were calculated according to the following formula: platelet count ÷ lymphocyte count (12). Neutrophil–lymphocyte ratios (NLR) were calculated according to the following formula: neutrophil count ÷ lymphocyte counts (12).

Coronary artery intervention

According to Judkins' technique, coronary artery interventions were performed via the patients' femoral arteries. Based on the current guidelines, all the patients received aspirin (300 mg), clopidogrel (300–600 mg), ticagrelor (180 mg), and prasugrel (60 mg) as antiplatelet therapy before coronary intervention (10,11). Heparin and, if necessary, tirofiban therapy were administered during the perioperative period. According to the patients' angiography results and clinical findings, the doctors selected current practice guidelines.

Transthoracic echocardiography

Echocardiographic measurements were performed using the Philips Affinitti 70 ultrasound system (Medical Healthcare Solutions, Inc.; Andover, MA, USA) with an S4-2 transducer probe. Transthoracic echocardiographic analyses were performed by two cardiologists who were blinded to the study groups. Single-lead echocardiographic recordings were simultaneously obtained during the echocardiographic recordings. Two-dimensional, M-mode, and color-flow Doppler echocardiography were performed according to the current guidelines (13). Left ventricular (LV) end-diastolic dimensions, interventricular septum, and left ventricular posterior wall thicknesses were measured from the parasternal-long-axis and apical four- and five-chamber views and averaged. LV ejection fractions were measured using the Biplane Simpson method in the apical four-chamber view.

Follow-up and study end points

The study's clinical end points included all-cause mortality and major adverse cardiovascular events. We assessed in-hospital mortality (during the participants' hospital stays) and long-term mortality (up to one year of follow-up). All-cause mortality was the study's primary end point. The major adverse cardiovascular events included rehospitalization for severe heart failure, nonfatal myocardial infarction (MI), and nonfatal stroke. We defined severe heart failure according to the New York Heart Association (NYHA) Classification Class IV. We defined ischemic stroke as obstruction within a blood vessel supplying blood to the brain evidenced by either magnetic resonance imaging (MRI) or computed tomography

(CT) scans and a new neurologic deficit lasting for at least 24 hours. We defined all-cause mortality as death from any cause during the one-year follow-up period. We reviewed the participants' medical records to confirm their primary clinical outcomes and mortality statistics. The patients were followed up on from September 2019 to January 2022.

Statistical analysis

We used IBM SPSS Statistics for Windows, version 18.0 (IBM Corp., Armonk, NY, USA), to perform the statistical analysis. We used the Kruskal–Wallis test to assess the normality of the variables' distributions. We expressed each quantitative variable with a normal distribution as its mean ± standard deviation, and we expressed each abnormally distributed variable as its median (25th–75th percentile). We expressed categorical variables as numbers and percentage values. We assessed the abnormally distributed variables using the Mann–Whitney U test, whereas we assessed the normally distributed variables with independent samples t-tests. We analyzed the categorical variables using chi-square tests. We obtained the survival curve using Kaplan–Meier analysis and the log-rank test. Logistic univariate regression and multivariate regression analysis identified factors related to clinical end points.

RESULTS

Our study population's basal demographic characteristics, laboratory results, and transthoracic echocardiographic findings are presented in Tables 1 and 2. There was no difference between the two groups in terms of basal demographic characteristics. Decisions of PCI occurred more often in Group 1 than in Group 2 ($p < 0.001$). The in-hospital mortality, first month mortality rate, the six-month mortality rate, and the first-year mortality rate were higher in Group 2 than in Group 1 ($p = 0.025$; $p = 0.032$, $p= 0.028$, and $p= 0.032$, respectively). The two groups' fasting glucose, high-density lipoprotein, triglycerides, and serum creatinine levels were similar. Group 1's total cholesterol and low-density lipoprotein levels and its neutrophil, lymphocyte, and platelet counts were significantly higher than those of Group 2. Group 2's median NLR and PLR values were significantly higher than those of Group 1. Moreover, Group 2's SII values and C-reactive protein (CRP) levels were higher than those of Group 1 ($p < 0.001$ and $p < 0.001$, respectively).

The logistic regression analysis results we achieved using one model, including continuous SII, PLR, CRP, serum creatinine, and categorical HT values, to detect dependent and independent predictors of in-hospital mortality in the elderly are presented in Table 3. According to multivariate logistic regression analyses, SII and PLR values ($p < 0.001$) were independent predictors of in-hospital mortality in elderly patients.

Twenty-two (3.34%) patients died during hospitalization in this study population, and 11 (1.6%) died during follow-up. Group 2 had significantly worse in-hospital mortality than Group 1 (Figure 2; logrank test $p = 0.013$).

Figure 2. The comparison of both groups Kaplan-Meier cumulative survival curves for in-hospital mortality

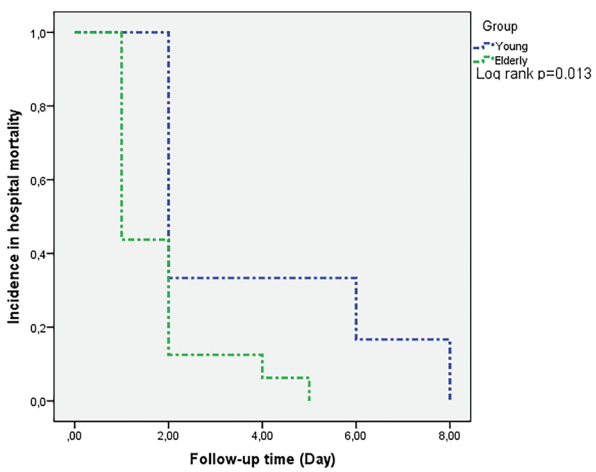


Table 1. Demographic and clinical characterictics of the groups

	Group 1 (n=338)	Group 2 (n=320)	*p**
Male	277 (82.7%)	264 (82.5%)	0.809*
Age	41.62 ±4,82	70.52±4.1	<0.001**
Type of ACS	STEMI=174 (51.5%)	STEMI=176 (55%)	0.377*
History of CAD	38 (11.2%)	36 (11.3%)	0,548*
HT	52 (15,6%)	46 (14.4%)	0.375*
HL	8 (2.4%)	4 (1.3%)	0.213*
DM	60 (18%)	64 (20%)	0.286*
Smoking	210 (62.9%)	194 (60.6%)	0.301*
Decision of PCI	PCI= 304 (91%)	PCI =246 (76.9%)	<0.001*
In hospital mortality	6 (1.8%)	16 (5%)	0.025*
Days of in hospital mortality	5.33 ±1.94	2±0.68	0.001**
Mortality rate of first month	0 (0%)	2 (0.62%)	0.032*
Mortality rate of 6. Month	2 (0.59%)	5 (1.56%)	0.028*
Mortality rate of first year	0 (0%)	2(0.62%)	0.032*
MACE of first month	16 (5.2%)	19 (5.8%)	0.528*
MACE of sixth month	21 (6.31%)	25 (7.81%)	0.253*

ACS:Acute coronary syndrome ; CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; DM: Diabetes mellitus; HL: Hyperlipidemia; HT: Hypertension; MACE: Major advers cardiovascular event; STEMI: ST elevation myocard infarctus

*: Fisher's Exact Test.

**: Independent sample Student t test

DISCUSSION

This study revealed that SII and PLR values are independent predictors of in-hospital mortality in elderly patients. To our knowledge, this study is the first in the literature to investigate the SII's predictive value in elderly patients with ACS.

Inflammation plays a highly important role in the development of many diseases, such as malignancy, metabolic diseases, and cardiovascular diseases. The determination of inflammation's active role in the development of atherosclerosis has drawn researchers' attention. Neutrophils, lymphocytes, and platelets also play significant roles in this process (14,15).

Neutrophil infiltration into endothelial tissue is associated with the initiation and progression of atherosclerosis, which causes damage to the endothelium. Moreover, neutrophils secrete inflamma-

Table 2. Laboratory tests and transthoracic echocardiography results of the groups

	Group 1 (n=338)	Group 2 (n=320)	*p*
Glucose (mg/dL)	106 (88.25-130.75)	109 (102.5-130)	0.181 **
Total cholesterol (mg/dL)	193.5 (163.25-227.5)	181 (150-212)	<0.001**
LDL (mg/dL)	120 (97.3-151)	114.2 (84.05-114.7)	<0.001**
HDL (mg/dL)	36 (31-43)	37 (34-42)	0.095**
Triglycerides (mg/dL)	165 (114-279.7)	146 (87-184)	0.129**
Serum creatinine (mg/dL)	0.91 (0.73-1.01)	0.98 (0.81-1.13)	0.251**
Neutrophil (N) count ($\times 10^3$/µL)	9.08 ±3.67	8.33±3.77	0.004*
Lymphocyte (L) count ($\times 10^3$/µL)	2.49 (1.81-3.3)	1.84 (1.3-2.54)	<0.001**
Platelets (P) ($\times 10^3$/µL)	264.85±79.83	248.77±70.57	0.022*
N/L ratio	2.96 (2.13-5.29)	3.92 (2.35-6.93)	<0.001**
P/L ratio	97.15 (72.19-150.81)	133.16 (92.59-178.67)	<0.001**
SII index	1134.77±284.09	1500.48±353.74	<0.001*
C – reactive protein (mg/dL)	0.83 (0.22-4.15)	1.92 (0.5-5.59)	<0.001**
Ejection Fraction (%)	50.97±10.75	49.48±10.58	0.103*

dL: deciliter;; HDL: High density lipoprotein; ıqr: Interquartile range; LDL: Low density lipoprotein; mg:Miligram; uL: microliter; SII: Systemic immune-inflammation index.

*: Independent sample T test

**: Mann Whitney U test

Table 3. Predictors of in-hospital mortality in elderly patients by logistic regression analysis

Variables	Univariate		Multivariate	
	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
HT	0.481 (0.148-1.561	0.250		
Serum creatinine (mg/dL)	5.808 (0.853-39.545)	0.072		
P/L ratio	0.993 (0.984-1.002)	0.044	0.975 (0.957-0.995)	0.013
SII	1 (1-2.801)	<0.001	1.005 (1.003-3.527)	<0.001
C-reactive protein (mg/dL)	0.890 (0.753-1.052)	0.173		

Nagelkerke R square= 0.809; -2 Log likelihood= 27.828; p= <0.001

dL: Deciliter; HT: Hypertension, mg: miligram; L: Lymphocyte; P: Platelet; SII: Systemic immune-inflammation index.

tory mediators, which are associated with acute inflammatory responses after tissue injury (16). Unlike neutrophils, a low lymphocyte count in a coronary artery patient is a poor prognostic indicator (17).

In this inflammatory process, lymphocytes are mostly associated with modulation of the immune system. Whereas neutrophils are associated with a destructive inflammatory response (18), platelets play an important role in inflammation, thrombosis, and atherogenesis. Additionally, platelets release various inflammatory mediators that can further activate platelets and create a vicious cycle (19,15).

After demonstrating that these cells may have a predictive role in the development of CAD, information such as NLR, PLR, and SII values has been brought to the forefront. It has been concluded that these ratios might be more valuable than evaluating cells alone. Therefore, many studies have been conducted on this subject. Sari et al. investigated the relationship among NLR, PLR, and CAD severity in patients undergoing coronary angiography and found that NLR and PLRs were significantly correlated with SYNTAX and Gensini scores (20). Another study, which contained 414 patients, revealed that the NLR is associated with CAD severity in patients with NSTEMI (21). In another study, admission NLR values were an independent predictor of all-cause mortality in patients with ACS (22).

Cicek et al. assessed the effectiveness of a combination of NLR and PLR values in predicting in-hospital and long-term mortality in patients with STEMI. They concluded that neither NLRs nor PLR alone were independent predictors of all-cause mortality. In contrast, the use of these ratios combined provided significant prognostic information (23). Our study's findings are supported by the abovementioned studies. In this study, the elderly patients' median NLR and PLR values were higher than those of the young patients. Additionally, PLR was an independent predictor of in-hospital mortality in the elderly group.

Thus far, inflammatory parameters, such as white blood cells, NLR, PLR, CRP, and some interleukins, have been reported to be associated with atherosclerosis (15,4). Seo et al. described the SII, which gathers neutrophil, lymphocyte, and platelet cell counts, as a prognostic marker in congestive heart failure (24). Yang et al. reported that the SII resulted in better risk prediction than traditional risk factors for death, congestive heart failure, and major adverse cardiovascular events in patients with CAD (25). Huang et al. evaluated 711 elderly AMI patients and found that the SII was a potential indicator for predicting all-cause mortality and major adverse cardiovascular events. Moreover, they discovered a significant correlation between SII values and cardiovascular-related variables, such as Gensini score. In our study, we compared the prediction abilities of the SII and some other parameters through univariate and multivariate logistic regression analyses (9). We adjusted all confounding factors and found that SII values had predictive ability regarding in-hospital mortality in elderly patients.

This study has some limitations. First, it was a single-center, retrospective cross-sectional study. Because of the study's nature, the patients did not undergo follow-up for more than one year, so no comments could be made regarding their long-term prognosis. The study had a relatively small sample size. The patients' medications were not taken into consideration. Therefore, prospective studies with larger populations are needed to validate our conclusions.

High SII values are independently associated with a high risk of in-hospital mortality in elderly patients with AMI. This index could be used as an easy, inexpensive, and practical predictor to identify high-risk elderly patients with AMI.

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