Original Article

The association between neutrophil-to-lymphocyte count ratio and mortality in septic patients: a retrospective analysis of the MIMIC-III database

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Background: Neutrophil-to-lymphocyte count ratio (NLCR) has been shown as a feasible parameter associated with outcomes of tumor patients and an accessible predictor of bacteremia. However, only a handful of research shed the light on the association between NLCR and outcomes of septic patients. This study is aimed to evaluate the association between NLCR and all-cause mortality in a population of adult septic patients.

Methods: We extracted clinical data from Medical Information Mart for Intensive Care (MIMIC)-III V1.4, a free, large-scale, single-center database. NLCR was computed individually. Patients were categorized by quartiles of NLCR. The associations between NLCR quartiles and 28-day all-cause mortality in septic patients were assessed using Cox proportional hazards models and subgroup analyzes. To evaluate the accuracy of NLCR in predicting 28-day mortality of sepsis, receiver operator characteristic curves (ROC), areas under the curve (AUC), and the Youden's J Index were calculated. Other outcomes included 7-day all-cause mortality, mortality in the intensive care units (ICU), in-hospital mortality and length of ICU stay.

Results: A total of 3,043 eligible patients were included in the study, of which, 760, 759, 766 and 758 patients were fallen in the first quartile (≤5.89), the second quartile (>5.89, ≤10.69), the third quartile (>10.69, ≤20.25) and the fourth quartile (>20.25) of NLCR, respectively. The 7-day mortality (13.4%, 9.9%, 13.6% and 14.2%; P=0.064) showed no difference in the four quartiles. In multivariate analysis, after adjusting for confounding factors, the highest NLCR quartile (>20.25) was associated with increased 28-day all-cause mortality [hazard ratio (HR) 1.22, 95% Cl: 1.01–1.49; P=0.046]. The areas under the receiver operating characteristic curves (AUROCs) for NLCR was 0.553 (95% CI: 0.529–0.576) for 28-day mortality.

Conclusions: High NLCR (>20.25) is independently related to increased 28-day all-cause mortality in adult septic patients of a limited sensibility and specificity. Further large multi-center prospective studies are needed to confirm such relationship and to validate whose clinical significance.

Keywords: Neutrophil-to-lymphocyte count ratio (NLCR); Medical Information Mart for Intensive Care (MIMIC); sepsis patients; mortality

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Introduction

Sepsis, a serious and life-threatening syndrome designated as immune disorder and organ dysfunction subsequent to the host response to infection, is notoriously known for its favor to patients in the intensive care unit (ICU) (1). A great leap that had been made over these years in the field of critical care medicine though, it was only contributed to a small step in lowering the mortality rate of septic patients which is still hovering at around 30% nowadays (2). Therefore, it's crucial for doctors to predict the prognosis of septic patients.

In 2001, Zahorec *et al.* were first to propose that neutrophil-to-lymphocyte count ratio (NLCR) could be used as an additional infection marker in clinical practice, and suggesting NLCR as an indicator of disease severity as well (3). NLCR boasts its simplicity, cost-efficiency and feasibility compared with many other previously proposed biomarkers, making which promising for clinicians to diagnose through (4).

Accumulating evidence shows that NLCR can be an independent predictor of poor survival in patients with tumor and cardiovascular disease (5,6). However, no consensus has been reached on the relationship between NLCR level and clinical prognosis of patients with sepsis up till now. One research found that higher NLCR measured at the time of admission to ICU was significantly related to higher 28-day mortality in either unselected critically ill patients or non-septic patients but not in patients with sepsis (7). Whereas several other studies linked NLCR to short- or long-term death of sepsis (8-12).

Accordingly, the clinical value of NLCR in patients with sepsis remain controversial. In this study, we obtained a large quantity of patient data from Medical Information Mart for Intensive Care III (MIMIC-III) database to analyze whether NLCR could be an independent predictor of all-cause mortality in adult septic patients.

Methods

Database

All data used in the study was extracted from the MIMIC-III version 1.4 (v1.4) which is a large, single-center, publicly available critical care database (13). It includes unidentified health-related data of more than 60,000 ICU stays at Beth Israel Deaconess Medical Center (BIDMC) from June 2001 to October 2012. MIMIC-III was built by researchers at the Massachusetts Institute of Technology (MIT) Laboratory for Computational Physiology and collaborating research groups. To get access to the database, we complete the course "Protecting Human Research Participants" at the website of National Institutes of Health and obtained the certification (Record ID: 28006489). The project was approved by the institutional review boards of the MIT and BIDMC and was granted a waiver of informed consent.

Patients population

Adult patients (≥18 years old) from medical ICU (MICU) and surgical ICU (SICU) with a diagnosis of sepsis defined by ICD-9-based Angus implementation (14) were selected from MIMIC-III v1.4 using computer code. Worth noticing, only first ICU admission of each patient with exact lymphocyte and neutrophils record within 24 hours after ICU admission were selected into final cohort. Patients unable to meet the inclusion criteria above were excluded.

Data extraction

Structured Query Language (SQL) and PostgreSQL tools (version 9.6) were used for data extraction. Data of following aspects were extracted directly or calculated with the data from the database: age, gender, ethnicity, first care unit, comorbidities, laboratory parameters, the time of patients' getting into and out of hospital and ICU and date of dead of patients. The comorbidities included atrial fibrillation (AFIB), coronary artery disease (CAD), congestive heart failure (CHF), diabetes, malignancy, chronic renal disease, liver disease. The laboratory parameters included hemoglobin, platelet, sodium, potassium, bicarbonate, chloride, creatinine, white blood cell counts, lymphocyte counts and neutrophil counts. Furthermore, the sequential organ failure assessment (SOFA) score (15) and simplified acute physiology score II (SAPSII) (16) were calculated for each patient with the SQL code provided by Johnson *et al.* (17). NLCR was computed based on the first laboratory parameters if there were more than one test of laboratory parameters mentioned above within 24 hours as a ratio of neutrophil/lymphocyte value. Patients were categorized into four groups (from the first quartile to the fourth quartile) according to the quartile of the initial NLCR value within 24 hours after ICU admission. The outcomes of our study included 7- and 28-day all-cause mortality, mortality in the

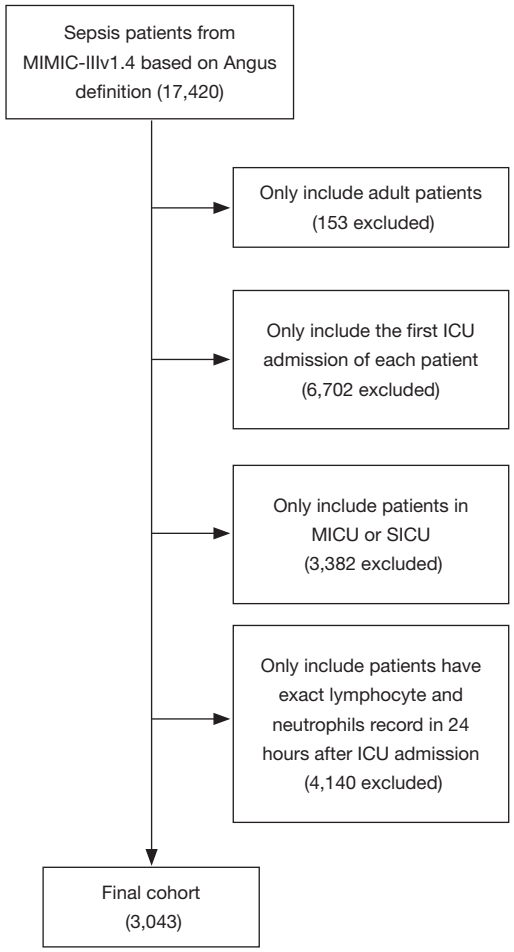

Figure 1 Study cohort. Illustration of inclusion criteria as utilized to select the final cohort of 3,043 patients. MIMIC-III V1.4, Medical Information Mart for Intensive Care III version 1.4; ICU, intensive care units; SICU, surgical intensive care units; MICU, medical intensive care units.

ICU, in-hospital mortality and length of ICU stay.

Statistical analysis

Baseline characteristics of all patients were stratified by NLCR quartiles. Continuous variables were presented as median and interquartile range (IQR) and Wilcoxon rank-sum test was used for comparisons between groups. Categorical data were expressed as absolute values and percentages and were compared using chi-square test or Fisher's exact test as appropriate. We compared the survival rates using log-rank tests and present the results as Kaplan-Meier curves. The outcomes data were compared with chi-square test or Wilcoxon rank-sum test as appropriate based on NLCR quartiles. Multivariable cox proportional hazards models were constructed to determine the independent effect of the quartiles of NLCR on 28-day mortality. Variables with P<0.05 in the univariate analysis were further incorporated into multivariate Cox proportional hazard models. Variables were selected by a method of Forward: LR. The probability for stepwise is 0.05 for entry and 0.10 for removal. The results were express as hazard ratios (HRs) with 95% confidence intervals (CIs). To evaluate the accuracy of the NLCR in predicting 28-day mortality of sepsis, receiver operating characteristic (ROC) curves were constructed and Youden's J Indexes were calculated for the initial NLCR as well as SOFA score and SAPS II score. The optimal cut-off value of NLCR is determined by the highest Youden's J Index.

Subgroup analyses were employed to evaluate the association between the NLCR and 28-day all-cause mortality, including age, gender, comorbidities, laboratory parameters, SOFA score and SAPSII score. The data were analyzed with SPSS software (v16.0; IBM, Armonk, NY). A two-tailed P<0.05 was considered statistically significant.

Results

Population characteristics

A total of 3,043 patients with complete data of neutrophil and lymphocyte available within 24 hours after ICU admission were included in this study. Complete designated endpoint data was available in all included patients. The procedure of data selection according to the criteria mention above is presented in *Figure 1*.

Baseline characteristics of the study population are shown in *Table 1*. The median age of the entire cohort was 67 years old (IQR, 54 to 79). Fifty-point-six percent of the patients were male. A vast majority of the patients were Caucasians (defined as "white" in the database). Eighty-six-point-one percent of patients were treated as medical inpatients, 13.9% as surgical admissions. The median of SOFA score was 6 (IQR, 4 to 8) and the median of SAPSII score was 41 (IQR, 33 to 53). Seven hundred and sixty, 759, 766 and 758 patients respectively belonged to the first quartile (≤5.89), the second quartile (>5.89, ≤10.69), the third quartile (>10.69, ≤20.25) and the fourth quartile (>20.25) of NLCR. Patients with NLCR >20.25 were more tend to be elderly with a history of AFIB and CHF while patients with NLCR <5.89 were more likely to have comorbidities of malignancy

Table 1 Characteristics of the study patients by NLCR level

Characteristics	Total (n=3,043)	NLCR levels				P
		≤5.89 (n=760)	>5.89, ≤10.69 (n=759)	>10.69, ≤20.25 (n=766)	>20.25 (n=758)	
Demographics						
Age (years), median [IQR]	67 [54, 79]	63 [51, 78]	65 [53, 79]	69 [54, 81]	69 [57, 81]	<0.001
Gender, n (%)						0.981
Male	1,539 (50.6)	387 (50.9)	387 (51.0)	384 (50.1)	381 (50.3)	
Female	1,504 (49.4)	373 (49.1)	372 (49)	382 (49.9)	377 (49.7)	
Ethnicity, n (%)						0.001
White	2,166 (71.2)	522 (68.7)	533 (70.2)	563 (73.5)	548 (72.3)	
Black	267 (8.8)	84 (11.1)	85 (11.2)	58 (7.6)	40 (5.3)	
Hispanic	91 (3.0)	29 (3.8)	21 (2.8)	20 (2.6)	21 (2.8)	
Other	519 (17.1)	125 (16.4)	120 (15.8)	125 (16.3)	149 (19.7)	
Care unit, n (%)						0.122
SICU	423 (13.9)	113 (14.9)	108 (14.2)	116 (15.1)	86 (11.3)	
MICU	2,620 (86.1)	647 (85.1)	651 (85.8)	650 (84.9)	672 (88.7)	
Time, n (%)*						0.298
≤6 h	1,831 (60.2)	432 (23.6)	442 (24.1)	486 (26.5)	471 (25.7)	
>6, ≤12 h	721 (23.7)	190 (26.4)	196 (27.2)	166 (23.0)	169 (23.4)	
>12, ≤18 h	339 (11.1)	95 (28.0)	85 (25.1)	79 (23.3)	80 (23.6)	
>18, ≤24 h	152 (5.0)	43 (28.3)	36 (23.7)	35 (23.0)	38 (25.0)	
Comorbidities, n (%)						
AFIB	789 (25.9)	158 (20.0)	201 (26.5)	195 (25.5)	235 (31.0)	<0.001
CAD	443 (14.6)	86 (11.3)	99 (13.0)	132 (17.2)	126 (16.6)	0.002
CHF	899 (29.5)	182 (23.9)	222 (29.2)	247 (32.2)	248 (32.7)	<0.001
Diabetes	851 (28.0)	203 (26.7)	221 (29.1)	223 (29.1)	204 (26.9)	0.57
Malignancy	741 (24.4)	226 (29.7)	167 (22.0)	152 (19.8)	196 (25.9)	<0.001
Liver	339 (11.1)	110 (14.5)	90 (11.9)	76 (9.9)	63 (8.3)	0.001
Renal	462 (15.2)	105 (13.8)	110 (14.5)	119 (15.5)	128 (16.9)	0.367
Laboratory parameters, median [IQR]						
Hemoglobin (g/dL)	10.4 [9.2, 11.8]	10.1 [8.8, 11.6]	10.4 [9.4, 11.9]	10.5 [9.4, 11.9]	10.5 [9.2, 11.9]	0.013
Platelet (10^3/μL)	199.0 [123.0, 286.0]	157.0 [88.0, 241.8]	202 [129.0, 290.0]	212.5 [144.0, 305.0]	208.5 [133.0, 305.0]	<0.001
Sodium (mEq/L)	139 [135, 142]	139 [136, 142]	139 [136, 142]	139 [136, 142]	138 [135, 141]	0.264
Potassium (mEq/L)	4.0 [3.6, 4.5]	4.0 [3.5, 4.5]	4.0 [3.6, 4.5]	4.1 [3.6, 4.5]	4.1 [3.6, 4.6]	0.022
Bicarbonate (mEq/L)	22 [19, 25]	22 [19, 26]	22 [19, 25]	22 [19, 25]	21 [18, 25]	0.005
Chloride (mEq/L)	106 [101, 110]	106 [102, 111]	106 [101, 110]	106 [101, 110]	105 [100, 109]	0.086

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (n=3,043)	NLCR levels				P
		≤5.89 (n=760)	>5.89, ≤10.69 (n=759)	>10.69, ≤20.25 (n=766)	>20.25 (n=758)	
White blood cell (10^3/μL)	12.3 [8.1, 18.1]	7.8 [4.2, 11.4]	11.4 [8.0, 20.3]	13.9 [10.1, 18.8]	17.6 [12.1, 24.8]	<0.001
Neutrophil (10^3/μL)	9.9 [6.2, 15.0]	5.0 [2.3, 7.6]	9.2 [6.5, 12.4]	12.0 [8.6, 16.0]	15.4 [10.4, 21.2]	<0.001
Lymphocyte (10^3/μL)	0.9 [0.5, 1.4]	1.4 [0.8, 2.1]	1.2 [0.8, 1.5]	0.8 [0.6, 1.1]	0.4 [0.3, 0.6]	<0.001
Creatinine (mg/dL)	1.2 [0.8, 2.1]	1.1 [0.7, 1.8]	1.2 [0.8, 2.0]	1.2 [0.8, 2.0]	1.4 [0.9, 2.3]	<0.001
Scoring systems, median [IQR]						
SOFA	6 [4, 8]	6 [3, 9]	5 [3, 8]	5 [3, 8]	6 [4, 9]	<0.001
SAPSII	41 [33, 53]	39 [31, 51]	40 [31, 51]	42 [33, 52]	46 [36, 56]	<0.001

*, time interval of complete blood count test after admission. NLCR, neutrophil-to-lymphocyte count ratio; SICU, surgical intensive care units; MICU, medical intensive care units; AFIB, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; SOFA, sequential organ failure assessment; SAPSII, simplified acute physiology score II; IQR, interquartile range.

and hepatic diseases.

Association of neutrophil-to-lymphocyte ratio with outcomes

The overall 28-day all-cause mortality of the whole cohort was 26.6% and was different in four NLCR quartiles (P<0.001) while 7-day all-cause mortality was 12.7% but showed no difference (P=0.064). Mortality in ICU (16.3%, 12.8%, 16.7%, 21.6%; P<0.001), in-hospital mortality (21.8%, 19.2%, 23.6%, 30.5%; P<0.001) and length of ICU stay (median: 3.1, 3.5, 3.7, 4.4 days; P<0.001) were different in four NLCR quartiles. And length of ICU stays showed a tendency of increasing with the NLCR quartiles (*Table 2*).

The association between NLCR quartiles and 28-day mortality was shown in the Kaplan-Meier curves in *Figure 2*. In univariate and multivariate analysis, NLCR was stratified by quartiles to determine whether NLCR was independent-associated with all-cause mortality (*Table 3*). In univariate model, the fourth quartile of NLCR increased the risk of 28-day mortality. In multivariate model, after adjusting for age, ethnicity, care unit, malignancy, liver disease, hemoglobin, potassium, creatinine, SOFA score and SAPSII score, the fourth quartile remained a statistically significant risk factor of 28-day all-cause mortality (HR 1.22, 95% CI: 1.01–1.49) (*Table 3*).

Discriminatory threshold of 28-day mortality

The discriminatory ability of SAPSII, SOFA and the NLCR to predict 28-day mortality is shown in *Figure 3*. The areas under the receiver operating characteristic curves (AUROCs) for NLCR was 0.553 (95% CI: 0.529–0.576) for 28-day mortality. The discriminatory NLCR thresholds were 14 (sensitivity =0.46, specificity =0.65) for 28-day mortality.

Subgroup analyses

Subgroup analyses were performed to assess the association between the NLCR and 28-day all-cause mortality (*Table 4*). In most strata, the results in each subgroup population were consistent with the main analysis. Patients with SOFA score <5 and patients with SAPSII score <40 presented an increased risk with high NLCR (>20.25) markedly (HR, 95% CI: 3.19, 1.97–5.15; 2.71, 1.70–4.34) (*Table 4*).

Discussion

We evaluated 3,043 patients to investigate the relationship between NLCR and all-cause mortality in patients with sepsis. We found that the high NLCR (>20.25) measured in 24 hours after admission to ICU was significantly associated with higher 28-day mortality in septic patients compared with the first quartile (NLCR ≤5.89). The findings remained robust after adjustment for multiple potential confounding variables, indicating that NLCR may be an independent risk factor of the outcome in septic patients. Our results were consistent with the previous study of NLCR tested in a population of oncology patients with

Table 2 Outcomes of patients according to the quartiles of NLCR quartiles

Outcome	Total (n=3,043)	First quartile (n=760)	Second quartile (n=759)	Third quartile (n=766)	Fourth quartile (n=758)	P
Mortality, n (%)						
7-day	387 (12.7)	101 (13.3)	75 (9.9)	104 (13.6)	107 (14.1)	0.064
28-day	809 (26.6)	179 (23.6)	167 (22.0)	203 (26.5)	260 (34.3)	<0.001
ICU	513 (16.9)	124 (16.3)	97 (12.8)	128 (16.7)	164 (21.6)	<0.001
Hospital	724 (23.8)	166 (21.8)	146 (19.2)	181 (23.6)	231 (30.5)	<0.001
Length of stay, median (IQR)						
ICU, days	3.7 (1.9, 8.1)	3.1 (1.7, 4.5)	3.5 (1.8, 8.5)	3.7 (2.0, 8.1)	4.4 (2.3, 8.8)	<0.001

NLCR, neutrophil-to-lymphocyte count ratio; ICU, intensive care units; IQR, interquartile range.

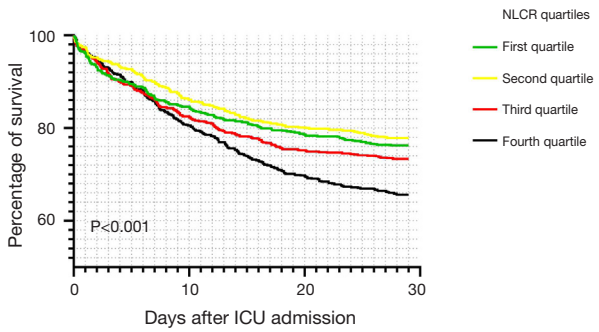

Figure 2 Kaplan-Meier curves showing the association between the NLCR quartiles and the 28-day mortality. ICU, intensive care units; NLCR, neutrophil-to-lymphocyte count ratio.

sepsis (3) but contrary to that of Salciccioli *et al.*'s finding (7), which contradicts the relationship between NLCR and 28-day mortality in septic patients. The difference in cohort sizes may explain the divergent conclusion as ours is almost twice as much as Salciccioli's. Besides, we found that the lowest NLCR group did not reflect the lowest mortality. Compared with the second quartile, the absolute neutrophil count of first quartile was significantly lower than the one of the second quartile. A study conducted by Bermejo-Martín *et al.* indicated that low circulating neutrophil count could negatively affect the outcome of septic shock patients due to whose inability to launch effective innate responses against the invading microbes (18). Increased neutrophil adhesion to vascular endothelium, resulting in endothelial damage and a decrease in circulating neutrophils (19) may aid in elucidating why the lowest NLCR group did not display the lowest mortality in our study.

NLCR reflects the relationship between the numbers of neutrophil and lymphocyte circulating in human body. The ratio can be used as an indicator of systemic inflammation as well (3). As a number of pathophysiologic processes in sepsis and septic shock are potentially associated with systemic inflammation, NLCR can also play a role in demonstrating sepsis and septic shock. Delayed apoptosis of neutrophil (20) and accelerated apoptosis of lymphocytes (21) were investigated during sepsis. Delayal of neutrophil apoptosis, as well as the upswing in immature neutrophil releasing, both contribute to the significant elevation of circulating neutrophils in septic patients, resulting in a boost of neutrophil-mediated killing, an innate immune response, and phenomenal tissue damage adversely (22). Moreover, it has been shown that neutrophils produce a massive amount of immunosuppressive cytokine IL-10 during sepsis (23), which may promote infection. Aside of neutrophils, lymphocytes are also vital for maintaining appropriate inflammatory responses. Growing apoptosis of lymphocytes in thymus and spleen lead to immunosuppression, multiple organ dysfunction and death (24), probably related to a prolonged, detrimental inflammatory state (25). Le Tulzo *et al.* (21) showed that higher mortality in septic patients are associated with failure to recover a normal non-apoptotic lymphocyte count. Another research focused on neonatal sepsis revealed that treatment reducing apoptosis of peripheral blood T lymphocytes could improve the prognosis of sepsis (26). And our hypothesis that NLCR is associated with outcomes is primarily based on the studies mentioned above. As our data showed, patients with higher NLCR had higher white blood cell count, higher neutrophil count, lower lymphocytes count and higher 28-day mortality. The mechanisms described above may provide a rationale for the result.

Table 3 Cox proportional hazard models exploring the association of NLCR quartiles with 28-day mortality

Factor	Univariate model		Multivariate model	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age (years)				
≤45	Reference	–	Reference	–
>45, ≤64	1.65 (1.24, 2.20)	0.001	1.17 (0.87, 1.57)	0.291
>64, ≤90	2.17 (1.66, 2.85)	<0.001	1.40 (1.04, 1.87)	0.025
>90	2.41 (1.71, 3.42)	<0.001	1.80 (1.25, 2.61)	0.002
Gender (male)	1.11 (0.97, 1.27)	0.143	–	–
Ethnicity				
White	Reference	–	Reference	–
Black	0.95 (0.73, 1.23)	0.705	0.94 (0.72, 1.22)	0.637
Hispanic	0.80 (0.51, 1.26)	0.333	1.02 (0.64, 1.61)	0.940
Other	1.45 (1.23, 1.72)	<0.001	1.45 (1.22, 1.72)	<0.001
Time*				
≤6 h	Reference	–	–	–
>6, ≤12 h	1.04 (0.88, 1.22)	0.674	–	–
>12, ≤18 h	1.07 (0.86, 1.34)	0.527	–	–
>18, ≤24 h	1.14 (0.83, 1.55)	0.423	–	–
Care unit (MICU)	0.69 (0.55, 0.86)	0.001	0.79 (0.63, 0.99)	0.043
Comorbidities				
AFIB	1.44 (1.24, 1.66)	<0.001	Not selected	–
CAD	1.06 (0.88, 1.29)	0.538	–	–
CHF	1.18 (1.02, 1.36)	0.029	Not selected	
Diabetes	0.95 (0.81, 1.10)	0.474	–	–
Malignancy	1.74 (1.50, 2.01)	<0.001	1.59 (1.36, 1.85)	<0.001
Liver	1.88 (1.57, 2.26)	<0.001	1.92 (1.57, 2.36)	<0.001
Renal	1.07 (0.89, 1.30)	0.453	–	–
Laboratory parameters				
Hemoglobin	0.92 (0.89, 0.96)	<0.001	0.96 (0.93, 1.00)	0.024
Platelet	1.00 (1.00, 1.00)	0.010	Not selected	–
Sodium	0.99 (0.98, 1.01)	0.316	–	–
Potassium	1.30 (1.21, 1.41)	<0.001	1.17 (1.08, 1.27)	<0.001
Bicarbonate	0.95 (0.94, 0.97)	<0.001	Not selected	–
Chloride	0.99 (0.98, 1.00)	0.197	–	–
Creatinine	1.08 (1.05, 1.12)	<0.001	0.92 (0.88, 0.97)	0.001
White Blood Cell	1.01 (1.00, 1.01)	<0.001	Not selected	–

Table 3 (*continued*)

Table 3 (*continued*)

Factor	Univariate model		Multivariate model	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Neutrophil	1.01 (1.01, 1.02)	<0.001	Not selected	–
Lymphocyte	0.96 (0.91, 1.02)	0.170	–	–
Scoring system				
SOFA	1.18 (1.16, 1.20)	<0.001	1.06 (1.03, 1.09)	<0.001
SAPSII	1.05 (1.05, 1.06)	<0.001	1.04 (1.03, 1.05)	<0.001
NLCR				
First quartile	Reference	–	Reference	–
Second quartile	0.91 (0.74, 1.13)	0.391	0.92 (0.75, 1.14)	0.460
Third quartile	1.14 (0.93, 1.39)	0.202	1.18 (0.96, 1.45)	0.112
Fourth quartile	1.50 (1.24, 1.82)	<0.001	1.22 (1.01, 1.49)	0.046

*, time interval of complete blood count test after admission. MICU, medical intensive care units; AFIB, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; SOFA, sequential organ failure assessment; SAPSII, simplified acute physiology score II; NLCR, neutrophil-to-lymphocyte count ratio; CI, confidence interval.

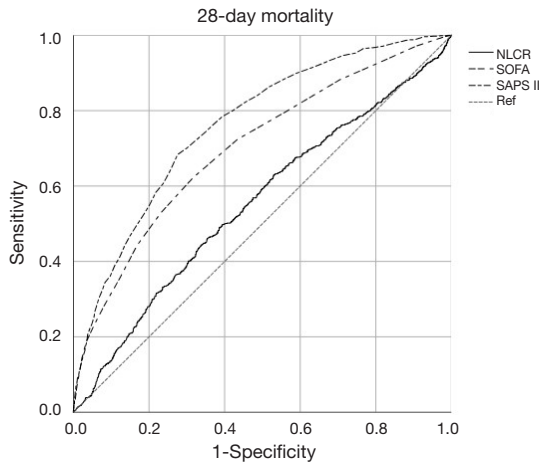

Figure 3 Receiver operating characteristic curves for the best neutrophil-to-lymphocyte count ratio (NLCR) thresholds to predict 28-day mortality. SOFA, sequential organ failure assessment; SAPSII, simplified acute physiology score II.

We also found that patients with SOFA score <5 and patients with SAPSII score <40 presented remarkably increased risk with high NLCR (>20.25), and high NLCR (>20.25) patients showing the highest 28-day mortality. It is a surprising result. Patients with SOFA score <5 and patients with SAPSII score <40 were not as serious as the patients with SOFA score ≥5 and patients with SAPSII score ≥40 respectively. We hypothesized that immune disorder might not play a major role in the group of more critical patients, while the existing organ dysfunction might affect more on the fatal outcomes. The insignificant ascending HR for 28-day mortality of the patients along with the increment of NLCR can be attributed to the hypothesis. On the contrary, patients with SOFA score <5 and patients with SAPSII score <40, who were less critical compared with patients with SOFA score ≥5 and patients with SAPSII score ≥40, immune factors maybe still play the leading role on the outcome and the patients' HR for 28-day mortality increased significantly as the NLCR increased. This result may imply that NLCR might be more valuable for septic patients who were of less critical conditions. Relevant studies should be carried out to test and verify the hypothesis.

Previous studies have reported that increased NLCR was associated with worse outcomes in patients with tumor of the brain (27), lung (28), breast (29), colon (30) and pancreas (31). Moreover, a prospective study found that higher NLCR was associated with higher death rate in patients with acute coronary syndrome (32). Some studies reported that NLCR was a predictor of bacteremia and can be used to detect the presence of sepsis (7,33). These studies implied that NLCR may be reflects the severity of many kinds of diseases. So far, research on the association

Table 4 Subgroup analysis of the associations between NLCR and 28-day mortality

Characteristics	No. of patients	NLRC				P
		≤5.89	>5.89, ≤10.69, HR (95% CI)	>10.69, ≤20.25, HR (95% CI)	>20.25, HR (95% CI)	
Age (years)						0.313
≤45	385	1.0 (ref)	0.56 (0.27, 1.15)	0.51 (0.24, 1.07)	1.15 (0.60, 2.20)	
>45, ≤64	966	1.0 (ref)	0.65 (0.46, 0.93)	0.75 (0.53, 1.06)	0.86 (0.60, 1.23)	
>64, ≤90	1,462	1.0 (ref)	0.86 (0.64, 1.16)	1.06 (0.81, 1.40)	1.46 (1.13, 1.90)	
>90	206	1.0 (ref)	0.66 (0.30, 1.4)	1.30 (0.65, 2.53)	1.11 (0.56, 2.22)	
Gender						0.238
Female	1,496	1.0 (ref)	0.98 (0.72, 1.33)	1.02 (0.75, 1.37)	1.62 (1.23, 2.13)	
Male	1,527	1.0 (ref)	0.86 (0.64, 1.15)	1.26 (0.96, 1.65)	1.41 (1.08, 1.83)	
AFIB						0.859
Yes	785	1.0 (ref)	0.90 (0.60, 1.33)	1.27 (0.88, 1.85)	1.51 (1.06, 2.15)	
No	2,238	1.0 (ref)	0.90 (0.70, 1.15)	1.07 (0.84, 1.36)	1.44 (1.15, 1.81)	
CAD						0.261
Yes	439	1.0 (ref)	1.38 (0.74, 2.58)	1.39 (0.76, 2.53)	2.39 (1.36, 4.21)	
No	2,584	1.0 (ref)	0.87 (0.69, 1.08)	1.12 (0.91, 1.39)	1.40 (1.14, 1.72)	
CHF						0.796
Yes	893	1.0 (ref)	0.89 (0.53, 1.52)	0.89 (0.53, 1.47)	1.05 (0.64, 1.72)	
No	2,130	1.0 (ref)	0.95 (0.74, 1.21)	1.18 (0.93, 1.50)	1.48 (1.17, 1.86)	
Diabetes						0.738
Yes	846	1.0 (ref)	0.80 (0.53, 1.19)	1.00 (0.68, 1.47)	1.49 (1.03, 2.14)	
No	2,177	1.0 (ref)	0.96 (0.75, 1.23)	1.21 (0.95, 1.53)	1.52 (1.21, 1.90)	
Malignancy						0.844
Yes	734	1.0 (ref)	0.92 (0.64, 1.32)	1.21 (0.86, 1.72)	1.69 (1.25, 2.30)	
No	2,289	1.0 (ref)	0.97 (0.75, 1.26)	1.20 (0.94, 1.54)	1.48 (1.16, 1.89)	
Liver						0.269
Yes	335	1.0 (ref)	1.00 (0.64, 1.55)	1.26 (0.80, 1.98)	1..13 (0.70, 1.83)	
No	2,688	1.0 (ref)	0.92 (0.72, 1.17)	1.18 (0.94, 1.48)	1.67 (1.35, 2.07)	
Renal						0.502
Yes	458	1.0 (ref)	1.00 (0.56, 1.80)	1.55 (0.91, 2.64)	2.00 (1.21, 3.30)	
No	2,565	1.0 (ref)	0.90 (0.72, 1.13)	1.08 (0.87, 1.35)	1.43 (1.16, 1.76)	
Hemoglobin (g/dL)						0.026
<11	1,905	1.0 (ref)	0.95 (0.73, 1.24)	1.41 (1.11, 1.79)	1.68 (1.33, 2.12)	
≥16	1,115	1.0 (ref)	0.85 (0.59, 1.21)	0.75 (0.52, 1.09)	1.20 (0.86, 1.67)	

Table 4 (*continued*)

Table 4 (*continued*)

Characteristics	No. of patients	NLRC				P
		≤5.89	>5.89, ≤10.69, HR (95% CI)	>10.69, ≤20.25, HR (95% CI)	>20.25, HR (95% CI)	
Platelet (10^3/μL)						0.207
<100	555	1.0 (ref)	1.03 (0.71, 1.48)	1.11 (0.75, 1.63)	1.14 (0.79, 1.64)	
≥100, ≤300	1,785	1.0 (ref)	1.00 (0.73, 1.35)	1.22 (0.91, 1.63)	1.70 (1.29, 2.24)	
>300	680	1.0 (ref)	1.14 (0.65, 1.98)	1.81 (1.08, 3.03)	2.46 (1.49, 4.05)	
Sodium						0.778
<135	614	1.0 (ref)	0.87 (0.56, 1.33)	0.91 (0.59, 1.42)	1.47 (1.01, 2.14)	
≥135, ≤145	2,116	1.0 (ref)	0.93 (0.71, 1.21)	1.19 (0.93, 1.53)	1.47 (1.16, 1.88)	
>145	291	1.0 (ref)	0.88 (0.51, 1.54)	1.47 (0.87, 2.50)	1.75 (1.02, 2.99)	
Potassium (mEq/L)						0.095
<3.5	504	1.0 (ref)	1.04 (0.58, 1.89)	1.19 (0.69, 2.08)	1.70 (1.01, 2.87)	
≥3.5, ≤5.5	2,358	1.0 (ref)	0.89 (.70, 1.13)	1.21 (0.97, 1.51)	1.55 (1.25, 1.92)	
>5.5	159	1.0 (ref)	0.72 (0.36, 1.43)	0.39 (0.17, 0.89)	0.66 (0.33, 1.35)	
Bicarbonate (mEq/L)						0.009
<21.4	1,405	1.0 (ref)	0.84 (0.63, 1.12)	1.04 (0.80, 1.35)	1.04 (0.80, 1.35)	
≥21.4, ≤27.3	1,167	1.0 (ref)	0.94 (0.66, 1.34)	1.10 (0.77, 1.57)	2.04 (1.48, 2.81)	
>27.3	448	1.0 (ref)	1.13 (0.60, 2.12)	1.42 (0.77, 2.61)	2.43 (1.38, 4.25)	
Chloride (mEq/L)						0.499
<96	208	1.0 (ref)	0.71 (0.35, 1.43)	0.71 (0.32, 1.54)	1.22 (0.65, 2.27)	
≥96, ≤106	1,466	1.0 (ref)	0.88 (0.64, 1.19)	1.13 (0.85, 1.51)	1.65 (1.27, 2.17)	
>106	1,350	1.0 (ref)	0.98 (0.71, 1.34)	1.23 (0.91, 1.67)	1.32 (0.97, 1.78)	
Creatinine (mg/dL)						0.025
<0.5	124	1.0 (ref)	1.17 (0.34, 4.03)	1.78 (0.56, 5.60)	4.61 (1.66, 12.81)	
≥0.5, ≤1.2	1,445	1.0 (ref)	0.96 (0.69, 1.34)	1.13 (0.81, 1.58)	1.84 (1.36, 2.50)	
>1.2	1,452	1.0 (ref)	0.85 (0.64, 1.12)	1.05 (0.81, 1.36)	1.12 (0.87, 1.43)	
SOFA score						0.002
<5	1,136	1.0 (ref)	1.35 (0.81, 2.26)	2.08 (1.28, 3.37)	3.19 (1.97, 5.15)	
≥5	1,887	1.0 (ref)	0.88 (0.70, 1.11)	1.02 (0.82, 1.28)	1.16 (0.94, 1.43)	
SAPSII						0.003
<40	1,352	1.0 (ref)	1.37 (0.83, 2.26)	1.51 (0.91, 2.50)	2.71 (1.70, 4.34)	
≥40	1,671	1.0 (ref)	0.80 (0.63, 1.01)	0.93 (0.75, 1.16)	1.03 (0.84, 1.27)	

AFIB, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; SOFA, sequential organ failure assessment; SAPSII, simplified acute physiology score II; NLCR, neutrophil-to-lymphocyte count ratio.

between NLCR and clinical outcome in patients with sepsis and the results is less controversial compared to those focus on different groups of diseases. In contrast to other studies of NLCR in critical ill patients without specific sepsis, we focused on septic population and our investigation revealed a significantly higher median NLCR. This is consistent with the proposed mechanism of NLCR representing ascended systemic inflammation and severity of sepsis seen in the ICU.

Although NLCR is not magnificently highly specific according to our results, it is an easily accessible, cheap and simple laboratory parameter reflecting the shift of the balance of neutrophil and lymphocyte. And we did find that patients included in the group of the highest NLCR (>20.25) have significantly higher 28-day mortality compared to those of the other three groups. Clinicians should draw more attention to septic patients with high NLCR as they tend to be of higher mortality. Early recognition of septic patients in higher risk with higher NLCR allow medical workers to take relevant actions ahead of the other complex and specific biomarkers are shown. NLCR is a worth mentioning yet not highly specific marker in patients with sepsis.

The major strength of our study was that it was, to our knowledge, the first to investigate the association between NLCR and all-cause mortality of patients with sepsis based on a large, diverse population and publicly available database, MIMIC-III. By using this database, the population in our study is larger than those ever adopted in previous research. Moreover, all of the data were recorded by the medical staff in BIDMC or imported by medical record system directly and what we did was just to extract the data we needed, which ensure our results to be reliable. Compared with previous relevant studies, the confounding factors are more balanced among the four group of NLCR. As NLCR is an easily measurable and simple parameter, based on our findings, it could be served as a supporter of the other mortality markers to improve the accuracy of prognostic prediction in septic patients.

Several limitations inevitably exist. First of all, the data of MIMIC-III are from one medical center, which means that this is actually a retrospective single-center study and selection bias is unavoidable. Secondly, our research presented a phenomenon without fully explaining its pathophysiological mechanism. Thirdly, some important clinical indicators including C-reactive protein and lactate are seriously missing, which may affect the result analysis. Finally, only NLCR of septic patients within 24 hours after admission to the ICU were measured in this study, without assessing the dynamic change of NLCR during the ICU stay, which could be better representative than the one-time NLCR measurement. We should emphasize the relationship between the changes of NLCR and outcomes of the septic patients in the future.

The pathophysiological and immunological mechanism of the relationship between NLCR and clinical outcomes in septic patients requires further study. A perfect biomarker for sepsis has not yet been identified. More immunological experiments and multi-center study on this easy-obtain parameter will be of great significance for early predict the outcomes of sepsis, which must be beneficial for the treatment of sepsis.

Conclusions

Higher NLCR was independently associated with increased 28-day all-cause mortality in adult septic patients but of a limited sensibility and specificity. Further large multicenter prospective studies are needed to confirm the relationship and validate whose clinical significance.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-1169). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The MIMIC III database has received ethical approval from the institutional review boards (IRBs) at BIDMC and MIT, and, because the database does not contain protected health information, a waiver of the requirement for informed consent was included in the IRB approval.

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