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Neutrophil-to-Lymphocyte Ratio as a Predictor of Mortality in Intensive Care Unit Patients: A Retrospective Analysis of the Medical Information Mart for Intensive Care III Database

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Competing interests

None declared.

Abstract

Objectives: Identifying high-risk patients in the intensive care unit (ICU) is important given the high mortality rate. However, existing scoring systems lack easily accessible, low-cost, and effective inflammatory markers. We aimed to identify inflammatory markers in routine blood tests to predict mortality in ICU patients and evaluate their predictive power.

Design: Retrospective cross-sectional study.

Setting: Single secondary care centre.

Participants: We analysed data from the Medical Information Mart for Intensive Care III database. A total of 21,822 ICU patients were enrolled and divided into survival and death groups based on in-hospital mortality.

Primary and secondary outcome measures: The predictive values of potential inflammatory markers were evaluated and compared using receiver operating characteristic curve analysis. After identifying the neutrophil-to-lymphocyte ratio (NLR) as having the best predictive ability, patients were re-divided into low (≤1), medium (1–6), and high (>6) NLR groups. Univariate and multivariate logistic regression analyses were performed to evaluate the association between the NLR and mortality. The area under the curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were used to assess whether incorporating the NLR could improve the predictive power of existing scoring systems.

Results: The NLR had the best predictive ability (AUC: 0.609; p <0.001). In-hospital mortality rates were significantly higher in the low (odds ratio [OR]: 2.09; 95% confidence interval [CI]: 1.64–2.66) and high (OR: 1.64; 95% CI: 1.50–1.80) NLR groups than in the medium NLR group. Adding the NLR to the Simplified Acute Physiology Score II improved the AUC from 0.789 to 0.798, with an NRI and IDI of 16.64% and 0.27%, respectively.

Conclusions: The NLR predicted mortality in ICU patients well. Both low and high NLRs were associated with elevated mortality rates. Including the NLR may improve the predictive power of the Simplified Acute Physiology Score II.

Strengths and limitations of this study

- This study included a large sample size and avoided selection bias by inclusion of all ICU patients.
- This study noticed that the mortality rate was also elevated in patients with a low NLR.
- The design was retrospective and important data may be missing; reasons for the missing data (especially those of neutrophil or lymphocyte counts) were challenging to determine based on the available information.
- The conclusions are qualitative rather than quantitative.

BACKGROUND

Patients admitted to the intensive care unit (ICU) are usually severely ill, with high mortality rates and high hospital costs.[1] Therefore, identifying patients with a high risk of mortality is essential. Existing scoring systems to predict the risk of mortality in the ICU, such as the Simplified Acute Physiology Score (SAPS) and Acute Physiology and Chronic Health Evaluation,[2] do not include effective inflammatory markers. C-reactive protein and procalcitonin concentrations are widely recognized as indicators of inflammation; however, routine testing is not always available for every ICU patient because of cost considerations, especially for patients without infectious complications. Thus, identifying low-cost, easily accessible, and effective inflammatory markers may help predict mortality in ICU patients.

A blood examination is one of the routine tests conducted for every patient admitted to the ICU. In addition to total white blood cell (WBC) and differential counts, combined markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have also attracted much attention in recent years. Numerous studies[3-11] have focused on the prognostic value of inflammatory markers in routine blood tests; however, the most sensitive indicator remains to be identified. More importantly, in clinical practice, we noted that some patients with a low NLR have a poor prognosis. However, when examining the literature, we found that although there are many studies on the NLR,[3-11] most of them concluded that a high NLR was associated with a poor prognosis, but ignored the prognostic value of a low NLR. Therefore, we conducted this study to verify which indicator is the best inflammatory marker in routine blood tests and to assess its prognostic value for mortality in ICU patients.

METHODS

Data Sources

Data for this study were obtained from the Medical Information Mart for Intensive Care III (MIMIC-III) database version 1.4 (https://mimic.physionet.org), which is a large, publicly available database comprising information on >40,000 patients who were admitted to the critical care unit of Beth Israel Deaconess Medical Center. Restrictions apply to the availability of these data, which were used under license for this study. Xie Wu completed the Collaborative Institutional Training Initiative program and was responsible for data extraction.

Participants

All patients aged ≥16 years who were admitted to the ICU were included. For patients with multiple ICU admissions, only the first admission was included. Patients with missing or abnormal values for key variables within 24 h after ICU admission were excluded. Abnormal values in this study referred to a WBC count >400 × 10^9/L, an NLR >100, or a PLR >8,000. Based on these inclusion and exclusion criteria, 21,822 patients were finally enrolled for data analysis.

Data Extraction

Data from the MIMIC-III database were extracted using structured query language within PostgreSQL (version 11.2, https://www.postgresql.org/). Demographic data, laboratory parameters, the clinical outcomes of patients, and survival data were collected from all participants, including data on: age; sex; ethnicity; ICU type; WBC, lymphocyte, neutrophil, and platelet counts; ICU and hospital lengths of stay; in-hospital mortality; and 90-day and 1-year

mortality. Severity at admission was measured using the SAPS II. Laboratory parameters were assessed during the first 24 h after admission. The NLR and PLR were calculated by dividing the neutrophil or platelet count by the lymphocyte count. The SAPS II was automatically calculated in the database according to published scoring criteria.[13] Extracted data were presented in comma-separated value files, linked by identifiers, and integrated into a table using Stata version 15.0 (Stata Corp., TX, USA).

Statistical Analyses

Statistical analyses were performed using Stata version 15.0 and MedCalc version 19.0.7 (MedCalc Inc., Mariakerke, Belgium). Continuous variables are presented as medians with interquartile ranges, and were compared using the Wilcoxon rank sum test or Kruskal–Wallis test. Categorical variables are presented as frequencies with percentages, and were compared using the Fisher's exact test or binomial probability test. Receiver operating characteristic curves were plotted to calculate the area under the curve (AUC), and were compared using the DeLong test. Optimal cut-off values for each inflammatory marker were determined using MedCalc version 19.0.7. Univariate and multivariate logistic regression analyses were performed to evaluate the prognostic value of the NLR for mortality. In the multivariate analysis, we adjusted for age, sex, ethnicity, ICU type, and the SAPS II. In addition to the traditional AUC, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to assess improvements in predictive power after adding the NLR. Subgroup analyses were performed to evaluate whether ICU type could influence the results. A $p < 0.05$ was considered statistically significant.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Between June 2001 and October 2012, a total of 38,597 patients (≥16 years) were admitted to the ICU. After the selection criteria were applied, 21,822 patients were included in the final analysis, with a mean (± standard deviation) age of 64.89 (± 17.80) years; 46.47% were female. The in-hospital mortality rate was 14.43%, while the 90-day and 1-year mortality rates were 20.78% and 28.57%, respectively. The median (interquartile range) lengths of ICU and hospital stay were 2.08 (1.21–4.13) and 6.63 (3.79–11.79) days, respectively.

Based on the in-hospital mortality data, patients were divided into survival and death groups. The baseline characteristics and clinical data are shown in **Table 1**. The death group was older and had more females than the survival group. Compared with overall in-hospital mortality, the mortality rate in the medical ICU (MICU) was significantly higher (14.43% *vs.* 16.31%, respectively). Blood examinations showed that the WBC count, neutrophil count, NLR, and PLR were significantly higher, whereas the lymphocyte and platelet counts were significantly lower, in the death group.

The AUC for all inflammatory markers and their optimal cut-off values are shown in **Supplemental Table 1**. The NLR had the greatest ability to predict in-hospital mortality (AUC: 0.609; p <0.001). The in-hospital mortality rates for different NLRs are shown in **Supplemental Figure 1**. We found that both a high (>6) and low (≤1) NLR were associated with a higher

mortality rate. Therefore, we selected the NLR as our best inflammatory marker, with cut-off values of 1 and 6.

We further divided patients into three groups based on the NLR—low (NLR ≤1; n = 580), medium (1 < NLR ≤ 6; n = 10,691), and high (NLR >6; n = 10,551) NLR groups—and compared the clinical outcomes (**Table 2**). Compared with the medium NLR group, the low and high NLR groups were both significantly associated with a poor prognosis. Their in-hospital, 90-day, and 1-year mortality rates were significantly higher, and the hospital and ICU stays were also significantly longer.

Table 3 presents the results of the logistic regression analyses for the association between the NLR and mortality. In the univariate analysis, the NLR was significantly associated with in-hospital, 90-day, and 1-year mortality. Very high or low NLRs may both be associated with elevated mortality rates. Similar results were obtained in the multivariate analysis after adjusting for age, sex, ethnicity, ICU type, and the SAPS II.

The predictive value of the NLR was evaluated by calculating the AUC, NRI, and IDI. As shown in **Figure 1**, the addition of the NLR to the SAPS II significantly improved the AUC from 0.789 (95% confidence interval [CI]: 0.785–0.796) to 0.798 (95% CI: 0.793–0.804; p <0.001, DeLong test). The NRI and IDI for the NLR in relation to the SAPS II were 16.64% (p <0.001) and 0.27% (p <0.001), respectively. We also performed a subgroup analysis based on ICU types (**Table 4**). The prognostic value of the NLR in the subgroups was similar to that of the total, except for patients with a low NLR in the trauma surgical ICU.

DISCUSSION

The main findings of this study are as follows. The NLR had the best predictive ability for in-hospital mortality in ICU patients. Further analyses based on the NLR revealed that patients with a high or low NLR were more likely to have higher mortality rates and longer ICU and hospital stays. The addition of the NLR significantly improved the predictive power of the SAPS II, and the results of the subgroup analysis based on ICU type were consistent with the overall population.

The predictive value of the NLR has been widely studied, particularly in cardiovascular disease,[5, 8] infectious disease,[7, 9] and cancer.[10, 11, 14] Most previous studies[3-11] have suggested that the higher the NLR, the worse the prognosis; however, other studies[15, 16] have suggested that a low NLR is also associated with a poor prognosis. If, as in previous studies, we divided patients equally into 3–5 groups based on their NLR, we could draw the same conclusion that a high NLR is indicative of a poor prognosis. However, before analysis, we noted that patients with a low NLR also seemed to have a poor prognosis. Thus, we implemented a different grouping scheme and confirmed our hypothesis by further analysis. Indeed, this finding was in line with clinical experience: the prognosis is generally good when the clinical indicators are within the normal range, and values that are too high or low are more likely to be associated with a poor prognosis. Several studies[14, 17] have suggested that the reason why an elevated NLR leads to a poor prognosis is mainly because of enhanced systemic inflammation and stress responses. However, the reason why a low NLR is associated with a poor prognosis remains unclear. We speculated that a decreased NLR may be due to a decrease in neutrophils that play a key role in the innate immune response, including directly killing pathogens by phagocytosis, releasing a variety of

cytokines, and activating T cells, among other roles.[18] Therefore, a reduction in circulating neutrophils can lower the body's response to microbial invasion. In addition, reduced circulating neutrophils can be ascribed to the increased neutrophil adhesion to the vascular endothelium, which can cause endothelial damage, leading to leukocyte aggregation and microvascular thrombosis.[19] Thus, the compromise of innate immunity and the increase in endothelial damage can collectively impair the prognosis of patients.

Many previous studies[3-11] have overlooked the possibility of a low NLR leading to a poor prognosis, which may be due to several reasons. First, compared to the overall trend towards a high NLR correlating with a poor prognosis, the association between a low NLR and a poor prognosis may have been neglected due to the small number of patients. There were only 580 patients with an NLR ≤1, which was 2.66% of the total population. Second, the main outcome indicators may have influenced the conclusions. Previous studies, which have mostly focused on late death (≥5 days), found that a high NLR can predict a poor prognosis. However, Riché *et al.*[16] reported that a low NLR is associated with an early death (< 5 days), whereas a high NLR is associated with a late death. Duggal *et al.*[17] also suggested that an elevated NLR is a biomarker for an increased length of ICU stay. Therefore, based on previous studies that focused on late death, it is reasonable to conclude that a high NLR is associated with increased mortality. However, in our study, around half of the in-hospital deaths (1,512/3,149; 48.02%) occurred within 5 days; thus, our study indicated that a low NLR is also associated with increased mortality. Third, the study population may have influenced the conclusions. Several studies have been conducted in patients with specific diseases,[11, 14] and those excluded often had a low NLR. Our study focused on all ICU patients with no case selection.

For patients in the MICU, many diseases can present with lymphocytosis and neutropenia, including haematological malignancies, such as acute lymphocytic leukaemia and myelodysplastic syndrome[20, 21]; haematopoietic system diseases, such as aplastic anaemia[22]; rheumatic diseases, such as systemic lupus erythematosus[23]; and infectious aetiologies, such as human immunodeficiency virus, hepatitis B virus, and Epstein–Barr virus. These patients are at an elevated risk of contracting bacterial and fungal infections, resulting in a poor prognosis.[24] This may also explain the over-representation of MICU patients with an NLR ≤1 (3.36%). In postoperative patients admitted to the surgical ICU, trauma surgical ICU, and cardiac surgery recovery unit, the NLR is usually high. First, surgical trauma itself can increase the NLR. Second, tissue damage caused by trauma or surgery can induce an acute inflammatory reaction, leading to the accumulation of neutrophils.[25] Third, surgery and anaesthesia expose the body to a state of stress, which induces the release of catecholamines and adrenocorticotropic hormones, causing the bone marrow, liver, and spleen to produce neutrophils constantly, resulting in a massive release of immature neutrophils into the bloodstream.[15] Moreover, cortisol inhibits the synthesis of lymphocyte nucleic acids, which leads to lymphopenia.[26] Therefore, postoperative patients have a higher NLR. If the NLR is still abnormally low in postoperative patients, then the predominantly neutrophilic inflammatory response has probably not been activated, leading to a transient type of lymphocytosis,[27] resulting in a poor prognosis. This result is consistent with those of a previous report,[28] which showed that the mortality rate is significantly higher in trauma patients with lymphocytosis.

In this study, the SAPS II was chosen as a tool for predicting mortality. Although the SAPS III has better predictive ability,[29] there were too many missing values, because it requires collecting data within 1 h after admission; therefore, we chose to use the SAPS II. Some studies suggested

that the PLR also has the ability to predict mortality; therefore, we evaluated the predictive power of the PLR and found that, despite having some predictive ability, it was not as effective as the NLR. When we added the PLR to the SAPS II together with the NLR, the AUC value did not increase significantly; therefore, we did not incorporate the PLR into this model.

The major strengths of our study are the large sample size and the inclusion of all ICU patients without selection bias. Further, we noticed that the mortality rate was also elevated in patients with a low NLR. More importantly, we found that adding the NLR to the SAPS II could improve its predictive power for ICU mortality, which is an important prompt for future scoring systems and may be of particular interest to critical care specialists.

There are also some limitations to this study. First, this was a retrospective study and some important data may be missing. Some patients were excluded because of missing neutrophil or lymphocyte data, and it was difficult to explore the reasons for missing data based on the information currently available. Second, the conclusions of this study were qualitative rather than quantitative. We can only infer that the addition of the NLR can improve the performance of the SAPS II because the NLR scores cannot be directly included in the SAPS II to construct a new scoring system. Finally, although we conducted a subgroup analysis of different ICU types, in-depth analyses were not undertaken as it was not the aim of our study.

CONCLUSIONS

Of the inflammatory markers identified from routine blood tests, the NLR was the best predictor of ICU mortality. Abnormally high or low NLRs were associated with increased mortality.

Finally, the addition of the NLR to the SAPS II can improve its predictive power for ICU mortality.

Author contributions

XW was fully responsible for all stages of the study, including design, data extraction, statistical analysis, and manuscript writing. FXY and SY was involved in the design of the original protocol. QPL and YNL participated in data curation and analyses. HBW and QL contributed to the discussion and interpretation of data. ZHS helped to draft the final manuscript. All authors read approved the final manuscript.

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Ethical Statement

Since MIMIC-III is a third-party, anonymized, publicly available database with pre-existing Institutional Review Board approval at BIDMC and MIT, we were exempted from obtaining approval from our institution.

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Tables

Table 1 Baseline characteristics according to survivors and death

	Overall (n=21,822)	Survival group (n=18,673)	Death group (n=3,149)	*P*
Age, years	66.68 (52.76, 79.55)	65.37 (51.65, 78.41)	75.05 (61.16, 83.58)	<0.001
Sex, n (%)				0.004
Female	10,140 (46.47)	8,602 (46.07)	1,538 (48.84)	
Male	11,682 (53.53)	10,071 (53.93)	1,611 (51.16)	
Ethnicity, n (%)				<0.001
White	15,875 (72.75)	13,619 (72.93)	2,256 (71.64)	
Black	2,080 (9.53)	1,857 (9.94)	223 (7.08)	
Other	3,867 (17.72)	3,197 (17.12)	670 (21.28)	
ICU type				<0.001
CCU	3,331 (15.26)	2,864 (15.34)	467 (14.83)	
CSRU	2,443 (11.20)	2,279 (12.20)	164 (5.21)	
MICU	10,411 (47.71)	8,713 (46.66)	1,698 (53.92)	
SICU	3,775 (17.30)	3,201 (17.14)	574 (18.23)	
TSICU	1,862 (8.53)	1,616 (8.65)	246 (7.81)	
SAPS II	34 (25, 43)	32 (24, 40)	48 (37.5, 60)	<0.001
Peripheral blood index				
WBC (10^9/L)	9.9 (7.1, 13.9)	9.7 (7.1, 13.6)	11.4 (7.6, 16.6)	<0.001
Lymphocyte (10^9/L)	1.30 (0.83, 1.91)	1.34 (0.87, 1.94)	1.06 (0.67, 1.62)	<0.001
Neutrophil (10^9/L)	7.56 (4.88, 11.45)	7.34 (4.82, 11.07)	9.16 (5.49, 13.60)	<0.001
Platelet (10^9/L)	208 (150, 275)	210 (155, 275)	192 (119, 277)	<0.001
NLR	5.75 (3.09, 11.13)	5.40 (2.95, 10.46)	8.32 (4.25, 14.75)	<0.001
PLR	177.9 (115.4, 287.4)	175.1(115.1, 280.0)	199.1 (117.8, 334.9)	<0.001

Data are presented as median and interquartile range or number and percentage.

ICU, intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery units; MICU, medical ICU; SICU, surgical ICU; TSICU trauma surgical ICU; SAPS, Simplified Acute Physiology Score; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 2 Clinical outcomes of the ICU patients

Clinical outcomes	Overall (n=21822)	NLR			*P*
		≤1 (n=580)	(1, 6] (n=10691)	> 6 (n=10,551)	
Hospital mortality, n (%)	3149 (14.43)	122 (21.03)	1,009 (9.44)	2,018 (19.13)	<0.001
90-Day mortality, n (%)	4534 (20.78)	155 (26.72)	1,511 (14.13)	2,868 (27.18)	<0.001
1-Year mortality, n (%)	6234 (28.57)	211 (36.38)	2,311 (21.62)	3,712 (35.18)	<0.001
ICU length of stay (d)	2.08 (1.21, 4.13)	2.04 (1.08, 4.38)	1.96 (1.13, 3.46)	2.38 (1.33, 5.04)	<0.001
Hospital length of stay (d)	6.63 (3.79, 11.79)	7.35 (3.34, 15.86)	6.08 (3.63, 10.79)	7.00 (3.96, 12.67)	<0.001

Data are presented as median and interquartile range or number and percentage.

Table 3 Association between NLR and mortality

Exposure	Non-adjusted		Adjusted	
	OR (95%CI)	*P*	OR (95%CI)	*P*
In-hospital mortality				
≤1	2.56 (2.07, 3.15)	<0.001	1.61 (1.26, 2.05)	<0.001
(1, 6]	1		1	
>6	2.27 (2.09, 2.46)	<0.001	1.59 (1.46, 1.74)	<0.001
90-Day mortality				
≤1	1.96 (1.65, 2.33)	<0.001	1.48 (1.18, 1.85)	<0.001
(1, 6]	1		1	
>6	2.08 (1.95, 2.22)	<0.001	1.60 (1.48, 1.43)	<0.001
1-Year mortality				
≤1	2.07 (1.74, 2.47)	<0.001	1.51 (1.23, 1.86)	<0.001
(1, 6]	1		1	
>6	1.97 (1.85, 2.09)	<0.001	1.38 (1.29, 1.48)	<0.001

Adjusted confounders: age, sex, ethnicity, ICU type and SAPS II.

Table 4 Subgroup analyses of the association between In-hospital mortality and NLR levels.

Subgroups		NLR		
		≤ 1	**(1, 6]**	**>6**
CCU	n (%)	74 (2.22)	1,712 (51.4)	1545 (46.38)
	OR (95%CI)	2.43 (1.21, 4.86)	1	1.82 (1.44, 2.31)
	P	0.012		<0.001
CSRU	n (%)	46 (1.88)	1,812 (74.17)	585 (23.95)
	OR (95%CI)	3.72 (1.45, 9.54)	1	3.25 (2.29, 4.61)
	P	0.006		<0.001
MICU	n (%)	350 (3.36)	4,635 (44,52)	5,426 (52.12)
	OR (95%CI)	1.77 (1.30, 2.41)	1	1.44 (1.27, 1.63)
	P	<0.001		<0.001
SICU	n (%)	73 (1.93)	1,767 (46.81)	1,935 (51.26)
	OR (95%CI)	2.43 (1.24, 4.78)	1	1.71 (1.39, 2.10)
	P	<0.001		<0.001
TSICU	n (%)	37 (1.99)	765 (41.08)	1,060 (56.93)
	OR (95%CI)	1.99 (0.79, 5.00)	1	1.55 (1.13, 2.12)
	P	0.144		0.007

Confounders adjustment were performed as before (Table 3).

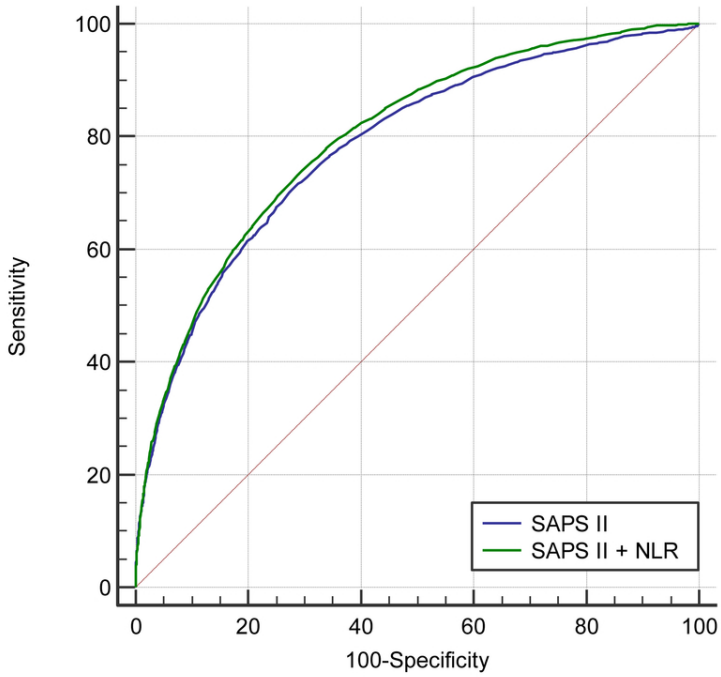
ICU, intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery units; MICU, medical ICU; SICU, surgical ICU; TSICU trauma surgical ICU.

Figure Legends

Supplemental Figure 1: Association of in-hospital mortality rates and different NLR levels.

Figure 1: Receiver operating characteristic curves for the SAPS II and the SAPS II+NLR.

SAPS, Simplified Acute Physiology Score; NLR, Neutrophil-to-Lymphocyte Ratio; AUC, area under the receiver-operating characteristic curve; IDI, integrated discrimination improvement; NRI, net reclassification improvement.



	SAPS II	SAPSII+NLR	P-value
AUC	0.789	0.798	< 0.001
	SAPS II vs. SAPSII+NLR		
NRI	16.64%		< 0.001
IDI	0.27%		< 0.001

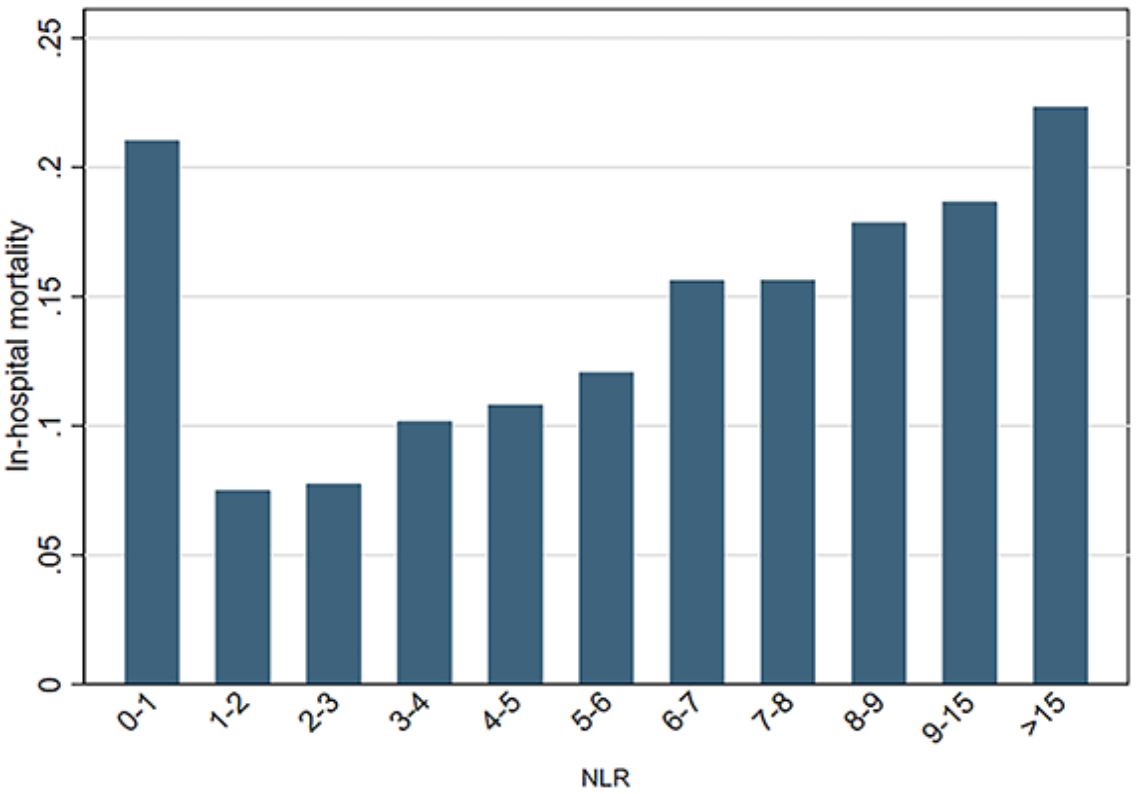
Figure 1

90x96mm (300 x 300 DPI)

Supplemental Table 1 The optimal cut-off values based on in-hospital mortality

Peripheral blood index	Cut-off value	AUC	*P*
WBC (10^9/L)	12	0.575	<0.001
Lymphocyte (10^9/L)	1.17	0.593	<0.001
Neutrophil (10^9/L)	9.57	0.576	<0.001
Platelet (10^9/L)	128	0.554	<0.001
NLR	6	0.609	<0.001
PLR	267	0.536	<0.001

WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.


In-hospital mortality
0
.05
.1
.15
.2
.25
0-1
1-2
2-3
3-4
4-5
5-6
6-7
7-8
8-9
9-15
>15
NLR

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Neutrophil-to-Lymphocyte Ratio as a Predictor of Mortality in Intensive Care Unit Patients: A Retrospective Analysis of the Medical Information Mart for Intensive Care III Database

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Neutrophil-to-Lymphocyte Ratio as a Predictor of Mortality in Intensive Care Unit Patients: A Retrospective Analysis of the Medical Information Mart for Intensive Care III Database

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Abstract

Objectives: Identifying high-risk patients in the intensive care unit (ICU) is important given the high mortality rate. However, existing scoring systems lack easily accessible, low-cost, and effective inflammatory markers. We aimed to identify inflammatory markers in routine blood tests to predict mortality in ICU patients and evaluate their predictive power.

Design: Retrospective case-control study.

Setting: Single secondary care centre.

Participants: We analysed data from the Medical Information Mart for Intensive Care III database. A total of 21,822 ICU patients were enrolled and divided into survival and death groups based on in-hospital mortality.

Primary and secondary outcome measures: The predictive values of potential inflammatory markers were evaluated and compared using receiver operating characteristic curve analysis. After identifying the neutrophil-to-lymphocyte ratio (NLR) as having the best predictive ability, patients were re-divided into low (≤1), medium (1–6), and high (>6) NLR groups. Univariate and multivariate logistic regression analyses were performed to evaluate the association between the NLR and mortality. The area under the curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were used to assess whether incorporating the NLR could improve the predictive power of existing scoring systems.

Results: The NLR had the best predictive ability (AUC: 0.609; p <0.001). In-hospital mortality rates were significantly higher in the low (odds ratio [OR]: 2.09; 95% confidence interval [CI]: 1.64–2.66) and high (OR: 1.64; 95% CI: 1.50–1.80) NLR groups than in the medium NLR group. Adding the NLR to the Simplified Acute Physiology Score II improved the AUC from 0.789 to 0.798, with an NRI and IDI of 16.64% and 0.27%, respectively.

Conclusions: The NLR predicted mortality in ICU patients well. Both low and high NLRs were associated with elevated mortality rates. Including the NLR may improve the predictive power of the Simplified Acute Physiology Score II.

Strengths and limitations of this study

- This study included a large sample size and avoided selection bias by inclusion of all ICU patients.
- This study noticed that the mortality rate was also elevated in patients with a low NLR.
- The design was retrospective and important data may be missing; reasons for the missing data (especially those of neutrophil or lymphocyte counts) were challenging to determine based on the available information.
- The conclusions are qualitative rather than quantitative.

BACKGROUND

Patients admitted to the intensive care unit (ICU) are usually severely ill, with high mortality rates and high hospital costs.[1] Therefore, identifying patients with a high risk of mortality is essential. Existing scoring systems to predict the risk of mortality in the ICU, such as the Simplified Acute Physiology Score (SAPS) and Acute Physiology and Chronic Health Evaluation,[2] do not include effective inflammatory markers. C-reactive protein and procalcitonin concentrations are widely recognized as indicators of inflammation; however, routine testing is not always available for every ICU patient because of cost considerations, especially for patients without infectious complications. Thus, identifying low-cost, easily accessible, and effective inflammatory markers may help predict mortality in ICU patients.

A blood examination is one of the routine tests conducted for every patient admitted to the ICU. In addition to total white blood cell (WBC) and differential counts, combined markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have also attracted much attention in recent years. Numerous studies[3-11] have focused on the prognostic value of inflammatory markers in routine blood tests; however, the most sensitive indicator remains to be identified. More importantly, in clinical practice, we noted that some patients with a low NLR have a poor prognosis. However, when examining the literature, we found that although there are many studies on the NLR,[3-11] most of them concluded that a high NLR was associated with a poor prognosis, but ignored the prognostic value of a low NLR. Therefore, we conducted this study to verify which indicator is the best inflammatory marker in routine blood tests and to assess its prognostic value for mortality in ICU patients.

METHODS

Data Sources

Data for this study were obtained from the Medical Information Mart for Intensive Care III (MIMIC-III) database version 1.4 (https://mimic.physionet.org), which is a large, publicly available database comprising information on >40,000 patients who were admitted to the critical care unit of Beth Israel Deaconess Medical Center. Restrictions apply to the availability of these data, which were used under license for this study. Xie Wu completed the Collaborative Institutional Training Initiative program and was responsible for data extraction (certification number: 35931746).

Participants

All patients who were admitted to the ICU were included. The exclusion criteria were as follows: (1) patients younger than 16 years old; (2) patients who are not the first hospitalization; (3) patients who had no blood routine test data within 24h of hospitalization; (4) patients with abnormal values for key variables; (5) patients with missing data greater than 10%. Abnormal values in this study were defined as extreme outliers, that is WBC count >400 × 10^9/L, NLR >100, and PLR >8,000. Based on these inclusion and exclusion criteria, 21,822 patients were finally enrolled for data analysis. The missing values of all selected variables are less than 10%, so we replaced the missing observations with the mean values.

Data Extraction

Data from the MIMIC-III database were extracted using structured query language within PostgreSQL (version 11.2, https://www.postgresql.org/). Demographic data, laboratory

parameters, the clinical outcomes of patients, and survival data were collected from all participants, including data on: age; sex; ethnicity; ICU type; WBC, lymphocyte, neutrophil, and platelet counts; ICU and hospital lengths of stay; in-hospital mortality; and 90-day and 1-year mortality. Severity at admission was measured using the SAPS II. Laboratory parameters were assessed during the first 24 h after admission. The NLR and PLR were calculated by dividing the neutrophil or platelet count by the lymphocyte count. The SAPS II was automatically calculated in the database according to published scoring criteria.[12] Extracted data were presented in comma-separated value files, linked by identifiers, and integrated into a table using Stata version 15.0 (Stata Corp., TX, USA).

Statistical Analyses

Statistical analyses were performed using Stata version 15.0 and MedCalc version 19.0.7 (MedCalc Inc., Mariakerke, Belgium). Continuous variables are presented as medians with interquartile ranges, and were compared using the Wilcoxon rank sum test or Kruskal–Wallis test. Categorical variables are presented as frequencies with percentages, and were compared using the Fisher's exact test or binomial probability test. Receiver operating characteristic curves were plotted to calculate the area under the curve (AUC), and were compared using the DeLong test. Optimal cut-off values for each inflammatory marker were determined using MedCalc version 19.0.7. Univariate and multivariate logistic regression analyses were performed to evaluate the prognostic value of the NLR for mortality. In the multivariate analysis, we adjusted for variables with a *p* value less than 0.2 in the univariate analysis or clinically significant, including age, sex, ethnicity, ICU type, and the SAPS II. In addition to the traditional AUC, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were

calculated to assess improvements in predictive power after adding the NLR. Subgroup analyses were performed to evaluate whether main diagnosis could influence the results. A p <0.05 was considered statistically significant.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Between June 2001 and October 2012, a total of 38,597 patients (≥16 years) were admitted to the ICU. After the selection criteria were applied, 21,822 patients were included in the final analysis, with a median (interquartile range) age of 66.68 (52.76, 79.55) years; 46.47% were female. The in-hospital mortality rate was 14.43%, while the 90-day and 1-year mortality rates were 20.78% and 28.57%, respectively. The median (interquartile range) lengths of ICU and hospital stay were 2.08 (1.21–4.13) and 6.63 (3.79–11.79) days, respectively.

Based on the in-hospital mortality data, patients were divided into survival and death groups. The baseline characteristics and clinical data are shown in **Table 1**. The death group was older and had more females than the survival group. Compared with overall in-hospital mortality, the mortality rate in the medical ICU (MICU) was significantly higher (14.43% *vs.* 16.31%, respectively). Blood examinations showed that the WBC count, neutrophil count, NLR, and PLR were significantly higher, whereas the lymphocyte and platelet counts were significantly lower, in the death group.

The AUC for all inflammatory markers and their optimal cut-off values are shown in **Supplemental Table 1**. The NLR had the greatest ability to predict in-hospital mortality (AUC: 0.609; p <0.001). The in-hospital mortality rates for different NLRs are shown in **Supplemental Figure 1**. We found that both a high (>6) and low (≤1) NLR were associated with a higher mortality rate. Therefore, we selected the NLR as our best inflammatory marker, with cut-off values of 1 and 6.

We further divided patients into three groups based on the NLR—low (NLR ≤1; n = 580), medium (1 < NLR ≤ 6; n = 10,691), and high (NLR >6; n = 10,551) NLR groups—and compared the clinical outcomes (**Table 2**). The baseline of the three groups were presented in **Supplemental Table 2.** Compared with the medium NLR group, the low and high NLR groups were both significantly associated with a poor prognosis. Their in-hospital, 90-day, and 1-year mortality rates were significantly higher, and the hospital and ICU stays were also significantly longer.

Table 3 presents the results of the logistic regression analyses for the association between the NLR and mortality. In the univariate analysis, the NLR was significantly associated with in-hospital, 90-day, and 1-year mortality. Very high or low NLRs may both be associated with elevated mortality rates. Similar results were obtained in the multivariate analysis after adjusting for age, sex, ethnicity, ICU type, and the SAPS II.

The predictive value of the NLR was evaluated by calculating the AUC, NRI, and IDI. As shown in **Figure 1**, the addition of the NLR to the SAPS II significantly improved the AUC from 0.789 (95% confidence interval [CI]: 0.785–0.796) to 0.798 (95% CI: 0.793–0.804; p <0.001, DeLong test). The NRI and IDI for the NLR in relation to the SAPS II were 16.64% (p <0.001) and

0.27% (p <0.001), respectively. We also performed a subgroup analysis based on main diagnosis (**Table 4**). The prognostic value of the NLR in the subgroups was similar to that of the total, except for patients with chronic liver disease.

DISCUSSION

The main findings of this study are as follows. The NLR had the best predictive ability for in-hospital mortality in ICU patients. Further analyses based on the NLR revealed that patients with a high or low NLR were more likely to have higher mortality rates and longer ICU and hospital stays. The addition of the NLR significantly improved the predictive power of the SAPS II, and the results of the subgroup analysis based on main diagnosis were consistent with the overall population.

The predictive value of the NLR has been widely studied, particularly in cardiovascular disease,[5, 8] infectious disease,[7, 9] and cancer.[10–11, 13] Most previous studies[3–11, 14–15] have suggested that the higher the NLR, the worse the prognosis; however, other studies[16–17] have suggested that a low NLR is also associated with a poor prognosis. If, as in previous studies, we divided patients equally into 3–5 groups based on their NLR, we could draw the same conclusion that a high NLR is indicative of a poor prognosis. However, before analysis, we noted that patients with a low NLR also seemed to have a poor prognosis. Thus, we implemented a different grouping scheme and confirmed our hypothesis by further analysis. Indeed, this finding was in line with clinical experience: the prognosis is generally good when the clinical indicators are within the normal range, and values that are too high or low are more likely to be associated with a poor prognosis. Several studies[13, 18] have suggested that the reason why an elevated NLR leads to a poor prognosis is mainly because of enhanced systemic inflammation

and stress responses. However, the reason why a low NLR is associated with a poor prognosis remains unclear. We speculated that a decreased NLR may be due to a decrease in neutrophils that play a key role in the innate immune response, including directly killing pathogens by phagocytosis, releasing a variety of cytokines, and activating T cells, among other roles.[19] Therefore, a reduction in circulating neutrophils can lower the body's response to microbial invasion. In addition, reduced circulating neutrophils can be ascribed to the increased neutrophil adhesion to the vascular endothelium, which can cause endothelial damage, leading to leukocyte aggregation and microvascular thrombosis.[20] Thus, the compromise of innate immunity and the increase in endothelial damage can collectively impair the prognosis of patients.

Many previous studies[3–11, 14–15] have overlooked the possibility of a low NLR leading to a poor prognosis, which may be due to several reasons. First, compared to the overall trend towards a high NLR correlating with a poor prognosis, the association between a low NLR and a poor prognosis may have been neglected due to the small number of patients. There were only 580 patients with an NLR ≤1, which was 2.66% of the total population. Second, the main outcome indicators may have influenced the conclusions. Previous studies, which have mostly focused on late death (≥5 days), found that a high NLR can predict a poor prognosis. However, Riché *et al.*[17] reported that a low NLR is associated with an early death (< 5 days), whereas a high NLR is associated with a late death. Duggal *et al.*[18] also suggested that an elevated NLR is a biomarker for an increased length of ICU stay. Therefore, based on previous studies that focused on late death, it is reasonable to conclude that a high NLR is associated with increased mortality. However, in our study, around half of the in-hospital deaths (1,512/3,149; 48.02%) occurred within 5 days; thus, our study indicated that a low NLR is also associated with

increased mortality. Third, the study population may have influenced the conclusions. Several studies have been conducted in patients with specific diseases,[11, 13] and those excluded often had a low NLR. Our study focused on all ICU patients with no case selection.

Commonly used ICU prognosis score include APACHE, SOFA, SAPS and so on[21-22]. In this study, the SAPS was chosen because of its lack of inflammatory indicators. Although the SAPS III has better predictive ability,[23] there were too many missing values, because it requires collecting data within 1 h after admission; therefore, we chose to use the SAPS II. Some studies suggested that the PLR also had the ability to predict mortality[24]; therefore, we evaluated the predictive power of the PLR and found that, despite having some predictive ability, it was not as effective as the NLR. When we added the PLR to the SAPS II together with the NLR, the AUC value did not increase significantly; therefore, we did not incorporate the PLR into this model. Although SAPS II is well-known, it lacks inflammatory indicators. As an easy-to-obtain, sensitive inflammatory indicator that does not increase the financial burden of patients, NLR has been reported by many previous studies and has high clinical significance. That's why we tried to add NLR to the SAPS II to evaluate whether it can increase its predictive performance. Although the AUC value does not increase very much from a numerical point of view, since this study is qualitative rather than quantitative, it is enough to illustrate the clinical value of NLR, and provide a certain reference for the future studies.

The major strengths of our study are the large sample size and the inclusion of all ICU patients without selection bias. Further, we noticed that the mortality rate was also elevated in patients with a low NLR. More importantly, we found that adding the NLR to the SAPS II could improve

its predictive power for ICU mortality, which is an important prompt for future scoring systems and may be of particular interest to critical care specialists.

There are also some limitations to this study. First, this was a retrospective study and some important data may be missing. Some patients were excluded because of missing neutrophil or lymphocyte data, and it was difficult to explore the reasons for missing data based on the information currently available. Second, the conclusions of this study were qualitative rather than quantitative. We can only infer that the addition of the NLR can improve the performance of the SAPS II because the NLR scores cannot be directly included in the SAPS II to construct a new scoring system, however, it has also attracted the attention of clinicians to be wary of abnormal NLR values. Finally, although we conducted a subgroup analysis of different diagnosis, in-depth analyses were not undertaken as it was not the aim of our study.

CONCLUSIONS

Of the inflammatory markers identified from routine blood tests, the NLR was the best predictor of ICU mortality. Abnormally high or low NLRs were associated with increased mortality. Finally, the addition of the NLR to the SAPS II can improve its predictive power for ICU mortality.

Contributorship statement

XW was fully responsible for all stages of the study, including design, data extraction, statistical analysis, and manuscript writing. FXY and SY was involved in the design of the original protocol. QPL and YNL participated in data curation and analyses. HBW and QL contributed to the discussion and interpretation of data. ZHS helped to draft the final manuscript. All authors read approved the final manuscript.

Competing interests

None declared.

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Data sharing statement

Full data set available from the corresponding author at yanfuxia@sina.com. However, reanalysis of the full data need to be approved by MIMIC III Institute.

Ethical Statement

Since MIMIC-III is a third-party, anonymized, publicly available database with pre-existing Institutional Review Board approval at BIDMC and MIT, we were exempted from obtaining approval from our institution.

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Tables

Table 1 Baseline characteristics according to survivors and death

	Overall (n=21,822)	Survival group (n=18,673)	Death group (n=3,149)	*P*
Age, years	66.68 (52.76, 79.55)	65.37 (51.65, 78.41)	75.05 (61.16, 83.58)	<0.001
Sex, n (%)				0.004
Female	10,140 (46.47)	8,602 (46.07)	1,538 (48.84)	
Male	11,682 (53.53)	10,071 (53.93)	1,611 (51.16)	
Ethnicity, n (%)				<0.001
White	15,875 (72.75)	13,619 (72.93)	2,256 (71.64)	
Black	2,080 (9.53)	1,857 (9.94)	223 (7.08)	
Other	3,867 (17.72)	3,197 (17.12)	670 (21.28)	
ICU type				<0.001
CCU	3,331 (15.26)	2,864 (15.34)	467 (14.83)	
CSRU	2,443 (11.20)	2,279 (12.20)	164 (5.21)	
MICU	10,411 (47.71)	8,713 (46.66)	1,698 (53.92)	
SICU	3,775 (17.30)	3,201 (17.14)	574 (18.23)	
TSICU	1,862 (8.53)	1,616 (8.65)	246 (7.81)	
SAPS II	34 (25, 43)	32 (24, 40)	48 (37.5, 60)	<0.001
Peripheral blood index				
WBC (10^9/L)	9.9 (7.1, 13.9)	9.7 (7.1, 13.6)	11.4 (7.6, 16.6)	<0.001
Lymphocyte (10^9/L)	1.30 (0.83, 1.91)	1.34 (0.87, 1.94)	1.06 (0.67, 1.62)	<0.001
Neutrophil (10^9/L)	7.56 (4.88, 11.45)	7.34 (4.82, 11.07)	9.16 (5.49, 13.60)	<0.001
Platelet (10^9/L)	208 (150, 275)	210 (155, 275)	192 (119, 277)	<0.001
NLR	5.75 (3.09, 11.13)	5.40 (2.95, 10.46)	8.32 (4.25, 14.75)	<0.001
PLR	177.9 (115.4, 287.4)	175.1(115.1, 280.0)	199.1 (117.8, 334.9)	<0.001

Data are presented as median and interquartile range or number and percentage.

ICU, intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery units; MICU, medical ICU; SICU, surgical ICU; TSICU trauma surgical ICU; SAPS, Simplified Acute Physiology Score; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 2 Clinical outcomes of the ICU patients

Clinical outcomes	Overall (n=21822)	NLR			*P*
		≤1 (n=580)	(1, 6] (n=10691)	> 6 (n=10,551)	
Hospital mortality, n (%)	3149 (14.43)	122 (21.03)	1,009 (9.44)	2,018 (19.13)	<0.001
90-Day mortality, n (%)	4534 (20.78)	155 (26.72)	1,511 (14.13)	2,868 (27.18)	<0.001
1-Year mortality, n (%)	6234 (28.57)	211 (36.38)	2,311 (21.62)	3,712 (35.18)	<0.001
ICU length of stay (d)	2.08 (1.21, 4.13)	2.04 (1.08, 4.38)	1.96 (1.13, 3.46)	2.38 (1.33, 5.04)	<0.001
Hospital length of stay (d)	6.63 (3.79, 11.79)	7.35 (3.34, 15.86)	6.08 (3.63, 10.79)	7.00 (3.96, 12.67)	<0.001

Data are presented as median and interquartile range or number and percentage.

Table 3 Association between NLR and mortality

Exposure	Non-adjusted		Adjusted	
	OR (95%CI)	*P*	OR (95%CI)	*P*
In-hospital mortality				
≤1	2.56 (2.07, 3.15)	<0.001	1.61 (1.26, 2.05)	<0.001
(1, 6]	1		1	
>6	2.27 (2.09, 2.46)	<0.001	1.59 (1.46, 1.74)	<0.001
90-Day mortality				
≤1	1.96 (1.65, 2.33)	<0.001	1.48 (1.18, 1.85)	<0.001
(1, 6]	1		1	
>6	2.08 (1.95, 2.22)	<0.001	1.60 (1.48, 1.43)	<0.001
1-Year mortality				
≤1	2.07 (1.74, 2.47)	<0.001	1.51 (1.23, 1.86)	<0.001
(1, 6]	1		1	
>6	1.97 (1.85, 2.09)	<0.001	1.38 (1.29, 1.48)	<0.001

Adjusted confounders: age, sex, ethnicity, ICU type and SAPS II.

Table 4 Subgroup analyses of the association between In-hospital mortality and NLR levels.

Subgroups		NLR		
		≤ 1	**(1, 6]**	**>6**
ARDS	n (%)	46 (1.88)	1,812 (74.17)	585 (23.95)
	OR (95%CI)	1.85 (1.24, 2.76)	1	1.27 (1.09, 1.49)
	P	0.003		0.002
CHD	n (%)	37 (1.99)	765 (41.08)	1,060 (56.93)
	OR (95%CI)	2.13 (1.12, 4.02)	1	1.90 (1.54, 2.33)
	P	0.021		<0.001
CKD	n (%)	37 (1.99)	765 (41.08)	1,060 (56.93)
	OR (95%CI)	3.62 (1.67, 7.86)	1	1.78 (1.33, 2.39)
	P	0.001		<0.001
CLD	n (%)	37 (1.99)	765 (41.08)	1,060 (56.93)
	OR (95%CI)	1.75 (0.16, 19.43)	1	2.57 (1.12, 5.89)
	P	0.648		0.025

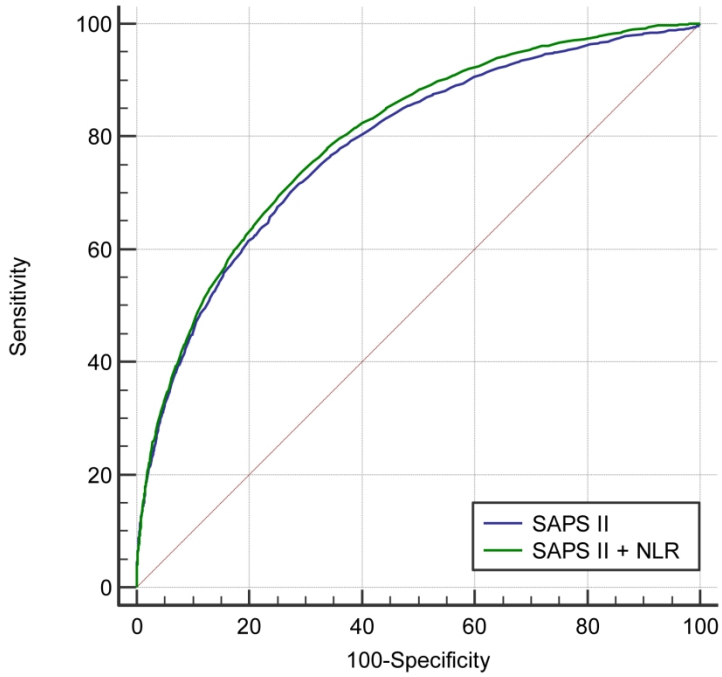
Confounders adjustment were performed as before (Table 3).

ARDS acute respiratory distress syndrome, CHD coronary heart disease, CKD chronic kidney disease, CLD chronic liver disease.

Figure Legends

Figure 1: Receiver operating characteristic curves for the SAPS II and the SAPS II+NLR.

SAPS, Simplified Acute Physiology Score; NLR, Neutrophil-to-Lymphocyte Ratio; AUC, area under the receiver-operating characteristic curve; IDI, integrated discrimination improvement; NRI, net reclassification improvement.



	SAPS II	SAPSII+NLR	P-value
AUC	0.789	0.798	< 0.001
	SAPS II vs. SAPSII+NLR		
NRI	16.64%		< 0.001
IDI	0.27%		< 0.001

Figure 1

Supplemental Table 1 The optimal cut-off values based on in-hospital mortality

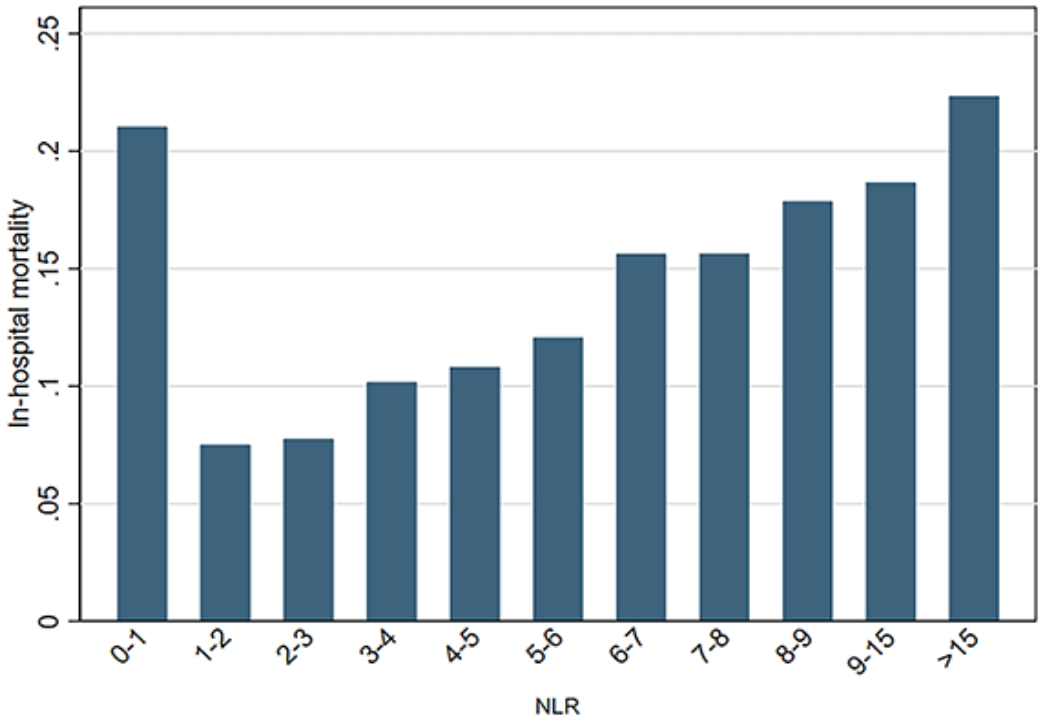
Peripheral blood index	Cut-off value	AUC	*P*
WBC (10^9/L)	12	0.575	<0.001
Lymphocyte (10^9/L)	1.17	0.593	<0.001
Neutrophil (10^9/L)	9.57	0.576	<0.001
Platelet (10^9/L)	128	0.554	<0.001
NLR	6	0.609	<0.001
PLR	267	0.536	<0.001

WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Supplemental Table 2 Baseline characteristics according to NLR level

	NLR			*P*
	≤1 (n=580)	**(1, 6] (n=10691)**	**＞6 (n=10,551)**	
Age, years	61.76 (48.02, 74.42)	64.99 (51.37, 78.06)	68.75 (54.56, 80.96)	<0.001
Female, n (%)	282 (48.62%)	4807 (44.96%)	5051 (47.87%)	<0.001
Ethnicity, n (%)				<0.001
White	354 (61.03%)	7595 (71.04%)	7929 (75.12%)	
Black	115 (19.83%)	1250 (11.69%)	1846 (17.27)	
Other	111 (19.14%)	1846 (17.27%)	1910 (18.10)	
ICU type				
CCU	74 (12.76%)	1712 (16.01%)	1545 (14.64%)	0.005
CSRU	46 (7.93%)	1812 (16.95%)	585 (5.54%)	<0.001
MICU	350 (60.34%)	4,635 (43.35%)	5,426 (51.43%)	<0.001
SICU	73 (12.59%)	1,767 (16.53 %)	1,935 (18.34%)	<0.001
TSICU	37 (6.38%)	765 (7.16 %)	1,060(10.05%)	<0.001
SAPS II	43 (31, 61)	37 (28, 50)	43 (32, 58.75)	<0.001
Peripheral blood index				
WBC (10^9/L)	6.4 (3.1, 11.9)	8 (6.1, 10.4)	12.8 (9.6, 17.1)	<0.001
Lymphocyte (10^9/L)	2.96 (1.31, 4.93)	1.76 (1.31, 2.32)	0.91 (0.61, 1.25)	<0.001
Neutrophil (10^9/L)	1.99 (0.48, 3.40)	5.44 (3.96, 7.41)	10.99 (8.06, 14.83)	<0.001
Platelet (10^9/L)	148.5 (67, 219.25)	202 (147, 266)	217 (159, 288)	<0.001

NLR, neutrophil-to-lymphocyte ratio; ICU, intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery units; MICU, medical ICU; SICU, surgical ICU; TSICU trauma surgical ICU; SAPS, Simplified Acute Physiology Score; WBC, white blood cell.



Supplemental Figure 1: Association of in-hospital mortality rates and different NLR levels.

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Neutrophil-to-Lymphocyte Ratio as a Predictor of Mortality in Intensive Care Unit Patients: A Retrospective Analysis of the Medical Information Mart for Intensive Care III Database

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Neutrophil-to-Lymphocyte Ratio as a Predictor of Mortality in Intensive Care Unit Patients: A Retrospective Analysis of the Medical Information Mart for Intensive Care III Database

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Abstract

Objectives: Identifying high-risk patients in the intensive care unit (ICU) is important given the high mortality rate. However, existing scoring systems lack easily accessible, low-cost, and effective inflammatory markers. We aimed to identify inflammatory markers in routine blood tests to predict mortality in ICU patients and evaluate their predictive power.

Design: Retrospective case-control study.

Setting: Single secondary care centre.

Participants: We analysed data from the Medical Information Mart for Intensive Care III database. A total of 21,822 ICU patients were enrolled and divided into survival and death groups based on in-hospital mortality.

Primary and secondary outcome measures: The predictive values of potential inflammatory markers were evaluated and compared using receiver operating characteristic curve analysis. After identifying the neutrophil-to-lymphocyte ratio (NLR) as having the best predictive ability, patients were re-divided into low (≤1), medium (1–6), and high (>6) NLR groups. Univariate and multivariate logistic regression analyses were performed to evaluate the association between the NLR and mortality. The area under the curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were used to assess whether incorporating the NLR could improve the predictive power of existing scoring systems.

Results: The NLR had the best predictive ability (AUC: 0.609; p <0.001). In-hospital mortality rates were significantly higher in the low (odds ratio [OR]: 2.09; 95% confidence interval [CI]: 1.64–2.66) and high (OR: 1.64; 95% CI: 1.50–1.80) NLR groups than in the medium NLR group. Adding the NLR to the Simplified Acute Physiology Score II improved the AUC from 0.789 to 0.798, with an NRI and IDI of 16.64% and 0.27%, respectively.

Conclusions: The NLR predicted mortality in ICU patients well. Both low and high NLRs were associated with elevated mortality rates. Including the NLR may improve the predictive power of the Simplified Acute Physiology Score II.

Strengths and limitations of this study

- This study included a large sample size and avoided selection bias by inclusion of all ICU patients.
- This study noticed that the mortality rate was also elevated in patients with a low NLR.
- The design was retrospective and important data may be missing; reasons for the missing data (especially those of neutrophil or lymphocyte counts) were challenging to determine based on the available information.
- The conclusions are qualitative rather than quantitative.

BACKGROUND

Patients admitted to the intensive care unit (ICU) are usually severely ill, with high mortality rates and high hospital costs.[1] Therefore, identifying patients with a high risk of mortality is essential. Existing scoring systems to predict the risk of mortality in the ICU, such as the Simplified Acute Physiology Score (SAPS) and Acute Physiology and Chronic Health Evaluation,[2] do not include effective inflammatory markers. C-reactive protein and procalcitonin concentrations are widely recognized as indicators of inflammation; however, routine testing is not always available for every ICU patient because of cost considerations, especially for patients without infectious complications. Thus, identifying low-cost, easily accessible, and effective inflammatory markers may help predict mortality in ICU patients.

A blood examination is one of the routine tests conducted for every patient admitted to the ICU. In addition to total white blood cell (WBC) and differential counts, combined markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have also attracted much attention in recent years. Numerous studies[3-11] have focused on the prognostic value of inflammatory markers in routine blood tests; however, the most sensitive indicator remains to be identified. More importantly, in clinical practice, we noted that some patients with a low NLR have a poor prognosis. However, when examining the literature, we found that although there are many studies on the NLR,[3-11] most of them concluded that a high NLR was associated with a poor prognosis, but ignored the prognostic value of a low NLR. Therefore, we conducted this study to verify which indicator is the best inflammatory marker in routine blood tests and to assess its prognostic value for mortality in ICU patients.

METHODS

Data Sources

Data for this study were obtained from the Medical Information Mart for Intensive Care III (MIMIC-III) database version 1.4 (https://mimic.physionet.org), which is a large, publicly available database comprising information on >40,000 patients who were admitted to the critical care unit of Beth Israel Deaconess Medical Center. Restrictions apply to the availability of these data, which were used under license for this study. Xie Wu completed the Collaborative Institutional Training Initiative program and was responsible for data extraction (certification number: 35931746).

Participants

All patients who were admitted to the ICU were included. The exclusion criteria were as follows: (1) patients who are not the first hospitalization; (2) patients younger than 16 years old; (3) patients who had no blood routine test data within 24h of hospitalization; (4) patients with abnormal values for key variables. Abnormal values in this study were defined as extreme outliers, that is WBC count >400 × 10^9/L, NLR >100, and PLR >8,000. Based on these inclusion and exclusion criteria, 21,822 patients were finally enrolled for data analysis.

Data Extraction

Data from the MIMIC-III database were extracted using structured query language within PostgreSQL (version 11.2, https://www.postgresql.org/). Demographic data, laboratory parameters, the clinical outcomes of patients, and survival data were collected from all participants, including data on: age; sex; ethnicity; ICU type; WBC, lymphocyte, neutrophil, and

platelet counts; ICU and hospital lengths of stay; in-hospital mortality; and 90-day and 1-year mortality. Severity at admission was measured using the SAPS II. Laboratory parameters were assessed during the first 24 h after admission. The NLR and PLR were calculated by dividing the neutrophil or platelet count by the lymphocyte count. The SAPS II was automatically calculated in the database according to published scoring criteria.[12] Extracted data were presented in comma-separated value files, linked by identifiers, and integrated into a table using Stata version 15.0 (Stata Corp., TX, USA).

Statistical Analyses

Statistical analyses were performed using Stata version 15.0 and MedCalc version 19.0.7 (MedCalc Inc., Mariakerke, Belgium). Continuous variables are presented as medians with interquartile ranges, and were compared using the Wilcoxon rank sum test or Kruskal–Wallis test. Categorical variables are presented as frequencies with percentages, and were compared using the Fisher's exact test or binomial probability test. Receiver operating characteristic curves were plotted to calculate the area under the curve (AUC), and were compared using the DeLong test. Optimal cut-off values for each inflammatory marker were determined using MedCalc version 19.0.7. Univariate and multivariate logistic regression analyses were performed to evaluate the prognostic value of the NLR for mortality. In the multivariate analysis, we adjusted for variables with a *p* value less than 0.2 in the univariate analysis or clinically significant, including age, sex, ethnicity, ICU type, and the SAPS II. In addition to the traditional AUC, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to assess improvements in predictive power after adding the NLR. Subgroup analyses

were performed to evaluate whether main diagnosis could influence the results. A p <0.05 was considered statistically significant.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Between June 2001 and October 2012, a total of 38,597 patients (≥16 years) were admitted to the ICU. After the selection criteria were applied, 21,822 patients were included in the final analysis. The flow diagram of this study is presented in **Figure 1**. There were no missing data except for age (missing for 0.2% of cases, n=42), and it was missing at random, so we replaced it with the mean value. The median (interquartile range) age of these patients was 66.68 (52.76, 79.55) years, and 46.47% were female. The in-hospital mortality rate was 14.43%, while the 90-day and 1-year mortality rates were 20.78% and 28.57%, respectively. The median (interquartile range) lengths of ICU and hospital stay were 2.08 (1.21–4.13) and 6.63 (3.79–11.79) days, respectively.

Based on the in-hospital mortality data, patients were divided into survival and death groups. The baseline characteristics and clinical data are shown in **Table 1**. The death group was older and had more females than the survival group. Compared with overall in-hospital mortality, the mortality rate in the medical ICU (MICU) was significantly higher (14.43% *vs.* 16.31%, respectively). Blood examinations showed that the WBC count, neutrophil count, NLR, and PLR were significantly higher, whereas the lymphocyte and platelet counts were significantly lower, in the death group.

The AUC for all inflammatory markers and their optimal cut-off values are shown in **Supplemental Table 1**. The NLR had the greatest ability to predict in-hospital mortality (AUC: 0.609; p <0.001). The in-hospital mortality rates for different NLRs are shown in **Supplemental Figure 1**. We found that both a high (>6) and low (≤1) NLR were associated with a higher mortality rate. Therefore, we selected the NLR as our best inflammatory marker, with cut-off values of 1 and 6.

We further divided patients into three groups based on the NLR—low (NLR ≤1; n = 580), medium (1 < NLR ≤ 6; n = 10,691), and high (NLR >6; n = 10,551) NLR groups—and compared the clinical outcomes (**Table 2**). The baseline of the three groups were presented in **Supplemental Table 2.** Compared with the medium NLR group, the low and high NLR groups were both significantly associated with a poor prognosis. Their in-hospital, 90-day, and 1-year mortality rates were significantly higher, and the hospital and ICU stays were also significantly longer.

Table 3 presents the results of the logistic regression analyses for the association between the NLR and mortality. In the univariate analysis, the NLR was significantly associated with in-hospital, 90-day, and 1-year mortality. Very high or low NLRs may both be associated with elevated mortality rates. Similar results were obtained in the multivariate analysis after adjusting for age, sex, ethnicity, ICU type, and the SAPS II.

The predictive value of the NLR was evaluated by calculating the AUC, NRI, and IDI. As shown in **Figure 2**, the addition of the NLR to the SAPS II significantly improved the AUC from 0.789 (95% confidence interval [CI]: 0.785–0.796) to 0.798 (95% CI: 0.793–0.804; p <0.001, DeLong test). The NRI and IDI for the NLR in relation to the SAPS II were 16.64% (p <0.001) and

0.27% (p <0.001), respectively. We also performed a subgroup analysis based on main diagnosis (**Supplemental Table 3**). The prognostic value of the NLR in the subgroups was similar to that of the total, except for patients with chronic liver disease.

DISCUSSION

The main findings of this study are as follows. The NLR had the best predictive ability for in-hospital mortality in ICU patients. Further analyses based on the NLR revealed that patients with a high or low NLR were more likely to have higher mortality rates and longer ICU and hospital stays. The addition of the NLR significantly improved the predictive power of the SAPS II, and the results of the subgroup analysis based on main diagnosis were consistent with the overall population.

The predictive value of the NLR has been widely studied, particularly in cardiovascular disease,[5, 8] infectious disease,[7, 9] and cancer.[10-11, 13] In this study, among the inflammatory indicators of the routine blood tests, NLR has the strongest ability to predict in-hospital death. NLR alone as a predictor has limited predictive power, and its AUC value is only 0.609. This may be related to that the prognosis of ICU patients are affected by many other confounding factors. However, after translating NLR into categorical variable and adjusting for the confounding factors, NLR showed a good ability to predict ICU outcomes. In addition, most previous studies[3-11, 14-15] have suggested that the higher the NLR, the worse the prognosis; however, other studies[16-17] have suggested that a low NLR is also associated with a poor prognosis. If, as in previous studies, we divided patients equally into 3–5 groups based on their NLR, we could draw the same conclusion that a high NLR is indicative of a poor prognosis. However, before analysis, we noted that patients with a low NLR also seemed to have a poor

prognosis. Thus, we implemented a different grouping scheme and confirmed our hypothesis by further analysis. Indeed, this finding was in line with clinical experience: the prognosis is generally good when the clinical indicators are within the normal range, and values that are too high or low are more likely to be associated with a poor prognosis. Several studies[13, 18] have suggested that the reason why an elevated NLR leads to a poor prognosis is mainly because of enhanced systemic inflammation and stress responses. However, the reason why a low NLR is associated with a poor prognosis remains unclear. We speculated that a decreased NLR may be due to a decrease in neutrophils that play a key role in the innate immune response, including directly killing pathogens by phagocytosis, releasing a variety of cytokines, and activating T cells, among other roles.[19] Therefore, a reduction in circulating neutrophils can lower the body's response to microbial invasion. In addition, reduced circulating neutrophils can be ascribed to the increased neutrophil adhesion to the vascular endothelium, which can cause endothelial damage, leading to leukocyte aggregation and microvascular thrombosis.[20] Thus, the compromise of innate immunity and the increase in endothelial damage can collectively impair the prognosis of patients.

Many previous studies[3-11, 14-15] have overlooked the possibility of a low NLR leading to a poor prognosis, which may be due to several reasons. First, compared to the overall trend towards a high NLR correlating with a poor prognosis, the association between a low NLR and a poor prognosis may have been neglected due to the small number of patients. There were only 580 patients with an NLR ≤1, which was 2.66% of the total population. Second, the main outcome indicators may have influenced the conclusions. Previous studies, which have mostly focused on late death (≥5 days), found that a high NLR can predict a poor prognosis. However, Riché *et al.*[17] reported that a low NLR is associated with an early death (< 5 days), whereas a high NLR

is associated with a late death. Duggal *et al.*[18] also suggested that an elevated NLR is a biomarker for an increased length of ICU stay. Therefore, based on previous studies that focused on late death, it is reasonable to conclude that a high NLR is associated with increased mortality. However, in our study, around half of the in-hospital deaths (1,512/3,149; 48.02%) occurred within 5 days; thus, our study indicated that a low NLR is also associated with increased mortality. Third, the study population may have influenced the conclusions. Several studies have been conducted in patients with specific diseases,[11, 13] and those excluded often had a low NLR. Our study focused on all ICU patients with no case selection.

Commonly used ICU prognosis score include APACHE, SOFA, SAPS and so on[21-22].In this study, the SAPS was chosen because of its lack of inflammatory indicators. Although the SAPS III has better predictive ability,[23] there were too many missing values, because it requires collecting data within 1 h after admission; therefore, we chose to use the SAPS II. As an easy-to-obtain, sensitive inflammatory indicator that does not increase the financial burden of patients, NLR has been reported by many previous studies and has high clinical significance. That's why we tried to add NLR to the SAPS II to evaluate whether it can increase its predictive performance. After adding NLR, the AUC of SAPS II increased from 0.789 to 0.798. Although the AUC value increase is statistically different, the increase is very small. Therefore, in order to illustrate the clinical importance of NLR, we also calculated NRI and IDI, and the results indicated that the addition of NLR significantly improved the prediction ability, with an NRI of 16.64% and IDI of 0.27%, respectively. What's more, some studies suggested that the PLR also had the ability to predict mortality[24]; therefore, we evaluated the predictive power of the PLR and found that, despite having some predictive ability, it was not as effective as the NLR. When

we added the PLR to the SAPS II together with the NLR, the AUC value did not increase significantly; therefore, we did not incorporate the PLR into this model.

The major strengths of our study are the large sample size and the inclusion of all ICU patients without selection bias. Further, we noticed that the mortality rate was also elevated in patients with a low NLR. More importantly, we found that adding the NLR to the SAPS II could improve its predictive power for ICU mortality, which is an important prompt for future scoring systems and may be of particular interest to critical care specialists.

There are also some limitations to this study. First, this was a retrospective study and some important data may be missing. Some patients were excluded because of missing neutrophil or lymphocyte data, and it was difficult to explore the reasons for missing data based on the information currently available. Second, the conclusions of this study were qualitative rather than quantitative. We can only infer that the addition of the NLR can improve the performance of the SAPS II because the NLR scores cannot be directly included in the SAPS II to construct a new scoring system, however, creating a new prognostic model is not a goal of this study, the main purpose of this study was to attract the attention of clinicians to be wary of abnormal NLR values. Finally, although we conducted a subgroup analysis of different diagnosis, in-depth analyses were not undertaken as it was not the aim of our study.

CONCLUSIONS

Of the inflammatory markers identified from routine blood tests, the NLR was the best predictor of ICU mortality. Abnormally high or low NLRs were associated with increased mortality.

Finally, the addition of the NLR to the SAPS II can improve its predictive power for ICU mortality.

Contributorship statement

XW was fully responsible for all stages of the study, including design, data extraction, statistical analysis, and manuscript writing. FXY and SY was involved in the design of the original protocol. QPL and YNL participated in data curation and analyses. HBW and QL contributed to the discussion and interpretation of data. ZHS helped to draft the final manuscript. All authors read approved the final manuscript.

Competing interests

None declared.

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Data sharing statement

Full data set available from the corresponding author at yanfuxia@sina.com. However, reanalysis of the full data need to be approved by MIMIC III Institute.

Ethical Statement

Since MIMIC-III is a third-party, anonymized, publicly available database with pre-existing Institutional Review Board approval at BIDMC and MIT, we were exempted from obtaining approval from our institution.

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Tables

Table 1 Baseline characteristics according to survivors and death

	Overall (n=21,822)	Survival group (n=18,673)	Death group (n=3,149)	*P*
Age, years	66.68 (52.76, 79.55)	65.37 (51.65, 78.41)	75.05 (61.16, 83.58)	<0.001
Sex, n (%)				0.004
Female	10,140 (46.47)	8,602 (46.07)	1,538 (48.84)	
Male	11,682 (53.53)	10,071 (53.93)	1,611 (51.16)	
Ethnicity, n (%)				<0.001
White	15,875 (72.75)	13,619 (72.93)	2,256 (71.64)	
Black	2,080 (9.53)	1,857 (9.94)	223 (7.08)	
Other	3,867 (17.72)	3,197 (17.12)	670 (21.28)	
ICU type				<0.001
CCU	3,331 (15.26)	2,864 (15.34)	467 (14.83)	
CSRU	2,443 (11.20)	2,279 (12.20)	164 (5.21)	
MICU	10,411 (47.71)	8,713 (46.66)	1,698 (53.92)	
SICU	3,775 (17.30)	3,201 (17.14)	574 (18.23)	
TSICU	1,862 (8.53)	1,616 (8.65)	246 (7.81)	
SAPS II	34 (25, 43)	32 (24, 40)	48 (37.5, 60)	<0.001
Peripheral blood index				
WBC (10^9/L)	9.9 (7.1, 13.9)	9.7 (7.1, 13.6)	11.4 (7.6, 16.6)	<0.001
Lymphocyte (10^9/L)	1.30 (0.83, 1.91)	1.34 (0.87, 1.94)	1.06 (0.67, 1.62)	<0.001
Neutrophil (10^9/L)	7.56 (4.88, 11.45)	7.34 (4.82, 11.07)	9.16 (5.49, 13.60)	<0.001
Platelet (10^9/L)	208 (150, 275)	210 (155, 275)	192 (119, 277)	<0.001
NLR	5.75 (3.09, 11.13)	5.40 (2.95, 10.46)	8.32 (4.25, 14.75)	<0.001
PLR	177.9 (115.4, 287.4)	175.1(115.1, 280.0)	199.1 (117.8, 334.9)	<0.001

Data are presented as median and interquartile range or number and percentage.

ICU, intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery units; MICU, medical ICU; SICU, surgical ICU; TSICU trauma surgical ICU; SAPS, Simplified Acute Physiology Score; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 2 Clinical outcomes of the ICU patients

Clinical outcomes	Overall (n=21822)	NLR			*P*
		≤1 (n=580)	(1, 6] (n=10691)	> 6 (n=10,551)	
Hospital mortality, n (%)	3149 (14.43)	122 (21.03)	1,009 (9.44)	2,018 (19.13)	<0.001
90-Day mortality, n (%)	4534 (20.78)	155 (26.72)	1,511 (14.13)	2,868 (27.18)	<0.001
1-Year mortality, n (%)	6234 (28.57)	211 (36.38)	2,311 (21.62)	3,712 (35.18)	<0.001
ICU length of stay (d)	2.08 (1.21, 4.13)	2.04 (1.08, 4.38)	1.96 (1.13, 3.46)	2.38 (1.33, 5.04)	<0.001
Hospital length of stay (d)	6.63 (3.79, 11.79)	7.35 (3.34, 15.86)	6.08 (3.63, 10.79)	7.00 (3.96, 12.67)	<0.001

Data are presented as median and interquartile range or number and percentage.

Table 3 Association between NLR and mortality

Exposure	Non-adjusted		Adjusted	
	OR (95%CI)	*P*	OR (95%CI)	*P*
In-hospital mortality				
≤1	2.56 (2.07, 3.15)	<0.001	1.61 (1.26, 2.05)	<0.001
(1, 6]	1		1	
>6	2.27 (2.09, 2.46)	<0.001	1.59 (1.46, 1.74)	<0.001
90-Day mortality				
≤1	1.96 (1.65, 2.33)	<0.001	1.48 (1.18, 1.85)	<0.001
(1, 6]	1		1	
>6	2.08 (1.95, 2.22)	<0.001	1.60 (1.48, 1.43)	<0.001
1-Year mortality				
≤1	2.07 (1.74, 2.47)	<0.001	1.51 (1.23, 1.86)	<0.001
(1, 6]	1		1	
>6	1.97 (1.85, 2.09)	<0.001	1.38 (1.29, 1.48)	<0.001

Adjusted confounders: age, sex, ethnicity, ICU type and SAPS II.

Figure Legends

Figure 1: Study flow diagram in the present study.

ICU, intensive care unit; NLR, Neutrophil-to-Lymphocyte Ratio.

Figure 2: Receiver operating characteristic curves for the SAPS II and the SAPS II+NLR.

SAPS, Simplified Acute Physiology Score; NLR, Neutrophil-to-Lymphocyte Ratio; AUC, area under the receiver-operating characteristic curve; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

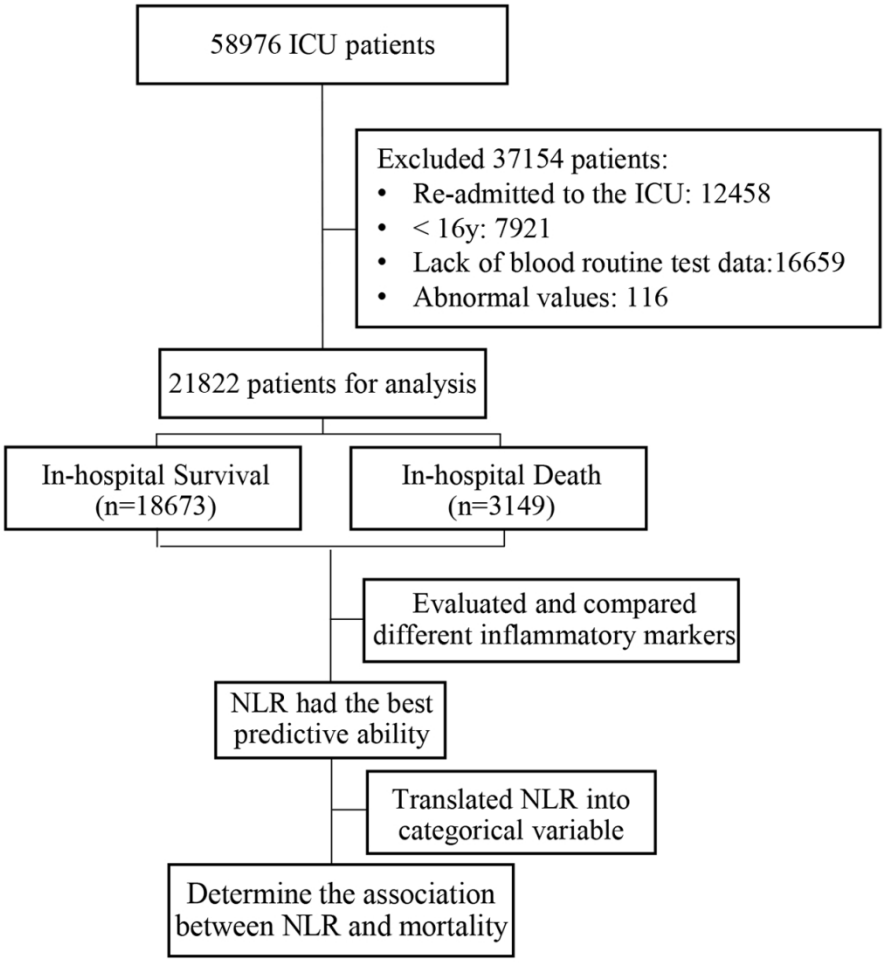
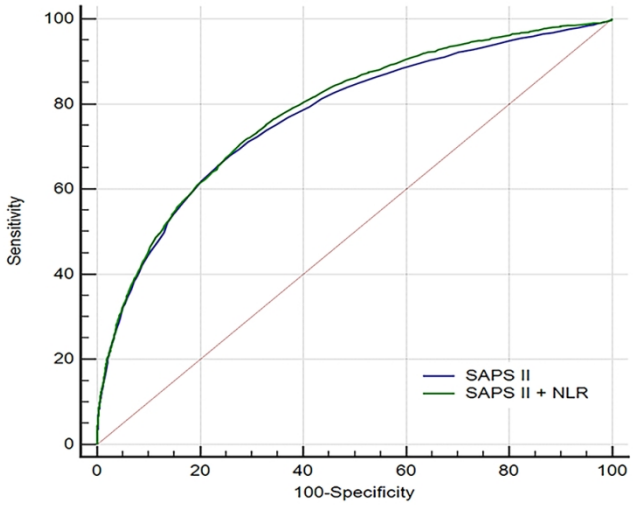

58976 ICU patients
Excluded 37154 patients:
• Re-admitted to the ICU: 12458
• < 16y: 7921
• Lack of blood routine test data:16659
• Abnormal values: 116
21822 patients for analysis
In-hospital Survival (n=18673)
In-hospital Death (n=3149)
Evaluated and compared different inflammatory markers
NLR had the best predictive ability
Translated NLR into categorical variable
Determine the association between NLR and mortality

Figure 1



	SAPS II	SAPSII+NLR	P-value
AUC	0.789	0.798	< 0.001
	SAPS II vs. SAPSII+NLR		
NRI	16.64%		< 0.001
IDI	0.27%		< 0.001

Figure 2

Supplemental Table 1 The optimal cut-off values based on in-hospital mortality

Peripheral blood index	Cut-off value	AUC	*P*
WBC (10^9/L)	12	0.575	<0.001
Lymphocyte (10^9/L)	1.17	0.593	<0.001
Neutrophil (10^9/L)	9.57	0.576	<0.001
Platelet (10^9/L)	128	0.554	<0.001
NLR	6	0.609	<0.001
PLR	267	0.536	<0.001

WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Supplemental Table 2 Baseline characteristics according to NLR level

	NLR			*P*
	≤1 (n=580)	**(1, 6] (n=10691)**	**＞6 (n=10,551)**	
Age, years	61.76 (48.02, 74.42)	64.99 (51.37, 78.06)	68.75 (54.56, 80.96)	<0.001
Female, n (%)	282 (48.62%)	4807 (44.96%)	5051 (47.87%)	<0.001
Ethnicity, n (%)				<0.001
White	354 (61.03%)	7595 (71.04%)	7929 (75.12%)	
Black	115 (19.83%)	1250 (11.69%)	1846 (17.27)	
Other	111 (19.14%)	1846 (17.27%)	1910 (18.10)	
ICU type				
CCU	74 (12.76%)	1712 (16.01%)	1545 (14.64%)	0.005
CSRU	46 (7.93%)	1812 (16.95%)	585 (5.54%)	<0.001
MICU	350 (60.34%)	4,635 (43.35%)	5,426 (51.43%)	<0.001
SICU	73 (12.59%)	1,767 (16.53 %)	1,935 (18.34%)	<0.001
TSICU	37 (6.38%)	765 (7.16 %)	1,060(10.05%)	<0.001
SAPS II	43 (31, 61)	37 (28, 50)	43 (32, 58.75)	<0.001
Peripheral blood index				
WBC (10^9/L)	6.4 (3.1, 11.9)	8 (6.1, 10.4)	12.8 (9.6, 17.1)	<0.001
Lymphocyte (10^9/L)	2.96 (1.31, 4.93)	1.76 (1.31, 2.32)	0.91 (0.61, 1.25)	<0.001
Neutrophil (10^9/L)	1.99 (0.48, 3.40)	5.44 (3.96, 7.41)	10.99 (8.06, 14.83)	<0.001
Platelet (10^9/L)	148.5 (67, 219.25)	202 (147, 266)	217 (159, 288)	<0.001

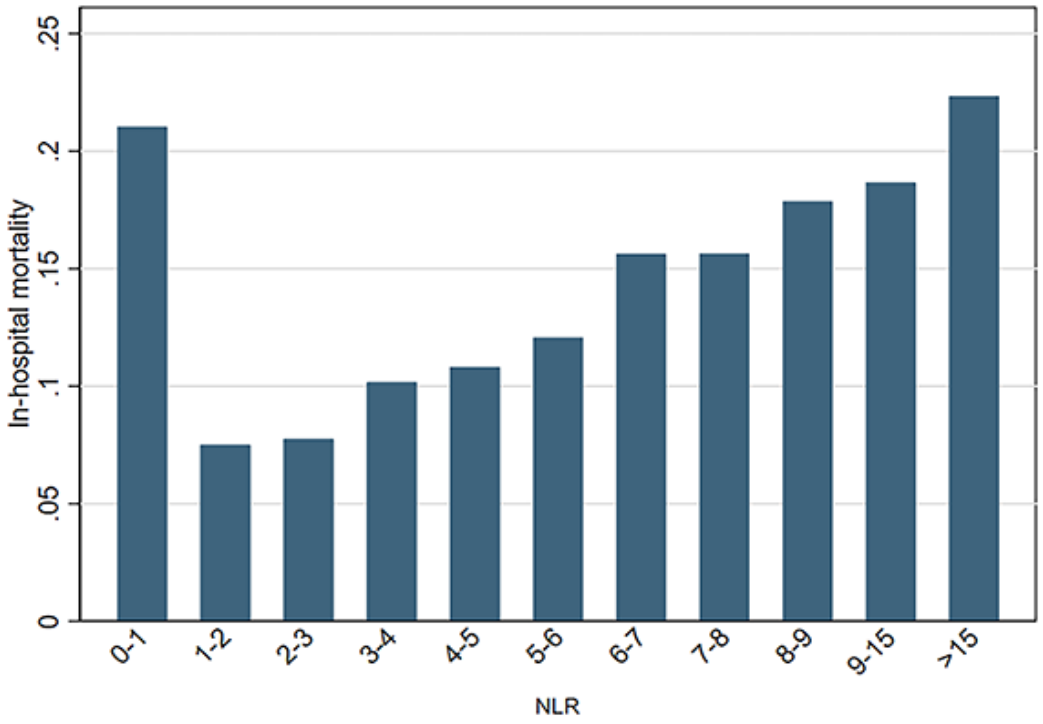
NLR, neutrophil-to-lymphocyte ratio; ICU, intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery units; MICU, medical ICU; SICU, surgical ICU; TSICU trauma surgical ICU; SAPS, Simplified Acute Physiology Score; WBC, white blood cell.

Supplemental Table 3 Subgroup analyses of the association between In-hospital mortality and NLR levels.

Subgroups		NLR		
		≤ 1	**(1, 6]**	**>6**
ARDS	n (%)	46 (1.88)	1,812 (74.17)	585 (23.95)
	OR (95%CI)	1.85 (1.24, 2.76)	1	1.27 (1.09, 1.49)
	P	0.003		0.002
CHD	n (%)	37 (1.99)	765 (41.08)	1,060 (56.93)
	OR (95%CI)	2.13 (1.12, 4.02)	1	1.90 (1.54, 2.33)
	P	0.021		<0.001
CKD	n (%)	37 (1.99)	765 (41.08)	1,060 (56.93)
	OR (95%CI)	3.62 (1.67, 7.86)	1	1.78 (1.33, 2.39)
	P	0.001		<0.001
CLD	n (%)	37 (1.99)	765 (41.08)	1,060 (56.93)
	OR (95%CI)	1.75 (0.16, 19.43)	1	2.57 (1.12, 5.89)
	P	0.648		0.025

Confounders adjustment were performed as before (Table 3).

ARDS acute respiratory distress syndrome, CHD coronary heart disease, CKD chronic kidney disease, CLD chronic liver disease.



Supplemental Figure 1: Association of in-hospital mortality rates and different NLR levels.