Prognostic value of systemic immune-inflammation index (SII) as a novel marker in patients with atrial fibrillation

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Abstract

Background Recently, inflammation plays an essential role in the prognosis of atrial fibrillation (AF) patients. Systemic immune-inflammation index (SII), reflecting the inflammation status, which is measured by the formula: neutrophil count × platelet count/lymphocyte count, is a powerful prognostic marker in several types of cancer and cardiovascular disease. However, no information regarding the prognostic value of SII in patients with AF is available. Methods and results We retrospectively enrolled 1768 AF patients in our study. Demographic characteristics, laboratory data and echocardiography were measured and collected on admission. The primary endpoints were death from all causes and death from cardiovascular diseases. The secondary endpoints were major bleeding and stroke. During a mean follow-up of 22.35 months, 155 patients occurred death from all causes. For further analysis, patients were categorized into two groups according to the optimal cutoff value of SII level determined by using receiver operating characteristics curve analysis. The incidence of death from all causes and death from cardiovascular diseases in high SII group is significantly higher compared with that in low SII group. However, no significant differences were detected between two groups for the secondary endpoints ($p>0.05$). On multivariable Cox analysis with adjustment of potential confounders, the risk of death from all causes and death from cardiovascular diseases increased by 77.6% and 51.2%, respectively, in high SII group. Conclusion Systemic immune-inflammation index was significantly associated poor outcomes and was an independent predictor for mortality in atrial fibrillation patients.

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Abstract

Background

Recently, inflammation plays an essential role in the prognosis of atrial fibrillation (AF) patients. Systemic immune-inflammation index (SII), reflecting the inflammation status, which is measured by the formula: neutrophil count × platelet count/lymphocyte count, is a powerful prognostic marker in several types of cancer and cardiovascular disease. However, no information regarding the prognostic value of SII in patients with AF is available.

Methods and results

We retrospectively enrolled 1768 AF patients in our study. Demographic characteristics, laboratory data and echocardiography were measured and collected on admission. The primary endpoints were death from all causes and death from cardiovascular diseases. The secondary endpoints were major bleeding and stroke. During a mean follow-up of 22.35 months, 155 patients occurred death from all causes. For further analysis, patients were categorized into two groups according to the optimal cutoff value of SII level determined by using receiver operating characteristics curve analysis (low SII group <451.01 or high SII group [?]451.01). The incidence of death from all causes and death from cardiovascular diseases in high SII group is significantly higher compared with that in low SII group, (14.3% vs. 5.3%,p <0.001; 9.3% vs. 3.8%, p <0.001, respectively). However, no significant differences were detected between two groups for the secondary endpoints (p >0.05). On multivariable Cox analysis with adjustment of potential confounders, the risk of death from all causes and death from cardiovascular diseases increased by 77.6% (hazard risk [HR]=1.776, 95% confidence interval [CI]: 1.109-3.065, p = 0.018) and 51.2% (HR=1.512, 95%CI: 1.011-3.742, p = 0.025), respectively, in high SII group.

Conclusion

Systemic immune-inflammation index was significantly associated poor outcomes and was an independent predictor for mortality in atrial fibrillation patients.

Key words systemic immune-inflammation index; atrial fibrillation; mortality; inflammation

Introduction

Worldwide, atrial fibrillation (AF) is one of the most prevalent cardiac arrhythmias in adults[1]. Owing to extended longevity and intensifying search for undiagnosed AF, approximately 4% experience AF in general population[2] and a 2.3-fold rise is expected[3]. AF, which is associated heart failure[4] and stroke[5], worsens patient quality of life[6] and increases significant burden to patients and societal health due to the high morbidity and mortality. Previous studies[7-11] have shown that inflammation is associated with AF development and progression in general population and patients after cardioversion, cardiac surgery and catheter ablation. Increasing evidence supports the essential role of inflammatory factors[10,12-14] in predicting the onset of AF and recurrence. Some inflammatory factors including platelet-to-lymphocyte ratio (PLR)[15,16], IL-6[17], IL-10[18] and high sensitivity C-reactive protein[19], were proven to be simple biomarkers to predict the incidence of AF in patients with or without history of AF. However, these biomarkers only involve one or two types of immune- inflammatory cells and may not accurately reflect inflammation status.

The systemic immune-inflammation index (SII) is a novel and integrated inflammatory index based on neutrophil, platelet and lymphocyte counts. SII was initially demonstrated to be associated with prognosis of various cancers, such as prostate cancer[20], hepatocellular carcinoma[21] and gastric cancer[22]. Up to now, the relationships of SII and coronary artery disease[23,24], heart failure[25] were reported by many studies. SII is now considered to comprehensively reflect inflammation status. However, the association between SII and AF still remains unclear. Therefore, we conducted this study to investigate the association between SII levels and AF to determine the prognostic value of SII in patients with AF.

Methods

Study design and population

Patients hospitalized for AF in the First Affiliated Hospital of Zhengzhou University from January 2017 to December 2019 were registered in this retrospective cohort study. Inclusion criteria were as follows: (1) age >18 years old; (2) history of symptomatic AF for at least 6 months and documented on electrocardiogram in the previous 1 year. Exclusion criteria were as follows: (1) patients with significant coronary artery disease verified by coronary angiogram; (2) congenital heart disease, valvular heart disease and serious dysfunction of kidney and liver; (3) suffering from infectious diseases and corticosteroid or nonsteroidal anti-inflammatory drug use in the previous 6 months; (4) patients with incomplete clinical data and unwilling or unable to commit to follow up requirements. The study protocol was approved by ethics committee. Because of the retrospective design of this study, the ethics committee waived the need of obtaining informed consent from all participants.

Data collection

The demographic characteristics and laboratory data were collected by reviewing patients' medical records. Echocardiography was performed on admission and left atrial diameter (LAD), left ventricular ejection fraction (LVEF) were obtained. Demographic characteristics included gender, age, race, height, weight, body mass index (BMI), smoking status, drinking, heart rate on admission and underlying disease. Peripheral blood samples were obtained by vacutainer tubes at the time of admission, after at least 12 hours of fasting. The following hematological parameters were measured using automated hematology analyzing devices: white blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), platelet count (PLT), differential white blood cell count (neutrophils, monocytes, lymphocytes, eosinophils and basophiles). Glucose, alanine aminotransferase (ALT), aspartic transaminase (AST), albumin, serum creatinine (Cr), uric acid (UA), blood urea nitrogen (BUN), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), estimated glomerular filtration rate (eGFR), D-dimer, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were also evaluated. Neutrophils, platelet count and lymphocytes were expressed as $x10^9$ cells/L. The SII was measured as neutrophil count x platelet count/lymphocyte count.

Outcome variables and follow-up

The primary endpoints were death from all causes and death from cardiovascular diseases. The secondary endpoints were major bleeding and stroke. The major bleeding events were characterized according to the Bleeding Academic Research Consortium definitions[26]types 2,3, or 5. Stroke was defined as a neurological deficit attributed to an acute focal injury of the central nervous system by vascular causes, including hemorrhage, embolism and thrombosis[5]. In our study, all participants were contacted and followed up by telephone. The mean follow-up time was 22.35 months.

Statistical analysis

For analysis, patients were categorized into two groups according to the optimal cutoff value of SII level determined by using receiver operating characteristics curve analysis (low SII group <451.01 or high SII group [?]451.01). The SPSS 22.0 software (IBM Corp., Armonk, NY) was used to perform all analyses. Continuous variables were reported as the mean +- standard deviation (SD) and categorical data were reported as frequencies and percentages. Differences in baseline characteristics between two groups were compared using a $\chi 2$ test or Fisher's exact test for categoric data and an independent t -test or Kruskal-Wallis test for continuous data, as appropriate. Kaplan-Meier survival curves were used for cumulative incidence rates of primary and secondary endpoints. The statistical differences between groups in Kaplan-Meier curves were determined using the log-rank test. The predictive value of SII level related to outcomes was assessed by the multivariable Cox regression model with adjustment for potential confounders, including age, diabetes mellitus, WBC, Hb, PLT, albumin, BUN, UA, Cr, HDL, eGFR, D-dimer, CRP, ESR, LAD and LVEF. The hazard ratios (HRs) and 95% confidence intervals (CIs) were also determined. All tests were 2-sided and a p value <0.05 was considered statistically significant.

Results

Baseline characteristics and outcomes

We initially enrolled 1851 patients with a diagnosis of atrial fibrillation who met the inclusion criteria. 35 patients were excluded because of incomplete SII data and 48 patients were excluded because they were lost to follow-up. Finally, a total of 1768 patients were selected to this study.

During a mean follow-up of 22.35 months, 155 cases of death from all causes occurred and 105 patients died from cardiovascular diseases. The baseline demographic characteristics and clinical data two groups are shown in Table 1. Patients in high SII group were older and more likely to have diabetes mellitus than patients in low SII group. Significant differences were detected in heart rate on admission, WBC, Hb, PLT, albumin, BUN, UA, Cr, HDL, eGFR, D-dimer, CRP, ESR, LAD and LVEF (all$p$ <0.05). Besides, the incidence of death from all causes in high SII group is 97 (14.3%) and in low SII group, it is 58 (5.3%) which is significantly different (p <0.001). The incidence of death from cardiovascular diseases between the two groups also showed a significant difference (9.3% vs. 3.8%,p <0.001). For the secondary endpoints, we did not find any difference in the incidence of major bleeding events and stroke ($p = 0.094$ and $p = 0.623$, respectively).

Kaplan-Meier survival curves for SII level and adverse outcomes are shown in Figure 1 and Figure 2. Compared with patients in low SII group, patients in high SII group showed a significantly increased risk of death from all causes and death from cardiovascular diseases (log rank$p < 0.001$ and $p = 0.001$).

After adjusting for potential cofounders, including age, diabetes mellitus, WBC, Hb, PLT, albumin, BUN, UA, Cr, HDL, eGFR, D-dimer, CRP, ESR and LAD, multivariable Cox regression analyses were performed to evaluate the prognostic value of SII and adverse outcomes. The risk of death from all causes and death from cardiovascular diseases increased by 77.6% (95% CI: 1.109-3.065, $p = 0.018$) and 51.2% (95% CI: 1.011-3.742, $p = 0.025$) in high SII group compared to that in low SII group, during the long-term follow-up (Table 2 and 3).

Discussion

This study mainly investigated the association between SII level and adverse outcomes in patients with AF, and tried to evaluate the prognostic value of SII as a new inflammatory factor in AF. The major finding was that high SII level was strongly associated with adverse outcomes and was an independent predictor for death from all causes and death from cardiovascular diseases in patients with AF. Our study is the first study to report the association and prognostic value of SII in patients with AF. This finding adds to current knowledge regarding the predictive relationship between SII and adverse outcomes in AF patients.

Previous studies[13,14,17,27] have established that inflammation plays a key role in development and progression of AF. Inflammatory factors, such as PLR[15], IL-6[17], IL-10[18] and CRP[19], were proven to be risk factors in AF and were potential predictors of prognosis in patients developed AF. As for SII, which combined neutrophil, lymphocyte and platelet count, serving as a detectable biomarker for systemic inflammatory activity and reflecting the inflammatory state[28]. Previously, SII emerged as a reliable and powerful predictor in various malignant diseases, including hepatocellular carcinoma[21], gastric cancer[22] and renal cell cancer[29]. Evidence is accumulating that SII level, apart from their well-known predictive value in cancer, were close related with in-hospital mortality in infective endocarditis[30] and the incidence of major cardiovascular events in coronary artery disease[23,31,32]. Until now, the association between SII level and AF is still unknown. Therefore, we utilized a novel predictor, SII, which was demonstrated to be significantly related to adverse outcomes in AF patients.

SII was measured based on the counts of three types of circulating immune cells: platelets, lymphocytes, and neutrophils. Our study showed that AF patients with high SII level had increased risk for mortality. Neutrophils, which constitute the largest proportion of leukocyte, are of great importance for initiating and modulating immune processes[33,34]. Lymphocytes are also an important component of white blood cells, mediate adaptive immunity and function in innate immunity. Both neutrophils and lymphocytes can mediate adaptive and innate immunity. Platelets could be considered as aspecific first line inflammatory biomarkers

which bind to leukocytes, influencing the function of inflammatory elements of these cells[35]. In several clinical studies, mediators of the inflammatory response were supported to be associated with remodeling of AF[36,37]. Inflammation can initiate AF, which subsequently generates an inflammatory response that further enhances atrial electrical and structural remodeling and perpetuates the arrhythmia.

Our study had several strengths. The sample size was relatively large to identify the significant association between SII and adverse outcomes in patients with AF. Moreover, we adjusted the potential confounders which might influence the prognostic value of SII in patients with AF. However, some limitations on this study also should be mentioned. First, because of the retrospective study design, results of our study need to be verified by multicenter, prospective studies. In addition, we only collected the baseline data of SII, rather than collecting data at multiple times.

Conclusion

Systemic immune-inflammation index was significantly associated poor outcomes and was an independent predictor for mortality in atrial fibrillation patients.

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Data availability statement

Due to confidentiality policies, data will not be shared.

Figure Legends

Figure 1 . Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of death from all causes. The X axis represents the follow-up time and the Y axis represents the Cumulative risk of death from all causes.

Figure 2. Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of death from cardiovascular diseases. The X axis represents the follow-up time and the Y axis represents the Cumulative risk of death from cardiovascular diseases.

Table 1 Baseline characteristics and clinical outcomes of patients with atrial fibrillation according to the SII level.

Variables	low SII group (n=1091)	high SII group (n=677)	$\chi 2$ or t	*P*
Age, years	65.55±11.24	66.94±11.50	2.552	0.011
Heart rate, beats/min	83.36±22.09	86.66±25.44	2.909	0.004
Male, n (%)	514 (47.1)	333 (49.2)	0.053	0.817
Smoking, n (%)	313 (28.7)	201 (29.7)	0.310	0.578
Drinking, n (%)	150 (17.8%)	180 (19.7%)	1.083	0.298
Hypertension, n (%)	408 (48.5)	476 (51.9)	2.093	0.148
Diabetes mellitus, n (%)	144 (17.1)	211 (23.1)	9.730	0.002
LAD, mm	44.37±10.04	45.64±15.40	1.954	0.049
LVEF, %	55.09±11.81	53.68±12.53	-2.364	0.018
WBC, 10^9/L	5.68±1.63	7.74±6.99	8.704	<0.001
RBC, 10^{12}/L	4.25±0.60	4.20±0.74	-2.005	0.045
Hemoglobin, g/L	131.47±20.40	128.35±22.85	-3.038	0.002
Platelet, 10^9/L	159.70±49.63	205.30±88.23	13.533	<0.001
BUN, mmol/L	7.03±3.59	9.20±1.17	6.054	<0.001
Cr, umol/L	80.57±32.36	103.26±83.78	7.598	<0.001
UA, umol/L	362.39±128.89	398.02±160.18	5.151	<0.001
Albumin, g/L	40.51±4.31	39.55±5.42	-4.073	<0.001
TC, mmol/L	3.60±1.04	3.71±3.20	0.928	0.354
TG, mmol/L	1.29±0.87	1.28±0.72	-0.393	0.695
HDL, mmol/L	1.12±0.62	1.04±0.32	-3.402	0.001
LDL, mmol/L	2.26±3.46	2.48±3.78	0.610	0.542
eGFR, ml/min	80.62±20.92	73.49±31.89	-2.268	0.024
D-dimer, ug/L	0.32±1.04	0.65±2.52	3.588	<0.001
CRP, mg/L	7.43±29.31	23.82±54.15	6.256	<0.001
ESR, mm/h	13.63±15.06	22.50±22.13	5.624	<0.001
Stroke, n (%)	49 (9.8)	43 (8.5)	0.148	0.700
Bleeding, n (%)	74 (8.7)	57 (6.2)	4.230	0.040
All-cause mortality, n (%)	58 (5.3)	97 (14.3)	27.700	<0.001
Cardiac mortality, n (%)	42 (3.8)	63 (9.3)	15.339	<0.001

Abbreviations: LAD, left atrial fibrillation; LVEF, left ventricular ejection fraction; WBC, white blood cell; RBC, red blood cell; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate;

Table 2Multivariate Cox regression analysis for death from all causes.

Variables	*B*	*SE*	*Wald*	*P*	*HR*	*95% CI*
Age	0.001	0.016	0.001	0.992	1.000	0.969 - 1.033
Diabetes mellitus	0.141	0.386	0.133	0.715	1.151	0.540 - 2.455
Heart rate	-0.012	0.008	2.623	0.105	0.988	0.973 - 1.003
LAD	0.033	0.015	4.877	0.027	1.033	1.004 - 1.063
LVEF	-0.033	0.013	7.071	0.008	0.967	0.944 - 0.991
WBC	-0.054	0.057	0.897	0.344	0.947	0.846 - 1.060
Hemoglobin	0.007	0.011	0.386	0.534	1.007	0.986 - 1.028
Platelet	-0.001	0.002	0.281	0.596	0.999	0.995 - 1.003
BUN	0.044	0.036	1.536	0.215	1.045	0.975 - 1.120
Cr	-0.003	0.004	0.784	0.376	0.997	0.989 - 1.004
UA	0.001	0.001	0.318	0.573	1.001	0.998 - 1.004
Albumin	-0.069	0.037	3.427	0.064	0.933	0.868 - 1.004
HDL	-0.475	0.627	0.575	0.448	0.622	0.182 - 2.124
eGFR	-0.008	0.011	0.550	0.458	0.992	0.972 - 1.013
D-dimer	0.368	0.184	4.003	0.045	1.445	1.008 - 2.071
CRP	-0.002	0.003	0.348	0.555	0.998	0.993 - 1.004
ESR	0.006	0.008	0.656	0.418	1.006	0.991 - 1.022
SII	1.789	0.727	5.621	0.018	1.776	1.109 - 3.065

Table 3 Multivariate Cox regression analysis for death from cardiovascular causes.

Variables	*B*	*SE*	*Wald*	*P*	*HR*	*95% CI*
Age	0.016	0.020	0.619	0.432	1.016	0.977 - 1.056
Diabetes mellitus	0.382	0.430	0.789	0.374	1.466	0.631 - 3.407
Heart rate	-0.004	0.009	0.200	0.655	0.996	0.978 - 1.014
LAD	0.023	0.019	1.419	0.234	1.023	0.986 - 1.062
LVEF	-0.042	0.016	7.041	0.008	0.959	0.930 - 0.989
WBC	-0.052	0.070	0.556	0.456	0.949	0.828 - 1.088
Hemoglobin	0.003	0.013	0.041	0.839	1.003	0.978 - 1.028
Platelet	-0.001	0.003	0.122	0.727	0.999	0.994 - 1.004
BUN	0.059	0.040	2.119	0.145	1.061	0.980 - 1.148
Cr	-0.005	0.005	1.260	0.262	0.995	0.986 - 1.004
UA	0.002	0.002	1.240	0.266	1.002	0.999 - 1.005
Albumin	-0.092	0.045	4.124	0.042	0.912	0.835 - 0.997
HDL	0.023	0.776	0.001	0.977	1.023	0.224 - 4.681
eGFR	-0.001	0.013	0.004	0.950	0.999	0.974 - 1.025
D-dimer	0.106	0.302	0.124	0.725	1.112	0.615 - 2.010
CRP	-0.001	0.003	0.169	0.681	0.999	0.992 - 1.005
ESR	0.006	0.009	0.410	0.522	1.006	0.988 - 1.024
SII	2.147	0.962	4.996	0.025	1.512	1.011 - 3.742

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Table 3.docx available at https://authorea.com/users/733001/articles/710988-prognostic-value-of-systemic-immune-inflammation-index-sii-as-a-novel-marker-in-patients-with-atrial-fibrillation