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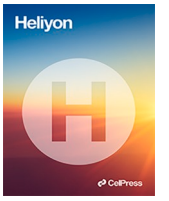

Research article

The neutrophil-to-lymphocyte ratio levels over time correlate to all-cause hospital mortality in sepsis

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ABSTRACT

Objective: This research aims to investigate the prognosis value using the time-weighted average neutrophil-to-lymphocyte ratio (TWA-NLR) for predicting all-cause hospital mortality among sepsis patients. Data were analyzed through the use of the eICU Collaborative Research Database (eICU-CRD 2.0) as well as Medical Information Mart for Intensive Care IV 2.2 (MIMIC-IV 2.2).
Methods: Septic patients from both eICU-CRD 2.0 as well as MIMIC-IV 2.2 databases were included. The neutrophil-to-lymphocyte ratios (NLR) were available for analysis, utilizing complete blood counts obtained on days one, four, and seven following ICU admission. The TWA-NLR was computed at the end of the seven days, and patients were then stratified based on TWA-NLR thresholds. 90-day all-cause mortality during hospitalization was the primary objective, with 60-day all-cause hospital mortality as a secondary objective. The correlation between TWA-NLR and sepsis patients' primary outcome was analyzed using univariable and multivariable Cox proportional hazard regressions. A restricted cubic spline (RCS) analysis was conducted in an attempt to confirm this association further, and subgroup analyses were employed to evaluate the correlation across various comorbidity groups.
Results: 3921 patients were included from the eICU-CRD 2.0, and the hospital mortality rate was 20.8 %. Both multivariable as well as univariable Cox proportional hazard regression analyses revealed that TWA-NLR was independently correlated with 90-day all-cause hospital mortality, yielding a hazard ratio (HR) of 1.02 (95 % CI 1.01–1.02, *P*-value<0.01) as well as 1.12 (95 % CI 1.01–1.15, *P*-value<0.01), respectively. The RCS analysis demonstrated a significant nonlinear relationship between TWA-NLR and 90-day all-cause hospital mortality risk. The study subjects were divided into higher (>10.5) and lower (≤10.5) TWA-NLR cohorts. A significantly decreased incidence of 90-day all-cause hospital mortality (HR = 0.56, 95 % CI 0.48–0.64, *P*-value<0.01) and longer median survival time (40 days vs 24 days, *P*-value<0.05) were observed in the lower TWA-NLR cohort. However, septic patients with chronic pulmonary (interaction of *P*-value = 0.009) or renal disease (interaction of *P*-value = 0.008) exhibited significant interactive associations between TWA-NLR and 90-day all-cause hospital mortality, suggesting the predictive power of TWA-NLR may be limited in these subgroups. The MIMIC-IV 2.2 was utilized as a validation cohort and exhibited a similar pattern.

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Conclusion: Our findings suggest that TWA-NLR is a powerful and independent prognostic indicator for 90-day all-cause hospital mortality among septic patients, and the TWA-NLR cutoff value may prove a useful method for identifying high-risk septic patients.

1. Introduction

Sepsis, a serious medical situation triggered by a variety of infections, leads to unregulated systemic production of excessive amounts of inflammatory mediators. Despite advancements in medicine and a deeper understanding of its underlying pathophysiology, sepsis persists as a leading reason for ICU admissions, with an estimated thirty million fatalities occurring annually [1–3]. The third international consensus has defined that sepsis as well as septic shock as rapidly progressive state of inflammation accompanied by immunosuppression [4]. Lymphocytes, comprising 20–40 % of the leukocytes, play a pivotal function in the adaptive immunity during sepsis [5]. Patients with higher lymphocyte counts during sepsis have been shown to experience more favorable outcomes [6].

Conversely, sepsis-induced lymphocyte apoptosis and impaired proliferation lead to lymphopenia, which correlates with increased mortality rates in ICU settings [7–11]. Recently, attention has turned to composite biomarkers that reflect the balance between different immune cell populations, such as the platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and

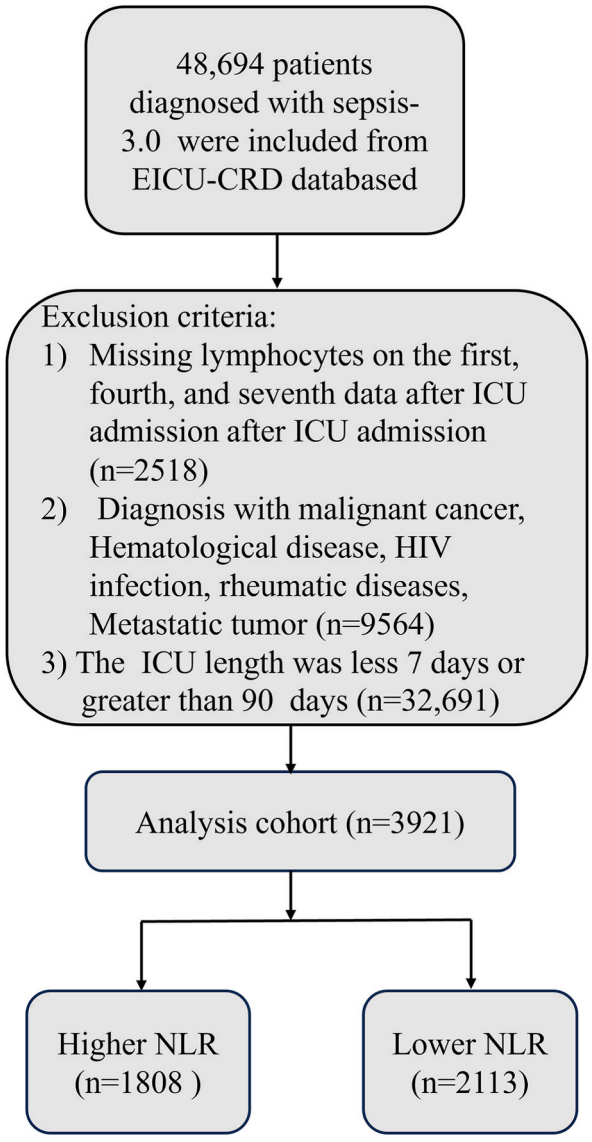

Fig. 1. A flow chart illustrating the regulatory model of patient enrollment and analysis workflow in the eICU-CRD 2.0 database.

Table 1
Baseline characteristics of sepsis patients in eICU-CRD.

	Survival	Non-Survival	***P* value**
	N = 3105	N = 816	
Age (years)	60.9 ± 15.8	66.7 ± 14.5	<0.001
Gender			0.958
Female	1364 (43.9 %)	357 (43.8 %)	
Male	1741 (56.1 %)	459 (56.2 %)	
BMI	28.7 [23.9–35.3]	28.1 [23.3–34.5]	0.880
TWA-WBC (10^9/L)	12.9 ± 5.52	14.5 ± 6.45	<0.001
TWA-lymphocytes (10^9/L)	1.15 ± 0.56	1.04 ± 0.56	<0.001
TWA-neutrophils (10^9/L)	10.5 ± 4.94	12.1 ± 5.63	<0.001
TWA-monocytes (10^9/L)	0.83 ± 0.39	0.84 ± 0.43	0.708
TWA-platelets (10^9/L)	206 (89.0)	176 (90.0)	<0.001
TWA-NLR	11.8 ± 9.71	15.8 ± 11.7	<0.001
TWA-LMR	1.90 ± 1.38	1.73 ± 1.35	0.002
TWA-PLR	211 [144–314]	214 [133–332]	0.520
WBC (10^9/L)	16.6 ± 9.50	17.2 ± 9.67	0.094
First-day neutrophils (10^9/L)	13.8 ± 8.28	14.3 ± 8.06	0.147
First-day lymphocytes (10^9/L)	1.94 ± 1.80	2.13 ± 3.72	0.163
First-day monocytes (10^9/L)	1.27 ± 1.06	1.28 ± 1.04	0.846
First-day platelets (10^9/L)	243 ± 125	234 ± 130	0.094
Sofa score	9.27 ± 3.41	11.4 ± 4.01	<0.001
Oasis score	34.4 ± 9.78	36.4 ± 9.91	<0.001
Heart rate	116 ± 23.9	116 ± 24.1	0.788
Respiratory rate	31.3 ± 9.03	32.4 ± 8.80	0.001
Systolic blood pressure (mmHg)	149 [130–168]	146 [130–166]	0.187
Diastolic blood pressure (mmHg)	89.0 [76.0–104]	89.0 [76.0–102]	0.850
Mean blood pressure (mmHg)	109 [95.3–125]	108 [95.3–123]	0.462
Temperature (°C)	37.8 ± 0.97	37.7 ± 0.98	0.036
Liver disease			<0.001
No	2996 (96.5 %)	758 (92.9 %)	
Yes	109 (3.51 %)	58 (7.11 %)	
Renal disease			<0.001
No	2625 (84.5 %)	642 (78.7 %)	
Yes	480 (15.5 %)	174 (21.3 %)	
Diabetes			0.818
No	2123 (68.4 %)	562 (68.9 %)	
Yes	982 (31.6 %)	254 (31.1 %)	
Myocardial infarct			0.772
No	2862 (92.2 %)	749 (91.8 %)	
Yes	243 (7.83 %)	67 (8.21 %)	
Congestive heart failure			0.003
No	2562 (82.5 %)	636 (77.9 %)	
Yes	543 (17.5 %)	180 (22.1 %)	
Cerebrovascular disease			0.048
No	2797 (90.1 %)	715 (87.6 %)	
Yes	308 (9.92 %)	101 (12.4 %)	
Chronic pulmonary disease			0.058
No	2511 (80.9 %)	635 (77.8 %)	
Yes	594 (19.1 %)	181 (22.2 %)	
Fio2 (%)	0.75 ± 0.27	0.78 ± 0.27	0.038
Pao2 (mmHg)	168 ± 108	172 ± 109	0.314
Paco2 (mmHg)	50.6 ± 20.2	49.8 ± 19.7	0.262
pH	7.40 ± 0.09	7.41 ± 0.09	0.028
Albumin (g/dl)	2.95 ± 0.74	2.82 ± 0.74	<0.001
Creatinine (mg/dl)	2.10 ± 2.03	2.21 ± 2.05	0.165
Glucose (mg/dl)	193 ± 117	195 ± 111	0.657
Hemoglobin (g/dl)	11.9 ± 2.52	11.6 ± 2.31	<0.001
Lactate (mmol/L)	3.01 ± 2.76	3.82 ± 3.41	<0.001
Potassium (mEq/L)	4.53 ± 0.82	4.61 ± 0.83	0.011
Sodium (mEq/L)	140 ± 6.05	141 ± 6.36	0.516
BUN (mg/dl)	36.7 ± 27.4	40.6 ± 27.8	<0.001
ALT (IU/L)	31.0 [19.0–61.0]	32.0 [19.0–65.0]	0.337

(*continued on next page*)

Table 1 (*continued*)

	Survival	Non-Survival	***P* value**
	N = 3105	N = 816	
AST (IU/L)	40.0 [24.0–89.0]	47.0 [27.0–109]	<0.001
Calcium (mg/dl)	8.62 ± 0.93	8.65 ± 1.02	0.487
Renal replacement therapy			<0.001
No	2537 (81.7 %)	616 (75.5 %)	
Yes	568 (18.3 %)	200 (24.5 %)	
Invasive ventilation			0.232
No	429 (13.8 %)	99 (12.1 %)	
Yes	2676 (86.2 %)	717 (87.9 %)	
The length of ICU stays (Days)	11.0 [8.50–15.8]	11.3 [8.75–16.0]	0.348

TWA: Time weighted average; WBC: white blood count.

neutrophil-to-lymphocyte ratio (NLR) [12,13]. Derived from white blood cell counts, the NLR has been identified as a powerful biomarker for systemic inflammatory and immune reactions for sepsis [14]. This easily accessible biomarker reflects the immunological dynamics of sepsis and demonstrates superior prognostic value compared to lymphocyte counts alone [15,16]. A positive correlational relationship between NLR and thirty-day mortality in bloodstream infections has been demonstrated, and a meta-analysis revealed that non-survivors exhibited elevated NLR levels relative to survivors of sepsis [17,18].

Despite these promising findings, the NLR over time and its relationship to hospital mortality in sepsis remains understudied. Most investigations have relied on single time-point NLR measurements, typically within the initial 24 h following ICU admission [19]. This approach may not reflect the dynamical nature of the immune reaction in sepsis, potentially limiting the prognostic accuracy of NLR.

To address this gap, our research is designed to verify the effect of a time-varying NLR upon hospital mortality among sepsis patients. We introduce the concept of time-weighted average neutrophil-to-lymphocyte ratios (TWA-NLR), which allows for a more comprehensive assessment of NLR fluctuations throughout the ICU stay. By exploring the potential relationship between TWA-NLR levels and 90-day all-cause hospital mortality among septic patients, we seek to enhance the prognostic utility of this biomarker and potentially improve patient risk stratification and management strategies. This novel approach may provide clinicians with a more tailored tool for monitoring sepsis progression and predicting outcomes, ultimately contributing to more effective and personalized treatment protocols in the critical care setting for sepsis patients.

2. Methods

2.1. Participants

Participants, age above or equal to 18 years, were recruited from the eICU-CRD 2.0 and MIMIC-IV 2.2 databases were included. Inclusion criteria were: 1) A confirmed or suspected infection, as well as a Sequential Organ Failure Assessment (SOFA) score of two or greater in accordance with the Sepsis-3.0 criteria [4]. 2) Complete blood count of peripheral blood documentation on the first, fourth, and seventh days of ICU admission. 3) An ICU stay duration of at least seven days.

The following exclusion criteria were applied: 1) An ICU duration of fewer than seven days or more than 90 days; 2) Presence of human immunodeficiency virus (HIV) infection, rheumatic disorders, metastatic tumors, cancer, and hematological diseases such as aplastic anemia; 3) Missing lymphocyte data on the first, fourth, and seventh days following ICU admission; 4) The initial ICU admission of patients with a history of multiple hospitalizations was selected for analysis in this research.

2.2. Extraction of data

The subsequent clinical information was obtained by means of Structured Query Language (SQL) statements:1) Biochemistry results within the first 24 h: blood glucose, albumin, creatinine, glucose, hemoglobin, lactate, potassium, sodium, blood urea nitrogen (BUN), calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT). 2) The first 24 h of demographic and vital parameters: heart rate, temperature (°C), respiratory rate, sex, age, diastolic blood pressure, sofa score, oasis score, systolic blood pressure, and BMI. 3) Analysis of blood gases within the first 24 h: the potential of Hydrogen (pH), the fraction of inspired Oxygen (FiO_2), arterial partial pressure of oxygen (PaO_2), and arterial partial pressure of carbon dioxide ($PaCO_2$). 4) Details of the ICU: the duration of ICU stays and the survival status of patients. 5) Comorbid conditions and treatments: renal replacement therapy, mechanical ventilation, congestive heart failure, chronic pulmonary, liver disease, myocardial infarction, and renal disease. 6) Blood cell counts: White blood count (WBC), lymphocytes, neutrophils, platelets, and monocytes were extracted on the first, fourth, and seventh days following admittance to the ICU. 7) The derived inflammatory indicators: PLR was calculated from the platelet to lymphocyte count ratio, LMR was from the ratio of the lymphocyte to monocyte count, and NLR was from the neutrophil to lymphocyte count ratio. 8) The TWA values of WBC, platelets, neutrophils, lymphocytes, monocytes, PLR, NLR, and LMR were computed as the ratio of their area under the curve to the number of days (seven days). The average value was used if a variable was recorded multiple times on the same day. The study's primary objective was the measurement of 90-day all-cause hospital death, while the secondary objective focused on 60-day hospital all-cause death.

Table 2
Baseline characteristics of sepsis patients according to TWA-NLR cutoff value in eICU-CRD.

	Total	Higher NLR	Lower NLR	*P* value
	N = 3921	N = 1808	N = 2113	
Age	64.0 [53.0–74.0]	66.0 [56.0–76.0]	61.0 [50.0–71.0]	<0.001
Gender				0.174
Female	1721 (43.9 %)	772 (42.7 %)	949 (44.9 %)	
Male	2200 (56.1 %)	1036 (57.3 %)	1164 (55.1 %)	
BMI	28.5 [23.8–35.1]	27.9 [23.4–34.2]	29.1 [24.1–36.0]	<0.001
TWA-WBC (10^9/L)	12.2 [9.31–16.0]	14.4 [11.2–18.6]	10.8 [8.30–13.6]	<0.001
TWA-lymphocytes (10^9/L)	1.04 [0.72–1.43]	0.77 [0.55–1.04]	1.29 [1.00–1.69]	<0.001
TWA-neutrophils (10^9/L)	9.90 [7.21–13.3]	12.5 [9.52–16.2]	8.17 [6.12–10.6]	<0.001
TWA-monocytes (10^9/L)	0.78 [0.55–1.05]	0.75 [0.51–1.05]	0.79 [0.58–1.05]	<0.001
TWA-platelets (10^9/L)	193 [134–255]	185 [123–245]	201 [144–262]	<0.001
TWA-LMR	1.54 [1.08–2.19]	1.23 [0.88–1.72]	1.80 [1.34–2.56]	<0.001
TWA-PLR	212 [141–317]	290 [188–426]	173 [121–237]	<0.001
WBC (10^9/L)	14.9 [10.4–21.0]	16.8 [12.0–23.5]	13.3 [9.60–18.8]	<0.001
First-day neutrophils (10^9/L)	12.3 [8.35–17.8]	14.4 [9.93–20.2]	10.7 [7.37–15.5]	<0.001
First-day lymphocytes (10^9/L)	1.41 [0.87–2.38]	1.12 [0.70–1.94]	1.67 [1.08–2.74]	<0.001
First-day monocytes (10^9/L)	1.05 [0.66–1.59]	1.05 [0.62–1.63]	1.04 [0.68–1.55]	0.896
First-day platelets (10^9/L)	219 [161–296]	219 [161–303]	219 [160–292]	0.519
Sofa score	9.00 [7.00–12.0]	10.0 [7.00–13.0]	9.00 [7.00–11.0]	<0.001
Oasis Score	35.0 [28.0–42.0]	35.0 [28.0–42.0]	35.0 [27.0–41.0]	0.003
Heart rate	115 [98.0–132]	116 [99.0–132]	115 [98.0–131]	0.065
Respiratory rate	30.0 [25.0–37.0]	31.0 [25.0–37.0]	30.0 [25.0–36.0]	0.014
Systolic blood pressure (mm Hg)	148 [130–168]	146 [129–168]	150 [131–169]	0.013
Diastolic blood pressure (mm Hg)	89.0 [76.0–103]	88.0 [74.0–102]	90.0 [77.0–104]	0.002
Mean blood pressure (mm Hg)	109 [95.3–124]	108 [94.0–123]	110 [96.3–125]	0.003
Temperature (°C)	37.6 [37.1–38.4]	37.5 [37.1–38.3]	37.7 [37.2–38.5]	<0.001
Liver disease				0.234
No	3754 (95.7 %)	1723 (95.3 %)	2031 (96.1 %)	
Yes	167 (4.26 %)	85 (4.70 %)	82 (3.88 %)	
Renal disease				0.021
No	3267 (83.3 %)	1479 (81.8 %)	1788 (84.6 %)	
Yes	654 (16.7 %)	329 (18.2 %)	325 (15.4 %)	
Diabetes				0.391
No	2685 (68.5 %)	1251 (69.2 %)	1434 (67.9 %)	
Yes	1236 (31.5 %)	557 (30.8 %)	679 (32.1 %)	
Myocardial infarct				<0.001
No	3611 (92.1 %)	1634 (90.4 %)	1977 (93.6 %)	
Yes	310 (7.91 %)	174 (9.62 %)	136 (6.44 %)	
Congestive heart failure				0.212
No	3198 (81.6 %)	1459 (80.7 %)	1739 (82.3 %)	
Yes	723 (18.4 %)	349 (19.3 %)	374 (17.7 %)	
Cerebrovascular disease				0.396
No	3512 (89.6 %)	1628 (90.0 %)	1884 (89.2 %)	
Yes	409 (10.4 %)	180 (9.96 %)	229 (10.8 %)	
Chronic pulmonary disease				<0.001
No	3146 (80.2 %)	1348 (74.6 %)	1798 (85.1 %)	
Yes	775 (19.8 %)	460 (25.4 %)	315 (14.9 %)	
Fio2 (%)	0.95 [0.50–1.00]	1.00 [0.50–1.00]	0.80 [0.50–1.00]	0.017
Pao2 (mmHg)	131 [89.0–215]	131 [89.0–215]	131 [89.0–214]	0.894
Paco2 (mmHg)	45.3 [37.5–57.0]	46.0 [38.0–58.0]	44.6 [37.4–56.5]	0.045
pH	7.41 [7.35–7.46]	7.40 [7.34–7.46]	7.41 [7.36–7.46]	<0.001
Albumin (g/dl)	2.90 [2.40–3.40]	2.80 [2.30–3.40]	3.00 [2.50–3.50]	<0.001
Creatinine (mg/dl)	1.42 [0.90–2.55]	1.60 [1.00–2.80]	1.30 [0.83–2.36]	<0.001
Glucose (mg/dl)	163 [127–222]	170 [132–224]	157 [123–219]	<0.001
Hemoglobin (g/dl)	11.7 [10.0–13.6]	11.6 [10.0–13.5]	11.8 [10.0–13.7]	0.147
Lactate (mmol/L)	2.10 [1.40–3.90]	2.30 [1.40–4.20]	2.10 [1.30–3.70]	<0.001
Potassium (mEq/L)	4.40 [4.00–5.00]	4.50 [4.00–5.00]	4.30 [3.90–4.90]	<0.001
Sodium (mEq/L)	140 [137–144]	140 [137–143]	140 [137–144]	<0.001
Bun (mg/dl)	30.0 [18.0–49.0]	34.0 [21.0–54.0]	26.0 [16.0–43.0]	<0.001
ALT (IU/L)	31.0 [19.0–62.0]	32.0 [19.0–65.0]	31.0 [19.0–59.0]	0.426
AST (IU/L)	41.0 [24.0–92.0]	43.0 [25.0–100]	40.0 [24.0–86.0]	0.007
Calcium (mg/dl)	8.60 [8.00–9.20]	8.60 [8.00–9.10]	8.60 [8.10–9.20]	0.129
Renal replacement therapy				<0.001
No	3153 (80.4 %)	1375 (76.1 %)	1778 (84.1 %)	
Yes	768 (19.6 %)	433 (23.9 %)	335 (15.9 %)	
Invasive ventilation				0.060
No	528 (13.5 %)	264 (14.6 %)	264 (12.5 %)	
Yes	3393 (86.5 %)	1544 (85.4 %)	1849 (87.5 %)	

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Table 2 (*continued*)

	Total	Higher NLR	Lower NLR	*P* value
	N = 3921	N = 1808	N = 2113	
The length of ICU stays (Days)	11.0 [8.54–15.8]	11.2 [8.75–16.4]	10.9 [8.38–15.5]	0.004
Survival status				<0.001
Death	816 (20.8 %)	507 (28.0 %)	309 (14.6 %)	
Survived	3105 (79.2 %)	1301 (72.0 %)	1804 (85.4 %)	

TWA: Time weighted average; WBC: white blood count.

Table 3
Cox regression analysis of the variables.

Variables	Univariable			Multivariable		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Age	1.03	1.02–1.03	<0.001	1.03	1.02–1.04	<0.001
TWA-Wbc	1.03	1.02–1.04	<0.001	1.02	1.01–1.04	0.008
TWA-lymphocyte	0.76	0.66–0.87	<0.001			
TWA-neutrophils	1.04	1.02–1.05	<0.001			
TWA-monocytes	1.03	0.87–1.21	0.76			
TWA-platelets	0.98	0.96–1.1	0.56			
TWA-NLR	1.02	1.01–1.02	<0.001	1.12	1.01–1.15	<0.001
TWA-LMR	0.92	0.86–0.97	0.005	0.97	0.92–1.03	0.3
TWA-PLR	0.91	0.9–1.13	0.1			
Fio2	0.99	0.76–1.28	0.92			
Pao2	0.86	0.85–1.15	0.053			
Paco2	1.00	0.99–1.00	0.24			
Ph	2.04	0.92–4.52	0.080			
Albumin	0.88	0.80–0.96	0.005	0.95	0.86–1.05	0.3
Creatinine	1.03	1.00–1.07	0.028			
Glucose	0.93	0.9–1.06	0.082			
Hemoglobin	0.95	0.92–0.98	<0.001	0.96	0.93–0.98	0.009
Lactate	1.06	1.04–1.08	<0.001	1.04	1.02–1.06	<0.001
Potassium	1.09	1.01–1.18	0.035	0.99	0.90–1.08	0.83
Sodium	1.00	0.99–1.01	0.67			
BUN	1.12	1.03–1.15	0.01	1.08	1.06–1.19	0.009
ALT	0.98	0.85–1.15	0.79			
AST	1.05	0.91–1.13	0.38			
Calcium	1.02	0.95–1.09	0.53			
Spo2	0.99	0.94–1.05	0.75			
BMI	1.12	0.98–1.23	0.051			
TWA-NLR category						
Higher TWA-NLR				Ref		
Lower TWA-NLR				0.56	0.48–0.64	<0.001

TWA: Time weighted average.

2.3. Statistical analysis of data

The continuous data were presented as w5ell as compared in two ways: either as the mean ± standard deviation (SD) or as the median (interquartile range). For normally distributed variables, the Student's t-test was employed for comparison. Conversely, for variables that were not normally distributed, the Mann-Whitney *U* test was applied. Categorical variables were expressed in terms of proportions and evaluated by the Chi-square or Fisher's exact tests. The independent prognostic effect of TWA-NLR on hospital mortality was assessed through univariable as well as multivariable Cox proportional hazard model analyses, employing the R package 'survival'. Results were presented in hazard ratios (HR) and 95 % confidence intervals (CI). Spearman correlation analyses were conducted using the 'corrplot' package to assess correlation coefficients. To further investigate the relationships between TWA-NLR and hospital mortality, clinically relevant and prognosis-associated variables such as time-weighted average white blood cell count (TWA-WBC), gender, age, BUN, and lactate were incorporated into the restricted cubic spline (RCS) model using the 'rms' package in R. The TWA-NLR was calculated to capture fluctuations in NLR during the ICU stay. Cutoff values for TWA-NLR were determined using maximally selected rank statistics with the 'maxstat' package [20]. Kaplan-Meier survival analysis was conducted to assess survival probabilities across two TWA-NLR level groups via the 'survminer' package. To verify the consistency of TWA-NLR's prognostic effect, we conducted subgroup analyses across various subgroups, including age, invasive ventilation, diabetes, cerebrovascular disease, renal disease, congestive heart failure, liver disease, renal replacement therapy, and chronic pulmonary disease. Variables missing for over 35 % were not considered in the analysis (Fig. S1). The rest 26 candidate predictors obtained during admission to ICU were chosen for further analysis. Missing values for these selected variables were imputed using the multiple imputations by predictive mean matching

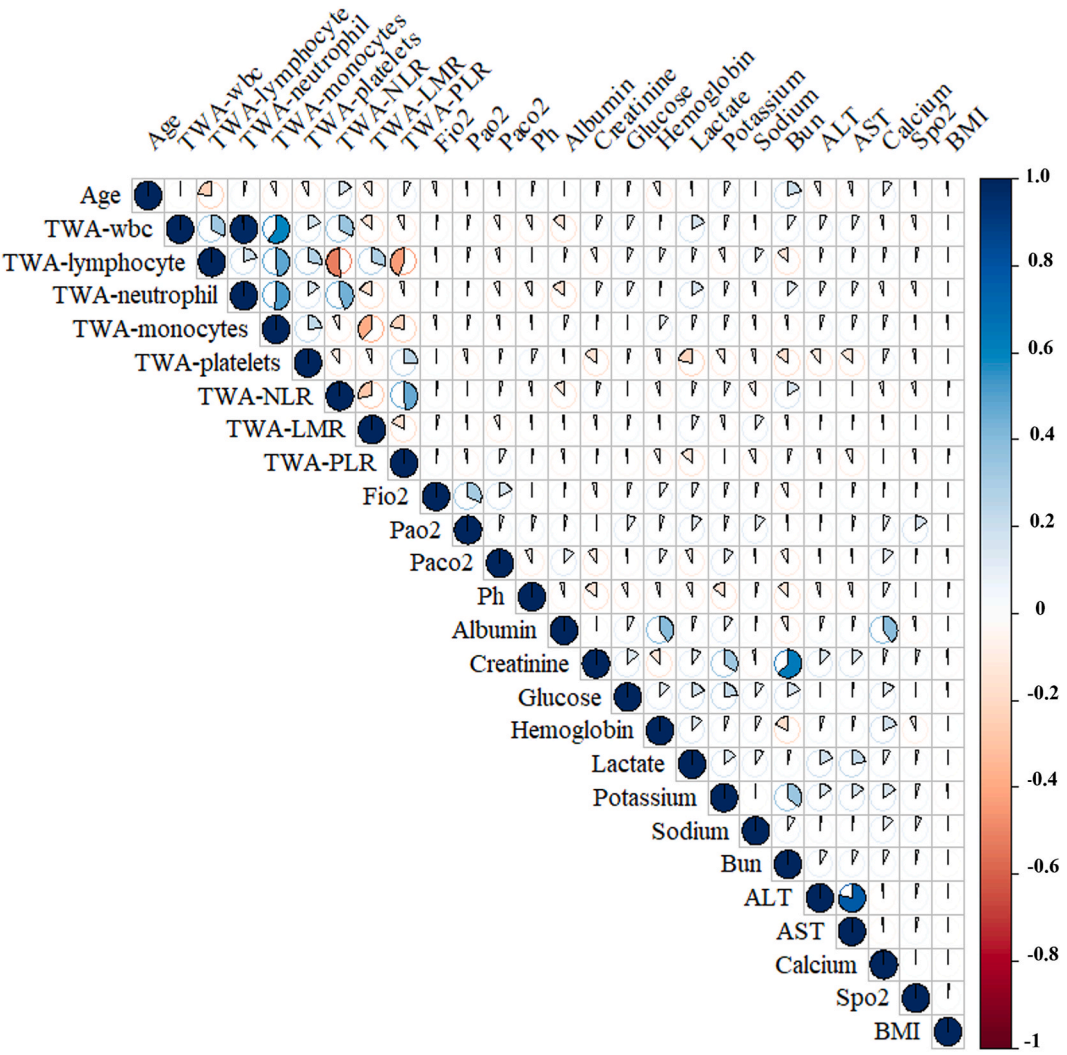

Fig. 2. Analysis of the correlation between clinical variables in the eICU-CRD 2.0 database.

(PMM) through the package 'mice'. Package 'timeROC' was used to calculate the accuracy of survival outcome prediction by TWA-NLR [21].

All analytical procedures were carried out by R programming language, version 4.1.3 (Beijing, China). We regard a two-tailed *P*-value of smaller than 0.05 to be meaningful for all analyses.

3. Results

3.1. Demographics and clinical features

Our study enrolled 3,921 patients from eICU-CRD 2.0 (Fig. 1) and 1,714 patients from MIMIC-IV 2.2 (Fig. S2), meeting our inclusion criteria. As illustrated in Table 1, the survival cohort demonstrated reduced levels of TWA-WBC, time-weighted average neutrophils (TWA-neutrophils), pH, BUN, potassium, AST, respiratory rate, TWA-NLR, Fio2, and were younger. Conversely, survivors showed higher levels of time-weighted average lymphocytes (TWA-lymphocytes), time-weighted average platelets (TWA-platelets), time-weighted lymphocyte-to-monocyte ratio (TWA-LMR), albumin, and hemoglobin. Additionally, this group demonstrated lower incidences of comorbid conditions, such as congestive heart failure (17.5 % vs. 22.1 %, *P*-value = 0.003), renal diseases (15.5 % vs. 21.3 %, *P*-value<0.001), liver disease (3.51 % vs. 7.11 %, *P*-value<0.001), and cerebrovascular disease (9.92 % vs. 12.4 %, *P*-value<0.001). Furthermore, the likelihood of requiring renal replacement therapy was greater in the non-survival group (24.5 % vs. 18.3 %, *P*-value<0.001). The length of stay in the ICU or the first-day WBC, lymphocytes, neutrophils, monocytes, and platelets levels were not significantly different.

To investigate further the effect of TWA-NLR on ICU mortality, septic patients were stratified in two cohorts based on their TWA-

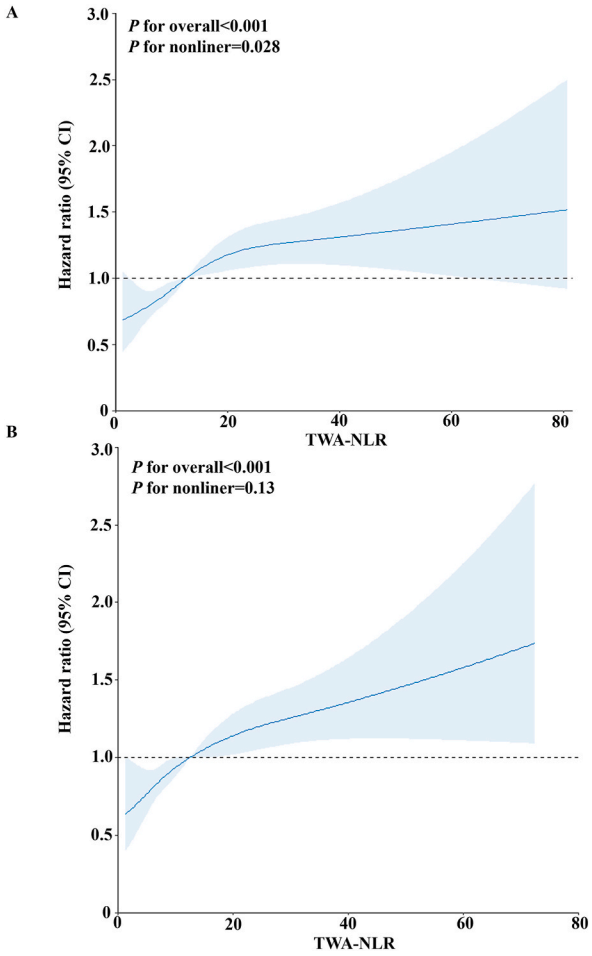

Fig. 3. The restricted cubic spline of TWA-NLR and the risk of all-cause mortality within 90 Days of hospitalization (A); Subgroup for renal replacement therapy (B) in the eICU-CRD 2.0 database.

NLR cutoff levels (Fig. S3). As illustrated in Table 2, the group with higher TWA-NLR group exhibited increased mortality rates (28.0 % vs. 14.6 %, *P*-value<0.001) as well as prolonged ICU stays (11.2 days vs 10.9 days, *P*-value = 0.004). Additionally, this group exhibited a higher rate of renal disease (18.2 % vs. 15.4 %, *P*-value = 0.021) as well as chronic pulmonary disease (25.4 % vs. 14.9 %, *P*-value<0.001). Simultaneously, the patients with higher TWA-NLR exhibited lower TWA-lymphocytes and TWA-platelets, and were more frequently subjected to renal replacement therapy (23.9 % vs. 15.9 %, *P*-value<0.001).

3.2. Associations between TWA-NLR and hospital mortality risk

In our univariable Cox regression analysis, several variables were initially identified as significantly associated with 90-day hospital mortality (Table 3). These prognostic factors included age, TWA-WBC, TWA-lymphocytes, TWA-neutrophils, TWA-NLR, TWA-LMR, albumin, creatinine, hemoglobin, lactate, potassium, and BUN. As depicted in Fig. 2, there were strong positive correlations among TWA-WBC, TWA-neutrophils, and TWA-monocytes. Conversely, a negative correlation was observed between TWA-NLR and TWA-lymphocytes. Additionally, BUN and creatinine were found to have a significant positive correlation. To mitigate the potential for collinearity in the multivariable Cox regression analysis, we selectively included factors such as TWA-WBC, TWA-NLR, BUN, age, TWA-LMR, albumin, hemoglobin, lactate, and potassium. Finally, the refined model, using a restricted cubic spline (RCS) approach, incorporated covariates such as TWA-WBC (hazard ratio [HR] 1.02, 95 % CI 1.01–1.04, *P*-value = 0.008), BUN (HR 1.08, 95 % CI 1.06–1.19, *P*-value = 0.009), age (HR 1.03, 95 % CI 1.02–1.04, *P*-value<0.001), hemoglobin (HR 0.96, 95 % CI 0.93–0.98, *P*-value = 0.009), as well as lactate (HR 1.04, 95 % CI 1.02–1.06, *P*-value<0.001). After adjusting for these factors, TWA-NLR continued to be a significant predictable element for mortality (HR 1.12, 95 % CI 1.01–1.15, *P*-value<0.001). The adjusted RCS model showed a significant nonlinear association between TWA-NLR and 90-day hospital mortality (Fig. 3A). Interestingly, in patients receiving renal replacement therapy, we observed a linear correlation between TWA-NLR and hospital mortality (Fig. 3B). This finding suggests that decreasing TWA-NLR levels correlates with improved prognosis in this specific patient subgroup, emphasizing the potential value of TWA-NLR in clinical assessment for these patients.

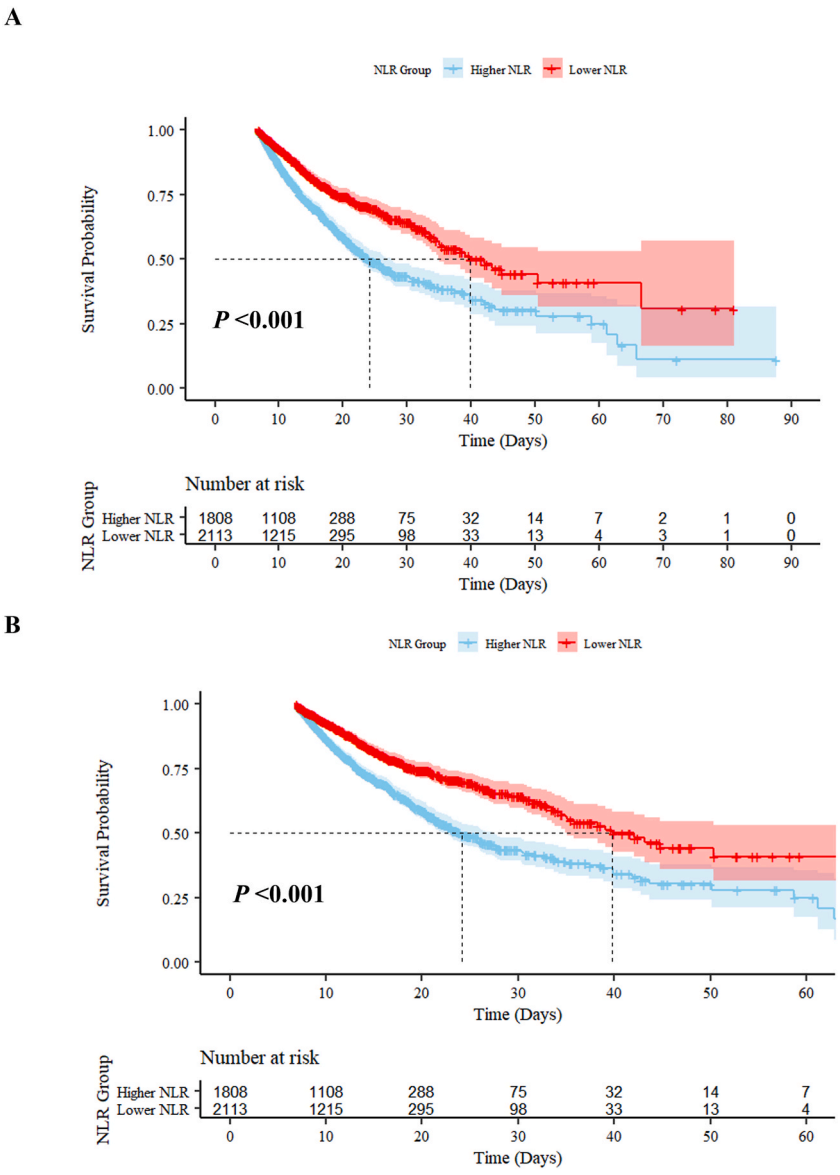

Fig. 4. Kaplan–Meier survival analysis curves for 90-day all-cause hospital mortality (A) and sixty days (B) in the eICU-CRD 2.0 database.

The Kaplan-Meier survival analysis, as illustrated in Fig. 4, demonstrates significant differences in hospital mortality rates at 60 (Figs. 4B) and 90 days (Fig. 4A) between two patient groups stratified by their TWA-NLR levels. The group with lower TWA-NLR demonstrated a significantly longer median survival time of 40 days compared to 24 days in the higher TWA-NLR group (Fig. 4A). This trend was similarly observed in the MIMIC-IV 2.2 database, where the lower TWA-NLR group displayed a longer median survival time (44 days vs. 24 days, *P*-value<0.001), reinforcing the survival benefit associated with lower TWA-NLR level (Fig. S4A). Moreover, follow-up data from the MIMIC-IV 2.2 revealed that the lower TWA-NLR group had a higher out-of-hospital survival rate and a longer median survival time (23 days vs. 19 days, *P*-value<0.001) (Fig. S4B). These findings emphasize the prognostic significance of TWA-NLR in evaluating the outcomes of patients in the hospital as well as after hospital discharge.

3.3. The prognostic capacity of TWA-NLR for all-cause hospital mortality among sepsis and subgroup analyses

To evaluate the prediction ability of the TWA-NLR for 90-day hospital mortality, a time-dependent receiver operating characteristic (ROC) curve analysis was conducted. TWA-NLR showed an area under the curve (AUC) that was 0.69, surpassing TWA-neutrophils (AUC: 0.57) and TWA-lymphocytes (AUC: 0.51) (Fig. 5A). The predictive model was further enhanced by adjusting for TWA-WBC, age, hemoglobin, lactate, and blood urea nitrogen (BUN), improving the AUC to 0.74. This adjusted model surpassed the Oxford Acute Severity of Illness Score (OASIS) (AUC: 0.66) as well as SOFA score (AUC: 0.65) (Fig. 5B). Similar patterns were observed on the

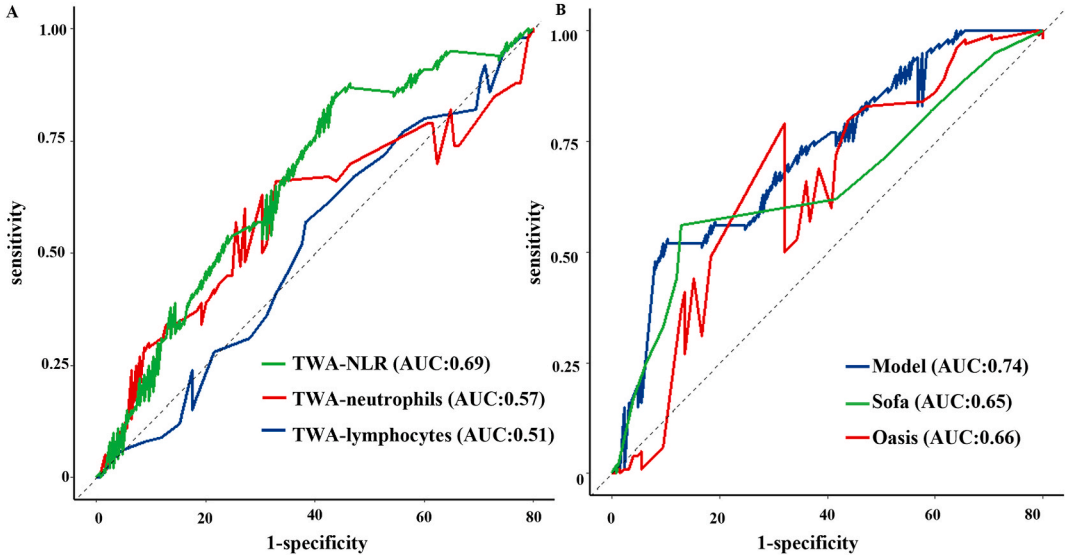

Fig. 5. Time-dependent ROC curves and time-dependent AUC values of the adjusted TWA-NLR (A) and model (B) for predicting 90-day all-cause hospital mortality in the eICU-CRD 2.0 database.

Table 4
Subgroup analysis of the associations between NLR and mortality.

Characteristics	ALL-cause mortality			*P* interaction
	Higher TWA-NLR	Lower TWA-NLR		
		HR (95%CI)	*P* value	
Age				0.934
≤60	Ref	0.6 (0.46–0.78)	<0.001	
>60	Ref	0.6 (0.51–0.72)	<0.001	
Gender				0.628
Female		0.57 (0.46–0.71)	<0.001	
Male		0.54 (0.44–0.65)	<0.001	
Invasive ventilation				0.589
No	Ref	0.51 (0.33–0.78)	<0.001	
Yes	Ref	0.57 (0.49–0.66)	<0.001	
Renal replacement therapy				0.258
No	Ref	0.53 (0.45–0.62)	<0.001	
Yes	Ref	0.64 (0.48–0.87)	<0.001	
Diabetes				0.44
No	Ref	0.54 (0.45–0.64)	<0.001	
Yes	Ref	0.62 (0.48–0.79)	<0.001	
Renal disease				0.008
No	Ref	0.51 (0.44–0.6)	<0.001	
Yes	Ref	0.80 (0.59–1.08)	0.147	
Liver disease				0.67
No	Ref	0.56 (0.48–0.65)	<0.001	
Yes	Ref	0.66 (0.38–1.15)	0.142	
Cerebrovascular disease				0.73
No	Ref	0.55 (0.47–0.64)	<0.01	
Yes	Ref	0.60 (0.41–0.90)	0.012	
Chronic pulmonary disease				0.009
No	Ref	0.52 (0.45–0.61)	<0.01	
Yes	Ref	0.83 (0.61–1.14)	0.248	

TWA: Time weighted average.

MIMIC-IV 2.2 database (Figs. S5A–B).

We performed an extensive subgroup analysis to assess the consistency in prognostic value of TWA-NLR across diverse patient subgroups. These subgroups included age, gender, use of invasive ventilation therapy, renal replacement therapy requirement, liver disease, diabetes, or cerebrovascular disease. As detailed in Table 4, our analysis revealed that most interactions were not statistically significant (interaction of *P*-value>0.05), affirming TWA-NLR's uniform prognostic significance across these subgroups. However,

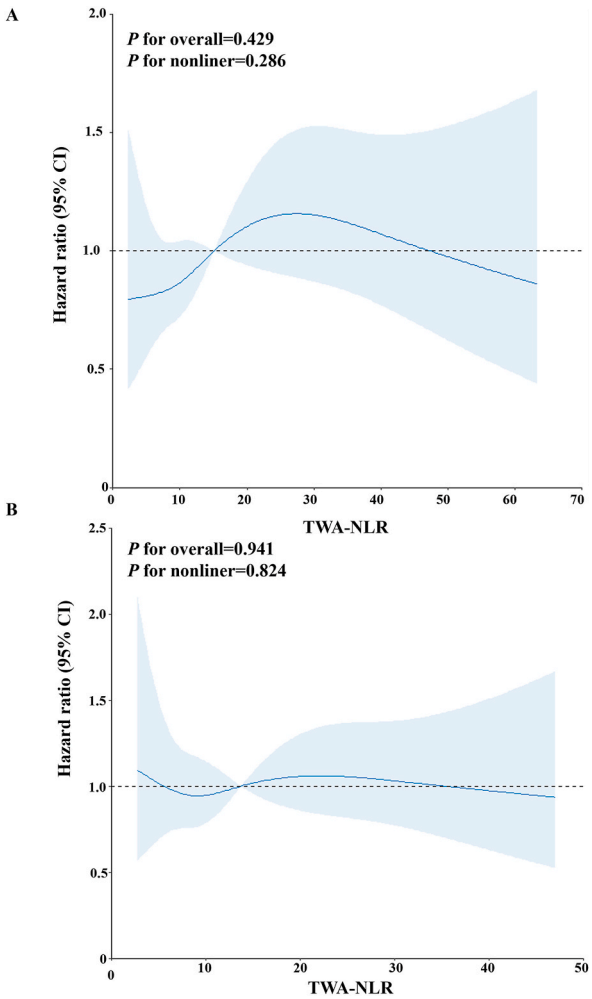

Fig. 6. Restricted cubic spline curve for chronic pulmonary disease subgroup (A) and renal disease (B) in the eICU-CRD 2.0 database.

significant interactions were observed in patients with renal disease (interaction of *P*-value = 0.008) and chronic pulmonary disease (interaction of *P*-value = 0.009), where TWA-NLR did not significantly predict hospital mortality, resulting in HR values of 0.83 (95 % CI 0.61–1.14, *P*-value = 0.248) for pulmonary disease and 0.80 (95 % CI 0.59–1.08, *P*-value = 0.147) for renal disease. Further analysis by restricted cubic spline analysis confirmed the lack of a significant association between TWA-NLR and 90-day hospital mortality in chronic pulmonary disease (Fig. 6A) and renal disease subgroups (Fig. 6B), suggesting that TWA-NLR's utility might be limited in specific chronic conditions.

4. Discussion

Sepsis is defined by systemic organ dysfunction and exaggeration of the immunological response to host infection, often leading to metabolic disturbances, severe immunosuppression, and alterations in lymphocyte distribution within lymphoid organs [22]. Initially, neutrophil and lymphocyte counts typically increase in response to microbial invasion. Neutrophils migrate toward the infection site as sepsis progresses, whereas lymphocyte levels decline due to immunosuppression. The variability in neutrophil counts and delayed lymphocyte decrease provide limited predictive value for sepsis outcomes [23,24]. Instead, the NLR has emerged as a valuable biomarker in adult sepsis, reflecting both innate as well as adaptive immunity balance and capturing the dynamics involved in the immune responses [25,26]. Recent studies have identified NLR as a more reliable predictor of patient survival than individual neutrophils or lymphocytes [27], and it has shown superior predictive value for mortality compared to other inflammation-related biomarkers like procalcitonin (PCT) and C-reactive protein (CRP) [28]. When combined with other inflammatory biomarkers, NLR may improve mortality predictions in sepsis patients [29,30]. The prognostic impact of NLR is mainly assessed through a single measured value within the first 24 h of ICU admission [31,32]. This single measurement fails to capture the fluctuating nature of sepsis, thereby limiting its diagnostic and prognostic utility [33]. To overcome this limitation, we employed a longitudinal approach using time-weighted averages [34,35] to monitor inflammatory markers such as WBC, platelets, neutrophils, lymphocytes, and monocytes at

admission and subsequently every 72 h for up to seven days. This methodology enabled us to track changes in these markers over time and their correlations with patient outcomes, offering a more detailed view of sepsis progression. Our results indicate a strong statistical association between elevated TWA-NLR levels and increased mortality rates and extended ICU stays. Conversely, lower TWA-NLR values correlated with significantly longer median survival times. The prognostic value of TWA-NLR proved consistent across various patient subgroups, demonstrating its robustness as a prognostic indicator across a diverse patient population. However, we noted significant interactions in patients with chronic pulmonary or renal diseases, indicating that these conditions might influence the correlation among TWA-NLR and mortality. In addition, the adjusted model outperformed traditional score systems, such as the OASIS and SOFA, in predicting 90-day in-hospital mortality. External validation with the MIMIC-IV 2.2 database further confirmed the reliability of our predictive model.

Several limitations of this study warrant consideration. First, the retrospective design and utilization of observational databases such as MIMIC-IV 2.2 and eICU-CRD 2.0 inherently introduce potential biases. Secondly, inadequate documentation of inflammatory biomarkers limits comprehensive analysis. Thirdly, the associations identified between TWA-NLR and mortality do not imply causation. To better understand this relationship, future research should aim to conduct prospective studies or randomized controlled trials.

5. Conclusion

In summary, our results reveal a substantial and independent correlation between increased TWA-NLR and the incidence of 90-day in-hospital mortality in sepsis patients. Notably, TWA-NLR demonstrates potential predictive capabilities for in-hospital as well as out-of-hospital mortality. These findings indicate that TWA-NLR may serve as a convenient and reliable diagnostic tool to help identify high-risk sepsis, allowing more specific and effective management of sepsis.

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Data and code statement

All the data present in our articles has been stored in the MIMIC-IV 2.2 (https://mimic.mit.edu/) and eICU-CRD 2.0 (https://eicu-crd.mit.edu/) database, which are freely available for analysis and download. Access to the MIMIC-IV 2.2 and eICU-CRD 2.0 databases involved successful completion of a qualifying exam and approval (certification number: 55849941). The related code and the data extracted are accessible from the corresponding author upon appropriate demand.

Ethics approval and consent to participate

The research was carried out following the ethical guidelines of the 1964 statement of Helsinki and its subsequent revisions or equivalent ethical guidelines. It is important to point out that the eICU-CRD 2.0 as well as MIMIC-IV 2.2 database received approval from the Beth Israel Deaconess Medical Center (2001-P-001699/14) as well as the Massachusetts Institute of Technology (0403000206). The eICU-CRD 2.0 as well as MIMIC-IV 2.2 database contain copies of the data utilized in this research. As a result, no ethical approval or informed consent did not need to be obtained for this research, and the study followed STROBE guidelines.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Guyu Zhang: Writing – original draft. **Tao Wang:** Investigation. **Le An:** Software. **ChenChen Hang:** Data curation. **XingSheng Wang:** Methodology. **Fei Shao:** Validation. **Rui Shao:** Funding acquisition. **Ziren Tang:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36195.

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