International Immunopharmacology 74 (2019) 105692

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

The neutrophil-lymphocyte ratio: A promising predictor of mortality in coronary care unit patients — A cohort study

Huankun Sun[a], Jiaqun Que[a], Yangpei Peng[a], Haihao Ye[a,b], Huaqiang Xiang[a], Yueyuan Han[a], Jie Wang[c,*,1], Kangting Ji[a,*,1]

[a] Department of Cardiology, The Second Affiliated Hospital and Yuying Children's Hospital, Wenzhou Medical University, Wenzhou 325000, Zhejiang, China
[b] Department of Cardiology, Wenzhou Hospital of Traditional Chinese Medicine, Wenzhou 325000, Zhejiang, China
[c] Department of Endocrinology, Affiliated Hospital of Yanbian University, Yanji 133002, Jilin, China

ARTICLE INFO

Keywords:
Coronary care unit
Mortality
Neutrophil-lymphocyte ratio
Prognosis

ABSTRACT

Background: Severe inflammation causes poor outcomes in coronary care unit (CCU) patients. The neutrophil-lymphocyte ratio (NLR), a biomarker used to monitor inflammation and the immune response, can predict a poor prognosis in various diseases. However, it remains unclear whether the NLR is associated with all-cause mortality in CCU patients. This study investigated the association between the NLR and CCU outcomes.

Methods: Clinical data were extracted from the Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC-III) database, which contains health data for over 50,000 patients. The primary outcome was 30-day mortality and the secondary outcome was 90-day mortality. Cox proportional hazard models were used to reveal the associations between NLR and outcomes. Multivariate analyses were used to control for confounders.

Results: We enrolled 3563 CCU patients. For 30-day mortality, the hazard ratio (HR) (95% confidence interval [CI]) for the second (NLR 4.80–10.08) and the third (NLR ≥ 10.09) tertiles were 1.57 (1.24, 1.97) and 2.76 (2.23, 3.41), respectively, compared to the first tertile (NLR < 4.80). In the model adjusted for multiple confounders, the fifth quintile (NLR ≥ 14.17) showed a slightly lower mortality risk [HR (95% CI) 1.44 (1.07, 1.94)] compared to the fourth (NLR 8.82–14.16) [HR (95% CI) 1.55 (1.15, 2.10)]. A similar trend was observed for 90-day mortality. The interactions between the acute kidney injury, respiratory failure, and pneumonia subgroups and 30-day mortality were significant.

Conclusions: The NLR was an independent predictor of 30- and 90-day mortality for CCU patients. The NLR is a promising clinical biomarker as an integrated, readily available predictor of CCU mortality.

1. Introduction

Cardiovascular disease is the leading cause of death worldwide. Increasing numbers of people are dying of ischemic heart disease, with an additional 1.6 million deaths in 2017 compared to a decade earlier [1]. Coronary care units (CCUs) are well-equipped system for the managing severe cardiovascular disease, to markedly reduce this burden. The first CCUs reduced mortality associated with acute myocardial infarction (AMI) by 40% [2,3]. Over the past 50 years, advances in CCUs have resulted in better outcomes, and the influence of early biomarkers on CCU prognosis is worthy of exploration [4].

Inflammation plays a major role in the pathogenesis of cardiovascular and other critical illnesses. The relative ratio of leukocyte subtypes reflects the initiation of inflammation. The neutrophil-lymphocyte ratio (NLR) is a recently introduced biomarker of inflammation based on both neutrophil and lymphocyte counts [5]. Neutrophils are activated in nonspecific inflammation, while the lymphocyte count indicates that the body is under stress or has weak immunity. The NLR uses both as a more comprehensive biomarker [6]. The systemic inflammatory response triggered by organ dysfunction in critical ill patients increases the NLR. The NLR is a better predictor of severity and outcome in patients with infectious and oncological diseases than conventional biomarkers such as C-reactive protein and the white blood cell (WBC) count [7–11].

The NLR also predicts both the risk and outcome in patients with cardiovascular events, which are the major cause of CCU admission. In patients with advanced heart failure, a low lymphocyte ratio, which indicates a high NLR, is associated with poorer long-term survival [12].

* Corresponding authors.
E-mail addresses: 393551062@qq.com (J. Wang), jikt@wzmc.edu.cn (K. Ji).
[1] Jie Wang and Kangting Ji contributed equally to this work.

https://doi.org/10.1016/j.intimp.2019.105692
Received 27 April 2019; Received in revised form 7 June 2019; Accepted 8 June 2019
Available online 19 June 2019

Another study showed that a high NLR is associated with a poor prognosis in patients with acute coronary syndrome (ACS) [13]. The NLR a useful predictor of the long-term mortality in patients undergoing percutaneous coronary intervention [14]. However, it remains unclear whether it is associated with all-cause mortality in CCU patients. In this study, we investigated the association between NLR and CCU outcomes.

2. Methods

2.1. Data source

The data studied were from the openly available Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC-III) database ver. 1.4. The MIMIC-III comprises deidentified health data for > 50,000 critical care patients admitted to Beth Israel Deaconess Medical Center (Boston, MA, USA) from 2001 to 2012 [15]. To access the database, we completed the National Institutes of Health's web-based course Protecting Human Research Participants.

This database was approved by the institutional review boards of Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (Boston, MA, USA). All personal information has been removed to protect the privacy of the included patients.

2.2. Population selection criteria

Of 58,976 recorded intensive care unit (ICU) patients in the MIMIC-III database, patients admitted to the CCU were included. Patients who were older than 18 years old at their first admission and hospitalized for > 2 days were selected. Patients were excluded if they met the criteria: had no data on the neutrophil or lymphocyte count within the first 24 h of admission, had > 5% missing data, and/or were diagnosed with hematological diseases such as leukemia or lymphoma.

2.3. Data extraction

Structure query language (SQL) was used to extract data from the database. The extracted data included age, sex, ethnicity, heart rate, respiratory rate, temperature, mean blood pressure (MBP), systolic blood pressure (SBP), diastolic blood pressure (DBP), percutaneous oxygen saturation (SPO_2), and vasoactive drug use. Comorbidities included coronary artery disease (CAD), chronic heart failure (CHF), atrial fibrillation (AF), endocarditis, sepsis, acute kidney injury (AKI), chronic renal disease, pneumonia, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), respiratory failure, malignancy, stroke, and chronic liver disease. Laboratory parameters included the neutrophil, and lymphocyte counts, hemoglobin, platelet, and WBC counts, anion gap, serum levels of bicarbonate, chloride, glucose, potassium, sodium, hematocrit, serum creatine (SCr), and blood urea nitrogen (BUN). The severity of illness was measured using the simplified Acute Physiology Score III (APS III) [16]. The follow-up was started from the date of admission and ended at death. The primary outcome was 30-day mortality and the secondary outcome was 90-day mortality. The extracted data were recorded within 24 h of admission to Beth Israel Deaconess Medical Center.

2.4. Statistical analyses

The study population was subdivided three groups according to the NLR. Data are presented are the mean ± standard deviation and interquartile range (IQR) for continuous variables, and as frequencies for categorical data. Differences among the NLR groups were compared using the Kruskal–Wallis test for continuous variables and the χ^2 test or Fisher's exact test (expected frequency < 10) for categorical variables.

The association between the NLR and mortality was determined using Cox proportional hazards models and presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The NLR values were divided into tertiles or quintiles, with the first tertile or quintile selected as the reference group. Multivariable analyses were used to control for confounders. Model 1 was adjusted for the confounders age, sex and ethnicity. In addition, Model 2 adjusted for the confounders age, sex, ethnicity, heart rate, SBP, DBP, respiratory rate, temperature, SPO_2, AKI, sepsis, AF, CAD, chronic liver disease, malignancy, respiratory failure, pneumonia, APS III score, vasopressin use, anion gap, serum bicarbonate, chloride, potassium, sodium, glucose, hematocrit, WBC, SCr, and BUN. These confounders were selected based on their associations with the outcomes or a change in the effect estimate exceeding 10% [17]. We performed stratification analyses to check if the association differed for subgroups classified using different parameters and comorbidities including CAD, CHF, AF, endocarditis, AKI, pneumonia, respiratory failure, ARDS, sepsis, COPD, chronic renal disease, malignancy, stroke, chronic liver disease, vasoactive drug use, APS III score, heart rate, SBP, DBP, MBP, respiratory rate, temperature, and SPO_2.

A two-sided $p < 0.05$ was considered statistically significant. R software (http://www.R-project.org) was used to perform the statistical analyses.

3. Results

3.1. Subject characteristics

In all, 3563 patients who met the selection criteria were enrolled. They were divided into three groups according to the NLR: < 4.80 (n = 1188); 4.80–10.08 (n = 1187); and ≥10.09 (n = 1188). Table 1 summarizes the characteristics of the NLR groups including, vital signs, laboratory parameters and comorbidities. Patients with a high NLR tended to be older, white, with a higher heart rate, lower blood pressure, respiratory rate, body temperature, SPO_2, and APS III scores, and a history of vasoactive drug use, AKI, sepsis, CHF, AF, chronic renal disease, COPD, malignancy, respiratory failure, and pneumonia. Patients with a higher NLR tended not to have CAD.

3.2. Association between NLR and 30- and 90-day mortality

There were 598 30-day deaths and 811 90-day deaths. A high NLR was associated with the risk for 30- and 90-day all-cause mortality in CCU patients (Table 2). For 30-day mortality, the HR (95% CI) for the second (4.80–10.08) and third (≥10.09) tertiles was 1.57 (1.24, 1.97) and 2.76 (2.23, 3.41), respectively, compared to the first tertile (< 4.80). Model 1, which was adjusted for age, sex and ethnicity, the HR (95% CI) of 30-day mortality for the second (4.80–10.08) and third (≥10.09) tertiles was 1.49 (1.18, 1.88) and 2.55 (2.06, 3.16), respectively, compared to the first tertile (< 4.80). In Model 2, which was adjusted for multiple confounders, the trend was similar to previous models. The HR (95% CI) for the second (4.80, 10.08) and third (≥10.09) tertiles was 1.37 (1.08, 1.73) and 1.45 (1.16, 1.83), respectively, compared to the reference (< 4.80). In quintile analyses, the fifth quintile (≥14.17) had a higher HR (95% CI) than the reference (< 3.34) in three models. However, in Model 2, the HR (95% CI) of the fourth quintile (8.82–14.16) was 1.55 (1.15, 2.10), which was higher than the HR (95% CI) [1.44 (1.07, 1.94)] of the fifth quintile (≥14.17). The association between NLR and the mortality risk was more significant in the relatively higher NLR quintiles (NLR ≥ 5.65), while the second (3.34–5.64) and third (5.65–8.81) quintiles showed no significantly increased mortality risk compared to the first quintile (< 3.34) in Model 2.

For 90-day mortality, a similar trend was observed. Model 2 (p trend 0.0003), the HR (95% CIs) for the second (4.80–10.08) and third (≥10.09) tertiles was 1.41 (1.15, 1.72) and 1.51 (1.24, 1.84), respectively, compared to the first tertile (< 4.80). In the quintile analyses, a similar decrease in HR (95% CI) [1.52 (1.18, 1.97)] of the fifth quintile

Table 1
Baseline characteristics of the study population.

Characteristics	Neutrophil–lymphocyte ratio			*p* value
	< 4.80	4.80–10.08	≥10.09	
NLR	2.9 ± 1.2	7.2 ± 1.5	20.6 ± 14.7	< 0.001
N	1188	1187	1188	
Age, years	66.8 ± 16.4	68.5 ± 15.9	70.0 ± 14.7	< 0.001
Sex, *n* (%)				0.32
Female	492 (41.4)	480 (40.4)	516 (43.4)	
Male	696 (58.6)	707 (59.6)	672 (56.6)	
Ethnicity, *n* (%)				< 0.001
White	839 (70.6)	847 (71.4)	867 (73.0)	
Black	131 (11.0)	81 (6.8)	57 (4.8)	
Other	218 (18.4)	259 (21.8)	264 (22.2)	
Vital signs				
Heart rate, beats/min	78.1 ± 16.6	82.0 ± 16.4	85.4 ± 17.2	< 0.001
SBP, mm Hg	117.9 ± 17.8	116.0 ± 17.1	113.1 ± 16.2	< 0.001
DBP, mm Hg	62.0 ± 11.6	60.4 ± 11.1	58.8 ± 10.6	< 0.001
MBP, mm Hg	78.8 ± 11.7	77.2 ± 11.2	75.3 ± 10.5	< 0.001
Respiratory rate, beats/min	18.5 ± 3.5	19.3 ± 3.9	20.1 ± 4.2	< 0.001
Temperature, °C	36.7 ± 0.6	36.8 ± 0.7	36.8 ± 0.8	< 0.001
SPO_2, %	97.1 ± 2.0	96.8 ± 2.3	96.9 ± 2.6	0.024
Laboratory parameters				
Neutrophil count, *n* (%)	64.9 ± 12.4	81.3 ± 5.2	88.3 ± 5.8	< 0.001
Lymphocyte count, *n* (%)	26.3 ± 10.9	11.8 ± 2.3	5.4 ± 2.0	< 0.001
Anion gap, mmol/l	13.1 ± 3.2	13.6 ± 3.2	14.2 ± 3.5	< 0.001
Serum bicarbonate, mmol/l	23.0 ± 4.3	22.5 ± 4.8	21.5 ± 5.6	< 0.001
Serum chloride, mmol/l	101.8 ± 5.1	101.4 ± 5.7	101.1 ± 6.5	0.021
Serum glucose, mg/dl	114.1 ± 38.4	120.4 ± 41.5	124.8 ± 46.8	< 0.001
Serum potassium, mmol/l	3.8 ± 0.5	3.8 ± 0.5	3.9 ± 0.6	0.313
Serum sodium, mmol/l	136.9 ± 4.2	136.5 ± 4.9	136.2 ± 5.2	0.008
Hematocrit, %	32.7 ± 6.2	32.0 ± 6.2	31.2 ± 5.6	< 0.001
Hemoglobin, g/dl	11.2 ± 2.2	10.9 ± 2.2	10.6 ± 1.9	< 0.001
Platelet count, 10^9/l	212.8 ± 92.7	215.9 ± 101.2	230.8 ± 113.1	< 0.001
WBC count, 10^9/l	8.6 ± 6.0	10.2 ± 4.1	13.2 ± 6.5	< 0.001
SCr, mg/dl	1.3 ± 1.4	1.5 ± 1.4	1.6 ± 1.4	< 0.001
BUN, mg/dl	23.7 ± 18.6	28.1 ± 19.8	33.6 ± 23.6	< 0.001
Vasoactive drug use, *n* (%)				< 0.001
Yes	344 (29.0)	354 (29.8)	521 (43.9)	
No	844 (71.0)	833 (70.2)	667 (56.1)	
Comorbidities, *n* (%)				
AKI				< 0.001
Yes	704 (59.3)	838 (70.6)	931 (78.4)	
No	484 (40.7)	349 (29.4)	256 (21.6)	
Sepsis				< 0.001
Yes	38 (3.2)	75 (6.3)	141 (11.9)	
No	1150 (96.8)	1112 (93.7)	1047 (88.1)	
Endocarditis				0.004
Yes	0 (0.0)	0 (0.0)	6 (0.5)	
No	1188 (100.0)	1187 (100.0)	1182 (99.5)	
CHF				< 0.001
Yes	290 (24.4)	374 (31.5)	395 (33.2)	
No	898 (75.6)	813 (68.5)	793 (66.8)	
AF				< 0.001
Yes	315 (26.5)	422 (35.6)	453 (38.1)	
No	873 (73.5)	765 (64.4)	735 (61.9)	
Chronic renal disease				0.004
Yes	176 (14.8)	217 (18.3)	237 (19.9)	
No	1012 (85.2)	970 (81.7)	951 (80.1)	
Chronic liver disease				0.7
Yes	34 (2.9)	41 (3.5)	39 (3.3)	
No	1154 (97.1)	1146 (96.5)	1149 (96.7)	
COPD				0.006
Yes	14 (1.2)	23 (1.9)	36 (3.0)	
No	1174 (98.8)	1164 (98.1)	1152 (97.0)	
CAD				< 0.001
Yes	677 (57.0)	604 (50.9)	566 (47.6)	
No	511 (43.0)	583 (49.1)	622 (52.4)	
Stroke				0.416
Yes	75 (6.3)	64 (5.4)	79 (6.6)	
No	1113 (93.7)	1123 (94.6)	1109 (93.4)	
Malignancy				0.013
Yes	108 (9.1)	120 (10.1)	151 (12.7)	
No	1080 (90.9)	1067 (89.9)	1037 (87.3)	
Respiratory failure				< 0.001
Yes	199 (16.8)	293 (24.7)	406 (34.2)	
No	989 (83.2)	894 (75.3)	782 (65.8)	
ARDS				0.251
Yes	18 (1.5)	15 (1.3)	25 (2.1)	
No	1170 (98.5)	1172 (98.7)	1163 (97.9)	
Pneumonia				< 0.001
Yes	170 (14.3)	288 (24.3)	403 (33.9)	
No	1018 (85.7)	899 (75.7)	785 (66.1)	
APS III	39.5 ± 18.2	43.7 ± 18.1	51.9 ± 22.3	< 0.001
Mortality, *n* (%)				
30-day				< 0.001
Yes	118 (9.9)	180 (15.2)	300 (25.3)	
No	1070 (90.1)	1007 (84.8)	888 (74.7)	
90-day				< 0.001
Yes	161 (13.6)	256 (21.6)	394 (33.2)	
No	1027 (86.4)	931 (78.4)	794 (66.8)	

Abbreviations: SBP systolic blood pressure, DBP diastolic blood pressure, MBP mean blood pressure SPO_2 percutaneous oxygen saturation, CHF chronic heart failure, AKI acute kidney injury, CAD coronary artery disease, ARDS acute respiratory distress syndrome, AF atrial fibrillation, COPD chronic obstructive pulmonary disease, WBC white blood cell, SCr serum creatine, BUN blood urea nitrogen, APS III acute physiology score III. Data were presented as the mean ± SD and *n* (%).

(≥14.17) was observed compared to the fourth [8.82–14.16; HR (95% CI) 1.60 (1.23, 2.07)], and the tendency (*p* trend 0.0032) was more significant than that for 30-day mortality (*p* trend 0.0212).

3.3. Subgroup analyses

Subgroup analysis revealed the associations between the NLR and 30-day mortality of CCU patients with different parameters and comorbidities (Table 3). The interactions between most subgroup factors and the risk for 30-day mortality were weakly significant, except for AKI ($p = 0.0344$), respiratory failure ($p = 0.0031$), and pneumonia ($p = 0.0479$). Patients with a history of AKI had a significant lower 30-day mortality risk for NLR 4.80–10.08 [HR (95% CI) 1.35 (1.04, 1.77)] and NLR ≥ 10.09 [HR (95% CI) 2.12 (1.66, 2.72)], While patients with respiratory failure had lower risks with NLR 4.80–10.08 [HR (95% CI) 1.02 (0.72, 1.46) vs HR (95% CI) 1.61 (1.18, 2.19)] and NLR ≥ 10.09 [HR (95% CI) 1.38 (1.00, 1.91) vs. HR (95% CI) 2.92 (2.19, 3.88)]. Similarly, pneumonia patients with NLR 4.80–10.08 [HR (95% CI) 0.94 (0.62, 1.44) vs. HR (95% CI) 1.65 (1.25, 2.18)] and NLR ≥ 10.09 [HR (95% CI) 1.57 (1.08, 2.29) vs. HR (95% CI) 2.74 (2.11, 3.57)] had a

Table 2
HRs (95% CIs) for all-cause mortality across groups of neutrophil-to-lymphocyte ratios.

Exposure	Non-adjusted			Model 1			Model 2		
	HR (95% CIs)	*p* value	*p* trend	HR (95% CIs)	*p* value	*p* trend	HR (95% CIs)	*p* value	*p* trend
30-Day all-cause mortality									
Tertiles			< 0.0001			< 0.0001			0.0050
< 4.80	1			1			1		
4.8–10.08	1.57 (1.24, 1.97)	0.0002		1.49 (1.18, 1.88)	0.0008		1.37 (1.08, 1.73)	0.0102	
≥10.09	2.76 (2.23, 3.41)	< 0.0001		2.55 (2.06, 3.16)	< 0.0001		1.45 (1.16, 1.83)	0.0013	
Quintiles			< 0.0001			< 0.0001			0.0212
< 3.34	1			1			1		
3.34–5.64	1.27 (0.91, 1.76)	0.1615		1.19 (0.85, 1.65)	0.3146		1.09 (0.77, 1.53)	0.6384	
5.65–8.81	1.71 (1.25, 2.34)	0.0007		1.61 (1.18, 2.20)	0.0029		1.34 (0.98, 1.85)	0.0697	
8.82–14.16	2.81 (2.10, 3.76)	< 0.0001		2.52 (1.88, 3.37)	< 0.0001		1.55 (1.15, 2.10)	0.0040	
≥14.17	3.25 (2.44, 4.32)	< 0.0001		2.93 (2.20, 3.91)	< 0.0001		1.44 (1.07, 1.94)	0.0172	
90-Day all-cause mortality									
Tertiles			< 0.0001			< 0.0001			0.0003
< 4.80	1			1			1		
4.8–10.08	1.66 (1.36, 2.02)	< 0.0001		1.59 (1.31, 1.94)	< 0.0001		1.41 (1.15, 1.72)	0.0010	
≥10.09	2.75 (2.29, 3.31)	< 0.0001		2.57 (2.14, 3.10)	< 0.0001		1.51 (1.24, 1.84)	< 0.0001	
Quintiles			< 0.0001			< 0.0001			0.0032
< 3.34	1			1			1		
3.34–5.64	1.40 (1.06, 1.85)	0.0179		1.31 (1.00, 1.74)	0.0542		1.19 (0.90, 1.59)	0.2290	
5.65–8.81	1.79 (1.37, 2.33)	< 0.0001		1.70 (1.30, 2.21)	0.0001		1.38 (1.05, 1.81)	0.0214	
8.82–14.16	2.79 (2.17, 3.58)	< 0.0001		2.52 (1.96, 3.23)	< 0.0001		1.60 (1.23, 2.07)	0.0004	
≥14.17	3.26 (2.55, 4.17)	< 0.0001		2.98 (2.33, 3.81)	< 0.0001		1.52 (1.18, 1.97)	0.0014	

Cox proportional hazards regression models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs).
Model 1 was adjusted for the confounders age, sex and ethnicity.
Model 2 was adjusted for the confounders age, sex and ethnicity, including age, gender, ethnicity, heart rate, SBP, DBP, respiratory rate, temperature, SPO_2, AKI, sepsis, AF, CAD, chronic liver disease, malignancy, respiratory failure, pneumonia, APS score, vasopressin use, anion gap, serum bicarbonate, serum chloride, serum glucose, serum potassium, serum sodium, hematocrit, WBC, SCr, and BUN.

decreased risk for 30-day mortality.

4. Discussion

This study, we determined the correlations between NLR and CCU mortality. Both 30- and 90-day mortality risks were increased in CCU patients with a high NLR. The reference value of NLR in healthy adults, proposed by Forget et al. [18], is 0.87–3.53 and was covered by our first tertile (< 0.48), while the highest values of NLR in a tertile or quintile exceeded 3- to 4-times the normal value, indicating a severe illness and loss of homeostasis. Balta et al. [19,20] reported that the NLR was a useful mortality marker in all conditions; however, it is uncertain whether it can be used as a marker of CCU mortality. Several studies have identified a relationship between NLR values and cardiovascular disease, which is the major problem in the CCU that may lead to a poor prognosis, although it is not fully responsible for death. A meta-analysis of 38 studies demonstrated the relevance of a high NLR and the risks of CAD, ACS, stroke, and composite cardiovascular events [21]. Gibson et al. [22] investigated the association between an elevated NLR and poor survival in 1938 patients undergoing coronary artery bypass grafting. Tamhane et al. [13] demonstrated a relationship between a high NLR and a poor 6-month mortality in patients with ACS. For patients with ST-elevated myocardial infarction undergoing primary coronary intervention, NLR is independently associated with the development of no reflow and in-hospital major adverse cardiac events [23], and predicts for both in-hospital and long-term adverse outcomes [24]. Similarly, it has been investigated as a predictor of both mortality and heart transplantation in patients with heart failure [25]. Therefore, patients with a higher NLR are not only at higher risk for cardiovascular diseases but also has poor outcomes. These studies may explain the correlation between NLR and CCU mortality observed in our study. The NLR correlates with cardiovascular diseases via multiple possible mechanisms. In left ventricular dysfunction and heart failure, systematic stress is triggered with elevated cortisol levels, altering the direction of leukocyte differentiation, leading to lymphopenia [26]. In the pathogenesis of atherosclerosis, neutrophils are involved in atherosclerotic plaque formation by secreting inflammatory cytokines, while lymphocyte regulatory T-cells have anti-atherosclerosis effects [27]. A higher NLR may also be related to AF [28], aortic stenosis [29], endothelial damage, and thromboembolism [30]. These evidences further support the association between NLR and cardiovascular disease and provide explanation for the burden of high NLR in CCU prognosis.

However, an extremely high NLR was related to lower mortality risk. For both 30- and 90-day mortality, the quintile with the highest NLR (≥14.17) showed a slight reduction compared to the second-highest quintile (8.82–14.16), though mortality risk remained high. Bermejo-Martín et al. [31] demonstrated that fewer circulating neutrophils, likely caused by increased neutrophil adhesion to the vascular endothelium in sepsis, was related to higher mortality. The activation of innate T cells can worsen the inflammatory state and may contribute to mortality in ICU patients with sepsis, stroke and respiratory diseases [32]. Both of these possible mechanisms lead to respectively a lower NLR, which may explain the highest mortality risk in the second-highest quintile of NLR.

In subgroup analyses of 30-day mortality, AKI, pneumonia, and respiratory failure were comorbidities that were related to a better prognosis in CCU patients. AKI, defined as a sudden loss of renal function within 7 days, is generally accompanied by poor in-hospital and long-term survival. A cohort study found that ICU patients with AKI surviving 30 days shows higher risks in one-year mortality compared to AKI free patients (20.5–23.8% vs. 10.7%) [33]. However, in another study, the association between 3-year mortality and AKI in 30-day was not significant [34]. Hence, the relationship between AKI and long-term outcome is unclear. It is thought that the long-term survival of AKI patients is not intrinsically related to AKI but is more closely related to advanced age and pre-comorbidities. This might explain our results. Comorbidities may increase the risk or death in non-AKI patients. Similarly, a reduced mortality risk was observed in patients with respiratory failure and pneumonia compared to other CCU patients. The improved survival might be promoted by systemic antimicrobial

Table 3
Subgroup analysis of the associations between 30-day all-cause mortality and the neutrophil–lymphocyte ratio.

Subgroups	*N*	Neutrophil–lymphocyte ratio			*p* for interaction
		< 4.80	4.80–10.08	≥10.09	
AKI					0.0344*
Yes	2473	1	1.35 (1.04, 1.77)	2.12 (1.66, 2.72)	
No	1089	1	1.64 (1.02, 2.64)	3.75 (2.42, 5.81)	
Sepsis					0.0991
Yes	254	1	0.81 (0.42, 1.56)	1.19 (0.66, 2.15)	
No	3309	1	1.51 (1.18, 1.94)	2.48 (1.97, 3.13)	
Endocarditis					
Yes	6	1	NA	NA	
No	3557	1	1.49 (1.18, 1.88)	2.54 (2.05, 3.14)	
CHF					0.4369
Yes	1059	1	1.43 (0.91, 2.25)	2.15 (1.40, 3.30)	
No	2504	1	1.54 (1.17, 2.02)	2.81 (2.19, 3.60)	
AF					0.5043
Yes	1190	1	1.41 (0.98, 2.04)	2.24 (1.59, 3.15)	
No	2373	1	1.49 (1.10, 2.01)	2.75 (2.09, 3.61)	
Chronic renal disease					0.3109
Yes	630	1	1.23 (0.74, 2.05)	1.85 (1.16, 2.95)	
No	2933	1	1.58 (1.21, 2.05)	2.78 (2.18, 3.54)	
Chronic liver disease					0.8899
Yes	114	1	1.18 (0.43, 3.18)	2.14 (0.86, 5.34)	
No	3449	1	1.51 (1.19, 1.91)	2.57 (2.06, 3.20)	
COPD					0.6659
Yes	73	1	0.79 (0.07, 9.37)	0.94 (0.08, 10.55)	
No	3490	1	1.49 (1.18, 1.89)	2.58 (2.08, 3.20)	
CAD					0.0573
Yes	1847	1	1.90 (1.32, 2.73)	3.17 (2.26, 4.45)	
No	1716	1	1.15 (0.85, 1.55)	1.95 (1.48, 2.57)	
Stroke					0.6493
Yes	218	1	1.21 (0.55, 2.70)	1.86 (0.94, 3.66)	
No	3345	1	1.53 (1.20, 1.96)	2.64 (2.11, 3.31)	
Malignancy					0.6171
Yes	379	1	1.30 (0.73, 2.31)	2.05 (1.23, 3.41)	
No	3184	1	1.54 (1.20, 1.99)	2.63 (2.07, 3.32)	
Respiratory failure					0.0031**
Yes	898	1	1.02 (0.72, 1.46)	1.38 (1.00, 1.91)	
No	2665	1	1.61 (1.18, 2.19)	2.92 (2.19, 3.88)	
ARDS					0.0776
Yes	58	1	0.54 (0.10, 2.85)	0.51 (0.12, 2.10)	
No	3505	1	1.54 (1.21, 1.95)	2.66 (2.14, 3.30)	
Pneumonia					0.0479*
Yes	861	1	0.94 (0.62, 1.44)	1.57 (1.08, 2.29)	
No	2702	1	1.65 (1.25, 2.18)	2.74 (2.11, 3.57)	
APS III score					0.1476
< 41	1727	1	1.34 (0.80, 2.22)	2.40 (1.48, 3.91)	
≥41	1836	1	1.28 (0.98, 1.66)	1.82 (1.43, 2.31)	

Confounders adjustment were performed as in Model 1 (Table 2). Cox proportional hazards regression models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs).

** $p < 0.01$.

* $p < 0.05$.

therapy and advanced ventilatory strategies. Moreover, in the AKI subgroup, mortality risk increased with the NLR, which has long been used as a predictor of AKI caused by various comorbidities, including burn surgery, cirrhotic patients, and patients with contrast use in percutaneous coronary intervention [35–37]. A retrospective review of 590 patients with a history of cardiovascular surgery showed that an elevated NLR on postoperative day 1 increased the risk or AKI and 1-year mortality [38]. Lai et al. [39] observed that NLR is independently associated with 30- and 90-day mortality in critically ill patients with AKI. Therefore, the higher NLR in AKI patients reflects severity and mortality.

We investigated the potential use of the NLR for predicting the mortality of patients admitted to the CCU, and proposed a new indicator for CCU monitoring and prognosis. The NLR is an easy-to-measure indicator that is convenient for clinic use. NLR measurement at admission may be used for risk stratification to provide a reference for early intervention. A large population was examined, adding to the strength of our study. However, several limitations of this study should be noted. As a single-center retrospective observational study, inherent biases in this study cannot be ignored. Moreover, the NLR was determined only in patients admitted to the CCU, resulting in unpreventable selection bias. In addition, other than clinical parameters and comorbidities, data on social and natural factors that may affect mortality, could not be obtained, leading to confounding bias. Moreover, the mechanisms through which subgroup factors interacted with the NLR and mortality risk were not fully elucidated. Further research on this is necessary. Finally, no inflammatory mediators other than NLR were measured in this study and the NLR was measured only once. The possible effects of different processes and dynamic changes in the inflammatory response cannot be addressed.

5. Conclusion

A high NLR was associated with increased all-cause mortality risk in CCU patients, although the highest NLR (≥10.17) was associated with slight decreases 30- and 90-day mortality risk compared to the second-

highest NLR (8.82–14.16) in quintile analyses. The NLR is a promising clinical biomarker as an integrated, readily available predictor of CCU mortality. Our findings need to be validated by studies of different populations, particularly large prospective studies with longer follow-up.

Disclosure

The funders of the project were not involved in study design; in the collection; in the data analysis; or in the writing of the report and publication.

Declaration of Competing Interests

Authors declare no competing interests.

References

[1] Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet 392 (2018) 1736–1788, https://doi.org/10.1016/s0140-6736(18)32203-7.

[2] M. Goldfarb, Risk-adjusted overall mortality as a quality measure in the cardiovascular intensive care unit, Cardiol. Rev. 26 (2018) 302–306, https://doi.org/10.1097/crd.0000000000000200.

[3] J. Loughran, T. Puthawala, B.S. Sutton, L.E. Brown, P.J. Pronovost, A.P. DeFilippis, The cardiovascular intensive care unit—an evolving model for health care delivery, J. Intensive Care Med. 32 (2017) 116–123, https://doi.org/10.1177/0885066615624664.

[4] W.B. Fye, Resuscitating a circulation abstract to celebrate the 50th anniversary of the Coronary Care Unit concept, Circulation 124 (2011) 1886–1893, https://doi.org/10.1161/circulationaha.111.033597.

[5] R. Zahorec, Ratio of neutrophil to lymphocyte counts—rapid and simple parameter of systemic inflammation and stress in critically ill, Bratisl. Lek. Listy 102 (2001) 5–14.

[6] B. Azab, M. Zaher, K.F. Weiserbs, E. Torbey, K. Lacossiere, S. Gaddam, R. Gobunsuy, S. Jadonath, D. Baldari, D. McCord, J. Lafferty, Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-ST-elevation myocardial infarction, Am. J. Cardiol. 106 (2010) 470–476, https://doi.org/10.1016/j.amjcard.2010.03.062.

[7] L.R. Ljungstrom, G. Jacobsson, R. Andersson, Neutrophil-lymphocyte count ratio as a biomarker of severe sepsis in Escherichia coli infections in adults, Crit. Care 17 (2013) P25, https://doi.org/10.1186/cc11963.

[8] C.P. de Jager, P.T. van Wijk, R.B. Mathoera, J. de Jongh-Leuvenink, T. van der Poll, P.C. Wever, Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit, Crit. Care 14 (2010) R192, https://doi.org/10.1186/cc9309.

[9] K.J. Halazun, A. Aldoori, H.Z. Malik, A. Al-Mukhtar, K.R. Prasad, G.J. Toogood, J.P. Lodge, Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases, Eur. J. Surg. Oncol. 34 (2008) 55–60, https://doi.org/10.1016/j.ejso.2007.02.014.

[10] R. Terradas, S. Grau, J. Blanch, M. Riu, P. Saballs, X. Castells, J.P. Horcajada, H. Knobel, Eosinophil count and neutrophil-lymphocyte count ratio as prognostic markers in patients with bacteremia: a retrospective cohort study, PLoS One 7 (2012) e42860, , https://doi.org/10.1371/journal.pone.0042860.

[11] L. Yang, Y. Huang, L. Zhou, Y. Dai, G. Hu, High pretreatment neutrophil-to-lymphocyte ratio as a predictor of poor survival prognosis in head and neck squamous cell carcinoma: a systematic review and meta-analysis, Head Neck (2018), https://doi.org/10.1002/hed.25583.

[12] D. Acanfora, M. Gheorghiade, L. Trojano, G. Furgi, E. Pasini, C. Picone, A. Papa, G.L. Iannuzzi, R.O. Bonow, F. Rengo, Relative lymphocyte count: a prognostic indicator of mortality in elderly patients with congestive heart failure, Am. Heart J. 142 (2001) 167–173.

[13] U.U. Tamhane, S. Aneja, D. Montgomery, E.K. Rogers, K.A. Eagle, H.S. Gurm, Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome, Am. J. Cardiol. 102 (2008) 653–657, https://doi.org/10.1016/j.amjcard.2008.05.006.

[14] B.K. Duffy, H.S. Gurm, V. Rajagopal, R. Gupta, S.G. Ellis, D.L. Bhatt, Usefulness of an elevated neutrophil to lymphocyte ratio in predicting long-term mortality after percutaneous coronary intervention, Am. J. Cardiol. 97 (2006) 993–996, https://doi.org/10.1016/j.amjcard.2005.10.034.

[15] A.E. Johnson, T.J. Pollard, L. Shen, L.W. Lehman, M. Feng, M. Ghassemi, B. Moody, P. Szolovits, L.A. Celi, R.G. Mark, MIMIC-III, a freely accessible critical care database, Sci. Data 3 (2016) 160035, , https://doi.org/10.1038/sdata.2016.35.

[16] P.G. Metnitz, R.P. Moreno, E. Almeida, B. Jordan, P. Bauer, R.A. Campos, G. Iapichino, D. Edbrooke, M. Capuzzo, J.R. Le Gall, SAPS 3—from evaluation of the patient to evaluation of the intensive care unit. Part 1: objectives, methods and cohort description, Intensive Care Med. 31 (2005) 1336–1344, https://doi.org/10.1007/s00134-005-2762-6.

[17] V.W.V. Jaddoe, L.L. de Jonge, A. Hofman, O.H. Franco, E.A.P. Steegers, R. Gaillard, First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study, BMJ [Br. Med. J.] 348 (2014) g14, https://doi.org/10.1136/bmj.g14.

[18] P. Forget, C. Khalifa, J.P. Defour, D. Latinne, M.C. Van Pel, M. De Kock, What is the normal value of the neutrophil-to-lymphocyte ratio? BMC. Res. Notes 10 (2017) 12, , https://doi.org/10.1186/s13104-016-2335-5.

[19] S. Balta, S. Demirkol, M. Unlu, Z. Arslan, T. Celik, Neutrophil to lymphocyte ratio may be predict of mortality in all conditions, Br. J. Cancer 109 (2013) 3125–3126, https://doi.org/10.1038/bjc.2013.598.

[20] S. Balta, M. Aparci, C. Ozturk, S. Demirkol, T. Celik, Neutrophil-lymphocyte ratio as an useful mortality marker, Am. J. Emerg. Med. 32 (2014) 1546–1547, https://doi.org/10.1016/j.ajem.2014.09.040.

[21] T. Angkananard, T. Anothaisintawee, M. McEvoy, J. Attia, A. Thakkinstian, Neutrophil lymphocyte ratio and cardiovascular disease risk: a systematic review and meta-analysis, Biomed. Res. Int. 2018 (2018) 2703518, , https://doi.org/10.1155/2018/2703518.

[22] P.H. Gibson, B.L. Croal, B.H. Cuthbertson, G.R. Small, A.I. Ifezulike, G. Gibson, R.R. Jeffrey, K.G. Buchan, H. El-Shafei, G.S. Hillis, Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting, Am. Heart J. 154 (2007) 995–1002, https://doi.org/10.1016/j.ahj.2007.06.043.

[23] M. Akpek, M.G. Kaya, Y.Y. Lam, O. Sahin, D. Elcik, T. Celik, A. Ergin, C.M. Gibson, Relation of neutrophil/lymphocyte ratio to coronary flow to in-hospital major adverse cardiac events in patients with ST-elevated myocardial infarction undergoing primary coronary intervention, Am. J. Cardiol. 110 (2012) 621–627, https://doi.org/10.1016/j.amjcard.2012.04.041.

[24] M.G. Kaya, M. Akpek, Y.Y. Lam, M. Yarlioglues, T. Celik, O. Gunebakmaz, M. Duran, S. Ulucan, A. Keser, A. Oguzhan, M.C. Gibson, Prognostic value of neutrophil/lymphocyte ratio in patients with ST-elevated myocardial infarction undergoing primary coronary intervention: a prospective, multicenter study, Int. J. Cardiol. 168 (2013) 1154–1159, https://doi.org/10.1016/j.ijcard.2012.11.074.

[25] K.V. Huehnergarth, D. Mozaffarian, M.D. Sullivan, B.A. Crane, C.W. Wilkinson, R.L. Lawler, G.B. McDonald, D.P. Fishbein, W.C. Levy, Usefulness of relative lymphocyte count as an independent predictor of death/urgent transplant in heart failure, Am. J. Cardiol. 95 (2005) 1492–1495, https://doi.org/10.1016/j.amjcard.2005.02.022.

[26] S.P. Thomson, L.J. McMahon, C.A. Nugent, Endogenous cortisol: a regulator of the number of lymphocytes in peripheral blood, Clin. Immunol. Immunopathol. 17 (1980) 506–514.

[27] S. Balta, T. Celik, D.P. Mikhailidis, C. Ozturk, S. Demirkol, M. Aparci, A. Iyisoy, The relation between atherosclerosis and the neutrophil-lymphocyte ratio, Clin. Appl. Thromb. Hemost. 22 (2016) 405–411, https://doi.org/10.1177/1076029615569568.

[28] Q. Shao, K. Chen, S.W. Rha, H.E. Lim, G. Li, T. Liu, Usefulness of neutrophil/lymphocyte ratio as a predictor of atrial fibrillation: a meta-analysis, Arch. Med. Res. 46 (2015) 199–206, https://doi.org/10.1016/j.arcmed.2015.03.011.

[29] E. Baysal, C. Burak, S. Cay, T. Aksu, B. Altintas, B. Yaylak, U. Sevuk, O. Bilge, The neutrophil to lymphocyte ratio is associated with severity of rheumatic mitral valve stenosis, J. Blood Med. 6 (2015) 151–156, https://doi.org/10.2147/jbm.S82423.

[30] E. Kurtipek, Z. Buyukterzi, M. Buyukterzi, M.S. Alpaydin, S.S. Erdem, Endothelial dysfunction in patients with pulmonary thromboembolism: neutrophil to lymphocyte ratio and platelet to lymphocyte ratio, Clin. Respir. J. 11 (2017) 78–82, https://doi.org/10.1111/crj.12308.

[31] J.F. Bermejo-Martín, E. Tamayo, G. Ruiz, D. Andaluz-Ojeda, R. Herrán-Monge, A. Muriel-Bombín, M. Fe Muñoz, M. Heredia- Rodríguez, R. Citores, J. Gómez-Herreras, J. Blanco, Express, G. groups, Circulating neutrophil counts and mortality in septic shock, Crit. Care 18 (2014) 407, https://doi.org/10.1186/cc13728.

[32] E.Y. Kim, W.M. Oldham, Innate T cells in the intensive care unit, Mol. Immunol. 105 (2019) 213–223, https://doi.org/10.1016/j.molimm.2018.09.026.

[33] H. Gammelager, C.F. Christiansen, M.B. Johansen, E. Tonnesen, B. Jespersen, H.T. Sorensen, One-year mortality among Danish intensive care patients with acute kidney injury: a cohort study, Crit. Care 16 (2012) R124, https://doi.org/10.1186/cc11420.

[34] H. Mildh, V. Pettila, A.M. Korhonen, S. Karlsson, T. Ala-Kokko, M. Reinikainen, S.T. Vaara, Three-year mortality in 30-day survivors of critical care with acute kidney injury: data from the prospective observational FINNAKI study, Ann. Intensive Care 6 (2016) 118, , https://doi.org/10.1186/s13613-016-0218-5.

[35] H.Y. Kim, Y.G. Kong, J.H. Park, Y.K. Kim, Acute kidney injury after burn surgery: preoperative neutrophil/lymphocyte ratio as a predictive factor, Acta Anaesthesiol. Scand. 63 (2019) 240–247, https://doi.org/10.1111/aas.13255.

[36] J. Gameiro, J. Agapito Fonseca, J. Monteiro Dias, M.J. Melo, S. Jorge, J. Velosa, J.A. Lopes, Prediction of acute kidney injury in cirrhotic patients: a new score combining renal, liver and inflammatory markers, Int. J. Nephrol. Renov. Dis. 11 (2018) 149–154, https://doi.org/10.2147/ijnrd.s163602.

[37] Y. Yuan, H. Qiu, X. Hu, T. Luo, X. Gao, X. Zhao, J. Zhang, Y. Wu, S. Qiao, Y. Yang, R. Gao, Predictive value of inflammatory factors on contrast-induced acute kidney injury in patients who underwent an emergency percutaneous coronary intervention, Clin. Cardiol. 40 (2017) 719–725, https://doi.org/10.1002/clc.22722.

[38] W.H. Kim, J.Y. Park, S.-H. Ok, I.-W. Shin, J.-T. Sohn, Association between the neutrophil/lymphocyte ratio and acute kidney injury after cardiovascular surgery: a retrospective observational study, Medicine (Baltimore) 94 (2015) e1867, https://doi.org/10.1097/MD.0000000000001867.

[39] L.L. Fan, Y.J. Wang, C.J. Nan, Y.H. Chen, H.X. Su, Neutrophil-lymphocyte ratio is associated with all-cause mortality among critically ill patients with acute kidney injury, Clin. Chim. Acta 490 (2019) 207–213, https://doi.org/10.1016/j.cca.2018.09.014.