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Association between inflammation markers and all-cause mortality in critical ill patients with atrial fibrillation: Analysis of the Multi-Parameter Intelligent Monitoring in Intensive Care (MIMIC-IV) database

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ABSTRACT

Background: Inflammation is related to cardiovascular disease. Among the many inflammatory markers, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII) were considered as novel predictors for atherosclerosis outcomes. We aimed to investigate the impact of these inflammatory markers on the prognosis of patients with atrial fibrillation (AF).

Methods: We obtained data on AF patients from the Medical Information Mart for Intensive Care (MIMIC)-IV database. These patients were classified into two groups based on their survival status within 30 days. Then, they were divided into three groups based on the tertile of baseline NLR, PLR, and SII, respectively. We comprehensively explored the relationship between those inflammatory indicators and all-cause mortality in patients with AF by Kaplan-Meier analysis, multivariate Cox regression analysis, receiver operating characteristic (ROC) analyses, restricted cubic spline regression (RCS), and subgroup analysis.

Results: A total of 4562 patients with AF were included. Statistically significant differences were found between survivor and non-survivor groups for NLR, PLR and SII. Patients in the high tertile of the NLR had a higher mortality rate than those in the low and intermediate tertiles, as did patients in the PLR and the SII. NLR, PLR and SII were independently associated with increased risk of all-cause mortality. RCS showed that the 30-day and 365-day risk of death were linearly associated with increases in NLR, PLR, and SII, respectively.

Conclusion: NLR, PLR, and SII have the potential to be used as indicators for stratifying the risk of mortality in critically ill patients with AF.

1. Introduction

Atrial fibrillation (AF) is one of the most common persistent cardiac arrhythmias [1,2]. There are currently 330 million people with AF worldwide, and the incidence of AF rises with age, reaching more than 10 % of people >80 years of age [2–4]. AF can increase the all-cause mortality of the population by 1.5–3.5 folds, bringing more obvious health effects and economic burden to patients and families, and it has become a global public health problem that needs to be solved urgently [3,5]. The development of AF is closely linked to inflammation [6,7]. The activated inflammasome has been observed in individuals diagnosed with AF and in animal models of AF [8]. In an inflammatory environment, immune-inflammatory cells infiltrate the atria and produce a large number of inflammatory mediators that cause damage to cardiomyocytes and promote fibroblast activation, which not only secrete collagen, but also release pro-inflammatory cytokines, which then induce inflammation and fibrosis, accelerating the formation of AF [9].

The immune system consists of two primary cell types: neutrophils and lymphocytes. Neutrophil counts indicate the duration of inflammation, while lymphocyte counts indicate the pathways involved in immune regulation. The Neutrophil to Lymphocyte Ratio (NLR) may provide a more accurate reflection of the various inflammatory conditions in the body [10,11]. Platelet-lymphocyte ratio (PLR) reflects the

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balance between platelet and lymphocyte levels in the organism, is a marker of whether platelets are bound or not, and represents the occurrence of thrombosis and pre-thrombotic states in the organism. It is a marker of inflammation derived in recent years and is used in the assessment of many inflammatory and cardiovascular diseases, such as coronary heart disease, myocardial infarction [12–14]. The Systemic Immune Inflammatory Index (SII) has emerged as a reliable and consistent novel marker of inflammation, capable of indicating both the localized immune response and the overall systemic inflammatory response within the body. This composite parameter, which combines platelets, neutrophils, and lymphocytes, provides a more comprehensive picture of the body's inflammatory state than a single inflammatory index [15].

Recently, it has been shown that NLR correlates with the development, maintenance, and prognosis of AF [16–18]. PLR can predict asymptomatic cerebral infarction in paroxysmal AF, whereas CRP and ESR are not associated with asymptomatic cerebral infarction in AF [14,19]. In patients with diabetes and AF, there was a direct association between SII and recurrence following the initial catheter ablation [20]. However, there is no available report on the impact of NLR, PLR, and SII on forecasting both near- and long-term prognosis in patients with AF.

2. Methods

2.1. Source of data

All the information in this research is acquired from the MIMIC III database, a vast and openly accessible database created and overseen by the MIT Computational Physiology Laboratory. The database contains data on every person admitted to the Intensive Care Unit (ICU) at Beth Israel Deaconess Medical Center (BIDMC) during the period of 2001-2012. The recorded information includes the duration of each patient's stay, laboratory tests, medication treatment, vital signs, and other detailed data. To ensure the confidentiality of patient data, all personal information is anonymized by substituting patient identification with random codes, eliminating the need for patient consent and ethical approval.

2.2. Population selection criteria

The study was conducted in patients with AF who were first admitted to the hospital. Based on the ICD-9 codes, a grand total of 12,256 patients with AF were identified. Following additional screening, patients who satisfy the subsequent conditions will be disqualified: (1) patients admitted with AIDS, metastatic solid tumor, sever liver disease, malignant cancer, paraplegia, acute kidney injury and dialysis; (2) patients lacking documented blood neutrophil, lymphocyte, and platelet information within 24 h of admission. In the end, a total of 4562 participants were registered for this research (Fig. 1).

2.3. Data extraction

Structured Query Language (SQL) with PostgreSQL (version 9.6) was utilized to extract all variables from the MIMIC III database. The variables examined in our study encompassed several categories: (1) Demographics, which included age, gender, and weight; (2) past medical history, encompassing conditions such as Hypertension, Diabetes, Myocardial infarction, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Dementia, Chronic obstructive pulmonary disease (COPD), Peptic ulcer disease, Renal disease, Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Grafting (CABG), Cardiac arrest, and Cardiogenic shock; (3) clinical treatment, involving the use of Amiodarone, Aspirin, Statin, Clopidogrel, Beta-blockers, ACE inhibitor and ARB, Digitalis, Diuretics, Norepinephrine,

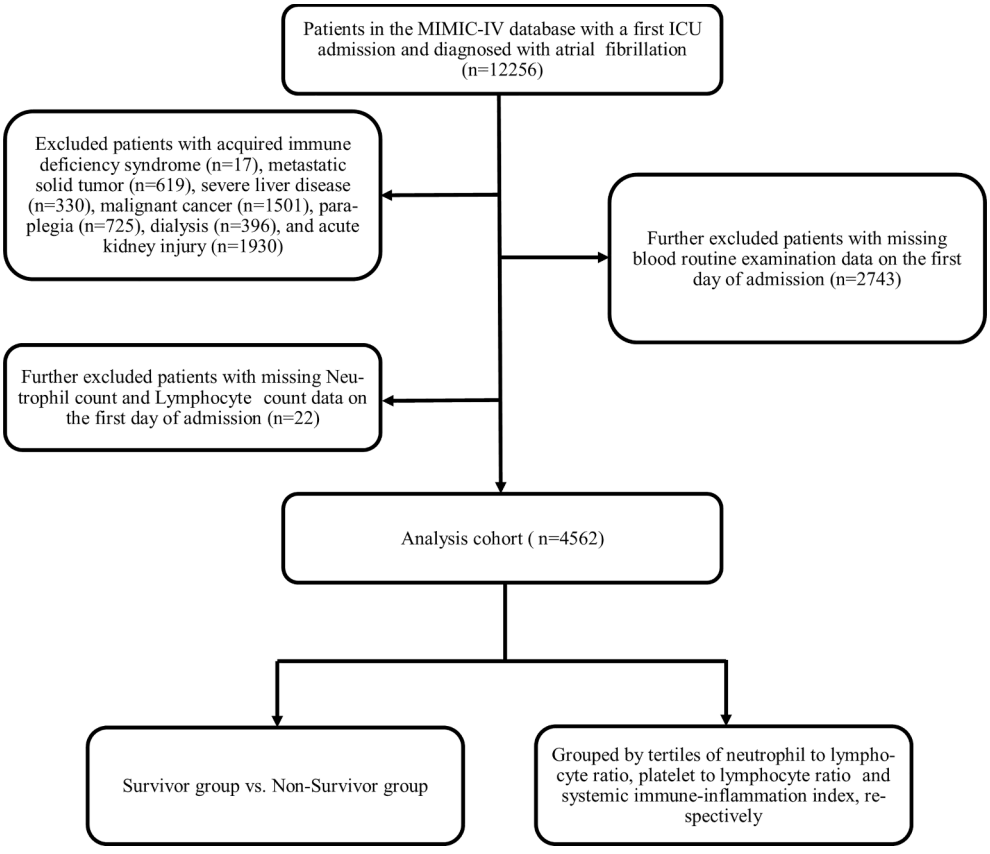

Fig. 1. Flow of included patients through the trial.

Phenylephrine, Vasopressin, Epinephrine, Dopamine, and Dobutamine; (4) vital signs, including temperature (T), respiratory rate (RR), heart rate (HR), mean blood pressure (MBP), systolic blood pressure (SBP), and diastolic blood pressure (DBP); (5) laboratory indicators, encompassing SaO2, PaO2, PaCO2, bicarbonate (HCO^{3-}), BE, anion gap (AG), lactate, PH, red blood cell (RBC), hemoglobin, white blood cell (WBC), neutrophils, lymphocytes, platelet, urea nitrogen, creatinine, glucose, sodium, potassium, calcium, chloride. Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment (SOFA) score, and Oxford Acute Severity of Illness Score (OASIS). The initial measurement of all blood biochemical variables was taken after admission to the hospital and before the patient received any therapy.

2.4. Grouping and outcome events

Patients were categorized into survival and non-survival groups based on whether they survived 30 or 365 days to compare the prognostic impact of inflammation levels on patients with AF. Then patients were divided into three groups based on tertiles of baseline NLR level, PLR level, and SII level. The endpoint was to analyze all-cause mortality in patients with AF at 30 and 365 days.

2.5. Statistical analysis

We evaluated the normal distribution of continuous variables using the Kolmogorov-Smirnov test. Mean ± SD was used to express continuous variables that were normally distributed, and those that were not normally distributed were expressed as interquartile spacing (IQR). For categorical variables, they were expressed as numbers (%). When analyzing characteristics at baseline, comparisons of continuous variables were made using the *t*-test or one-way ANOVA, while comparisons of categorical variables were made using Pearson's $\chi 2$ test and Fisher's test. To explore the relationship between inflammation metrics and clinical outcomes, we also performed adjusted and unadjusted model analyses of baseline inflammation metrics (as categorical metrics in tertiles) and endpoints using Cox regression analysis. Next, Survival curves were plotted using the Kaplan-Meier method and the groups were compared using the log-rank test. To evaluate the prognostic capability of NLR, PLR, and SII for 30-day mortality upon admission, the Receiver Operating Characteristic (ROC) analysis was employed. Moreover, a subgroup analysis was conducted to examine the impact of NLR, PLR, and SII on various subgroups, such as gender, age, heart failure, dementia, COPD, renal disease, CABG, and cardiogenic shock. R Studio was used for all the analyses. A statistically significant result is indicated by a two-tailed test with $P < 0.05$.

3. Results

3.1. Baseline characteristics

The study included 4562 patients who were critically ill and had AF. The median age of the enrolled participants was 76 years (IQR: 67–84), of which 409 (60.41 %) were male. The median values of NLR, PLR and SII were 6.85 (IQR: 4.10–12.13), 143.45 (IQR: 81.28–259.79) and 1217.93 (IQR: 629.48–2575.55), respectively. The mortality rates patients within 30-day and 365-day were 12.25 % and 25.69 %, respectively. Table 1 shows the differences in baseline characteristics between those who survived and those who did not at 30 days. In the non-survivor group, there was a higher proportion of males, higher disease severity scores, often combined heart failure, and higher levels of creatinine, RBC, platelet, and WBC. The NLR, PLR and SII levels were considerably elevated in the non-survivor group compared to the survivor group (6.40 vs. 11.04, $P < 0.001$, 134.35 vs. 240.54, $P < 0.001$, 1109.08 vs. 2297.55, $P < 0.001$, respectively). Baseline clinical characteristics of patients stratified by 365-day survival status were summarized in Supplementary Table 1. In the non-survivor group, the levels

Table 1
Baseline characteristics between survivors and non-survivors by 30-day survival status.

Variables	Overall(N = 4562)	30-d survivors (N = 4003)	30-d non-survivors (N = 559)	P value
Age (year)	76 [67, 84]	75 [67, 83]	83 [75, 89]	<0.001
Gender (%)				<0.001
Female	1806 (39.59)	1541 (38.50)	265 (47.41)	
Male	2756 (60.41)	2462 (61.50)	294 (52.59)	
Weight (kg)	79.00 [66.50, 94.18]	80.00 [67.40, 95.00]	70.80 [59.55, 86.75]	<0.001
Aspirin (%)				<0.001
No	1369 (30.01)	1103 (27.55)	266 (47.58)	
Yes	3193 (69.99)	2900 (72.45)	293 (52.42)	
Clopidogrel (%)				0.840
No	4031 (88.36)	3539 (88.41)	492 (88.01)	
Yes	531 (11.64)	464 (11.59)	67 (11.99)	
Statin (%)				<0.001
No	1803 (39.52)	1510 (37.72)	293 (52.42)	
Yes	2759 (60.48)	2493 (62.28)	266 (47.58)	
Betablocker (%)				<0.001
No	646 (14.16)	489 (12.22)	157 (28.09)	
Yes	3916 (85.84)	3514 (87.78)	402 (71.91)	
Amiodarone (%)				<0.001
No	2775 (60.83)	2390 (59.71)	385 (68.87)	
Yes	1787 (39.17)	1613 (40.29)	174 (31.13)	
ACEI/ARB (%)				0.163
No	4160 (91.19)	3641 (90.96)	519 (92.84)	
Yes	402 (8.81)	362 (9.04)	40 (7.16)	
Digitalis (%)				0.001
No	4012 (87.94)	3545 (88.56)	467 (83.54)	
Yes	550 (12.06)	458 (11.44)	92 (16.46)	
Diuretics (%)				<0.001
No	938 (20.56)	791 (19.76)	147 (26.30)	
Yes	3624 (79.44)	3212 (80.24)	412 (73.70)	
Norepinephrine (%)				<0.001
No	3679 (80.64)	3286 (82.09)	393 (70.30)	
Yes	883 (19.36)	717 (17.91)	166 (29.70)	
Phenylephrine (%)				<0.001
No	3280 (71.90)	2822 (70.50)	458 (81.93)	
Yes	1282 (28.10)	1181 (29.50)	101 (18.07)	
Vasopressin (%)				<0.001
No	4308 (94.43)	3800 (94.93)	508 (90.88)	
Yes	254 (5.57)	203 (5.07)	51 (9.12)	
Dopamine (%)				<0.001
No	4415 (96.78)	3889 (97.15)	526 (94.10)	
Yes	147 (3.22)	114 (2.85)	33 (5.90)	
Epinephrine (%)				<0.001
No	4113 (90.16)	3578 (89.38)	535 (95.71)	
Yes	449 (9.84)	425 (10.62)	24 (4.29)	
Dobutamine (%)				<0.001

(*continued on next page*)

Table 1 (*continued*)

Variables	Overall(N = 4562)	30-d survivors (N = 4003)	30-d non-survivors (N = 559)	P value
No	4491 (98.44)	3955 (98.80)	536 (95.89)	
Yes	71 (1.56)	48 (1.20)	23 (4.11)	
CCI (score)	6 [5,7]	6 [4,7]	6 [5,8]	<0.001
Diabetes (%)				
No	3114 (68.26)	2724 (68.05)	390 (69.77)	0.442
Yes	1448 (31.74)	1279 (31.95)	169 (30.23)	
Hypertension (%)				
No	1064 (23.32)	926 (23.13)	138 (24.69)	0.447
Yes	3498 (76.68)	3077 (76.87)	421 (75.31)	
MI (%)				
No	3435 (75.30)	3048 (76.14)	387 (69.23)	0.001
Yes	1127 (24.70)	955 (23.86)	172 (30.77)	
HF (%)				
No	2408 (52.78)	2171 (54.23)	237 (42.40)	<0.001
Yes	2154 (47.22)	1832 (45.77)	322 (57.60)	
Cerebrovascular disease (%)				
No	3868 (84.79)	3444 (86.04)	424 (75.85)	<0.001
Yes	694 (15.21)	559 (13.96)	135 (24.15)	
Dementia (%)				
No	4319 (94.67)	3833 (95.75)	486 (86.94)	<0.001
Yes	243 (5.33)	170 (4.25)	73 (13.06)	
COPD (%)				
No	3198 (70.10)	2829 (70.67)	369 (66.01)	0.027
Yes	1364 (29.90)	1174 (29.33)	190 (33.99)	
Renal disease (%)				
No	3435 (75.30)	3055 (76.32)	380 (67.98)	<0.001
Yes	1127 (24.70)	948 (23.68)	179 (32.02)	
Cardiac arrest (%)				
No	4426 (97.02)	3920 (97.93)	506 (90.52)	<0.001
Yes	136 (2.98)	83 (2.07)	53 (9.48)	
Cardiogenic shock (%)				
No	4230 (92.72)	3757 (93.85)	473 (84.62)	<0.001
Yes	332 (7.28)	246 (6.15)	86 (15.38)	
CABG (%)				
No	3590 (78.69)	3046 (76.09)	544 (97.32)	<0.001
Yes	972 (21.31)	957 (23.91)	15 (2.68)	
Lactate (mmol/l)	1.60 [1.10, 2.20]	1.50 [1.10, 2.10]	2.00 [1.40, 3.10]	<0.001
PH	7.38 [7.33, 7.42]	7.39 [7.34, 7.42]	7.36 [7.28, 7.42]	<0.001
SaO2 (mmHg)	96 [89, 98]	96 [91, 98]	95 [72, 98]	<0.001
PaO2 (mmHg)	148 [63, 352]	170 [66, 365]	91 [48, 180]	<0.001
PaCO2 (mmHg)	41 [37,47]	41 [37,47]	43 [36,51]	0.006
PaO2/FiO2	230.00 [125.00, 336.00]	236.00 [129.00, 338.33]	193.00 [96.57, 321.50]	<0.001
Base excess (mmol/l)	0.00 [−2.00, 2.00]	0.00 [−2.00, 2.00]	0.00 [−5.00, 2.00]	0.001
Anion gap (mmol/l)	14 [12,17]	14 [12,17]	16 [14,19]	<0.001
Bicarbonate (mmol/l)	23 [21,26]	23 [21,25]	23 [20,27]	0.862
BUN (mg/dl)	21 [15,34]	21 [15,32]	31 [20,50]	<0.001
Calcium (mg/dl)	8.40 [7.90, 8.90]	8.40 [7.90, 8.90]	8.50 [8.00, 9.00]	0.045
Chloride (mmol/l)	104 [100, 108]	105 [100, 108]	102 [98, 106]	<0.001
Creatinine (mg/dl)	1.00 [0.80, 1.40]	1.00 [0.80, 1.40]	1.30 [0.90, 1.90]	<0.001
Glucose (mg/dl)	127 [107, 160]	125 [107, 156]	142 [112, 193]	<0.001
Sodium (mmol/l)	139 [136, 141]	139 [136, 141]	139 [136, 142]	0.035
Potassium (mmol/l)	4.30 [3.90, 4.70]	4.30 [3.90, 4.70]	4.40 [3.90, 5.00]	0.007
WBC (10^9/L)	11.20 [8.10, 15.40]	11.10 [8.10, 15.20]	12.10 [8.55, 17.40]	<0.001
Hemoglobin (g/dL)	10.70 [9.00, 12.50]	10.60 [9.00, 12.50]	11.20 [9.20, 12.00]	0.003
RBC (10^12/L)	3.57 [3.01, 4.17]	3.55 [3.00, 4.15]	3.72 [3.14, 4.28]	<0.001
Platelets (10^9/L)	183 [134, 246]	178 [132, 242]	209 [161, 283]	<0.001
Lymphocytes (10^9/L)	1.28 [0.80, 1.94]	1.35 [0.86, 2.00]	0.88 [0.56, 1.38]	<0.001
Neutrophils (10^9/L)	9.13 [6.27, 12.92]	9.00 [6.20, 12.64]	10.21 [7.03, 14.88]	<0.001
NLR	6.85 [4.10, 12.13]	6.40 [3.96, 11.09]	11.04 [6.60, 20.00]	<0.001
PLR	143.45 [81.28, 259.79]	134.35 [76.88, 241.09]	240.54 [137.20, 386.81]	<0.001
SII	1217.93 [629.48, 2575.55]	1109.08 [597.28, 2305.04]	2297.55 [1271.63, 4670.29]	<0.001
OASIS (score)	33 [27,39]	32 [27,38]	40 [34,47]	<0.001
SAPSII (score)	37 [31,45]	37 [31,44]	45 [37,54]	<0.001
SOFA (score)	5 [3,7]	5 [3,7]	7 [4,10]	<0.001
HR (bpm)	82[73, 93]	81 [73, 92]	87 [76, 100]	<0.001
SBP (mmHg)	113 [106, 123]	114 [106, 123]	112 [104, 125]	0.098
DBP (mmHg)	59 [54, 66]	59 [54, 66]	60 [53, 67]	0.936
MBP (mmHg)	75 [70, 81]	75 [70, 81]	74 [68, 82]	0.016
Temperature (℃)	36.7 [36.5, 37.0]	36.7 [36.5, 37.0]	36.8 [36.5, 37.1]	0.024
RR (bpm)	19 [17,21]	19 [17,21]	21 [18,23]	<0.001

Data are Median (interquartile range), or number (%) of patients. ACEI/ARB, Angiotensin Converting Enzyme Inhibitors/Angiotonin Receptor Blocker; CCI, Charlson Comorbidity Index; COPD, Chronic Obstructive Pulmonary Disease; HF, Heart Failure; MI, Myocardial Infarction; CABG, Coronary Angioplasty Bypass Grafting; WBC, White Blood Cell; SII, Systemic Immune Inflammation Index; PLR, Platelet to Lymphocyte Ratio; NLR, Neutrophil to Lymphocyte Ratio; RBC, Red Blood Cell; SOFA, Sequential Organ Failure Assessment; SAPSII, Simplified Acute Physiology Score II; OASIS, Oxford Acute Severity of Illness Score; HR, Heart Rate; RR, Respiratory Rate; MBP, Mean Blood Pressure; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

of NLR, PLR, and SII were also significantly elevated compared to the survivor group (6.00 vs. 9.67, $P < 0.001$, 123.51 vs. 218.19, $P < 0.001$, 1041.51 vs. 1907.30, $P < 0.001$, respectively).

Then, patients were divided into three groups based on NLR tertiles, PLR tertiles and SII tertiles, respectively, in order to observe the relationship between these inflammatory indicators and prognosis. The Supplementary Table 3 displayed the baseline characteristics of critically ill patients with AF, categorized into three groups based on the NLR tertiles. Compared to the lower group, patients in the top third of NLR exhibited elevated lactate levels, greater severity of illness scores upon admission, often in combination with heart failure, dementia, COPD, renal disease, and cardiogenic shock, higher mortality rates, and elevated WBC levels. Compared to individuals in the lower tertile of NLR, those in the higher tertile had higher mortality (both 30-day and 365-day, for all $P < 0.001$). The PLR and SII tertile grouping results were similar to NLR tertile grouping results. (Supplementary Table 4 and Supplementary Table 5).

3.2. Primary outcomes

The Kaplan-Meier analysis indicated that individuals with an elevated NLR, PLR, or SII faced an increased likelihood of mortality from any cause within either a 30-day or 365-day (log-rank $P < 0.001$ for all, as shown in Fig. 2). Correlations between NLR, PLR, SII and mortality were tested respectively using Cox proportional hazards analysis. Our findings indicated that patients in the upper tertile of NLR faced a significantly higher hazard of death within 30 days in all four established Cox proportional hazards models: unadjusted model 1 [hazard ratios [HR], (95 % confidence intervals [CI]) 4.15 (3.26–5.28) $P < 0.001$], partially adjusted model 2 [HR (95 % CI) 3.62 (2.84–4.61) $P < 0.001$], partially adjusted model 3 [HR (95 % CI) 2.44 (1.91–3.13) $P < 0.001$], and fully adjusted model 4 [HR (95 % CI) 1.88 (1.45–2.42) $P < 0.001$], when compared to individuals in the lowest tertile (Table 2). Additionally, the high NLR group was found to be an independent factor affecting the risk of mortality within 365 days in the four established Cox proportional hazards models. These models include the unadjusted model 1 [HR (95 % CI) 2.91 (2.51–3.39) $P < 0.001$], partly adjusted model 2 [HR (95 % CI) 2.58 (2.22–3.00) $P < 0.001$], partly adjusted model 3 [HR (95 % CI) 1.73 (1.48–2.02) $P < 0.001$], and fully adjusted model 4 [HR (95 % CI) 1.39 (1.18–1.63) $P < 0.001$]. These results were observed when comparing the high NLR group to subjects in the lowest tertile (Supplementary Table 2). Similar results were observed in the multivariate Cox proportional risk analysis of PLR, SII and mortality (Table 2 and Supplementary Table 2). ROC curves showed that the SII had a higher predictive value for 30-day mortality in AF patients compared to NLR, and there was no significant difference between SII and PLR (AUC 95 % CI, 0.69 (0.67–0.71) vs. 0.68 (0.65–0.70), $P = 0.037$; vs. 0.68 (0.66–0.71), $P = 0.574$) (Fig. 3). Nevertheless, the prognostic significance of SII for one-year mortality in individuals with AF is lower than that of PLR, and there is no significant difference compared to NLR (AUC 95 % CI, 0.66 (0.64–0.67) vs. 0.67 (0.66–0.69), $P = 0.001$; vs. 0.65 (0.63–0.67), $P = 0.057$) (Fig. 3). The predictive value of PLR for 30-day mortality in patients with AF was not different from NLR (AUC 95 % CI, 0.68 (0.65–0.70) vs. 0.68 (0.66–0.71), $P = 0.386$). However, the predictive value of PLR for 365-day mortality in patients with AF was better than that of NLR (AUC 95 % CI, 0.67 (0.66–0.69) vs. 0.65 (0.63–0.67), $P < 0.001$) (Fig. 3). Furthermore, analysis using restricted cubic spline regression showed that the 30-day and 365-day risk of death were linearly associated with increases in NLR, PLR, and SII, respectively (P for non-linearity ≤ 0.001, all) (Fig. 4). Patients with AF had an increased 30-day risk of death when the NLR exceeded 3.15 and the PLR exceeded 58.67. The 365-day risk of death in patients with AF was increased when the NLR exceeded 4.38 and the PLR exceeded 55.81. When SII exceeded 488.99, patients with AF had an increased risk of death at both 30 and 365 days.

3.3. Subgroup analysis

The NLR, PLR, and SII risk stratification measures for the primary outcomes were performed for the different subgroups of enrolled participants (including gender, age, heart failure, dementia, COPD, renal disease, CABG, and cardiogenic shock) (Figs. 5, 6, and 7). Regardless of gender, age, heart failure, COPD, kidney disease, CABG, and cardiogenic shock, a higher tertile of NLR was found to be significantly linked to an increased risk of death at 30-day and 365-day in AF patients. In AF patients without dementia, a higher tertile of NLR showed a significant association with increased risk of mortality at 30 and 365 days [HR (95 % CI) 4.53(3.49–5.89), HR (95 % CI) 3.05(2.60–3.59), respectively] (Fig. 5 and Supplementary Fig. 1). Similarly, regardless of gender, age, heart failure, COPD, renal disease, CABG, or cardiogenic shock, the uppermost tertile of PLR and SII exhibited a substantial correlation with an increased likelihood of 30 days and 365 days mortality in patients with AF. In AF patients without dementia, higher PLR was accompanied by higher 30-day and 365-day risk of death [HR (95 % CI) 5.28 (4.00–6.99), HR (95 % CI) 4.31(3.61–5.16), respectively], as for SII [HR (95 % CI) 4.98(3.80–6.54), HR (95 % CI) 3.22(2.73–3.79), respectively] (Figs. 6, 7 and Supplementary Figs. 2 and 3).

4. Discussion

In recent times, numerous clinical investigations have explored the correlation between the marker of inflammation and the incidence and death rate of cardiovascular disease in the overall population or different groups of patients [21–25]. However, few studies have

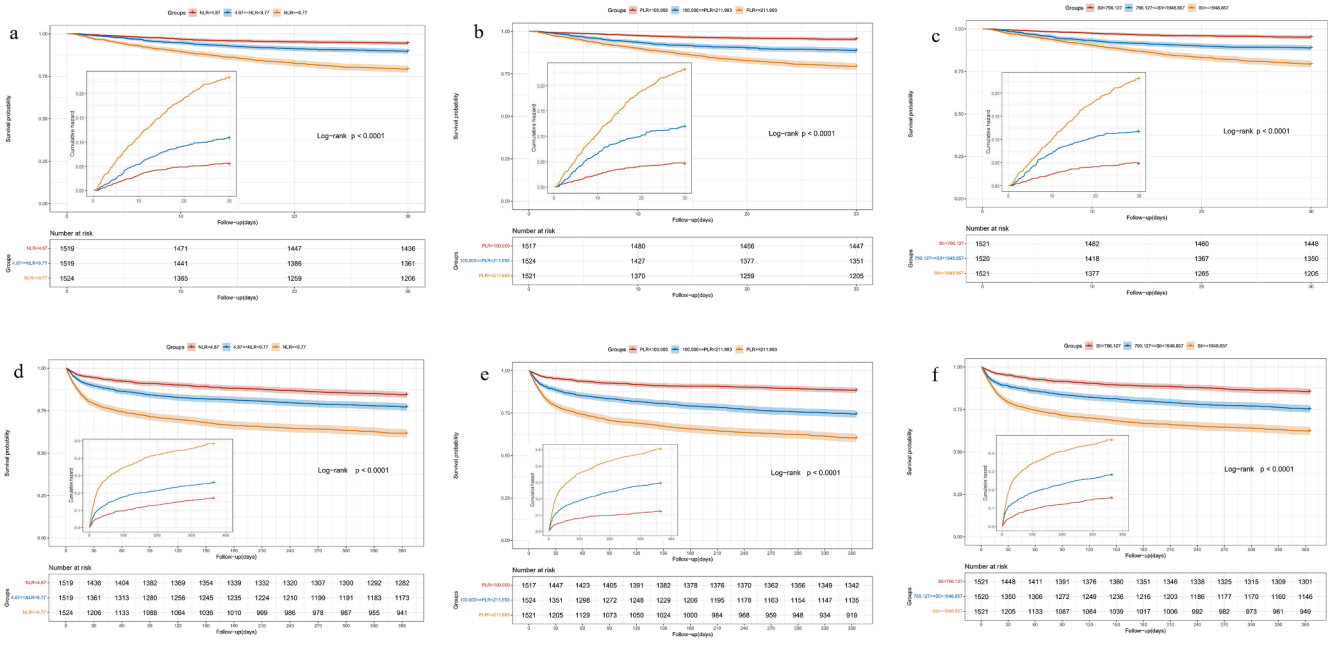

Fig. 2. Cumulative incidence and Kaplan-Meier curve of all-cause mort ality stratified by inflammation marker levels. (a), (b), (c) 30-day mortality stratified by NLR, PLR and SII levels, respectively. (d), (e), (f) 365-day mortality stratified by NLR, PLR and SII levels, respectively. Cumulative survival rates were calculated by the Kaplan-Meier method and compared with the log-rank test.

Table 2
Cox proportional hazard models for 30-day all-cause mortality.

Variables	Q1	NLR Q2		NLR Q3		PLR Q2		PLR Q3		SII Q2		SII Q3	
		HR (95 %CI)	P	HR (95 %CI)	P	HR (95 %CI)	P	HR (95 %CI)	P	HR (95 %CI)	P	HR (95 %CI)	P
Model 1	Ref.	1.95(1.50–2.54)	<0.001	4.15(3.26–5.28)	<0.001	2.56(1.94–3.37)	<0.001	4.90(3.78–6.34)	<0.001	2.43(1.84–3.19)	<0.001	4.69(3.64–6.05)	<0.001
Model 2	Ref.	1.96(1.50–2.55)	<0.001	3.62(2.84–4.61)	<0.001	2.23(1.69–2.95)	<0.001	3.83(2.95–4.99)	<0.001	2.36(1.80–3.11)	<0.001	4.05(3.13–5.23)	<0.001
Model 3	Ref.	1.70(1.30–2.22)	<0.001	2.44(1.91–3.13)	<0.001	1.49(1.12–1.99)	0.006	2.25(1.71–2.96)	<0.001	1.84(1.39–2.42)	<0.001	2.60(2.00–3.38)	<0.001
Model 4	Ref.	1.51(1.16–1.98)	0.003	1.88(1.45–2.42)	<0.001	1.35(1.01–1.80)	0.042	1.79(1.36–2.37)	<0.001	1.58(1.19–2.08)	0.001	1.92(1.47–2.51)	<0.001

Model 1: Variables.
Model 2: Variables, Age, Sex.
Model 3: Variables, Age, Sex, Aspirin used, Betablocker used, Amiodarone used, Digitalis used, Diuretics used, Norepinephrine used, Phenylephrine used, Epinephrine used, Statin used, Congestive heart failure, Dementia, COPD, Renal disease, CABG, Cardiogenic shock, Charlson comorbidity index.
Model 4: Variables, Age, Sex, Aspirin used, Betablocker used, Amiodarone used, Digitalis used, Diuretics used, Norepinephrine used, Phenylephrine used, Epinephrine used, Statin used, Congestive heart failure, Dementia, COPD, Renal disease, CABG, Cardiogenic shock, Charlson comorbidity index, Weight, RR, Temperature, DBP, HR, Sodium, Glucose, Creatinine, Chloride, Calcium, Pao2/fio2, PH, SAPSII.

documented a correlation between inflammatory markers and death in critically ill individuals with AF. In the present study, we evaluated the correlation between the inflammation indicator (NLR, PLR, and SII) and prognosis in a group of critically ill individuals with AF from a cohort in the United States. The findings of this research suggested that an elevated marker of inflammation was linked to mortality from all-cause within 30 days and 365 days in critically ill patients diagnosed with AF. Despite corrected for confounding risk factors, the presence of the inflammation marker remained significantly linked to mortality rates at both 30-day and 365-day intervals. Therefore, the indicator of inflammation could potentially serve as a valuable tool for healthcare professionals when making decisions, and it could also act as a risk factor on its own in critically ill individuals with AF.

Up to now, the precise mechanism of AF remains unclear. However, it is widely accepted that inflammation plays a crucial part in the development and maintenance of AF and has been proven to be associated with metabolic disorders [26,27], atherosclerotic disease [28–30], and AF [9,27]. A mendelian randomization study has demonstrated a causal relationship between peripheral lymphocyte counts, especially $CD4^+$ T cells, and AF [31]. A *meta*-analysis indicated that elevated levels of NLR were linked to a higher likelihood of AF recurrence and incidence [32]. In another research, it was found that NLR had a connection with the occurrence of new-onset AF in individuals diagnosed with acute myocardial infarction [33]. In a study that followed a group of patients over time, researchers examined the significance of PLR levels in predicting the recurrence of AF and found that PLR could serve as a cost-effective and valuable indicator for recurrence in individuals with nonvalvular persistent AF who underwent electrical cardioversion within a 6-month period [34]. Patients with elevated preoperative PLR were at higher risk of developing AF after CABG surgery [35]. Additionally, the current investigation revealed a correlation between elevated PLR tertiles and the likelihood of 30-day mortality in AF patients who underwent CABG. Nevertheless, another investigation indicated that there was no correlation between increased preoperative PLR and postoperative AF in individuals who underwent CABG surgery [36].

Research has indicated that SII is a more accurate forecaster for malignant ventricular arrhythmias that occur during hospitalization in individuals with ST-segment elevation myocardial infarction (STEMI) compared to inflammatory indicators like neutrophil count, CRP, albumin, and CRP to albumin ratio [37]. The sensitivity and specificity of SII for the prediction of new-onset AF after STEMI were 60 % and 78.1 %, respectively [38]. Another study demonstrated that SII has the potential to serve as a biomarker in the prediction of ischemic stroke patients with AF [39]. These studies indicated NLR, PLR and SII held promise to predict clinical outcomes in patients with AF. Our findings align with these results, further validating that the aforementioned markers of inflammation can anticipate the prognosis of patients with AF in both the short and long term. Additionally, they serve as independent risk factors for the prognosis of AF patients. Previous research has indicated that SII demonstrates a greater correlation with levels of systemic inflammation and immune status compared to NLR and PLR. Consequently, the predictive efficacy of SII surpasses that of NLR and PLR. Nevertheless, our findings indicate that NLR, PLR, and SII lack substantial variations when it comes to forecasting the short-term and long-term outcomes for individuals diagnosed with AF. Zhang et al. investigated the correlation between the development of dementia and peripheral immune markers, such as immune cell counts and their derived ratios (NLR, PLR, SII, and LMR). The study found that higher levels of innate immune markers were linked to a higher risk of dementia [40]. However, our findings revealed no correlation between NLR, PLR, and SII levels and the short-term and long-term prognosis of AF patients with dementia.

The exact biological process that explains the connection between the inflammation indicator and the occurrence and advancement of AF and death is still unknown. An explanation could be that the higher

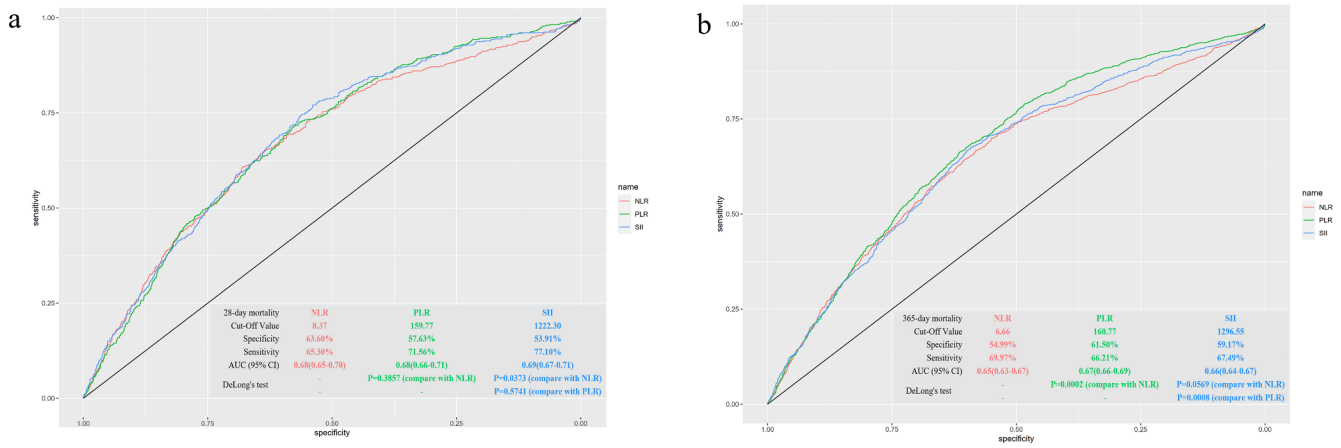

Fig. 3. Receiver operating characteristic (ROC) curves of NLR, PLR and SII predictive value for 30-day (a) and 365-day (b) mortality.

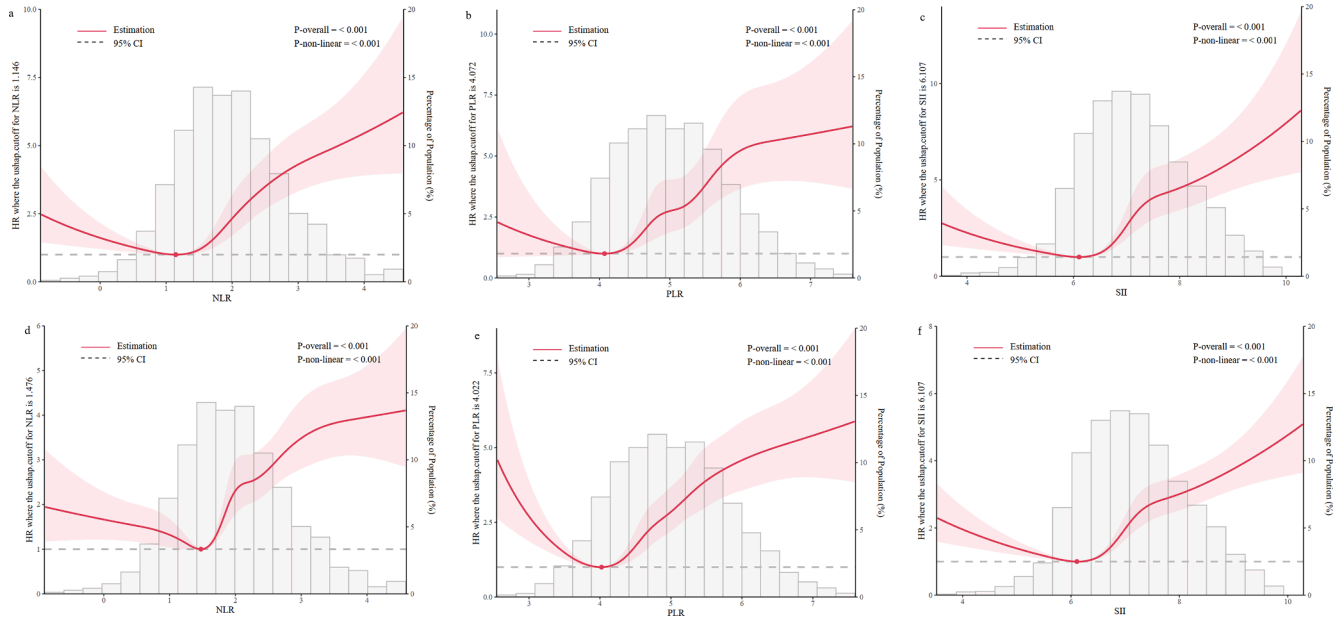

Fig. 4. Restricted cubic spline curve for the NLR, PLR and SII hazard ratio, respectively. Since NLR, PLR, and SII are all extremely non-normal distributions, we performed the ln transformation and then conducted the RCS analysis. (a), (b), (c) Restricted cubic spline for NLR, PLR and SII on 30-day mortality risk, respectively. (d), (e), (f) Restricted cubic spline for NLR, PLR and SII on 365-day mortality risk, respectively. HR, hazard ratio; CI, confidence interval.

count of neutrophils, platelets, and lymphocytes in the outer circulation may release various inflammatory substances like C-reactive protein (CRP), interleukin (IL)-2, IL-6, IL-8, IL-17, monocyte chemotactic protein (MCP)-1.These substances can quickly trigger subsequent cytokines such as tumor necrosis factor α (TNF-α) through a cascade of events similar to a waterfall [22,41–43]. Several clinical studies have shown that patients with AF have elevated levels of the above inflammatory factors [44–48]. Simultaneously, numerous fundamental investigations have indicated that inflammatory signaling pathways are involved in atrial electrical architecture and structural remodeling, which underlie the formation of AF [6,17,49–51].

Although some observations from basic and clinical studies have also confirmed that anti-inflammatory drugs reduce new-onset AF as well as recurrence after radiofrequency ablation of AF, there are no drugs that target biomarkers of inflammation in patients with AF, and most of the medications used for the prevention of AF are blithely assumed to have an anti-inflammatory effect due to the pleiotropic nature of the drugs, such as statin, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, aldosterone receptor antagonists, omega-3 [52–55]. Glucocorticosteroids (GCS) have rapid, potent, and nonspecific anti-inflammatory effects. Many previous studies have shown that GCS therapy for AF can achieve a certain degree of efficacy [56,57]. However, GCS stimulates bone marrow hematopoiesis to increase erythrocytes, hemoglobin, platelets, and to increase the number of neutrophils; inhibits the body's immunity to promote lymphocyte destruction and disintegration, and reduces the number of circulating lymphocytes; therefore, the body's NLR, PLR, and SII are elevated after GCS treatment, and we found that high levels of NLR, NLR, and SII were associated with poorly prognosis in patients with AF. There is a contradiction here, which may be attributed to the fact that GCS increase the number of neutrophils but inhibit their function, and they also induce the synthesis of anti-inflammatory factors. Moreover, Colchicine is an alkaloid extracted from the lily plant colchicine, which was first used in the treatment of gout for its anti-inflammatory effects, and in recent years research on colchicine for the prevention of AF has attracted the attention of scholars [58]. Previous studies have shown colchicine to be safe and effective in reducing the incidence of AF after cardiac surgery, recurrence of AF after radiofrequency ablation, and

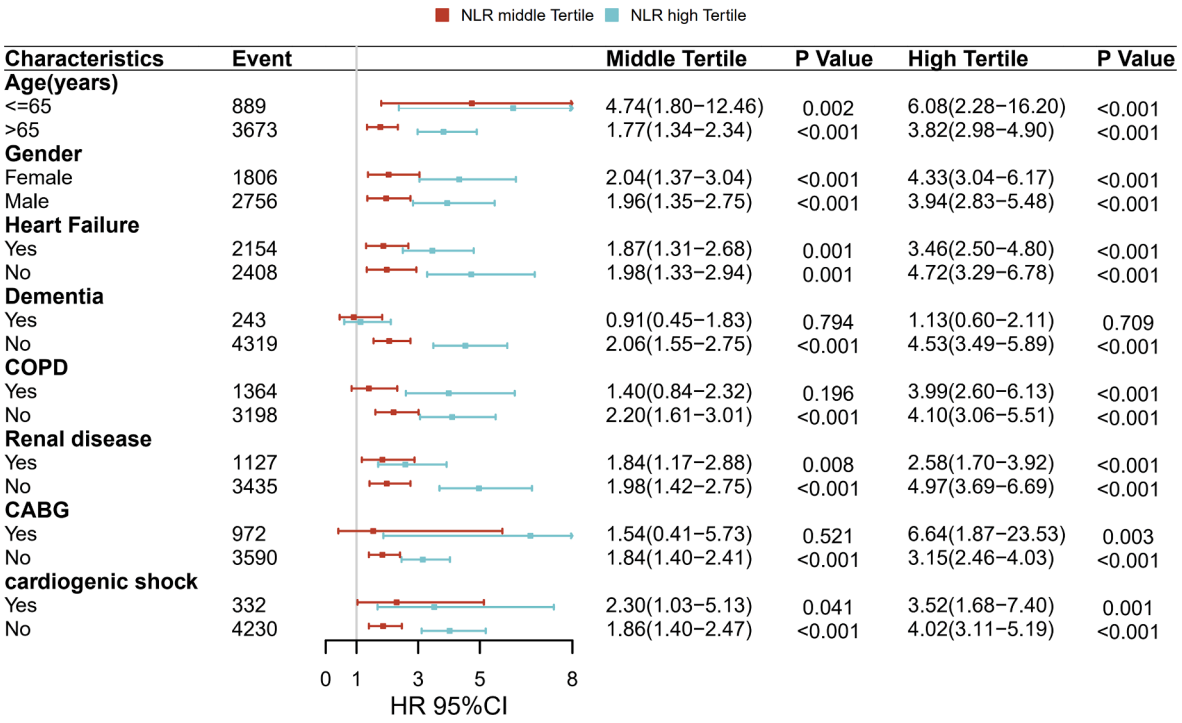

Fig. 5. Forest plots of hazard ratios of NLR tertile for the 30-day mortality in different subgroups. HR, hazard ratio; CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease; CABG, Coronary Angioplasty Bypass Grafting.

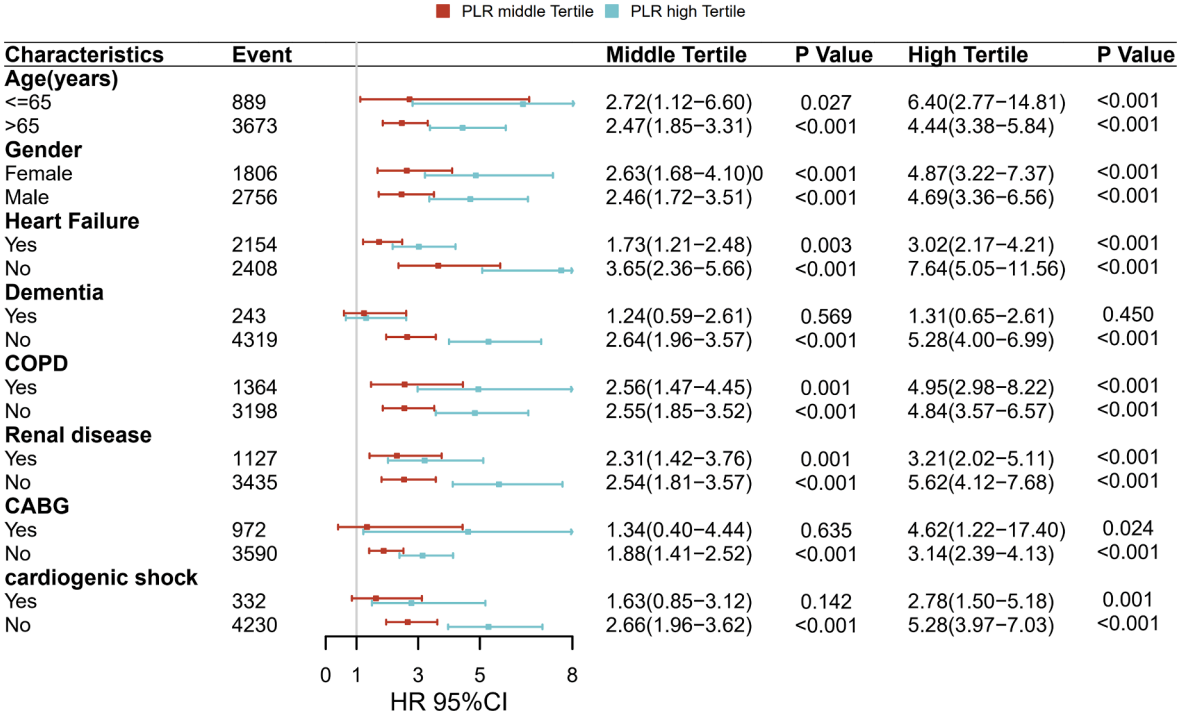

Fig. 6. Forest plots of hazard ratios of PLR tertile for the 30-day mortality in different subgroups. HR, hazard ratio; CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease; CABG, Coronary Angioplasty Bypass Grafting.

suggested that this was due to the control of localized inflammation after cardiac surgery by colchicine [59,60]. However, some studies have found that colchicine only reduces the incidence of postoperative pericardiotomy syndrome, but does not reduce the incidence of postoperative AF and increases the risk of most benign noninfectious diarrhea [61,62]. Thus, the evidence for routine colchicine in the prevention of AF is still controversial, and coupled with the issue of colchicine's side effects, further research is needed to determine whether colchicine can be safely and effectively used in the prevention of AF.

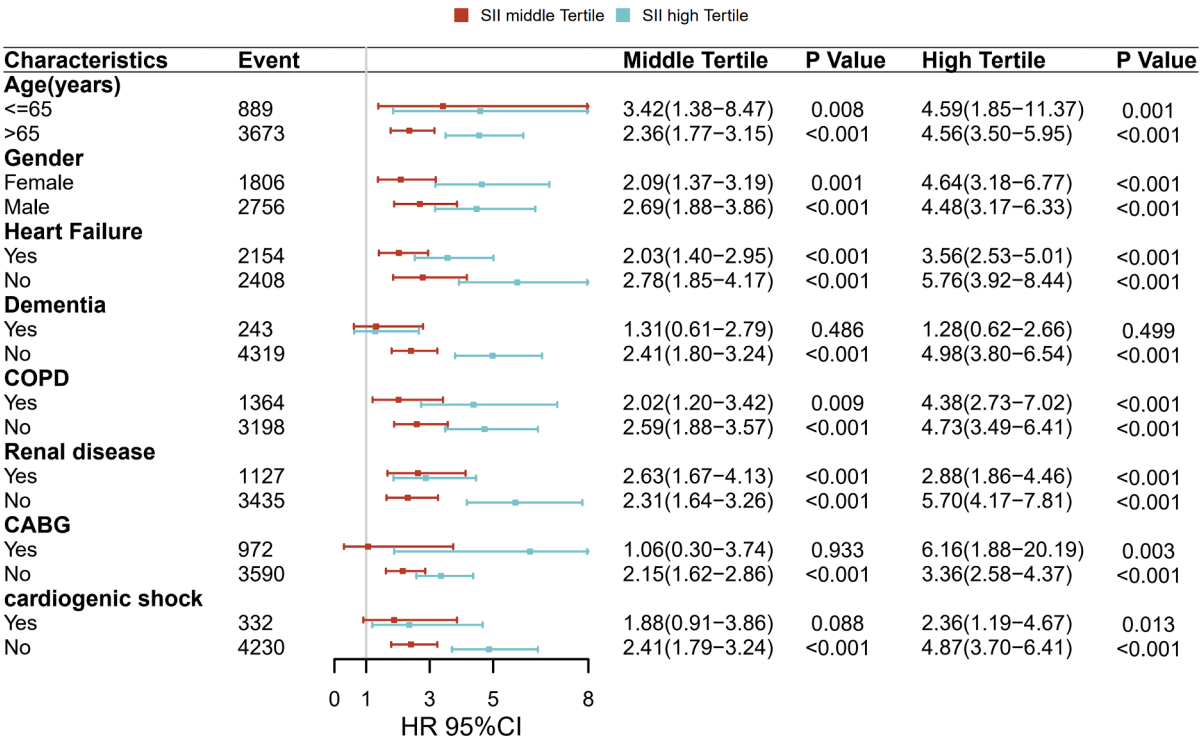

Fig. 7. Forest plots of hazard ratios of SII tertile for the 30-day mortality in different subgroups. HR, hazard ratio; CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease; CABG, Coronary Angioplasty Bypass Grafting.

5. Limitation

A significant advantage of this research is that we confirmed in a cohort from the United States that heightened markers of inflammation are significant risk factors on their own for higher mortality rates among critically ill patients with AF. Nevertheless, there exist certain constraints to this research. Because of the retrospective design, this study was unable to establish causality. Despite the utilization of multivariate adjustment and subgroup analyses, it is possible that clinical outcomes may still be influenced by unaccounted confounding factors. This database did not provide information on potential confounders like AF subtype and cause of death. Furthermore, this study solely examined inflammatory markers upon admission. Dynamic changes in inflammatory markers during hospitalization and in the intensive care unit were not available. Hence, it is imperative to assess the prognostic value of alterations in markers of inflammation in forthcoming research.

6. Conclusions

To summarize, our findings showed that NLR, PLR, and SII could potentially be used as markers for assessing the risk of mortality in critically ill patients with AF, both in the short-term and long-term. Additionally, the predictive value of PLR for 30-day survival status in critically ill patients with AF was better than that of SII and NLR, whereas the predictive value of SII for 365-day survival status in critically ill patients with AF was superior to that of NLR and PLR. Patients with AF had an increased risk of 30-day mortality when the NLR exceeded 3.15, the PLR exceeded 58.67, and the SII exceeded 448.99.

7. Date Availability

The data that support the findings of this study are openly available in MIMIC III database at https://mimic.mit.edu.

8. Author contributions statement

QL, JN, MMC, CDL and CFS designed the study. CDL extracted the data from MIMIC III database. QL, JN, and MMC completed data analysis and graphing. The manuscript was drafted by QL and JN, and revised by CDL, MMC, and CFS. The final version to be published received approval from all authors.

CRediT authorship contribution statement

Qian Li: Conceptualization, Methodology, Visualization, Writing – original draft. **Jian Nie:** Conceptualization, Methodology, Visualization, Writing – original draft. **Miaomiao Cao:** Formal analysis, Project administration, Writing – review & editing. **Chaodi Luo:** Data curation, Formal analysis, Project administration, Writing – review & editing. **Chaofeng Sun:** Conceptualization, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101372.

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