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Research Article

Association Between Neutrophil To-Lymphocyte Ratio (NLR) and Outcome of Septic Patients with Atrial Fibrillation (AF): A Retrospective Observational Study Based on Medical Information Mart for Intensive Care IV

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Abstract

Background: This study aimed to evaluate the association between the Neutrophil to-Lymphocyte Ratio (NLR) and outcome of septic patients with atrial fibrillation.

Methods: Patients with sepsis and AF from the Medical Information Mart For Intensive Care-IV (MIMIC-IV) database had their baseline data and in-hospital prognosis retrieved. Multivariable logistics regression analyses were applied to calculate adjusted Odds Ratios (OR) with 95% Confidence Intervals (CI). Survival curves were plotted, and subgroup analyses were stratified by relevant covariates. To address the linearity relationship, curve fitting were performed.

Results: Of the 7,241 patients, 5,864 patients with sepsis and AF were included. The overall in-hospital mortality rate was 21.1% (1,235/4,629). Adjusted for confounding factors in the multivariable logistics regression analysis models, when NLR was used as a categorical variable, patients in the highest NLR tertile had increased in-hospital mortality compared to patients in the lowest NLR tertile (HR=1.31, 95% CI: 1.09–1.58). A linear relationship between NLR and in-hospital mortality was found in patients with sepsis and AF. K-M curves showed the in-hospital mortality rate was highest in group 3 (NLR 8.4) than in the other two groups. Stratified analyses indicated that the correlation between the NLR and in-hospital mortality was stable.

Conclusion: There is a linear relationship between NLR and in-hospital mortality in intensive care of septic patients with atrial fibrillation. A higher NLR in ICU patients is associated with in-hospital mortality in the United States. However, further research is needed to confirm the findings.

Keywords: Intensive care unit; Infection; Platelet-lymphocyte ratio; Red cell distribution width; Massachusetts institute of technology

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INTRODUCTION

Sepsis is a clinical syndrome characterized by an overactive immune response to infection, posing a grave threat to the lives and well-being of patients [1-3] . Around 20% to 30% of patients admitted to an Intensive Care Unit (ICU) are diagnosed with sepsis. Of these, approximately 25% to 40% do die before being discharged from the hospital despite the decline in

hospital mortality rates associated with sepsis [4,5].

Atrial Fibrillation (AF) refers to the rapid and irregular beating of the heart's atria. AF is the most common arrhythmia among patients admitted to the ICU, the incidence of new-onset AF ranges from 23% to 40% [6]. Due to the irregular heart rhythm, blood clots may form in the atria or atrial appendages, increasing the risk of bacterial or viral infection and exacerbating sepsis. On the other hand, patients with sepsis may experience changes in cardiac function and electrical activity due to systemic inflammatory responses, which in turn can lead to the occurrence of atrial fibrillation, and compared to patients without AF, sepsis patients with AF have worse clinical outcomes [7-9].

The nature of sepsis is a host-mediated systemic inflammatory response to infection [10,11]. The impairment and dysfunction of immune cells are believed to be the primary contributing factors to secondary infections and unfavorable outcomes in sepsis patients. Previous studies have indicated that some systemic inflammatory biomarkers were associated with sepsis and poor prognosis, including Platelet-Lymphocyte Ratio (PLR), Lymphocyte-Monocyte Ratio (LMR), Red Cell Distribution Width (RDW), and Neutrophil to Lymphocyte Ratio (NLR) [12-19]. However, few studies have explored the prognostic correlation between biomarkers in sepsis patients with concomitant atrial fibrillation and neutrophil and lymphocyte counts. The objective of this study was to investigate the association between the NLR and hospital outcomes in sepsis patients with AF, aiming to provide a new foundation and reference for the clinical management of sepsis.

MATERIALS AND METHODS

Data source

We enrolled patients with sepsis and atrial fibrillation from the MIMIC-IV database of the Massachusetts Institute of Technology (MIT). More than 70,000 adult patients were admitted to the ICU of Beth Israel Deaconess Medical Center in Boston between 2008 and 2019. The requirement for informed consent or ethical approval was waived because the data were obtained from publicly available sources with de-identified information. The first author, Kui Tang, completed the training on "Human Subject Protection"and gained full access to the database (certification number 59259021). Raw data were extracted using Structured Query Language with PostgreSQL 13.0 and Navicat Premium 15.

Participants

Patients aged >18 years who fulfilled the Sepsis-3 criteria were eligible for our study. Sepsis was defined as an increase of ≥ 2 points in the Sequential Organ Failure Assessment (SOFA) score, plus documented or suspected infection [20,21]. Septic was defined as (ICD) code 78552 (9th revision) and ICD code R6521 (10th revision). The diagnosis of atrial fibrillation was based on ICD-9. If patients were admitted to the ICU more than once, we only adopted the date of their first ICU admission [22].

Variates

Variables considered confounders of sepsis outcomes based on existing literature and clinical judgment were included [23,24]. Demographic and admission information: Age, sex, race, insurance, language, marital status, height, weight, BMI, Charlson and severity at admission, as measured by the Acute Physiology Score (APS) III score and Sequential Organ Failure Assessment (SOFA) score.

Vital signs: Heart rate, Mean Arterial Pressure (MAP), and SPO^2 at ICU admission.

Interventions: Invasive ventilation.

Laboratory results: Glucose, neutrophil count, lymphocyte count, hemoglobin, White Blood Cell (WBC) count, Red Blood Cell (RBC), Red Cell Distribution Width (RDW), hematocrit, albumin, chlorid, aniongap, PCO_2, PO_2, total CO_2, free calcium, Partial Thromboplastin Time (PTT), plasma Prothrombin Time (PT), creatinine, urea nitrogen, platelet count, lactate, and pH. NLR was calculated using the neutrophil count (K/uL)/lymphocyte count (K/uL). If the above data were tested multiple times within 24 h, we chose the first set of parameters.

Outcome

The outcome was in-hospital mortality, which is defined as survival status at hospital discharge. Patients without any outcome information were excluded from the final cohort.

Statistical analysis

Descriptive analysis was performed for categorical variables to assess the significance of differences between groups stratified by NLR tertile (<4.0; 4.0–8.4; ≥ 8.4) using the Kruskal– Wallis test or one-way analysis of variance. Baseline characteristic data

are presented as proportions (%) and were compared using chi-square tests for categorical variables. Normally distributed continuous data are presented as mean ± Standard Deviation (SD) and compared using Student's t-test between groups, while skewed distribution data are presented as the median and Inter Quartile Range (IQR) and compared using the Wilcoxon rank-sum test.

A multivariate logistics proportional hazard model was used to assess the independent association between the NLR and in-hospital mortality. We constructed three models: Model 1, no covariance were adjusted. Model 2 adjusted only for age and sex. Model 3 was additionally adjusted for weight, height, BMI, HR, SBP, DBP, WBC, neutrophil count, RDW, Albumin, Glucose, Aniongap, PH, PO_2, lactate, free calcium, PTT, invasive ventilation, MI, hypertriglyceridemia, and AKI. In all models, linear trends were tested using NLR tertile as categorical variables by assigning the median values of the tertile to the variable.

A logistics proportional hazards regression model was used to assess the linear relationship between NLR and the outcome of sepsis and AF. Based on the curve fitting (restricted cubic spline), we conducted a two- piecewise linear regression model to identify threshold effects.

A sensitivity analysis was performed to ensure the robustness of the data analysis. NLR was transformed into a categorical variable and a p-value for the trend was calculated. The purpose of this test was to validate the results of treating the NLR as a continuous variable and to determine the possibility of linearity.

Hospital survival was assessed using Kaplan-Meier survival curves according to NLR tertile and evaluated using the logrank test. Stratified and interaction analyses were applied based on sex (male or female), age (<65 or ≥ 65 years), BMI (< 25 · 25-30 · > =30) · MI (yes or no), CKD (yes or no),and hypertension (yes or no). Subgroup analyses were adjusted for age, sex, weight, height, BMI, HR, SBP, DBP, WBC, neutrophilcount, RDW, Albumin, Glucose, Aniongap, PH, PO_2, lactate, freecalcium, PTT, invasive ventilation, MI, hypertriglyceridemia, and AKI.

The percentages of covariates with missing data were less than 25% for all analyses. The missing values of the covariates were imputed *via* multiple imputations. We created and analyzed three datasets together. Data analyses were performed using packages R 4.1.2 (The R Foundation)1 software and Free Statistics software versions 1.5. P-values < 0.05 were considered significant.

RESULTS

Baseline characteristics of the study population

According to the screening criteria, 5,864 patients were included whose demographic characteristics were shown in Table 1. As previously mentioned, participants were divided into three groups based on NLR<4.0 (n=1,244); 4.0 ≤ NLR<8.4 (n=1,537); and NLR ≥ 8.4 (n=3,083). The average age of the patients was 76.2 ± 11.4 years old and approximately 57.8% of them were men. There were no significant differences among the different groups concerning SBP, BMI, charlson score, SPO_2, PCO_2, temperature, RDW, PTT, hypertension, DM, MI, CKD and COPD (all p>0.05). Patients with a higher NLR tended to be male, have a heavier weight, higher SOFA score, glucose and aniongap, more WBC count, with invasive ventilation, heart failure, MI, CKD, but with lower PO_2, neutrophil count and platelet count.

Association between NLR and in hospital mortality

A univariable logistics regression analysis was used to select the variables of prognostic value for in-hospital mortality Figure 1. Age, gender, weight, height, BMI, SOFA, charlson, SBP, WBC, neutrophil count, RDW, glucose, aniongap, PH, lactate, free calcium, PTT, invasive ventilation, and MI were all signifcantly associated with in-hospital mortality in patients with sepsis and AF (P<0.05, Table 2). Figure 2 displayed the K-M curves of three groups. The in-hospital mortality rate was highest in group 3 (NLR≧8.4) than in the other two groups.

Table 3 shows an unadjusted and a multivariable-adjusted correlation between NLR and in-hospital mortality. When NLR was analyzed as categorical variables, the highest NLR (model 3 vs. model 1) was associated with a higher risk of in-hospital mortality after adjusting all covariates (adjusted odds ratio, 1.31; 95% Confidence Interval (CI), 1.09–1.58; p<0.001). No covariate were adjusted in Model 1, age and sex were adjusted in Model 2, and all covariates were adjusted in Model 3. A linear relationship was observed between the NLR and in-hospital mortality in patients with sepsis and AF (Figure 3).

V+C3:J47ariables	Total (n=5,864)	<4.0 (n=1,244)	4.0-8.4 (n=1,537)	> 8.4 (n=3,083)	p	statistic
NLR	8.9 (4.5, 18.5)	2.4 (1.2, 3.3)	5.9 (5.0, 7.1)	17.7 (11.7, 31.0)	<0.001	4849.415
Age, years	76.2 ± 11.4	76.5 ± 11.5	75.8 ± 11.4	76.3 ± 11.4	0.279	1.277
Gender (%)	_	_	_	_	0.691	0.739

Male	3389 (57.8)	712 (57.2)	879 (57.2)	1798 (58.3)	_	_
Female	2475 (42.2)	532 (42.8)	658 (42.8)	1285 (41.7)	_	_
Weight (Kg)	82.5 ± 23.7	80.8 ± 22.1	82.6 ± 23.0	83.2 ± 24.7	0.01	4.56
Height (cm)	168.9 ± 10.9	168.4 ± 10.8	168.5 ± 10.7	169.3 ± 11.0	0.013	4.371
BMI	28.8 ± 7.4	28.4 ± 6.8	29.0 ± 7.3	28.9 ± 7.7	0.06	2.815
HR (bpm)	86.9 ± 16.0	85.5 ± 16.6	85.9 ± 15.4	87.9 ± 16.1	<0.001	13.563
SBP (mmHg)	114.9 ± 14.9	118.9 ± 16.7	115.2 ± 13.6	113.1 ± 14.5	< 0.001	67.664
DBP (mmHg)	56.6 ± 9.7	57.8 ± 10.5	56.8 ± 9.5	56.0 ± 9.4	<0.001	14.919
Temperature (°C)	36.7 ± 2.2	36.7 ± 1.7	36.7 ± 2.0	36.8 ± 2.5	0.281	1.27
SOFA	5.0 (3.0, 8.0)	5.0 (3.0, 7.0)	5.0 (3.0, 8.0)	6.0 (4.0, 9.0)	<0.001	39.682
Charlson	6.4 ± 2.6	6.5 ± 2.7	6.4 ± 2.5	6.4 ± 2.6	0.389	0.945
WBC (K/uL)	13.6 ± 9.7	11.1 ± 13.3	12.5 ± 5.8	15.1 ± 9.3	<0.001	89.956
RBC (K/uL)	3.5 ± 0.6	3.3 ± 0.6	3.4 ± 0.6	3.5 ± 0.7	< 0.001	29.809
Hemoglobin (g/dL)	10.4 ± 1.9	10.2 ± 1.9	10.3 ± 1.7	10.5 ± 1.9	<0.001	12.995
RDW,n (%)	15.5 ± 2.3	15.6 ± 2.4	15.4 ± 2.3	15.6 ± 2.3	0.069	2.68
Hematocrit,n (%)	31.7 ± 5.5	31.2 ± 5.7	31.5 ± 5.2	31.9 ± 5.6	<0.001	9.7
Albumin (g/dL)	3.1 ± 0.6	3.2 ± 0.6	3.1 ± 0.6	3.0 ± 0.6	<0.001	26.451
Glucose (mq/dL)	142.1 ± 53.2	135.8 ± 47.6	137.6 ± 47.5	146.8 ± 57.4	< 0.001	26.355
Aniongap (mEq/L)	14.9 ± 4.0	14.3 ± 3.7	14.5 ± 3.8	15.3 ± 4.2	<0.001	35.846
PH	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	<0.001	28.253
PCO2 (mmHg)	41.7 ± 9.6	41.9 ± 11.1	41.8 ± 9.3	41.6 ± 9.1	0.531	0.633
PO2 (mmHg)	137.7 ± 79.6	152.2 ± 87.5	146.4 ± 82.2	127.5 ± 73.2	<0.001	56.423
Free calcium (mmol/L)	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.001	6.523
PTT (sec)	40.4 ± 19.2	39.7 ± 18.7	40.7 ± 19.4	40.6 ± 19.2	0.292	1.231
Neutrophil count (K/uL)	9.7 (6.4, 14.2)	4.8 (2.3, 7.2)	8.8 (6.5, 11.8)	12.6 (9.2, 17.6)	<0.001	2013.531
Lymphocytes (K/uL)	1.1 (0.6, 1.7)	2.1 (1.4, 2.9)	1.5 (1.1, 2.0)	0.7 (0.4, 1.0)	<0.001	2530.875
Platelet count (K/uL)	175.3 (128.0, 240.0)	148.8 (112.0, 201.8)	171.0 (126.0, 232.0)	190.4 (140.5, 258.5)	<0.001	230.822
Lactate (mmol/L)	1.9 (1.4, 2.6)	1.7 (1.3, 2.4)	1.8 (1.4, 2.5)	1.9 (1.4, 2.7)	<0.001	43.467
Hypertension	_	_	_	_	0.619	0.959
No	3389 (57.8)	724 (58.2)	872 (56.7)	1793 (58.2)	_	_
Yes	2475 (42.2)	520 (41.8)	665 (43.3)	1290 (41.8)	_	_
DM	_	_	_	_	0.86	0.301
No	3974 (67.8)	846 (68)	1033 (67.2)	2095 (68)	_	_
Yes	1890 (32.2)	398 (32)	504 (32.8)	988 (32)	_	_
Heart failure	_	_	_	_	0.037	6.578
No	3047 (52.0)	686 (55.1)	792 (51.5)	1569 (50.9)	_	_
Yes	2817 (48.0)	558 (44.9)	745 (48.5)	1514 (49.1)	_	_
Myocardial infarction	_	_	_	_	0.681	0.767
No	5311 (90.6)	1133 (91.1)	1395 (90.8)	2783 (90.3)	_	_
Yes	553 (9.4)	111 (8.9)	142 (9.2)	300 (9.7)	_	_
CKD	_	_	_	_	0.694	0.731
No	4253 (72.5)	914 (73.5)	1113 (72.4)	2226 (72.2)	_	_
Yes	1611 (27.5)	330 (26.5)	424 (27.6)	857 (27.8)	_	_
COPD	_	_	_	_	0.554	1.18
No	5262 (89.7)	1123 (90.3)	1385 (90.1)	2754 (89.3)	_	_
Yes	602 (10.3)	121 (9.7)	152 (9.9)	329 (10.7)	_	_
AKI	_	_	_	_	0.005	10.688
No	1005 (17.1)	250 (20.1)	263 (17.1)	492 (16)	_	_
Yes	4859 (82.9)	994 (79.9)	1274 (82.9)	2591 (84)	_	_
Invasive ventilation, n (%)	_	_	_	_	<0.001	25.34
No	4436 (75.6)	997 (80.1)	1183 (77)	2256 (73.2)	_	_
Yes	1428 (24.4)	247 (19.9)	354 (23)	827 (26.8)	_	_
In hospital mortality	_	_	_	_	<0.001	46.355
No	4629 (78.9)	1036 (83.3)	1265 (82.3)	2328 (75.5)	_	_
Yes	1235 (21.1)	208 (16.7)	272 (17.7)	755 (24.5)	_	_

Table 1: Patient characteristics according to tertiles of neutrophil to lymphocyte ratio.

Item	HR (95%CI)	P (Wald's test)	P (LR-test)
Age	1.02 (1.01,1.03)	<0.001	<0.001

Gender(Female vs. Male)	1.19 (1.04,1.37)	0.012	0.012
Weight (Kg)	0.9956 (0.9928,0.9985)	0.003	0.002
Height (cm)	0.9927 (0.9865,0.999)	0.023	0.023
BMI	0.99 (0.98,1)	0.021	0.018
SOFA	1.11 (1.09,1.13)	<0.001	<0.001
Charlson	1.08 (1.05,1.11)	<0.001	<0.001
HR (bpm)	1.0091 (1.005,1.0132)	<0.001	<0.001
SBP (mmHg)	0.9921 (0.9875,0.9966)	<0.001	<0.001
DBP (mmHg)	0.9954 (0.9885,1.0023)	0.186	0.182
Temp (℃)	0.98 (0.95,1)	0.094	0.113
WBC (K/uL)	1.0058 (1.0021,1.0095)	0.002	0.01
RBC (K/uL)	1.03 (0.93,1.14)	0.584	0.585
Neutrophil count (K/uL)	1.02 (1.01,1.03)	<0.001	<0.001
Lymphocytes (K/uL)	0.99 (0.9616,1.0193)	0.501	0.309
NLR	1.0008 (0.9995,1.0021)	0.208	0.251
Platelet count (K/uL)	1.0001 (0.9995,1.0008)	0.656	0.657
Hemoglobin (g/dL)	1.0076 (0.9727,1.0439)	0.672	0.673
RDW	1.09 (1.06,1.12)	<0.001	<0.001
Hematocrit	1.01 (1,1.02)	0.061	0.063
Albumin (g/dL)	0.85 (0.76,0.95)	0.004	0.004
Glucose (mg/dL)	1.0033 (1.0022,1.0044)	<0.001	<0.001
Aniongap (mEq/L)	1.09 (1.08,1.1)	<0.001	< 0.001
PH	0.01 (0,0.02)	<0.001	<0.001
PCO2 (mmHg)	0.9995 (0.9926,1.0065)	0.895	0.895
PO2 (mmHg)	0.9952 (0.994,0.9963)	<0.001	<0.001
Lactate (mmol/L)	1.14 (1.12,1.17)	<0.001	<0.001
Free calcium (mmol/L)	0.15 (0.07,0.32)	<0.001	<0.001
PTT (sec)	1.009 (1.0061,1.0118)	<0.001	<0.001
Invasive ventilation(Yes vs. No)	1.21 (1.05,1.39)	0.008	0.008
Hypertension(Yes vs. No)	0.88 (0.76,1.01)	0.067	0.065
DM(Yes vs. No)	0.97 (0.84,1.12)	0.649	0.648
Heart failure(Yes vs. No)	1.06 (0.92,1.21)	0.425	0.425
MI(Yes vs. No)	1.4 (1.15,1.71)	<0.001	0.001
CKD(Yes vs. No)	1.06 (0.91,1.23)	0.464	0.466
COPD(Yes vs. No)	1.05 (0.85,1.29)	0.662	0.664
AKI(Yes vs. No)	1.31 (0.86,2)	0.21	0.192

Note: BMI: Body Mass Index; SOFA: Sequential Organ Failure Assessment; HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; WBC: White Blood Cell; RBC: Red Blood Cell; NLR: Neutrophil to-Lymphocyte Ratio; RDW: Red Cell distribution Width; DM: Diabetes Mellitus; MI: Myocardial Infarction; PTT: Partial Thromboplastin Time; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; AKI: Acute Kidney Injury.

Table 2: Univariable Cox regression analysis of in hospital mortality of septic patients with atrial fibrillation.

	Model 1		Model 2		Model 3	
Exposure	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
In hospital mortality						
<4.0	1(Ref.)		1(Ref.)		1(Ref.)	
4.0-8.4	0.98 (0.82~1.17)	0.829	1 (0.83~1.2)	0.99	0.99 (0.80~1.23)	0.784
≧ 8.4	1.43 (1.22~1.66)	<0.001	1.44 (1.23~1.67)	<0.001	1.31(1.09~1.58)	<0.001
P for trend	1.24 (1.15~1.34)	<0.001	1.24 (1.15~1.33)	<0.001	1.04 (0.95~1.13)	<0.001

Table 3: Relationship between neutrophil to lymphocyte ratio and in hospital mortality in different models

Results of subgroup analyses

The subgroup analysis was conducted to reveal the correlation between NLR and in-hospital mortality across age, gender, BMI, comorbidities, and the results were shown in Figure 4. No significant interactions were observed between NLR and age, gender, BMI, MI, CKD and hypertension (p>0.05).

DISCUSSION

Our study demonstrated that high NLR was related to increased in-hospital mortality of septic patients with atrial fibrillation, and there was a linear relationship between NLR and in-hospital mortality, stratified analyses indicated stable

correlation between the NLR and in-hospital mortality. The findings of this retrospective observational study based on the MIMIC-IV database provide compelling evidence of a significant association between the Neutrophil to-Lymphocyte Ratio (NLR) and the outcome of septic patients with Atrial Fibrillation (AF).

Sepsis is a host-mediated systemic inflammatory response to infection, and evidence of immune cell activation and host response dysfunction has been observed in severe sepsis patients[10,11,25,26]. There are existing literature that have identified the cell ratio as an important indicator for predicting mortality rates. The Platelet-to- Lymphocyte Ratio (PLR) has been embraced by medical professionals as a widely used and cost-effective tool for diagnosing and predicting mortality rates. Additionally, PLR has been found to enhance the diagnostic role of the Neutrophil-to-Lymphocyte Ratio (NLR) [12]. Kriplani et al. [13] evaluated the Lymphocyte-Monocyte Ratio (LMR) in patients undergoing Percutaneous Nephro Lithotomy (PNL) and found that patients who developed Systemic Inflammatory Response Syndrome (SIRS) had a lower LMR (2.5 ± 1.7 vs. 3.2 ± 1.8, OR 1.18, 95% CI 1.04-1.34, p=0.006). They suggested that LMR could serve as an independent, easily obtainable, and cost-effective predictive marker for early identification of SIRS/sepsis after PNL, particularly patients with LMR<3.23 should be closely monitored for early detection of postoperative infections and complications. Increased Red Cell Distribution Width (RDW) also has been found to be significantly associated with higher in-hospital mortality rates and 4-year mortality rates. Importantly, the prognostic value of RDW for 4-year mortality rates is independent of traditional severity scoring, suggesting that RDW can predict in-hospital and 4-year mortality rates in adult critically ill patients and provide additional prognostic value beyond traditional severity scoring [27]. Besides, Daniel Dankl found an association of RDW with mortality in septic patients and proposed he optimal RDW cutoff for the prediction of hospital mortality was 16% [16].

NLR can be calculated by dividing the absolute neutrophil count by the absolute lymphocyte count obtained from a complete blood count of peripheral blood. Neutrophils are white blood cells primarily involved in inflammatory and infection defense. An increase in neutrophil count usually indicates an ongoing inflammatory response or infection. Lymphocytes, on the other hand, are a type of immune cell. They play a crucial role in recognizing and attacking pathogens, as well as maintaining immune balance. The quantity and function of lymphocytes are closely related to the immune status of the body. The NLR is used in assessing the severity of inflammation, predicting disease progression, and prognosis. Higher NLR values typically indicate immune system dysregulation or intensified inflammatory response [26,28-31]. Numerous studies have reported associations between NLR and adverse outcomes in critically ill patients. Zahorec [25] mentioned that the NLR is useful in distinguishing the severity of diseases and predicting mortality rates. Patients with an NLR value greater than 30 are considered to be in critical condition, with a higher mortality rate. On the other hand, patients with an NLR value lower than7 have significantly reduced probability of sepsis occurrence, leading to a lower mortality rate as well [32-34]. In this study, we analysed NLR as a continuous and categorical variable based on the literature. Numerous covariates were found to be associated with in- hospital mortality, including age, gender, weight, height, BMI, SOFA, charlson, HR, SBP, WBC, neutrophilcount, RDW, albumin, glucose, aniongap, PH, PO_2, lactate, freecalcium, PTT, and MI. After adjusting for all covariates, the highest NLR group had a 31% increase in in- hospital mortality compared to the lowest group, which is consistent with previous research findings. Atrial FIbrillation (AF) is a common cardiac arrhythmia characterized by rapid and irregular electrical activity in the atria of the heart. Clinical data consistently show an increased incidence of AF in patients with sepsis, shedding light on their association and clinical implications. Although NLR is a commonly used indicator to assess the severity of inflammation in sepsis patients, it is rarely used as a biomarker in AF population. Confirmed NLR has been associated with adverse prognosis in various cardiovascular diseases, including acute coronary syndrome and other coronary artery diseases, coronary artery bypass grafting, hospitalization for heart failure [35-39]. In a randomized, double-blind trial involving 19,697 non-severe atrial fibrillation patients, Fagundes et al. found that a high proportion of 72.9% had NLR distribution between 1.5-4.0, while only 15.8% had NLR greater than 4.0. However, higher NLR values were consistently associated with a higher risk of adverse clinical outcomes, including stroke, cardiovascular death, myocardial infarction, and all- cause mortality [40]. In the present study, we included patients with sepsis complicated by AF. According to the literature, we divided the NLR into three groups: <4.0, 4.0-8.4, and ≧ 8.4. The results showed that the majority (3,083/5,864) of patients had NLR values in the third group (NLR ≧ 8.4), which indirectly reflects the severity of inflammation in septic patients. Besides, a higher NLR was found to be significantly associated with increased mortality rates and prolonged hospital stays in septic shock patients with concurrent atrial fibrillation.

Several mechanisms have been proposed to explain the link between sepsis and AF. Firstly, sepsis induces a pro-inflammatory state through the release of cytokines, such as interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-α). This excessive inflammatory response can disrupt the normal electrical conduction pathways of the heart, leading to the development of AF [41]. In addition, sepsis can cause myocardial dysfunction, myocardial ischemia, and oxidative stress, which further contribute to the occurrence and persistence of AF [42-44]. Furthermore, sepsis-related alterations in

autonomic tone and neurohormonal activation may also play a role in the development of AF [45]. The sympathetic over activation and parasympathetic withdrawal associated with sepsis can lead to an imbalance in the autonomic nervous system, promoting the initiation and maintenance of AF [46]. Additionally, elevated levels of circulating catecholamines and abnormal calcium handling in cardiomyocytes during sepsis have been implicated in the pathogenesis of AF [47]. The presence of AF in septic patients has been associated with worse outcomes, including increased mortality, longer hospital stays, and a higher incidence of stroke [41].

In the present study, we recruited 5,864 septic patients with AF. Both logistics regression and Kaplan–Meier survival curves showed that higher NLR is related to increased mortality, which is consistent with previous literature, and it's a linear relationship between NLR and in-hospital mortality in septic patients with AF. Moreover, the subgroup analysis results indicated that the correlation between the NLR and in- hospital mortality was stable. The linear relationship between NLR and in-hospital mortality observed in our study suggests that NLR could serve as a valuable prognostic marker for septic patients with AF in the intensive care setting. This information holds potential clinical relevance for risk stratification and treatment decision-making in this patient population.

Nonetheless, it is essential to acknowledge the limitations of our study, including its retrospective design and reliance on data from a single database. Future research, incorporating prospective designs and data from multiple sources, is warranted to validate our findings and explore the clinical utility of NLR in septic patients with AF.

CONCLUSION

In conclusion, our study contributes to the growing body of evidence supporting the association between NLR and clinical outcomes in septic patients with AF. The wealth of literature on this topic, including the studies cited above and others, underscores the importance of further investigation into the prognostic value of NLR in critical care settings, ultimately aiming to improve patient care and outcomes.

AUTHOR CONTRIBUTIONS

All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

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