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The nonlinear correlation of neutrophil-lymphocyte ratio on 1-year mortality risk in patients with severe acute heart failure

Yunchao Deng[1], Jian Lin[1], Chuang Li[1], Rong Tian[1] and Bo Liu[1*]

Abstract

Background This retrospective cohort study was designed to examine the relationship between the neutrophil-lymphocyte ratio (NLR) and the 1-year risk of death in patients with acute heart failure (AHF) in the intensive care unit (ICU).

Methods We retrospectively analyzed 1,176 patients with AHF from the MIMIC-IV database. Cox regression was used to evaluate the relationship between NLR and 1-year mortality risk after adjusting for covariates. Nonlinear associations and optimal NLR cutoff values were determined using restricted cubic splines. Propensity score matching was used to eliminate imbalances in the baseline confounders. Kaplan-Meier survival analysis further confirmed the correctness of the threshold. The ROC was used to evaluate the diagnostic accuracy of the NLR for long-term outcomes. Subgroup analyses were performed to assess the generality of NLR in specific populations.

Results The mortality rate was lowest in the lower tertile NLR group (< 5.43) and highest in the upper tertile group (> 13.53, P for trend < 0.001). NLR showed a nonlinear correlation with mortality (P for Non-linearity = 0.0075), with the risk increasing significantly when NLR exceeded 11.11. The AUC of NLR for predicting 1-year mortality was 0.579 (95%CI 0.542–0.617). The NLR was not significantly different from long-term outcomes in most groups, but the association was stronger in patients with AHF who did not have sepsis.

Conclusion Elevated NLR, a marker of heightened systemic inflammation, was associated with a higher risk of 1-year mortality in ICU patients with AHF.

Clinical trial number Not applicable.

Keywords Acute heart failure, Intensive care unit, Neutrophil lymphocyte ratio, MIMIC IV

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Background

Acute heart failure (AHF) is an urgent and serious complication of cardiovascular diseases, characterized by rapid deterioration of cardiac pumping function, posing a significant threat to the patient's life and health [1]. Acute heart failure often leads to high mortality rates in the Intensive Care Unit (ICU) and is associated with an increased consumption of medical resources [2]. Therefore, identifying effective prognostic indicators for timely intervention is crucial for improving the prognosis of such patients.

In recent years, with in-depth research on the pathogenesis of cardiovascular diseases, increasing evidence suggests that the inflammatory process is of great importance in the onset, evolution, and deterioration of AHF [3]. Neutrophils and lymphocytes, as key participants in the inflammatory response, with their ratio (Neutrophil Lymphocyte Ratio, NLR), are considered effective indicators of inflammatory status [4].

NLR, as a convenient and cost-effective inflammatory biomarker, is not only associated with infectious diseases [5, 6] but has also been confirmed to be related to various diseases and cancers in different systems (respiratory, circulatory, digestive, and urinary systems) [7–10]. Relevant studies also indicate that an elevation in the NLR is associated with disease severity and adverse outcomes [11, 12]. Although studies have explored the relationship between NLR and other cardiovascular diseases [13–15], research has not focused on the nonlinear correlation relationship between NLR and the risk of death at 1 year in patients with AHF in the ICU.

In view of this, our retrospective cohort study focused on the optimal NLR values for evaluating the long-term prognosis of patients with AHF in the ICU, particularly the 1-year mortality risk. Through a thorough analysis of the relationship between NLR and patient outcomes, we hope to provide clinicians with a novel and convenient prognostic assessment tool to assist in clinical decision making, ultimately improving the quality of life and long-term prognosis of patients with AHF.

Methods

Data sources

All data used in our study were obtained from the Medical Information Mart for Intensive Care (MIMIC) run by the Beth Israel Deaconess Medical Center (BIDMC). The one we applied was MIMIC IV 2.0. MIMIC IV 2.0 is a large, publicly available clinical database that encompasses patient data from the ICU of BIDMC from 2001 to 2019. The database was jointly developed by the Massachusetts Institute of Technology (MIT) and BIDMC, and its use for research purposes was approved by the Institutional Review Board (IRB). This study strictly adhered to relevant ethical standards and privacy protection principles and received IRB approval prior to data approval. We carried out a complete data analysis to ensure the security of patient information, anonymity, and de-identification of all data. At the same time, we selected eICU data as an external validation cohort. In addition, the requirement for informed consent was waived owing to the study design [16].

Research population and definition

From the MIMIC IV 2.0 database, we selected patients diagnosed with Acute Heart Failure (AHF). The diagnostic criteria for AHF were based on the International Classification of Diseases, 9th revision (ICD-9) codes 428.21, 428.31, 428.41, and 10th Revision (ICD-10) codes I50.21, I50.31, I50.41, and I50.811. Inclusion criteria specified patients who were first transferred to the ICU and met the diagnostic criteria for AHF. Exclusion criteria included baseline absence of neutrophil or lymphocyte measurements, extreme NLR values (beyond the mean ± 3 standard deviations), and ICU stay of < 24 h.

Data collection and processing

We systematically collected key variables, including demographic data, vital signs during the first 24-hours of ICU admission, comorbidity information, hematology test results, severity scores, and treatment interventions. For missing values in the data, we employed multiple imputations with the random forest method to ensure data completeness. For outliers, we conducted a thorough examination and cleaning to ensure data accuracy. In addition, the key indicator NLR was obtained by the ratio of the mean neutrophil count and the mean lymphocyte count obtained on the first day after admission to ICU. NLR = mean neutrophil counts (10^9)/mean lymphocyte counts (10^9).

Statistical analysis

In the data analysis phase, we first performed descriptive statistics to determine the basic characteristics and distribution of the study population.

We employed the restricted cubic spline method to make a thorough inquiry into the nonlinear relationship between the NLR and mortality risk. To further explore the nonlinear correlation between NLR and AHF in the ICU, we used a propensity score matching (PSM) approach. The propensity score matching method matched the two groups of people according to the selected confounding factors so that the confounding factors of the two groups of people were as balanced as possible to reduce the confounding effect of confounding factors on the results. First, a logistic regression model was constructed with NLR, which was converted into categorical variables according to the threshold, as the dependent variable, and baseline covariates such as age,

sex, comorbidities, and vital signs as the independent variables. The model was used to estimate the propensity score for each patient. Then, we use the greedy nearest neighbor algorithm for matching while imposing 0.05 SD constraints on the propensity score to ensure the robustness of the matching. Then, a matching ratio of 1:1 was selected to evaluate the matching quality after matching by comparing the differences in baseline covariates between groups. We visualized the survival differences between patients with various NLR levels using Kaplan-Meier survival curves, both pre- and post-matching, and compared them using the log-rank test. Additionally, we plotted the Receiver Operating Characteristic (ROC) curve and computed the area under the curve (AUC) of the ROC to identify the best NLR threshold for predicting mortality risk.

To enhance the robustness of our results, we conducted a subgroup analysis to examine the effects (such as age, sex, underlying disease, etc.) on the prognosis of ICU patients with acute heart failure across various patient groups to more comprehensively understand the clinical significance of NLR as a prognostic indicator.

We performed all statistical analyses using R version 4.2.3 and SPSS version 27.0, considering a two-sided P-value of less than 0.05, to indicate statistical significance.

Results

Baseline characteristics of the study population

A total of 1,176 patients with AHF were included strictly in accordance with the inclusion and exclusion criteria of this study (Fig. 1), and the baseline characteristics are detailed in Table 1. Overall, 71% ($n = 842$) of the patients survived for one year after their initial hospitalization. The average age of patients who died within one year was 75.6 years, significantly higher than the 67.4 years of surviving patients ($P < 0.01$). Furthermore, deceased patients had a lower body mass index (BMI) (26.2 vs. 28.5 kg/m^2, $P < 0.01$).

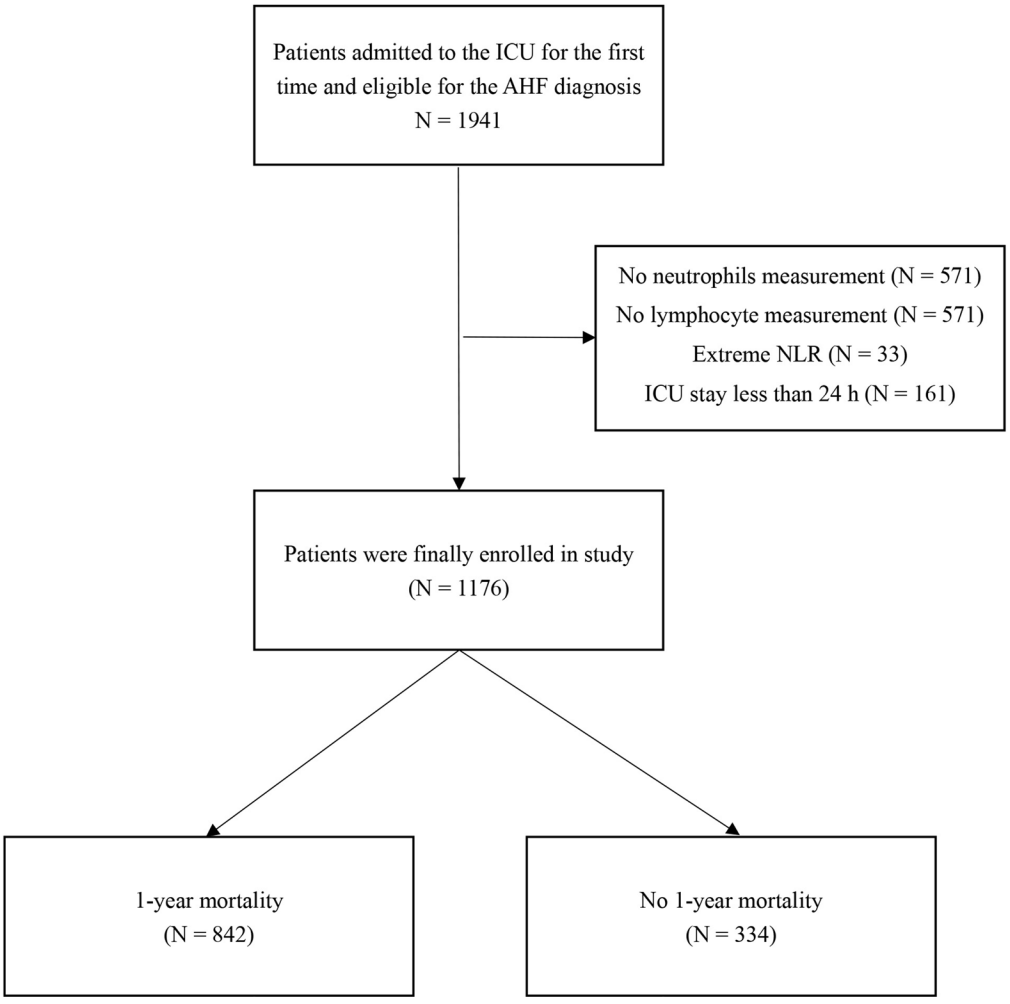

Fig. 1 Flow chart of patient eventually selection included in this study. AHF: Acute heart failure; ICU: Intensive care unit; NLR: Neutrophil lymphocyte ratio

Table 1 The baseline characters of inclued patients

Variable	Overall (*N* = 1176)	Survivor (*N* = 842)	Non-survivor (*N* = 334)	*P* Value
Gender, male (%)	654 (55.61)	483 (57.36)	171 (51.20)	0.06
Age	69.94 (58.92–79.03)	67.41 (55.45–77.06)	75.6 (66.29–84.43)	< 0.01
BMI	27.92 (24.25–32.41)	28.46 (25.14–33.05)	26.23 (22.85–30.19)	< 0.01
HR	87.33 (77.32-100.62)	86.53 (77.33–99.44)	90.02 (77.24-101.98)	0.1
MBP	76.51 (70.62-84)	77.11 (71.6-84.57)	74.61 (68.84–82.2)	< 0.01
RR	20.51 (18.13–23.52)	20.44 (18.06–23.41)	20.74 (18.24–24.03)	0.4
BT	36.82 (36.58–37.09)	36.84 (36.63–37.11)	36.75 (36.5-37.05)	0.05
SPO2	96.56 (95.17-98)	96.65 (95.21–98.07)	96.46 (95.13–97.94)	0.05
Lac	1.93 (1.54–2.5)	1.9 (1.5–2.4)	2.07 (1.63–2.92)	< 0.01
Ph	7.37 (7.33–7.41)	7.37 (7.34–7.41)	7.36 (7.31–7.41)	< 0.01
PO2	100.5 (74.98-139.41)	102.72 (78-144.25)	95.92 (68.2-129.93)	0.01
PCO2	40.32 (36.65-44)	40.5 (36.67–43.88)	39.83 (36.18–44.75)	0.12
Base excess	-1.06 (-3.82-0.38)	-1 (-3.28-0.43)	-1.53 (-5-0.33)	0.38
Total CO2	24.5 (21.66–26.77)	24.78 (22-26.68)	23.73 (20.68-27)	0.27
Hematocrit	33.7 (29.07–38.6)	34.18 (29.63–39.32)	32.03 (27.8-37.15)	< 0.01
Hemoglobin	11.01 (9.49–12.71)	11.23 (9.7-13.05)	10.55 (9-12.04)	< 0.01
WBC	12.46 (8.95–16.31)	12.45 (9.25–16.03)	12.58 (8.18–17.15)	0.14
RBC	3.7 (3.2–4.28)	3.79 (3.28–4.38)	3.55 (2.95–4.1)	< 0.01
PLC	202.17 (151.25-270.81)	205.42 (157.19-268.25)	194.5 (139.5–275)	0.15
Basophils	0.07 (0.02–2.77)	0.09 (0.02–3.28)	0.05 (0.01–1.77)	< 0.01
Eosinophils	0.3 (0.01–6.21)	0.43 (0.02–7.27)	0.1 (0-3.18)	0.34
Lymphocytes	45.55 (1.42-124.06)	56.1 (1.57-134.58)	29.48 (0.99-106.98)	0.01
Monocytes	17.59 (0.83–51.23)	20.95 (0.84–51.75)	3.66 (0.81–47.14)	0.75
Neutrophils	404.96 (11.06-1062.47)	439.34 (11.41-1060.11)	77.15 (10.11-1071.97)	0.68
NLR	8.16 (4.7-14.26)	7.64 (4.53–12.84)	9.7 (5.52–18.22)	< 0.01
RDW	14.54 (13.58–15.92)	14.3 (13.43–15.47)	15.41 (14.25–16.97)	< 0.01
MCV	91 (87-95.21)	90.5 (87-94.96)	91.5 (87-96.63)	0.06
MCH	30.07 (28.55–31.3)	30.1 (28.61–31.26)	29.97 (28.37–31.39)	0.36
MCHC	32.85 (31.86–33.75)	32.98 (32.03–33.95)	32.5 (31.51–33.46)	< 0.01
ALT	47.5 (23-93.8)	47.46 (24-85.81)	49 (21.12-110.84)	0.67
AST	67.92 (35-144.3)	66.26 (35–132)	72.78 (35-204.5)	0.16
ALP	88 (68.5–114)	84.77 (66–107)	97.07 (75.09-129.58)	< 0.01
TB	0.71 (0.5–1.05)	0.7 (0.5-1)	0.8 (0.5–1.23)	< 0.01
CKMB	16.87 (6-37.18)	17.25 (6.67–37.13)	16.07 (5.33–37.17)	0.38
BUN	23.5 (17-36.52)	22 (16.21-32)	31.29 (20.27–46.19)	< 0.01
SCR	1.13 (0.85–1.65)	1.1 (0.83–1.5)	1.3 (0.9–2.23)	< 0.01
Calcium	8.34 (7.9–8.77)	8.36 (7.95–8.77)	8.28 (7.8–8.77)	0.18
Chloride	103.33 (99.79-106.46)	103.33 (100.33–106.5)	103 (98.67-106.24)	0.15
Sodium	138.31 (135.75–140.4)	138.33 (136-140.25)	138 (135.08–141)	0.84
Potassium	4.25 (3.9–4.67)	4.21 (3.9–4.6)	4.3 (3.95–4.83)	< 0.01
Anion gap	15.07 (13-17.5)	15 (13-17.13)	15.67 (13.5-18.67)	< 0.01
Bicarbonate	22.5 (19.67-25)	22.67 (20–25)	21.67 (19–25)	0.07
Glucose	137 (115-177.26)	136.5 (115.5-173.92)	141.46 (114.62-184.77)	0.38
INR	1.27 (1.13–1.5)	1.25 (1.11–1.45)	1.3 (1.17–1.69)	< 0.01
PTT	34.36 (28.64–50.91)	33.4 (28.33–49.77)	36.02 (29.53–52.07)	0.04
PT	14.1 (12.6–16.5)	13.9 (12.5-15.74)	14.62 (13-18.28)	< 0.01
UO	1640 (981.5-2601.5)	1799 (1090-2767.5)	1330 (737.5-2267.5)	< 0.01
SOFA	6 (3–9)	5 (3–8)	7 (5–10)	< 0.01
SRIS	3 (2–3)	3 (2–3)	3 (2–4)	0.07
MI (%)	520 (44.22)	368 (43.71)	152 (45.51)	0.62
COPD (%)	357 (30.36)	232 (27.55)	125 (37.43)	< 0.01
DM (%)	406 (34.52)	295 (35.04)	111 (33.23)	0.6
RD (%)	295 (25.09)	188 (22.33)	107 (32.04)	< 0.01

Table 1 (continued)

Variable	Overall (*N* = 1176)	Survivor (*N* = 842)	Non-survivor (*N* = 334)	*P* Value
LD (%)	131 (11.14)	90 (10.69)	41 (12.28)	0.5
Hypertension (%)	824 (70.07)	586 (69.60)	238 (71.26)	0.62
Sepsis (%)	758 (64.46)	511 (60.69)	247 (73.95)	< 0.01
RRT (%)	41 (3.49)	24 (2.85)	17 (5.09)	0.09
Ventilation (%)	1051 (89.37)	750 (89.07)	301 (90.12)	0.67

BMI: Body mass index; HR: Heart rate; MBP: Mean arterial blood pressure; RR: Respiratory rate; BT: Body temperature; SPO2: Pulse oxygen saturation; Lac: Lactic acid; WBC: White blood cell count; RBC: Red blood cell count; PLC: Platelet count; NLR: Neutrophil lymphocyte ratio; RDW: Red blood cell distribution width; MCV: Mean corpuscular volume; MCH: Mean corpuscular concentration of hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; TB: Total bilirubin; CKMB: Creatine phosphokinase isoenzyme; BUN: Blood urea nitrogen; SCR: Serum creatinine; INR: International normalized ratio; PT: Prothrombin time; PTT: Partial thromboplastin time; UO: urine output; SOFA: Sequential organ failure assessment; SIRS: Systemic inflammatory syndrome; MI: Myocardial infarction; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; RD: Renal disease; LD: Liver disease; RRT: Renal replacement therapy

In terms of comorbidities, the deceased group had significantly higher rates of chronic obstructive pulmonary disease (COPD; 37.4% vs. 27.6%) and renal disease (32.0% vs. 22.3%) than the surviving group ($P < 0.01$). With regard to the severity of clinical diseases and organ dysfunction, deceased patients exhibited significant derangement during hospitalization.

Specifically, the death group had higher lactate levels than the survival group (2.07 mmol/L vs. 1.90 mmol/L), more severe renal injury (higher BUN, creatinine levels), and significantly higher levels of total bilirubin and liver enzymes compared to the survival group (all $P < 0.05$). Additionally, deceased patients showed more pronounced abnormalities in coagulation function, international normalized ratio (INR), hematocrit (HCT), red blood cell (RBC) count, and other hematological parameters (all $P < 0.05$). Finally, during hospitalization, the severity of acute illnesses and SOFA scores were significantly higher in deceased patients than in survivors (median, 7 vs. 5; $P < 0.01$). It is noteworthy that deceased patients exhibited significantly elevated inflammatory markers, including a higher white blood cell count and NLR (NLR, 9.7 vs. 7.6, $P < 0.01$).

Risk factors for one-year mortality risk in AHF patients

Through Cox regression analysis (Table 2), we explored potential risk factors for one-year mortality in ICU patients with AHF. In univariate analysis, we found several clinical factors and biomarkers significantly correlated with one-year mortality ($p < 0.05$). Subsequently, we included these potential risk factors in multivariate analysis and, after adjusting for potential confounding factors, found that age, comorbid COPD, bicarbonate, BUN, lactate, NLR, red cell distribution width (RDW), partial thromboplastin time (PTT), oxygen saturation (SPO2), and SOFA score were independent risk factors, while BMI was an independent protective factor (all $p < 0.05$). Specifically, the more pronounced systemic inflammation marked by high NLR remained significantly associated with increased risk of one-year mortality after adjusting for potential confounding factors (HR 1.14, 95% CI 1.12–1.16, $p = 0.042$).

Nonlinear association of NLR with mortality risk

To further investigate the association between NLR and mortality risk, we divided NLR into tertiles based on the inter-tertile range: Lower Tertile (T1), representing the lowest third, Middle Tertile (T2), middle third, and Upper Tertile (T3) the highest third. This created a categorical variable known as the tertile of neutrophil-lymphocyte ratio (TNLR). The analysis results (Fig. 2) showed a significant difference in the mortality rates among the different TNLR groups during the follow-up period ($P < 0.001$). Pairwise comparisons using the chi-square test also indicated that the mortality rate in T3 was significantly higher than that in T1 and T2, suggesting a higher mortality rate in patients with a higher NLR (P for trend < 0.001).

To investigate this nonlinear relationship in more depth, we used restricted cubic splines with four nodes based on the results of the goodness-of-fit test of the model (Table S1). The analysis results indicated a significant non-linear correlation between NLR at the time of ICU admission and the peril of one-year fatality rate (P for non-linearity = 0.0075, P for total < 0.001, Fig. 3).

High levels of NLR are a risk factor for patients of AHF in the ICU

According to the nonlinear correlation described earlier, the risk of death increased significantly when the NLR was greater than 11.11(second quartile). To further confirm these findings, we eliminated confounders that might influence patient outcomes using a method called propensity score matching (PSM). After PSM, the possible confounders affecting the 782 patients were largely balanced (Fig. 4). Subsequently, according to the threshold value (11.11) obtained from the above results, we converted the continuous variable NLR into a subtype variable; that is, patients were separated into lower-level and upper-level NLR groups. Through Kaplan-Meier survival analysis, we found that before and after PSM, the

Table 2 Results of risk factor analysis

		Univariate		Multivariate	
Characteristics	**Number (%)**	**HR 95%CI**	**P Value**	**HR 95%CI**	**P Value**
Basophils	1.84 (3.05)	0.919 (0.877, 0.963)	< 0.001	0.968 (0.924, 1.014)	0.173
Age	68.12 (15.38)	1.032 (1.024, 1.04)	< 0.001	1.03 (1.02, 1.039)	< 0.001
BMI	29.28 (7.86)	0.963 (0.946, 0.979)	< 0.001	0.979 (0.961, 0.996)	0.019
MBP	78.16 (11.00)	0.979 (0.969, 0.99)	< 0.001	0.999 (0.987, 1.011)	0.869
SPO2	96.42 (2.29)	0.946 (0.904, 0.991)	0.018	0.92 (0.878, 0.965)	0.001
Lac	2.28 (1.44)	1.165 (1.111, 1.221)	< 0.001	1.171 (1.084, 1.265)	< 0.001
Ph	7.37 (0.07)	0.042 (0.009, 0.203)	< 0.001	2.062 (0.261, 16.279)	0.493
PO2	114.76 (60.68)	0.997 (0.995, 0.999)	0.008	0.999 (0.996, 1.001)	0.192
WBC	13.50 (7.47)	1.015 (1.001, 1.03)	0.035	1.003 (0.989, 1.018)	0.658
RBC	3.76 (0.78)	0.695 (0.601, 0.804)	< 0.001	0.901 (0.619, 1.311)	0.585
NLR	11.11 (9.64)	1.25 (1.2, 1.3)	< 0.001	1.14 (1.12, 1.16)	0.042
hematocrit	34.03 (6.67)	0.962 (0.946, 0.978)	< 0.001	1.203 (0.974, 1.486)	0.087
hemoglobin	11.17 (2.26)	0.866 (0.824, 0.911)	< 0.001	0.551 (0.287, 1.057)	0.073
RDW	15.05 (2.19)	1.172 (1.132, 1.213)	< 0.001	1.123 (1.071, 1.178)	< 0.001
MCHC	32.79 (1.51)	0.844 (0.787, 0.904)	< 0.001	1.21 (0.97, 1.51)	0.091
AST	255.57 (1303.62)	1 (1, 1)	0.035	1 (1, 1)	0.384
ALP	103.85 (92.58)	1.001 (1, 1.001)	0.006	1 (1, 1.001)	0.278
TB	1.01 (1.33)	1.11 (1.05, 1.172)	< 0.001	1.005 (0.943, 1.071)	0.875
Anion gap	15.56 (3.65)	1.059 (1.03, 1.088)	< 0.001	0.984 (0.941, 1.029)	0.473
bicarbonate	22.56 (4.58)	0.974 (0.95, 0.998)	0.036	1.043 (1.014, 1.074)	0.004
BUN	29.88 (20.07)	1.017 (1.013, 1.021)	< 0.001	1.014 (1.007, 1.02)	< 0.001
SCR	1.61 (1.59)	1.08 (1.027, 1.135)	0.003	0.947 (0.851, 1.055)	0.325
Potassium	4.32 (0.59)	1.392 (1.172, 1.653)	< 0.001	1.125 (0.909, 1.392)	0.279
INR	1.50 (0.95)	1.117 (1.046, 1.192)	0.001	0.671 (0.35, 1.287)	0.23
PT	16.26 (8.73)	1.017 (1.009, 1.024)	< 0.001	1.046 (0.981, 1.115)	0.173
PTT	43.66 (22.66)	1.006 (1.001, 1.01)	0.013	1.007 (1.002, 1.012)	0.003
UO	1973.93 (1467.76)	1 (1, 1)	< 0.001	1 (1, 1)	0.188
SOFA	6.36 (3.97)	1.093 (1.066, 1.12)	< 0.001	1.083 (1.044, 1.124)	< 0.001
SIRS	2.82 (0.86)	1.15 (1.012, 1.307)	0.032	0.999 (0.856, 1.165)	0.986
COPD	357 (30.4)	1.461 (1.171, 1.824)	0.001	1.375 (1.084, 1.744)	0.009
RD	295 (25.1)	1.498 (1.19, 1.885)	0.001	0.934 (0.702, 1.242)	0.639
Sepsis	758 (64.5)	1.751 (1.371, 2.235)	< 0.001	1.138 (0.861, 1.505)	0.363

BMI: Body mass index; MBP: Mean arterial blood pressure; SPO2: Pulse oxygen saturation; Lac: Lactic acid; WBC: White blood cell count; RBC: Red blood cell count; NLR: Neutrophil lymphocyte ratio; RDW: Red blood cell distribution width; MCHC: Mean corpuscular hemoglobin concentration; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; TB: Total bilirubin; BUN: Blood urea nitrogen; SCR: Serum creatinine; INR: International normalized ratio; PT: Prothrombin time; PTT: Partial thromboplastin time; UO: urine output; SOFA: Sequential organ failure assessment; SIRS: Systemic inflammatory syndrome; COPD: Chronic obstructive pulmonary disease; RD: Renal disease

survival probability of patients with high NLR was significantly lower than that of patients with low NLR (Fig. 5, $P < 0.05$).

To assess the predictive value of NLR for one-year mortality risk in ICU-admitted patients with AHF, we conducted a ROC curve analysis (Fig. 6). The results showed that the AUC for the NLR model was 0.579 (95% CI: 0.542–0.617), indicating moderate predictive ability for mortality risk. Additionally, based on the Youden index from the ROC analysis, we determined the optimal cut-off value to be 11.11, which is consistent with the results from the restricted cubic spline.

Subgroup analysis

In this study, we performed a detailed subgroup analysis to better understand the impact of the NLR on the outcome of patients with AHF in the ICU and to explore how this impact varied across patient populations. Factors such as age, BMI, myocardial infarction, hypertension, diabetes, kidney disease, and sepsis were selected as stratified factors. We then performed COX regression analysis at each level according to stratification and calculated the interactions between the layers. We found no significant difference in the effect of NLR on long-term outcomes in patients with sepsis, except in this specific group. In sepsis stratification, we found that NLR had a more significant effect on patients without sepsis (Fig. 7, $P < 0.001$, P for interaction < 0.05).

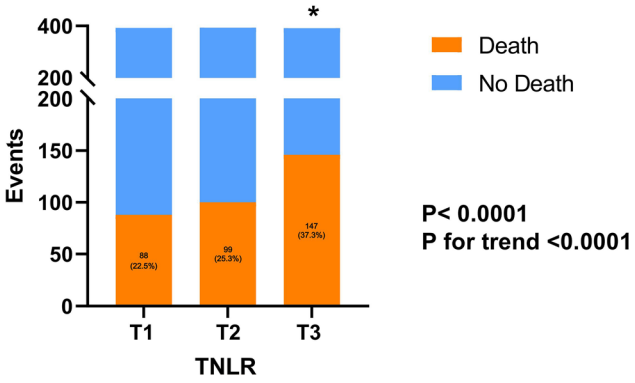

Fig. 2 The mortality rate during follow-up was compared between different tertiles. T1: The lowest third of the data; T2: The middle third of the data; T3: The highest third of the data; TNLR: Tertile of neutrophil lymphocyte ratio

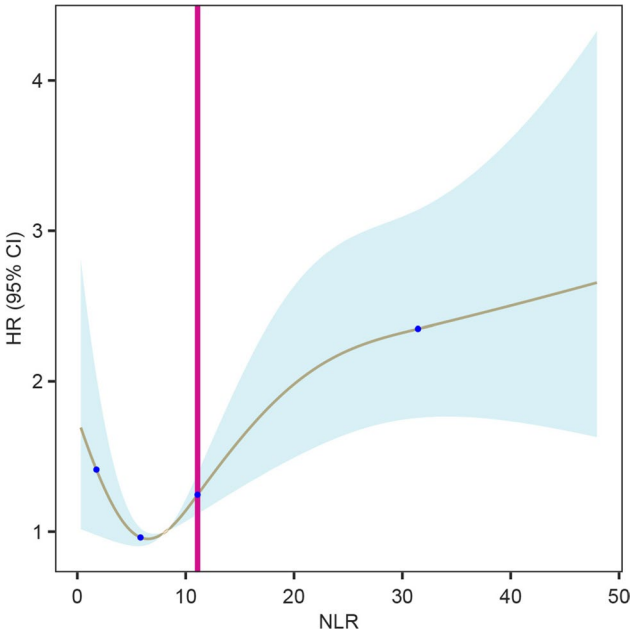

Fig. 3 The nonlinear relationship between NLR and death risk. NLR: Neutrophil lymphocyte ratio; HR: Hazard ratio; CI: Confidence interval

External validation

To validate the generalizability of our findings, we enrolled 839 patients from the eICU database to construct an external validation cohort. The baseline characteristics of this cohort were broadly comparable to the original derivation cohort (Table S2). In the external validation cohort, the NLR cutoff of 11.11 exhibited comparable discriminative power (AUC = 0.601, 95% CI: 0.574–0.651), and the high-NLR group demonstrated a significantly lower survival probability compared to the low-NLR group (log-rank $P = 0.0012$; see Figure S1).

Discussion

This study has several key findings: (1) NLR was significantly elevated in patients with AHF in the ICU with poor consequences; (2) Elevated NLR increases the risk of death within one year; (3) NLR exhibits a non-linear association with patient mortality risk, with a sharp increase when NLR exceeds 11.11.

Our study aimed to explore factors related to the one-year mortality risk of patients with AHF in the ICU, with a particular focus on the predictive value of NLR as a systemic inflammation marker. Through a comprehensive analysis of 1,176 patients with AHF, we identified a range of clinical factors and biomarkers that were significantly associated with the risk of death.

First, NLR, as a simple, cost-effective, and widely available systemic inflammation marker, has been increasingly shown to be useful in predicting the prognosis of various diseases in recent research [17, 18]. Our results further demonstrate that NLR exhibits additional risk stratification capability for predicting long-term mortality in patients with AHF, especially in the severe ICU setting. Monitoring NLR allows clinicians to identify high-risk patients more accurately, enabling more proactive treatment and interventions.

The predictive value of NLR is likely closely related to the systemic inflammatory state it reflects [19]. Systemic inflammation is crucial for the occurrence, development, and prognosis of cardiovascular diseases [20]. During the pathological process of AHF, inflammatory reactions can lead to myocardial cell damage, worsening heart function, and the occurrence of a series of adverse cardiovascular events [21–23]. Studies suggest that proinflammatory cytokines, lipopolysaccharides, and hypoxia signals can affect lymphocyte function and prolong neutrophil apoptosis [24]. Therefore, an increase in the NLR, indicating elevated inflammation, may further exacerbate myocardial injury and heart failure, leading to a higher risk of mortality. Biomarkers such as RDW and lactate, which also reflect inflammation, support this view [25–27]. Interestingly, our study also found that PTT increases the risk of death, possibly due to chronic hypoxia-induced systemic inflammatory responses causing coagulation factor concentration imbalance and arterial/venous endothelial dysfunction [28].

Moreover, existing observational studies support the value of the NLR in predicting outcomes in patients with AHF. For instance, a study including nearly patients with AHF found a significantly increased mortality rate during hospitalization in patients with elevated NLR at admission [29]. Another long-term follow-up study showed that patients with AHF with a higher NLR had a significantly increased long-term mortality rate [24, 30]. These findings indicate that NLR can not only be used to predict short-term outcomes in patients with AHF, but also

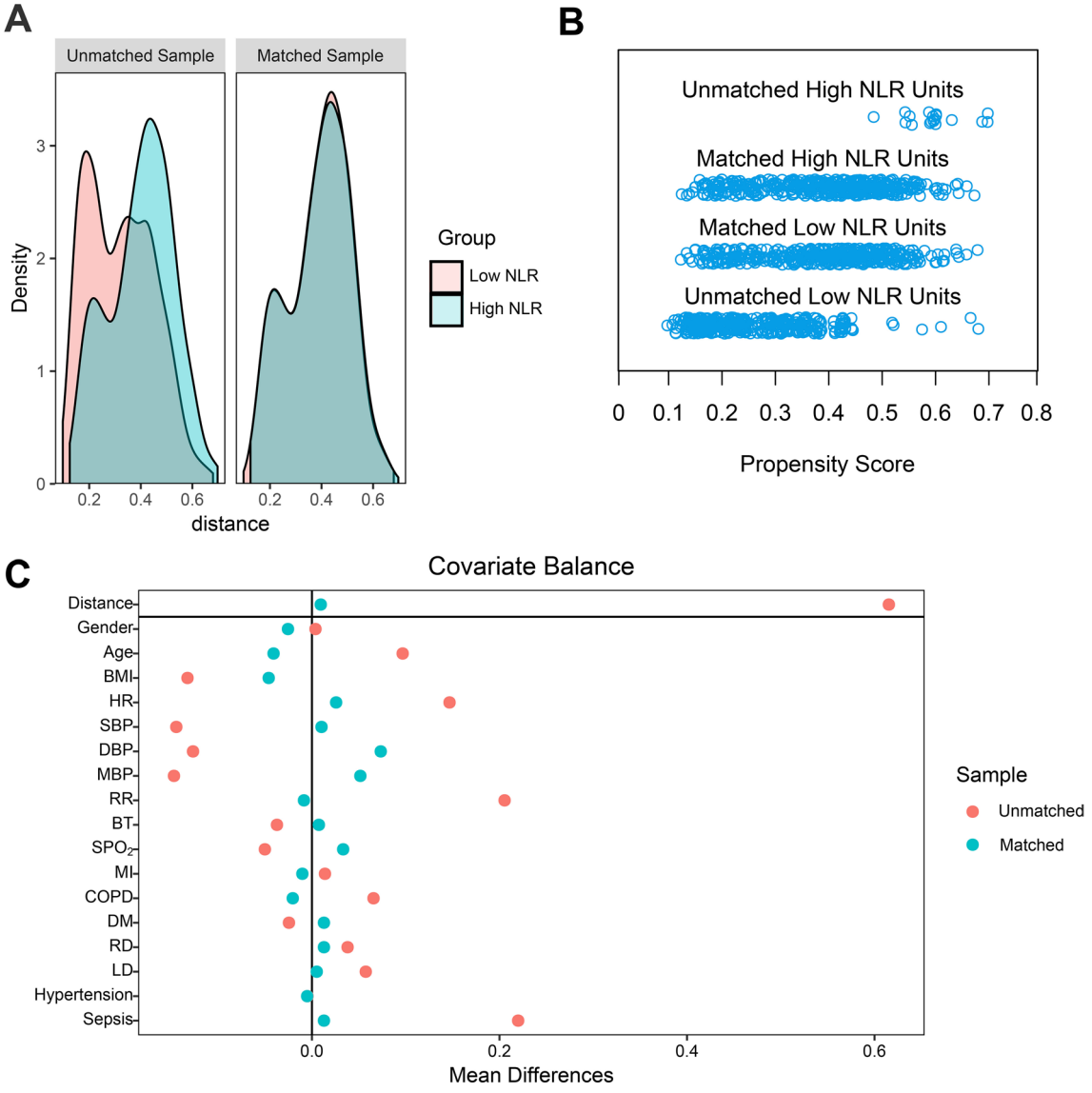

Fig. 4 (**A**). The kernel density plot indicates that the propensity scores of the two groups were best matched after adjustment. (**B**). Point plots indicate the matches for each patient between the two groups as well as those that were not matched. (**C**). The love point shows the situation of each variable before and after matching, after matching each variable has basically reached the equilibrium state. Survival analysis ROC curve. ROC: Receiver operating characteristic

provide crucial information about long-term survival. It is worth noting that our study showed a non-linear association between NLR and mortality risk. When the NLR exceeds a certain threshold (11.11 in this study), the risk of death significantly rises, setting our study apart from previous research.

Age was identified as a vital factor for one-year mortality in patients with AHF. This aligns with previous studies [31, 32], indicating that physiological decline in elderly patients, increased comorbidities, and decreased adaptability to stress might lead to a poorer prognosis [33].

Furthermore, we found that a high BMI is an independent protective factor for AHF patients in the ICU. First, a higher BMI may provide patients with better metabolic reserves, enabling them to better tolerate the increased catabolic state during the acute phase of the disease [34, 35]. Second, obese patients typically exhibit higher levels of leptin, which, under critical conditions, can modulate immune responses and reduce levels of inflammatory cytokines such as TNF-α and IL-6, thereby attenuating the inflammatory response [36]. Obese patients are also often characterized by abnormal visceral fat distribution and endocrine dysregulation, which may lead to alterations in endothelial function and activation of the renin-angiotensin as well as the sympathetic nervous systems; such activations could play a beneficial role in maintaining hemodynamic stability in critically ill patients [37]. Simultaneously, although obese patients have lower

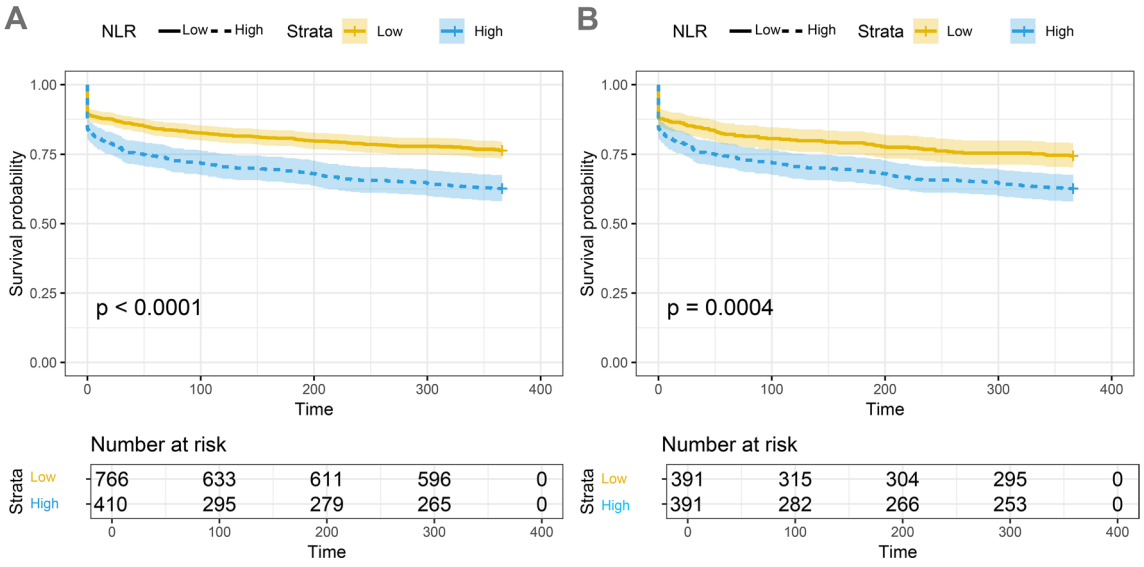

Fig. 5 The curves of Kaplan–Meier's survival analysis. (**A**). The curves of Kaplan–Meier's survival analysis in the unmatched cohort. (**B**). The curves of Kaplan–Meier's survival analysis in the matched cohort

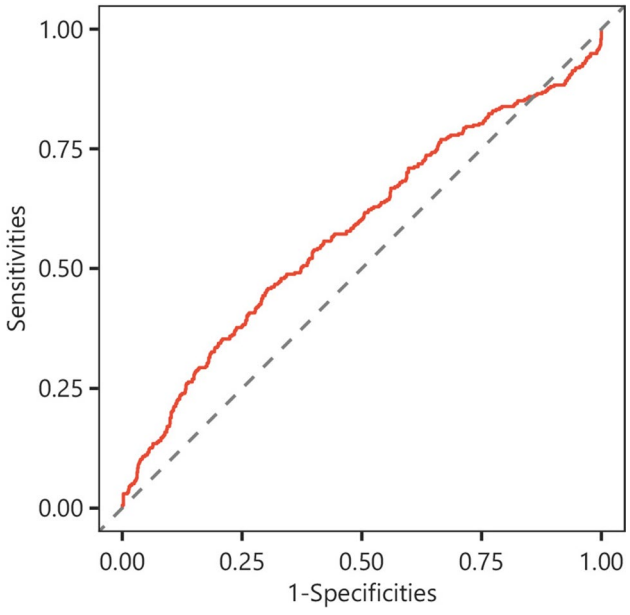

Fig. 6 Receiver operating curve for the MIMIC cohort

plasma adiponectin levels and are more prone to comorbidities such as hypertension and diabetes mellitus, these factors also result in them receiving more intensive treatment and nursing support during routine management and critical care, which may ultimately improve their prognosis [38, 39].

Our study found that comorbid chronic obstructive pulmonary disease (COPD) significantly increased the one-year mortality risk in AHF patients. Research indicates that these two diseases often coexist [40] and share several common risk factors [41, 42]. The persistent airway inflammation and hypoxia status in COPD, along with dynamic hyperinflation and increased chest pressure, may impair ventricular filling, leading to diastolic dysfunction, exacerbating the course of AHF and resulting in an adverse prognosis [43]. Therefore, the impact of these comorbidities should be thoroughly considered and controlled during the treatment of patients with AHF.

In conclusion, our findings suggest that in clinical practice, especially in daily care and treatment in the ICU, greater attention and therapeutic interventions should be given to AHF patients with higher NLR.

Clinical implications

Our findings have important clinical implications for the treatment and management of patients with AHF in the ICU. Incorporating the NLR into AHF patient risk assessment strategies could offer valuable insights into cardiovascular risk profiles. Given its cost-effectiveness and widespread availability, the NLR index is a practical and easily implementable tool for identifying high-risk individuals who may receive intensified monitoring and early interference.

Moreover, we used a variety of different dimensions, such as cubic splines, propensity score matching, and subgroup analysis, to confirm the strong association between the NLR and long-term mortality risk in patients with AHF in the ICU. Moreover, the nonlinear correlation was another important finding of our study. This will facilitate personalized treatment decisions. By integrating the NLR into routine clinical practice, healthcare providers can enhance risk prediction accuracy and tailor management strategies to suit the needs of this often-overlooked high-risk population.

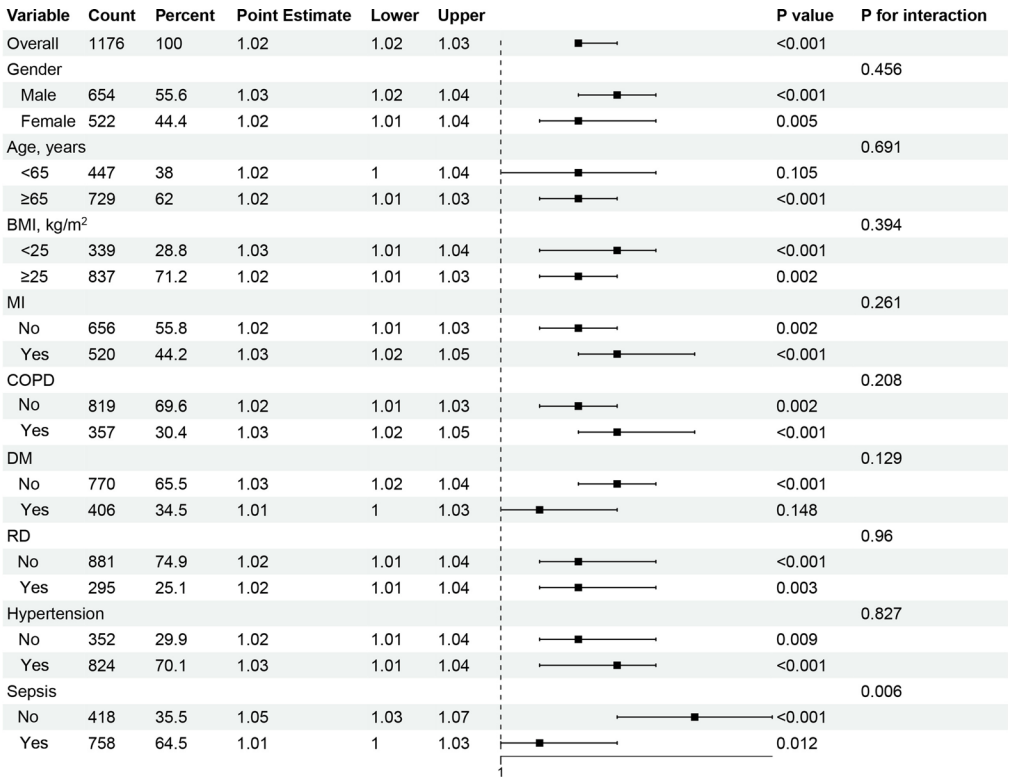

Fig. 7 The forest plot of subgroup analysis

Limitations

Finally, our study had several limitations. First, it was a single-center study, which may have introduced selection bias and regional constraints. Second, despite adjusting for multiple potential confounding factors, the impact of unmeasured confounders on results cannot be ruled out. Additionally, because this study was observational, causal relationships could not be established. Future research should include larger sample sizes and multicenter prospective studies to validate our findings and explore potential mechanisms.

Conclusions

In conclusion, our study results indicate that NLR, as a simple and widely available inflammatory biomarker, possesses additional risk stratification capability for predicting the long-term mortality risk of AHF patients in the ICU. These findings will help clinicians to more accurately assess patient prognosis and formulate more personalized treatment plans.

Abbreviations

BMI	Body Mass Index
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BT	Body Temperature
BUN	Blood Urea Nitrogen
CKMB	Creatine Phosphokinase Isoenzyme
COPD	Chronic Obstructive Pulmonary Disease
DM	Diabetes Mellitus
HR	Heart rate
INR	International Normalized Ratio
Lac	Lactic Acid
LD	Liver Disease
MBP	Mean Arterial Blood Pressure
MCH	Mean Corpuscular Concentration of Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MI	Myocardial Infarction
NLR	Neutrophil Lymphocyte Ratio
PLC	Platelet Count
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell Count
RD	Renal Disease
RDW	Red Blood Cell Distribution Width
RR	Respiratory Rate
RRT	Renal Replacement Therapy
SCR	Serum Creatinine
SIRS	Systemic Inflammatory Syndrome
SOFA	Sequential Organ Failure Assessment
SPO2	Pulse Oxygen Saturation
TB	Total Bilirubin
UO	Urine Output
WBC	White Blood Cell Count

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04734-4.

Supplementary Material 1

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Author contributions
Y.D. Conceptualization and Writing– Original Draft. J.L. Software usage and Analysis. C.L. Resources and Investigation. R.T. Visualization and Methodology. B.L. Writing– Review & Editing and Supervision.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The MIMIC-IV database systematically collected data from sepsis patients in the ICUs of Beth Israel Deaconess Medical Center in Boston, Massachusetts, USA, from 2008 to 2019. This project has received approval from the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. This database is an open data set. Bo Liu, the corresponding author of this study, has completed the application and obtained the authorization (Record ID: 62175707). All health data of patients in this database have been de-identified, thereby obviating the need for obtaining informed consent from the patients. This study was conducted in accordance with the principles of the 2013 Helsinki Declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Tomasoni D, Lombardi CM, Sbolli M, Cotter G, Metra M. Acute heart failure: more questions than answers. Prog Cardiovasc Dis. 2020;63:599–606.
2. Gall E, Pezel T, Lattuca B, Hamzi K, Puymirat E, Piliero N et al. Profile of patients hospitalized in intensive cardiac care units in France: ADDICT-ICCU registry. Arch Cardiovasc Dis. 2024;:S1875-2136(24)00024-X.
3. La Vecchia G, Del Buono MG, Bonaventura A, Vecchiè A, Moroni F, Cartella I, et al. Cardiac involvement in patients with multisystem inflammatory syndrome in adults. J Am Heart Assoc. 2024;13:e032143.
4. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to lymphocyte ratio: an emerging marker of the relationships between the immune system and diseases. Int J Mol Sci. 2022;23:3636.
5. Regolo M, Sorce A, Vaccaro M, Colaci M, Stancanelli B, Natoli G, et al. Assessing humoral Immuno-Inflammatory pathways associated with respiratory failure in COVID-19 patients. J Clin Med. 2023;12:4057.
6. Kakehi E, Uehira R, Ohara N, Akamatsu Y, Osaka T, Sakurai S, et al. Utility of the new early warning score (NEWS) in combination with the neutrophil–lymphocyte ratio for the prediction of prognosis in older patients with pneumonia. Fam Med Community Health. 2023;11:e002239.
7. Feng X, Xiao H, Duan Y, Li Q, Ou X. Prognostic value of neutrophil to lymphocyte ratio for predicting 90-Day poor outcomes in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2023;18:1219–30.
8. Vo HH, Truong-Thi NN, Ho-Thi HB, Vo HMC, Tran-Thi KT, Nguyen MD. The value of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, red cell distribution width, and their combination in predicting acute pancreatitis severity. Eur Rev Med Pharmacol Sci. 2023;27:11464–71.
9. Li H, Lu X, Xiong R, Wang S. High Neutrophil-to-Lymphocyte ratio predicts cardiovascular mortality in chronic Hemodialysis patients. Mediators Inflamm. 2017;2017:9327136.
10. Grilz E, Posch F, Königsbrügge O, Schwarzinger I, Lang IM, Marosi C, et al. Association of Platelet-to-Lymphocyte ratio and Neutrophil-to-Lymphocyte ratio with the risk of thromboembolism and mortality in patients with cancer. Thromb Haemost. 2018;118:1875–84.
11. Asperges E, Albi G, Zuccaro V, Sambo M, Pieri TC, Calia M, et al. Dynamic NLR and PLR in predicting COVID-19 severity: A retrospective cohort study. Infect Dis Ther. 2023;12:1625–40.
12. de Dios E, Rios-Navarro C, Perez-Sole N, Gavara J, Marcos-Garces V, Rodríguez E, et al. Similar clinical course and significance of Circulating innate and adaptive immune cell counts in STEMI and COVID-19. J Clin Med. 2020;9:3484.
13. Vakhshoori M, Nemati S, Sabouhi S, Yavari B, Shakarami M, Bondariyan N, et al. Neutrophil to lymphocyte ratio (NLR) prognostic effects on heart failure; a systematic review and meta-analysis. BMC Cardiovasc Disord. 2023;23:555.
14. Zhang J-L, Yang R, Zhu Y, Shao Y, Ji Y, Wang F-F. Association between the neutrophil-to-lymphocyte ratio and risk of in-hospital heart failure and arrhythmia in patients with acute myocardial infarction. Front Cardiovasc Med. 2023;10:1275713.
15. García-Escobar A, Vera-Vera S, Tébar-Márquez D, Rivero-Santana B, Jurado-Román A, Jiménez-Valero S, et al. Neutrophil-to-lymphocyte ratio an inflammatory biomarker, and prognostic marker in heart failure, cardiovascular disease and chronic inflammatory diseases: new insights for a potential predictor of anti-cytokine therapy responsiveness. Microvasc Res. 2023;150:104598.
16. Johnson A, Bulgarelli L, Pollard T, Horng S, Celi LA, Mark R. MIMIC-IV (version 2.0). 2022.
17. Tekin A, Wireko FW, Gajic O, Odeyemi YE. The neutrophil/lymphocyte ratio and outcomes in hospitalized patients with Community-Acquired pneumonia: A retrospective cohort study. Biomedicines. 2024;12:260.
18. Jin S, Yin J-B, Li W, Zang L-L. Effect of neutrophil to lymphocyte ratio on prognosis of elderly patients with severe sepsis combined with diabetes mellitus. BMC Geriatr. 2024;24:211.
19. Vaduganathan M, Greene SJ, Butler J, Sabbah HN, Shantsila E, Lip GYH, et al. The immunological axis in heart failure: importance of the leukocyte differential. Heart Fail Rev. 2013;18:835–45.
20. Chen Y-C, Liu C-C, Hsu H-C, Hung K-C, Chang Y-J, Ho C-N, et al. Systemic immune-inflammation index for predicting postoperative atrial fibrillation following cardiac surgery: a meta-analysis. Front Cardiovasc Med. 2024;11:1290610.
21. Chioncel O, Mebazaa A, Harjola V-P, Coats AJ, Piepoli MF, Crespo-Leiro MG, et al. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC heart failure Long-Term registry. Eur J Heart Fail. 2017;19:1242–54.
22. Swirski FK, Nahrendorf M, Etzrodt M, Wildgruber M, Cortez-Retamozo V, Panizzi P, et al. Identification of Splenic reservoir monocytes and their deployment to inflammatory sites. Science. 2009;325:612–6.
23. Tracchi I, Ghigliotti G, Mura M, Garibaldi S, Spallarossa P, Barisione C, et al. Increased neutrophil lifespan in patients with congestive heart failure. Eur J Heart Fail. 2009;11:378–85.
24. Zhu X, Cheang I, Xu F, Gao R, Liao S, Yao W, et al. Long-term prognostic value of inflammatory biomarkers for patients with acute heart failure: construction of an inflammatory prognostic scoring system. Front Immunol. 2022;13:1005697.
25. Ferreira AI, Silva JE, Melo N, Oliveira D, Silva C, Lume M, et al. Prognostic impact of red blood cell distribution width in chronic heart failure patients with left ventricular dysfunction. J Cardiovasc Med (Hagerstown). 2023;24:746–51.
26. Hu W, Yuan L, Wang X, Zang B, Zhang Y, Yan X, et al. Predictive value of arterial blood lactic acid concentration on the risk of in-Hospital All-Cause death in patients with acute heart failure. Int J Clin Pract. 2022;2022:7644535.
27. Ouyang J, Wang H, Huang J. The role of lactate in cardiovascular diseases. Cell Commun Signal. 2023;21:317.
28. Siniarski A, Gąsecka A, Borovac JA, Papakonstantinou PE, Bongiovanni D, Ehrlinder H, et al. Blood coagulation disorders in heart failure: from basic science to clinical perspectives. J Card Fail. 2023;29:517–26.
29. Di Rosa M, Sabbatinelli J, Soraci L, Corsonello A, Bonfigli AR, Cherubini A, et al. Neutrophil-to-lymphocyte ratio (NLR) predicts mortality in hospitalized geriatric patients independent of the admission diagnosis: a multicenter prospective cohort study. J Transl Med. 2023;21:835.
30. Davison BA, Takagi K, Edwards C, Adams KF, Butler J, Collins SP, et al. Neutrophil-to-Lymphocyte ratio and outcomes in patients admitted for acute heart failure (As seen in the BLAST-AHF, Pre-RELAX-AHF, and RELAX-AHF Studies). Am J Cardiol. 2022;180:72–80.
31. Miró Ò, Llorens P, Aguiló S, Alquézar-Arbé A, Fernández C, Burillo-Putze G et al. Epidemiological aspects, clinical management and short-term outcomes

in elderly patients diagnosed with acute heart failure in the emergency department in Spain: results of the EDEN-34 study. Rev Clin Esp (Barc). 2024;:S2254-8874(24)00037– 7.
32. Yan M, Liu H, Xu Q, Yu S, Tang K, Xie Y. Development and validation of a prediction model for in-hospital death in patients with heart failure and atrial fibrillation. BMC Cardiovasc Disord. 2023;23:505.
33. Fernando SM, Brodie D, Barbaro RP, Agerstrand C, Badulak J, Bush EL, et al. Age and associated outcomes among patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory failure: analysis of the extracorporeal life support organization registry. Intensive Care Med. 2024. https://doi.org/10.1007/s00134-024-07343-5.
34. Wang S, Ren J. Obesity paradox in aging: from prevalence to pathophysiology. Prog Cardiovasc Dis. 2018;61:182–9.
35. Ng PY, Eikermann M. The obesity conundrum in sepsis. BMC Anesthesiol. 2017;17:147.
36. Kuperman EF, Showalter JW, Lehman EB, Leib AE, Kraschnewski JL. The impact of obesity on sepsis mortality: a retrospective review. BMC Infect Dis. 2013;13:377.
37. Seravalle G, Grassi G. Obesity and hypertension. Pharmacol Res. 2017;122:1–7.
38. O'Brien JM, Philips GS, Ali NA, Aberegg SK, Marsh CB, Lemeshow S. The association between body mass index, processes of care, and outcomes from mechanical ventilation: a prospective cohort study. Crit Care Med. 2012;40:1456–63.
39. Nasraway SA, Hudson-Jinks TM, Kelleher RM. Multidisciplinary care of the obese patient with chronic critical illness after surgery. Crit Care Clin. 2002;18:643–57.
40. van Dijk SHB, Brusse-Keizer MGJ, Effing T, van der Valk PDLPM, Ploumen EH, van der Palen J, et al. Exploring patterns of COPD exacerbations and comorbid Flare-Ups. Int J Chron Obstruct Pulmon Dis. 2023;18:2633–44.
41. MacDonald MI, Shafuddin E, King PT, Chang CL, Bardin PG, Hancox RJ. Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. Lancet Respir Med. 2016;4:138–48.
42. Pellicori P, Cleland JGF, Clark AL. Chronic obstructive pulmonary disease and heart failure: A breathless conspiracy. Heart Fail Clin. 2020;16:33–44.
43. Hawkins NM, Nordon C, Rhodes K, Talukdar M, McMullen S, Ekwaru P, et al. Heightened long-term cardiovascular risks after exacerbation of chronic obstructive pulmonary disease. Heart. 2024. https://doi.org/10.1136/heartjnl-2023-323487.

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