Research article

The early predictive roles of NLR and NE% in in-hospital mortality of septic patients

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ABSTRACT

Background: This study aimed to retrospectively investigate the early predictive value of inflammation-related parameters in-hospital mortality of septic patients.

Methods: We retrospectively recruited 606 patients from Wuhan Union Hospital from January 2009 to October 2022. The inflammation-related parameters including neutrophil-to-lymphocyte ratio (NLR), neutrophil percentage (NE%), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) in survivals and non-survivals on day 1, 2, 3 and 7 after hospitalization were collected and analyzed.

Results: NLR and NE% in non-survivals (n = 185) were significantly higher than those in survivals (n = 421). The area under the receiver operating characteristic curve (AUC) of NLR or NE% was 0.880 or 0.852 on day 1, 0.770 or 0.790 on day 2, 0.784 or 0.777 on day 3, and 0.732 or 0.741 on day 7. The optimal cut-off values of NLR or NE% for predicting in-hospital mortality were 10.769 or 87.70% on day 1, 17.544 or 90.69% on day 2, 14.395 or 85.00% on day 3, and 9.105 or 83.93% on day 7. The day 1, 2 and 3 NLR and NE% were significant predictors of in-hospital mortality in the Cox proportional hazards models.

Conclusions: NLR ≥10.769 and NE% ≥ 87.70% could be used early biomarkers for predicting in-hospital mortality of septic patients.

Trial registration

This trial was retrospectively registered at ClinicalTrials.gov (NCT05636202). Registered November 08, 2022.

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Abbreviations	
NLR	Neutrophil-to-lymphocyte ratio
NE%	Neutrophil percentage
PLR	Platelet-to-lymphocyte ratio
MLR	Monocyte-to-lymphocyte ratio
ROC	Receiver operating characteristic
AUC	Area under the receiver operating characteristic curve
ICU	Intensive care unit
HR	Hazard ratio
CRP	C-reactive protein
PCT	Procalcitonin
APACHE II	Acute physiology and chronic health evaluation
IQR	Interquartile range
SOFA	Sepsis-related organ failure assessment
WBC	White blood cells
PT	Prothrombin time
APTT	Activated partial thromboplastin time
OR	Odd ratio

1. Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by the host's malfunctioning response to infection [1], which has become one of the major problems in the world's public health. Sepsis is a severe medical syndrome with high morbidity and mortality rates, posing a significant public health challenge, which costs over $20 billion each year in the United States healthcare system [2,3]. In the past decades, more than 250 biomarkers related to the diagnosis and prognosis of sepsis have been identified [4]. The development of effective biomarkers for the diagnosis of sepsis is undoubtedly helpful for us to timely and accurately understand the diagnosis, progression, and prognosis of sepsis.

The neutrophil-to-lymphocyte ratio (NLR), as an inflammatory indicator, is inexpensive and easily accessible parameter and could be widely used. NLR has been studied in many diseases such as melanoma [5], laryngeal carcinoma [6], and acute myocardial infarction [7]. In severe infectious diseases, particularly in sepsis, a substantial increase in peripheral blood neutrophils has been discovered, which reflects the severity of the inflammatory response [8,9]. Neutrophil reverse migration following the initial neutrophil infiltration into inflammatory scenarios may further exacerbate the increase in the peripheral blood neutrophils [8]. Lymphocyte apoptosis-induced reduction of peripheral blood lymphocytes is a significant feature of sepsis that could lead to adaptive immunosuppression [10]. In all, NLR is a cheap and rapidly available predictor of sepsis and has shown a significant correlation with other relatively expensive and non-rapidly existing markers of inflammation and sepsis [11,12].

Importantly, research on NLR in sepsis has received wide attention in recent years. NLR within 24 h before intensive care unit (ICU) admission could be used as a marker for early diagnosis of sepsis. 226 septic patients were enrolled in a single-center study and it was found that NLR more than 5.0 and the neutrophil percentage (NE%) more than 10% were risk factors for sepsis, the ROC curve values for the percentage of neutrophils was 0.98 [13]. In addition to the diagnostic value of NLR, through a 5-year single-center retrospective study, low NLR was found to be an independent risk factor for in-hospital mortality in septic patients (n = 174), and high NLR was associated with the probability of bacteremia [14]. A meta-analysis in 2019 indicates that peripheral blood leucocyte ratios, including NLR, lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratios (PLR), could be useful infection biomarkers and associated with clinical prognosis of sepsis [15]. A meta-analysis in 2020 also indicates that the higher NLR was linked to poor prognosis in septic patients (n = 10,685) (hazard ratio (HR) = 1.75) [16]. NLR at admission is shown to be an independent predictor of in-hospital mortality of septic patients (n = 174) [14]. NLR, PLR and LMR can be useful predictors for early identification of post-percutaneous nephrolithotomy (PNL) sepsis [17]. However, the exact role of NLR in the early prediction of the prognosis of septic patients remain controversial [14,18]. No correlation was found between NLR at admission of emergency department and 28-day hospital mortality of septic patients [14,19]. NLR at admission is less suitable than conventional inflammatory markers C-reactive protein (CRP) and procalcitonin (PCT) to detect the presence of sepsis in ICU patients [20]. NLR at ICU admission is also less reliable than CRP, PCT, lactic acid and acute physiology and chronic health evaluation (APACHE II) score in assessing the severity and in predicting 28-day mortality of critical illness [21].

In this study, we enrolled 606 septic patients to determine the role of NLR in the early prediction of in-hospital mortality of septic patients. We have conducted an extensive analysis of baseline data. In addition, considering that PLR, NE% and monocyte to lymphocyte ratio (MLR) have been confirmed to be also associated with the mortality of septic patients [22–24], while retrospectively analyzing the role of NLR, we also studied the roles of PLR, MLR, neutrophil percentage, and other inflammation-related parameters on the first, second, third, and seventh days after hospitilization in the in-hospital mortality of septic patients.

2. Methods

2.1. Study design and participants

This study was a single center retrospective study screening 22,261 septic patients admitted to the headquarters and three divisions of Wuhan Union Hospital from January 1, 2009 to October 1, 2022. Inclusion criteria: adult patients ($\geq$18 years old) with the diagnosis of sepsis or septic shock according to the sepsis 2.0 criteria [25] or sepsis 3.0 criteria [26]. Patients admitted to hospital before February 23, 2017 diagnosed with sepsis according to the sepsis 2.0 criteria need to be re-diagnosed by sepsis 3.0 criteria.

Exclusion criteria: (1) patients aged <18 years; (2) pregnant or lactating women; (3) patients with hematological diseases, tumors after radiotherapy and chemotherapy, or immune system diseases; (4) patients with incomplete routine blood records on the first day after hospitalization. A total of 606 patients met the inclusion and exclusion criteria.

The study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Permission number: 0732), and it conforms to the provisions of the Declaration of Helsinki. Patient consent was waived for all participants enrolled in this study because of the retrospective study design. This study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.2. Study collection

We reviewed the electronic medical records, nurse notes, laboratory test results, and imaging findings of all patients who diagnosed with sepsis in our hospital from January 1, 2009 to October 1, 2022. All data were checked by two researchers.

We collected the gender, age, comorbidities, source of infection, laboratory parameters (blood routine, blood biochemical and electrolyte, cardiac biomarkers and blood coagulation parameters, CRP and PCT) on day 1, 2, 3 and 7 after hospitalization, discharge conditions (alive or death), and length of hospital stay.

2.3. Detection methods and statistical methods

Categorical variables are expressed as numbers (%). All variables were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were described as mean $\pm$ SD. The median (interquartile range, IQR) was used for description if the distribution did not meet the normal distribution. The measurement data conforming to normal distribution were compared by independent sample *t*-test. Otherwise, the Mann-Whitney test was used. Proportions of categorical variables were compared using the chi-square test, Yates continuity correction chi-square test, or Fisher's exact probability method. The receiver operating characteristic (ROC) curve was used to analyze the cut-off value, sensitivity and specificity of each variable. Odds ratios with 95% confidence intervals were calculated to determine the strength of the association between risk factors and outcomes. For this purpose, the most promising independent variable (univariate analysis) was included as a single risk factor in binary logistic regression analysis (multivariate analysis). The proportional hazards model was used to explore the relationship between factors and
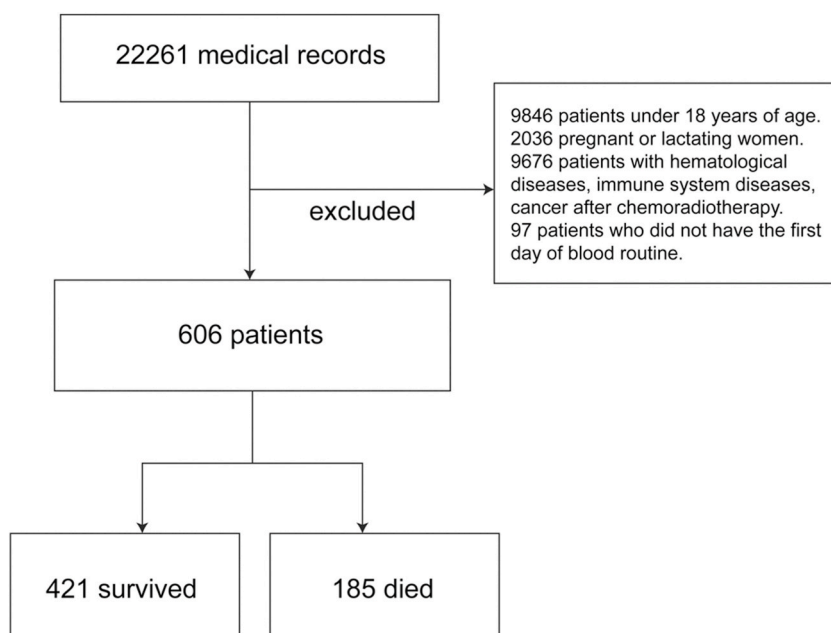

Fig. 1. Flowchart of the enrolled patients.

Table 1
General characteristics in sepsis.

		Total (n = 606)	Survived (n = 421)	Non-survived (n = 185)	P value
Gender	Male	375 (61.88%)	252 (59.86%)	123 (66.49%)	–
	Female	231 (38.12%)	169 (40.14%)	62 (33.51%)	–
Age, years		56.67 ± 16.88	55.92 ± 16.7	58.39 ± 17.17	0.093
Number of ICU patients		275 (45.38%)	156 (37.05%)	119 (64.32%)	< 0.001
Surgery	Abdominal surgery	55 (9.08%)	20 (4.75%)	35 (18.92%)	< 0.001
	Non-abdominal surgery	40 (6.60%)	26 (6.18%)	14 (7.57%)	0.459
SOFA scores (Day 1)		8 (5, 10)	5 (5, 8)	11 (9, 14)	< 0.001
Comorbidities, n (%)					
Respiratory system		303 (50.0%)	198 (47.03%)	105 (56.76%)	< 0.05
Urinary system		242 (39.93%)	145 (34.44%)	97 (52.43%)	< 0.001
Digestive system		250 (41.25%)	137 (32.54%)	113 (61.08%)	< 0.001
Cardiovascular system		211 (34.82%)	124 (29.45%)	87 (47.03%)	< 0.001
Source of infection, n (%)					
Pulmonary		163 (26.90%)	76 (18.05%)	87 (47.03%)	< 0.001
Abdominal		13 (2.15%)	5 (1.19%)	7 (3.78%)	< 0.05
Bloodstream		15 (2.48%)	4 (0.95%)	9 (4.86)	< 0.05
Urinary		2 (0.33%)	0 (0%)	2 (1.08%)	< 0.05
White blood cell ($\times 10^{12}$/L)	Day 1	9.74 (6.39–4.18)	8.34 (5.58–11.89)	14.54 (9.36–20.88)	< 0.001
	Day 2	9.60 (6.20–14.89)	7.89 (5.58–11.64)	14.20 (10.00–20.65)	< 0.001
	Day 3	9.94 (6.64–15.76)	8.04 (5.74–12.15)	14.11 (9.29–20.80)	< 0.001
	Day 7	10.82 (7.22–14.89)	9.57 (6.13–11.90)	90.00 (74.00–101.00)	< 0.001
Platelet ($\times 10^9$/L)	Day 1	141.00 (74.00–241.00)	160.00 (90.00–252.50)	113.00 (52.00–202.50)	< 0.001
	Day 2	143.00 (62.50–260.50)	196.00 (80.00–295.50)	103.50 (44.25–155.25)	< 0.001
	Day 3	114.00 (53.00–240.00)	153.00 (66.00–279.75)	76.00 (36.00–154.00)	< 0.001
	Day 7	104.50 (60.00–216.25)	126.00 (72.00–266.00)	84.00 (58.00–156.00)	< 0.05
Neutrophil (%)	Day 1	82.3 (72.85–88.86)	77.45 (68.20–83.60)	90.80 (87.80–93.60)	< 0.001
	Day 2	82.3 (69.70–90.05)	74.60 (62.62–83.95)	91.30 (85.55–94.05)	< 0.001
	Day 3	83.70 (72.40–90.50)	76.00 (65.20–84.14)	90.28 (85.70–93.60)	< 0.001
	Day 7	85.90 (80.13–90.73)	81.80 (72.30–87.10)	88.40 (85.20–91.90)	< 0.001
Lymphocyte (%)	Day 1	10.35 (6.10–16.63)	13.50 (9.10–20.25)	4.80 (3.30–6.55)	< 0.001
	Day 2	10.80 (4.90–20.20)	15.30 (9.85–26.10)	4.55 (3.03–6.83)	< 0.001
	Day 3	9.20 (5.20–17.70)	15.20 (8.93–24.50)	5.40 (3.10–7.70)	< 0.001
	Day 7	7.70 (4.67–11.43)	9.90 (5.60–17.80)	5.90 (3.40–9.30)	< 0.001
Monocyte (%)	Day 1	5.8 (3.10–8.40)	6.71 (4.50–9.48)	3.15 (1.90–5.40)	< 0.001
	Day 2	5.30 (2.90–8.20)	6.70 (4.51–9.20)	2.85 (1.78–4.70)	< 0.001
	Day 3	5.10 (2.90–7.70)	6.50 (4.40–8.78)	3.20 (1.80–5.13)	< 0.001
	Day 7	4.74 (2.60–7.18)	5.70 (3.70–7.90)	3.70 (2.00–5.85)	< 0.05
Neutrophil ($\times 10^9$/L)	Day 1	7.70 (4.60–12.09)	6.37 (3.71–9.42)	12.99 (8.01–19.22)	< 0.001
	Day 2	7.61 (4.27–13.17)	5.73 (3.66–9.42)	12.43 (8.95–19.25)	< 0.001
	Day 3	8.11 (4.65–14.25)	5.42 (3.78–10.03)	12.56 (8.24–19.14)	< 0.001
	Day 7	9.05 (5.93–12.36)	7.92 (4.53–10.41)	10.53 (7.15–15.70)	< 0.001
Lymphocyte ($\times 10^9$/L)	Day 1	1.00 (0.68–1.44)	1.11 (0.83–1.53)	0.64 (0.37–1.01)	< 0.001
	Day 2	1.03 (0.62–1.60)	1.27 (0.84–1.80)	0.66 (0.39–1.05)	< 0.001
	Day 3	1.10 (0.60–1.50)	1.23 (0.80–1.81)	0.69 (0.41–1.09)	< 0.001
	Day 7	0.91 (0.49–1.24)	1.01 (0.61–1.36)	0.76 (0.42–1.08)	< 0.05
Monocyte ($\times 10^9$/L)	Day 1	0.52 (0.32–0.82)	0.56 (0.35–0.82)	0.43 (0.22–0.81)	0.282
	Day 2	0.52 (0.30–0.77)	0.55 (0.35–0.77)	0.41 (0.22–0.78)	0.216
	Day 3	0.53 (0.31–0.76)	0.53 (0.36–0.76)	0.50 (0.24–0.75)	0.756
	Day 7	0.48 (0.29–0.77)	0.49 (0.32–0.77)	0.45 (0.23–0.91)	0.369
NLR	Day 1	7.64 (4.21–13.90)	5.75 (3.40–8.63)	18.25 (13.28–28.86)	< 0.001
	Day 2	7.76 (3.49–17.88)	4.90 (2.43–8.80)	20.03 (12.63–31.07)	< 0.001
	Day 3	9.07 (4.03–17.02)	4.97 (2.63–9.37)	16.46 (11.30–29.99)	< 0.001
	Day 7	11.15 (7.22–19.51)	8.11 (3.90–13.32)	15.14 (9.12–24.76)	< 0.001
PLR	Day 1	145.97 (73.84–242.37)	140.88 (74.24–232.30)	157.29 (71.33–307.33)	< 0.001
	Day 2	154.44 (75.83–246.33)	149.37 (77.50–232.41)	161.54 (71.71–270.40)	< 0.05
	Day 3	129.76 (63.03–225.97)	131.89 (65.58–218.99)	122.41 (59.05–228.95)	0.324
	Day 7	153.57 (69.45–285.62)	157.14 (79.07–289.81)	149.01 (60.24–267.18)	0.343
MLR	Day 1	0.54 (0.32–0.84)	0.48 (0.31–0.73)	0.71 (0.42–1.13)	< 0.001
	Day 2	0.48 (0.29–0.80)	0.43 (0.26–0.65)	0.67 (0.35–1.04)	< 0.001
	Day 3	0.47 (0.29–0.81)	0.42 (0.29–0.67)	0.65 (0.30–1.09)	< 0.001
	Day 7	0.60 (0.30–0.89)	0.60 (0.32–0.74)	0.61 (0.30–1.14)	0.162
PT (s)	Day 1	15.5 (13.9–18.1)	14.60 (13.43–16.68)	17.25 (14.45–22.15)	< 0.001
	Day 2	16.30 (14.50–19.98)	14.90 (13.70–17.30)	18.60 (15.95–22.30)	< 0.001
	Day 3	16.30 (14.30–18.90)	15.00 (14.00–17.90)	17.30 (15.40–24.15)	< 0.05
	Day 7	15.3 (14.10–18.30)	14.60 (13.30–16.70)	16.85 (14.73–25.93)	< 0.05
APTT (s)	Day 1	41.10 (36.3–49.1)	39.60 (35.95–45.30)	46.45 (38.30–56.35)	< 0.001
	Day 2	43.00 (37.45–52.73)	40.05 (35.50–46.98)	48.25 (40.18–60.55)	< 0.001
	Day 3	43.55 (37.63–53.50)	42.00 (37.05–49.00)	47.30 (38.80–61.10)	0.098

(continued on next page)

Table 1 (*continued*)

		Total (n = 606)	Survived (n = 421)	Non-survived (n = 185)	P value
	Day 7	41.00 (36.30–50.10)	38.10 (34.90–43.70)	45.15 (36.63–59.15)	< 0.05
Total bilirubin (μmol/L)	Day 1	16.45 (10.18–38.13)	13.55 (9.00–23.98)	29.55 (16.12–72.98)	< 0.001
	Day 2	19.70 (10.33–51.58)	13.60 (9.00–28.53)	29.80 (15.05–84.25)	< 0.05
	Day 3	23.70 (12.35–69.80)	16.70 (10.70–36.30)	37.50 (15.80–88.20)	0.067
	Day 7	20.25 (10.26–54.20)	16.45 (9.03–29.85)	30.85 (12.35–77.78)	< 0.05
Creatinine (μmol/L)	Day 1	79.84 (60.43–170.73)	72.10 (58.30–130.70)	125.6 (70.75–248.45)	< 0.001
	Day 2	98.90 (63.10–196.90)	81.15 (59.68–148.50)	141.90 (78.30–258.10)	< 0.001
	Day 3	119.40 (67.00–225.60)	92.90 (60.83–211.58)	137.20 (71.45–238.65)	0.526
	Day 7	92.80 (57.78–200.83)	76.50 (57.70–152.75)	135.00 (59.65–221.20)	0.231
Albumin (g/L)	Day 1	28.5 (24.30–33.10)	30.10 (25.98–33.90)	25.9 (21.15–29.70)	< 0.001
	Day 2	27.3 (23.43–31.30)	28.80 (25.78–32.53)	24.95 (22.18–28.53)	< 0.001
	Day 3	27.30 (23.45–31.15)	28.40 (25.05–32.30)	25.60 (22.90–29.80)	< 0.001
	Day 7	27.85 (24.10–31.20)	29.15 (25.80–31.90)	26.05 (22.35–30.43)	< 0.05
Urea nitrogen (mmol/L)	Day 1	8.25 (4.90–16.20)	6.42 (4.30–12.60)	13.24 (7.59–21.22)	0.489
	Day 2	10.83 (5.24–19.12)	7.19 (4.32–15.03)	14.68 (9.10–23.67)	< 0.001
	Day 3	13.30 (7.62–21.77)	10.55 (6.14–19.00)	15.30 (9.56–23.28)	< 0.05
	Day 7	14.86 (24.10–31.20)	9.90 (5.35–17.57)	17.94 (9.42–33.00)	< 0.001
CK-MB (ng/mL)	Day 1	2.25 (0.90–9.43)	1.70 (0.65–7.10)	3.90 (1.20–12.50)	0.502
	Day 2	2.30 (0.90–11.85)	2.00 (0.70–11.38)	2.60 (1.10–11.93)	0.295
	Day 3	3.5 (0.86–13.85)	1.80 (0.55–10.80)	4.30 (1.10–16.50)	0.113
	Day 7	1.05 (0.60–2.45)	0.70 (0.38–2.10)	1.5 (0.6–3.2)	0.468
Procalcitonin (ng/mL)	Day 1	3.00 (0.69–30.17)	1.91 (0.47–32.83)	3.65 (1.04–21.14)	0.756
	Day 2	7.91 (1.72–36.51)	7.50 (0.81–18.25)	8.4 (2.81–39.14)	0.125
	Day 3	7.92 (2.72–25.89)	4.65 (0.60–13.01)	9.28 (3.18–30.49)	0.179
	Day 7	1.49 (0.47–11.07)	1.49 (0.51–5.66)	–	0.344
C-reactive protein (mg/L)	Day 1	134.50 (54.63–207.15)	123.50 (54.48–185.50)	170.33 (56.45–245.00)	0.125
	Day 2	137.00 (57.65–198.50)	94.05 (32.10–159.25)	185.00 (101.00–234.00)	0.169
	Day 3	103.61 (48.48–176.75)	82.70 (24.00–145.67)	134.50 (63.58–183.00)	0.184
	Day 7	62.00 (36.80–82.50)	49.60 (31.05–76.18)	–	0.188
Length of hospital stay		12 (8, 19)	12 (9, 18)	14 (6, 22)	0.081

SOFA, Sequential Organ Failure Assessment; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; CK-MB, creatine kinase Mb. Data are expressed as the mean ± SD, median (interquartile range), or number (%).

survival time and survival outcome. A two-sided P value of 0.05 was considered statistically significant. SPSS 27.0 software (SPSS, Tokyo, Japan) was used for statistical analysis.

3. Results

3.1. Baseline clinical characteristics

We reviewed all existing medical records of patients with a discharge diagnosis of sepsis from January 2009 to October 2022, a total of 22,261 patients were included. We excluded 9846 patients aged <18 years, 2036 pregnant or lactating women, 9676 patients with hematological diseases, immune system diseases, or cancer after chemoradiotherapy, and 97 patients without complete routine blood records on the first day after hospitalization. Finally, we included 606 patients, of whom 421 (69.47%) survived and 185 (30.53%) died during hospitalization (Fig. 1). The 421 survivals included 252 (66.49%) males and 169 (33.51%) females, and the average age was 55.92 ± 16.70 years. There were 123 (59.86%) males and 62 (40.14%) females in the non-survivals, with an average age of 58.39 ± 17.17 years. The median overall survival days for all patients was 12 days [IQR 9–19], the median overall survival days in the survivals were 12 [IQR 9–18] days, the median overall survival days in the non-survivals were 14 [IQR 6–22] days (Table 1). It is important to note that more ICU patients (37.05% *vs.* 64.32%; $p < 0.001$) and patients undergoing abdominal surgery (4.75% *vs.* 18.92%; $p < 0.001$) in the non-survivals were observed compared to that in the survivals. Similarly, sepsis-related organ failure assessment (SOFA) score on day 1 after hospitalization were significantly higher in non-survivals (median 11 [IQR 9–14]) relative to survivals (median 5 [IQR 5–8]). Non-survivals had more comorbidities and positive etiological results during hospitalization ($p < 0.001$ or $p < 0.05$; Table 1).

3.2. Laboratory tests

Compared with that in the survivals, white blood cells (WBC), platelet, NE%, lymphocyte percentage, monocyte percentage, absolute neutrophil count, absolute lymphocyte count, NLR, prothrombin time (PT), and albumin in the non-survivals were all significantly higher on day 1, 2, 3 and 7 ($p < 0.001$ or $p < 0.05$; Table 1). In addition, PLR, MLR, creatinine, activated partial thromboplastin time (APTT), and total bilirubin were all remarkably higher in the non-survivals on day 1 and 2 ($p < 0.001$ or $p < 0.05$). The median NLR on day 1, 2, 3 and 7 were 7.643 [IQR 4.214–13.900], 7.758 [IQR 3.493–17.875], 9.079 [IQR 4.031–17.020], and 11.152 [IQR 7.217–19.507], respectively. The median NE% on day 1, 2, 3 and 7 were 82.30% [IQR 72.85%–88.88%], 82.30% [IQR 69.70%–

Table 2
Comparisons of the hematologic variables.

Parameters		OR	95% CI		P value
			lower bound	upper bound	
White blood cells ($\times 10^{12}$/L)	Day 1	1.134	1.101	1.167	< 0.001
	Day 2	1.107	1.076	1.139	< 0.001
	Day 3	1.114	1.078	1.151	< 0.001
	Day 7	1.122	1.05	1.199	< 0.001
Platelets ($\times 10^{9}$/L)	Day 1	0.997	0.995	0.998	< 0.001
	Day 2	0.995	0.994	0.997	< 0.001
	Day 3	0.995	0.993	0.997	< 0.001
	Day 7	0.996	0.993	0.999	< 0.05
Neutrophils (%)	Day 1	1.274	1.222	1.330	< 0.001
	Day 2	1.105	1.080	1.130	< 0.001
	Day 3	1.194	1.148	1.241	< 0.001
	Day 7	1.076	1.029	1.125	< 0.05
Lymphocytes (%)	Day 1	0.694	0.649	0.742	< 0.001
	Day 2	0.769	0.729	0.812	< 0.001
	Day 3	0.783	0.740	0.827	< 0.001
	Day 7	0.866	0.805	0.931	< 0.001
Monocytes (%)	Day 1	0.723	0.674	0.776	< 0.001
	Day 2	0.701	0.647	0.760	< 0.001
	Day 3	0.812	0.755	0.873	< 0.001
	Day 7	0.877	0.785	0.980	< 0.05
Neutrophils ($\times 10^{9}$/L)	Day 1	1.186	1.144	1.229	< 0.001
	Day 2	1.105	1.080	1.130	< 0.001
	Day 3	1.194	1.148	1.241	< 0.001
	Day 7	1.076	1.029	1.125	< 0.05
Lymphocytes ($\times 10^{9}$/L)	Day 1	0.327	0.227	0.470	< 0.001
	Day 2	0.283	0.196	0.408	< 0.001
	Day 3	0.352	0.243	0.510	< 0.001
	Day 7	0.596	0.352	1.007	0.053
Monocytes ($\times 10^{9}$/L)	Day 1	0.836	0.609	1.148	0.268
	Day 2	0.789	0.547	1.138	0.205
	Day 3	0.932	0.624	1.393	0.732
	Day 7	1.353	0.649	2.819	0.420
NLR	Day 1	1.234	1.188	1.283	< 0.001
	Day 2	1.112	1.087	1.137	< 0.001
	Day 3	1.132	1.097	1.168	< 0.001
	Day 7	1.093	1.043	1.146	< 0.001
PLR	Day 1	1.002	1.001	1.003	< 0.001
	Day 2	1.001	1.000	1.002	< 0.05
	Day 3	1.001	0.999	1.002	0.251
	Day 7	1.001	0.999	1.003	0.372
MLR	Day 1	2.195	1.520	3.168	< 0.001
	Day 2	2.647	1.791	3.911	< 0.001
	Day 3	2.093	1.381	3.171	< 0.001
	Day 7	1.417	0.814	2.465	0.217
PT (s)	Day 1	1.096	1.049	1.144	< 0.001
	Day 2	1.145	1.071	1.224	< 0.001
	Day 3	1.057	1.014	1.101	< 0.05
	Day 7	1.175	1.031	1.339	< 0.05
APTT (s)	Day 1	1.032	1.014	1.049	< 0.001
	Day 2	1.045	1.021	1.069	< 0.001
	Day 3	1.010	0.998	1.023	0.098
	Day 7	1.045	1.003	1.089	< 0.05
Ttotal bilirubin (μmol/L)	Day 1	1.008	1.005	1.012	< 0.001
	Day 2	1.005	1.002	1.009	< 0.05
	Day 3	1.003	1.000	1.007	0.075
	Day 7	1.010	1.002	1.018	< 0.05
	Day 1	1.002	1.001	1.004	< 0.001
Creatinine (μmol/L)	Day 2	1.003	1.001	1.005	< 0.001
	Day 3	1.001	0.999	1.002	0.525
	Day 7	1.002	0.999	1.005	0.251
Albumin (g/L)	Day 1	0.913	0.882	0.994	< 0.001
	Day 2	1.107	1.076	1.139	< 0.001
	Day 3	1.114	1.078	1.151	< 0.001
	Day 7	0.887	0.819	0.959	< 0.05
Urea nitrogen (mmol/L)	Day 1	1.001	0.997	1.005	0.517
	Day 2	1.059	1.034	1.084	< 0.001
	Day 3	1.035	1.009	1.062	< 0.05

Table 2 (*continued*)

Parameters		OR	95% CI		P value
			lower bound	upper bound	
	Day 7	1.056	1.020	1.093	< 0.001
CK-MB (ng/mL)	Day 1	1.002	0.995	1.010	0.528
	Day 2	1.006	0.995	1.017	0.301
	Day 3	1.023	0.994	1.053	0.126
	Day 7	1.023	0.953	1.098	0.530
Procalcitonin (ng/mL)	Day 1	0.997	0.979	1.016	0.752
	Day 2	1.012	0.997	1.027	0.122
	Day 3	1.012	0.994	1.029	0.184
	Day 7	1.034	0.981	1.089	0.212
C-reactive protein (mg/L)	Day 1	1.003	0.999	1.007	0.127
	Day 2	1.009	1.004	1.014	< 0.001
	Day 3	1.005	1.000	1.010	0.061
	Day 7	1.020	0.996	1.044	0.102

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; CK-MB, creatine kinase Mb; CI, confidence interval.

90.05%], 83.70% [IQR 72.40%–90.50%], and 85.90% [IQR 80.13%–90.73%], respectively (Table 1).

3.3. Analysis of related OR value to predicting in-hospital mortality

Through constructing univariate logistic regression analyses, we found that NLR and NE% had larger odds of death, the odd ratio (OR) values of NLR on day 1, 2, 3 and 7 were 1.234 (95% CI 1.188–1.283; *p* < 0.001), 1.112 (95% CI 1.087–1.137; *p* < 0.001), 1.132 (95% CI 1.097–1.168; *p* < 0.001), 1.093 (95% CI 1.043–1.146; *p* < 0.001), respectively. The OR values of NE% on day 1, 2, 3 and 7 were 1.274 (95% CI 1.222–1.330; *p* < 0.001), 1.105 (95% CI 1.080–1.130; *p* < 0.001), 1.194 (95% CI 1.148–1.241; *p* < 0.001), and 1.076 (95% CI 1.029–1.125; *p* < 0.05). Therefore, both NLR and NE% were risk factors for in-hospital mortality of septic patients. Furthermore, the increased WBC, absolute neutrophil count and MLR, as well as the decreased platelets, absolute lymphocyte count, lymphocyte percentage and monocyte percentage could be used as risk factors for death in septic patients at day 1, 2 and 3 after hospitalization (all *p* < 0.001; Table 2).

3.4. Inflammation-related parameters and in-hospital mortality

In the univariate Cox proportional hazards model, day 1 to day 7 NLR, day 1 to day 3 MLR, and day 1 to day 3 NE% were associated with in-hospital mortality (Table 3).

ROC curves were calculated to investigate the predictive value of peripheral circulating inflammation-related parameters in septic patients on day 1 (Fig. 2A), day 2 (Fig. 2B), day 3 (Fig. 2C) and day 7 (Fig. 2D) after hospitalization. The ROC curve analyses revealed that the area under ROC curves (AUC) values for predicting in-hospital mortality were 0.880 for day 1 NLR (95% CI 0.816–0.943), 0.770 for day 2 NLR (95% CI 0.684–0.856), 0.784 for day 3 NLR (95% CI 0.700–0.868), 0.732 for day 5 NLR (95% CI 0.641–0.823), 0.852 for day 1 NE% (95% CI 0.780–0.924), 0.790 for day 2 NE% (95% CI 0.708–0.873), 0.777 for day 3 NE% (95% CI 0.691–0.862),

Table 3
Cox regression models to predict mortality.

Time	Parameters	Hazard ratio	95% CI		P value
			lower bound	upper bound	
Day 1	NLR	1.006	1.003	1.008	< 0.001
	PLR	1.000	1.000	1.001	0.330
	MLR	1.189	1.087	1.301	< 0.001
	Neutrophil (%)	1.129	1.102	1.156	< 0.001
Day 2	NLR	1.018	1.013	1.022	< 0.001
	PLR	1.000	0.999	1.001	0.451
	MLR	1.563	1.291	1.892	< 0.001
	Neutrophil (%)	1.006	1.004	1.009	< 0.001
Day 3	NLR	1.096	1.071	1.122	< 0.001
	PLR	1.000	0.998	1.001	0.526
	MLR	1.308	1.158	1.478	< 0.001
	Neutrophil (%)	1.096	1.071	1.122	< 0.001
Day 7	NLR	1.005	1.000	1.009	< 0.05
	PLR	1.000	0.999	1.001	0.496
	MLR	1.074	0.977	1.182	0.139
	Neutrophil (%)	1.020	0.989	1.051	0.213

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; CI, confidence interval.
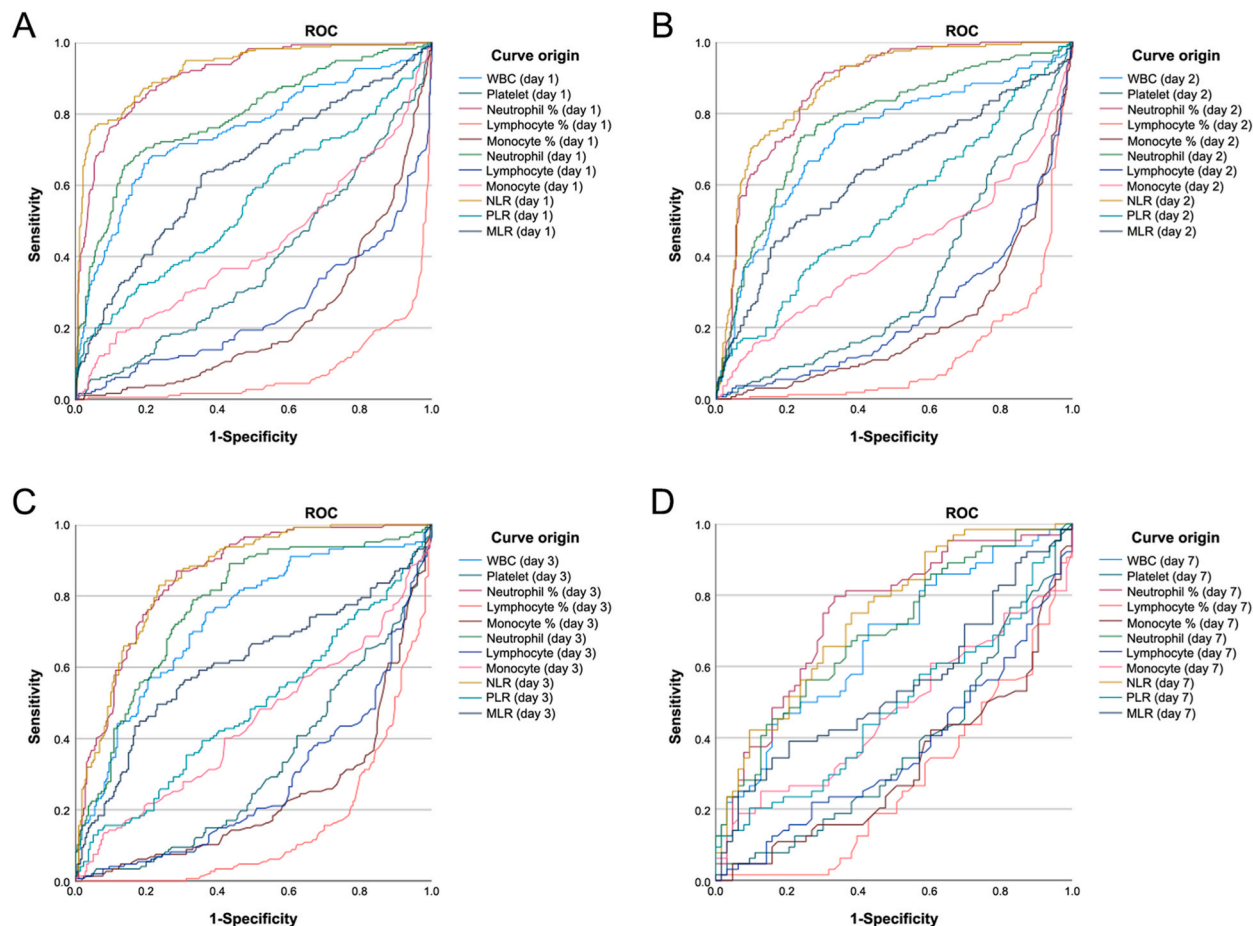
Fig. 2. The receiver operating characteristic (ROC) curve analysis of the studied biomarkers on day 1 (A), day 2 (B), day 3 (C) and day 7 (D) after hospitalization for predicting in-hospital mortality in septic patients.

and 0.741 for day 5 NE% (95% CI 0.648–0.833) (Table 4). The best clinical cut-off value, sensitivity and specificity for each parameter are shown in Table 4. The results showed that day 1 to day 7 NLR and NE% were promising parameters with good sensitivity, specificity values in septic patients.

Table 4
Comparison of the area under the receiver operator characteristic curves.

Parameters		AUC	Sensitive (%)	Specificity (%)	95% CI	Cut-off	P value
NLR	Day 1	0.880	0.828	0.804	0.816–0.943	10.769	< 0.001
	Day 2	0.770	0.615	0.907	0.684–0.856	17.544	< 0.001
	Day 3	0.784	0.707	0.821	0.700–0.868	14.395	< 0.001
	Day 7	0.732	0.741	0.625	0.641–0.823	9.105	< 0.001
PLR	Day 1	0.616	0.707	0.607	0.511–0.721	124.286	0.033
	Day 2	0.601	0.862	0.411	0.496–0.706	70.368	0.064
	Day 3	0.567	0.793	0.357	0.461–0.673	71.426	0.461
	Day 7	0.452	0.086	1.000	0.345–0.559	592.177	0.345
MLR	Day 1	0.659	0.610	0.667	0.557–0.761	0.572	0.004
	Day 2	0.576	0.464	0.759	0.467–0.685	0.806	0.171
	Day 3	0.576	0.643	0.593	0.468–0.685	0.573	0.167
	Day 7	0.531	0.232	1.000	0.422–0.640	1.181	0.574
Neutrophil (%)	Day 1	0.852	0.763	0.873	0.780–0.924	87.70%	< 0.001
	Day 2	0.790	0.508	0.945	0.708–0.873	90.69%	< 0.001
	Day 3	0.777	0.814	0.655	0.691–0.862	85.00%	< 0.001
	Day 7	0.741	0.797	0.691	0.648–0.833	83.93%	< 0.001

AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, Monocyte to lymphocyte ratio; CI, confidence interval.

4. Discussion

Sepsis manifests as a dysregulated immune response to infection (documented or suspected), leading to organ dysfunction. Timely assessment for patients with potentially poor prognosis could warn clinicians about the ongoing pathological process early and to give appropriate care and treatment in time, such as providing intensive care (treatment and monitoring) or referral to another hospital, which could optimize the allocation of limited health care resources. The host response biomarkers play a key role in the early diagnosis, early risk stratification, and early intervention [27]. Such as serum Butyrylcholinesterase (BChE), a widely available, low-cost biomarker, its levels have been linked to the inflammatory response [28], with lower levels often observed in septic patients. BChE may serve as a potential biomarker for assessing inflammation and liver dysfunction, and it could have implications for drug metabolism during sepsis treatment [29,30]. Nevertheless NLR is a cheaper, simpler, rapider and more easily available inflammation-related parameter.

Whether NLR is a valid predictor of poor prognosis in sepsis remains controversy [31]. A retrospective study in 2019 showed no significant association of NLR at admission of emergency department with 28-day mortality in sepsis [14]. The cut-off value of NLR for prediction also various in different studies (Supplementary Table 1). However, several reviews have mentioned the association of a NLR with mortality in sepsis [11,27,32]. It has been proposed that dynamic monitoring of NLR should be done daily to observe its dynamic changes in critical illness [11]. Moreover, he suggested that dramatic increasing of NLR values above 11 indicates continued deterioration of the condition, whereas improving the clinical course of sepsis, lower risk of mortality are associated with decline of NLR values below 7 [11]. Therefore, the dynamic changes of NLR in early sepsis reflecting the intensity of immune-inflammatory reaction are very important. As far as we know, our present study is the first to analyze the predictive value of NLR in in-hospital mortality of septic patients on the first three consecutive days and the seventh day after hospitalization. In our analyses at four time points, we found that NLR could be used as a risk factor for in-hospital mortality in septic patients with high sensitivity and specificity, and its cut-off values were 10.769 on day 1, 17.5435 on day 2, 14.3954 on day 3, and 9.1047 on day 7 after hospitalization.

In addition to NLR, PLR and MLR have been reported to be associated with sepsis mortality [33,34]. However, in our analysis, PLR or MLR at hospitalization is less reliable than NLR or NE% in predicting in-hospital mortality, which is consistent with the findings of Djordjevic et al., in 2018 [35]. Additionally, we found that NE% was also highly correlated with the in-hospital mortality of sepsis. The AUC values were 0.852, 0.790, 0.777 and 0.741, and the cut off values were 87.70, 90.69, 85.00 and 83.93 on day 1, 2, 3 and 7 after hospitalization, respectively. In our univariate Cox proportional hazards model, we did not find a correlation between NE% on day 7 and in-hospital mortality. We speculated that it might be related to the massive missing data on day 7, or it might be related to the fact that the late stage of sepsis was mainly characterized by severe immunosuppression rather than excessive inflammatory response.

In the early stage of sepsis, a large number of immune cells are activated, including neutrophils, monocytes, natural killer cells, dendritic cells and lymphocytes [36]. In the early stage of sepsis, the number of neutrophils increases rapidly owing to delayed neutrophil apoptosis [36]. Increased circulating neutrophils lead to a dysregulated immune response by releasing inflammatory cytokines and reactive oxygen species at sites distal to the infectious site, contributing to multiple organ failure. As for lymphocyte, it is also actively involved in the immune response in the early stage of sepsis, but the number of lymphocytes is far lower than that of neutrophils, accounting for 20–40% of the WBC in the blood. Uncontrolled apoptosis of T lymphocytes-induced decrease in the absolute counts is critical in the pathogenesis of sepsis [37,38]. NLR has been shown to be capable of reflecting the intensity of critical immune-inflammatory reaction [11]. In addition, evidence has shown that dynamic changes of NLR precede the clinical status for several hours and may warn early recognition and timely intervention targeting the ongoing pathological process [11]. With the continuous clinical improvement of sepsis, the decreased neutrophils and the increased lymphocytes in the peripheral blood could cause NLR decrease continuously [11,39].

Our study has some limitations. First, this is a retrospective, single-center study, which cannot predict future events and may have some inherent biases. Second, NLR data were missing to a certain extent on the second, third and seventh day after hospitalization, especially on the seventh day after hospitalization, this might have led to some decrease in the accuracy of our analysis. Therefore, large scale, prospective, multicenter and high-quality clinical studies that continuously monitor the dynamic changes of NLR at an early stage of sepsis are needed to be conducted to further clarify the role of NLR in early prediction of the clinical prognosis of sepsis.

5. Conclusion

Among inflammation-related parameters, the most effective biomarkers for the early prediction of in-hospital mortality of septic patients among inflammation-related parameters were NLR and NE% on the first three consecutive days and the seventh day after hospitalization, which may be relevant for the management of septic patients. NLR at admission is a convenient and inexpensive blood routine index, we recommend the NLR of 10.769 and NE% of 87.7% or greater on the first day of admission as a warning indicators of high mortality in septic patients, and the persistent increase in NLR and NE% may represent the deterioration of sepsis. However, the combination of a biomarker panel with clinical information may be particularly useful in the early prediction of the prognosis of septic patients.

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CRediT authorship contribution statement

Xiaoyue Wen: Writing – original draft, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yujing Zhang:** Software, Formal analysis, Conceptualization. **Jiaxin Xu:** Investigation. **Chaoying Song:** Software, Investigation, Formal analysis. **You Shang:** Supervision, Resources. **Shiying Yuan:** Supervision, Resources, Funding acquisition, Conceptualization. **Jiancheng Zhang:** Writing – review & editing, Supervision, Resources, Funding acquisition, Formal analysis, Conceptualization.

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.e26563.

References

[1] M. Huang, S. Cai, J. Su, The pathogenesis of sepsis and potential therapeutic targets, Int. J. Mol. Sci. 20 (21) (2019), https://doi.org/10.3390/ijms20215376.

[2] F. Mulita, E. Liolis, K. Akinosoglou, L. Tchabashvili, I. Maroulis, C. Kaplanis, et al., Postoperative sepsis after colorectal surgery: a prospective single-center observational study and review of the literature, Przegląd Gastroenterol. 17 (1) (2022) 47–51, https://doi.org/10.5114/pg.2021.106083.

[3] A.M. Taeb, M.H. Hooper, P.E. Marik, Sepsis: current definition, pathophysiology, diagnosis, and management, Nutr. Clin. Pract. 32 (3) (2017) 296–308, https://doi.org/10.1177/0884533617695243.

[4] P. Póvoa, L. Coelho, F. Dal-Pizzol, R. Ferrer, A. Huttner, A. Conway Morris, et al., How to use biomarkers of infection or sepsis at the bedside: guide to clinicians, Intensive Care Med. 49 (2) (2023) 142–153, https://doi.org/10.1007/s00134-022-06956-y.

[5] M. Capone, D. Giannarelli, D. Mallardo, G. Madonna, L. Festino, A.M. Grimaldi, et al., Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab, J Immunother Cancer 6 (1) (2018) 74, https://doi.org/10.1186/s40425-018-0383-1.

[6] P. Li, H. Li, S. Ding, J. Zhou, P.L.R. Nlr, LMR and MWR as diagnostic and prognostic markers for laryngeal carcinoma, Am J Transl Res 14 (5) (2022) 3017–3027.

[7] J. Liu, W. Ao, J. Zhou, P. Luo, Q. Wang, D. Xiang, The correlation between PLR-NLR and prognosis in acute myocardial infarction, Am J Transl Res 13 (5) (2021) 4892–4899.

[8] J. Ji, J. Fan, Neutrophil in reverse migration: role in sepsis, Front. Immunol. 12 (2021) 656039, https://doi.org/10.3389/fimmu.2021.656039.

[9] M.G. Manz, S. Boettcher, Emergency granulopoiesis, Nat. Rev. Immunol. 14 (5) (2014) 302–314, https://doi.org/10.1038/nri3660.

[10] J.J. Grailer, F. Fattahi, R.S. Dick, F.S. Zetoune, P.A. Ward, Cutting edge: critical role for c5ars in the development of septic lymphopenia in mice, J. Immunol. 194 (3) (2015) 868–872, https://doi.org/10.4049/jimmunol.1401193.

[11] R. Zahorec, Neutrophil-to-lymphocyte ratio, past, present and future perspectives, Bratisl. Lek. Listy 122 (7) (2021) 474–488, https://doi.org/10.4149/BLL_2021_078.

[12] F.U. Rehman, A. Khan, A. Aziz, M. Iqbal, S. Mahmood, N. Ali, Neutrophils to lymphocyte ratio: earliest and efficacious markers of sepsis, Cureus 12 (10) (2020) e10851, https://doi.org/10.7759/cureus.10851.

[13] E.C. Martins, L. Silveira, K. Viegas, A.D. Beck, J.G. Fioravantti, R.V. Cremonese, et al., Neutrophil-lymphocyte ratio in the early diagnosis of sepsis in an intensive care unit: a case-control study, Rev Bras Ter Intensiva 31 (1) (2019) 64–70, https://doi.org/10.5935/0103-507X.20190010.

[14] J. Ni, H. Wang, Y. Li, Y. Shu, Y. Liu, Neutrophil to lymphocyte ratio (nlr) as a prognostic marker for in-hospital mortality of patients with sepsis: a secondary analysis based on a single-center, retrospective, cohort study, Medicine (Baltim.) 98 (46) (2019) e18029, https://doi.org/10.1097/MD.0000000000018029.

[15] C.D. Russell, A. Parajuli, H.J. Gale, N.S. Bulteel, P. Schuetz, C. de Jager, et al., The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: a systematic review and meta-analysis, J. Infect. 78 (5) (2019) 339–348, https://doi.org/10.1016/j.jinf.2019.02.006.

[16] Z. Huang, Z. Fu, W. Huang, K. Huang, Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: a meta-analysis, Am. J. Emerg. Med. 38 (3) (2020) 641–647, https://doi.org/10.1016/j.ajem.2019.10.023.

[17] A. Kriplani, S. Pandit, A. Chawla, J. de la Rosette, P. Laguna, R.S. Jayadeva, et al., Neutrophil-lymphocyte ratio (nlr), platelet-lymphocyte ratio (plr) and lymphocyte-monocyte ratio (lmr) in predicting systemic inflammatory response syndrome (sirs) and sepsis after percutaneous nephrolithotomy (pnl), Urolithiasis 50 (3) (2022) 341–348, https://doi.org/10.1007/s00240-022-01319-0.

[18] Y. Liu, J. Zheng, D. Zhang, L. Jing, Neutrophil-lymphocyte ratio and plasma lactate predict 28-day mortality in patients with sepsis, J. Clin. Lab. Anal. 33 (7) (2019) e22942, https://doi.org/10.1002/jcla.22942.

[19] R.B. Chebl, M. Assaf, N. Kattouf, S. Haidar, M. Khamis, K. Abdeldaem, et al., The association between the neutrophil to lymphocyte ratio and in-hospital mortality among sepsis patients: a prospective study, Medicine (Baltim.) 101 (30) (2022) e29343, https://doi.org/10.1097/MD.0000000000029343.

[20] K. Westerdijk, K.S. Simons, M. Zegers, P.C. Wever, P. Pickkers, C. de Jager, The value of the neutrophil-lymphocyte count ratio in the diagnosis of sepsis in patients admitted to the intensive care unit: a retrospective cohort study, PLoS One 14 (2) (2019) e0212861, https://doi.org/10.1371/journal.pone.0212861.

[21] T. Zhou, N. Zheng, X. Li, D. Zhu, Y. Han, Prognostic value of neutrophil- lymphocyte count ratio (nlcr) among adult icu patients in comparison to Apache ii score and conventional inflammatory markers: a multi center retrospective cohort study, BMC Emerg. Med. 21 (1) (2021) 24, https://doi.org/10.1186/s12873-021-00418-2.

[22] E. Can, S. Hamilcikan, C. Can, The value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio for detecting early-onset neonatal sepsis, J. Pediatr. Hematol. Oncol. 40 (4) (2018) e229–e232, https://doi.org/10.1097/MPH.0000000000001059.

[23] T. Tian, B. Wei, J. Wang, Study of c-reactive protein, procalcitonin, and immunocyte ratios in 194 patients with sepsis, BMC Emerg. Med. 21 (1) (2021) 81, https://doi.org/10.1186/s12873-021-00477-5.

[24] M.S. Meshaal, A. Nagi, A. Eldamaty, W. Elnaggar, M. Gaber, H. Rizk, Neutrophil-to-lymphocyte ratio (nlr) and platelet-to-lymphocyte ratio (plr) as independent predictors of outcome in infective endocarditis (ie), Egypt Heart J 71 (1) (2019) 13, https://doi.org/10.1186/s43044-019-0014-2.

[25] R.P. Dellinger, M.M. Levy, A. Rhodes, D. Annane, H. Gerlach, S.M. Opal, et al., Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012, Intensive Care Med. 39 (2) (2013) 165–228, https://doi.org/10.1007/s00134-012-2769-8.

[26] M. Singer, C.S. Deutschman, C.W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, et al., The third international consensus definitions for sepsis and septic shock (sepsis-3), JAMA 315 (8) (2016) 801–810, https://doi.org/10.1001/jama.2016.0287.

[27] T. Barichello, J.S. Generoso, M. Singer, F. Dal-Pizzol, Biomarkers for sepsis: more than just fever and leukocytosis-a narrative review, Crit. Care 26 (1) (2022) 14, https://doi.org/10.1186/s13054-021-03862-5.

[28] G.-I. Verras, F. Mulita, K. Bouchagier, V.-D. Dafnomili, G. Skroubis, I. Perdikaris, et al., Development of a predictive model for surgical site infections in colorectal patients based on butyrylcholinesterase plasma levels, Eur. J. Surg. Oncol. 49 (1) (2023) e15, https://doi.org/10.1016/j.ejso.2022.11.082.

[29] F. Mulita, G.-I. Verras, K. Bouchagier, V.-D. Dafnomili, I. Perdikaris, P. Perdikaris, et al., Butyrylcholinesterase levels as a predictive factor of septic complications development in the postoperative period of colorectal patients: univariate analysis and predictive modeling, Eur. J. Surg. Oncol. 49 (1) (2023) e15, https://doi.org/10.1016/j.ejso.2022.11.083.

[30] A.R. Zivkovic, K.M. Tourelle, T. Brenner, M.A. Weigand, S. Hofer, K. Schmidt, Reduced serum cholinesterase activity indicates splenic modulation of the sterile inflammation, J. Surg. Res. 220 (2017) 275–283, https://doi.org/10.1016/j.jss.2017.07.024.

[31] J.D. Salciccioli, D.C. Marshall, M.A. Pimentel, M.D. Santos, T. Pollard, L.A. Celi, et al., The association between the neutrophil-to-lymphocyte ratio and mortality in critical illness: an observational cohort study, Crit. Care 19 (1) (2015) 13, https://doi.org/10.1186/s13054-014-0731-6.

[32] A. Buonacera, B. Stancanelli, M. Colaci, L. Malatino, Neutrophil to lymphocyte ratio: an emerging marker of the relationships between the immune system and diseases, Int. J. Mol. Sci. 23 (7) (2022), https://doi.org/10.3390/ijms23073636.

[33] S. Mangalesh, S. Dudani, A. Malik, The systemic immune-inflammation index in predicting sepsis mortality, Postgrad. Med. 135 (4) (2023) 345–351, https://doi.org/10.1080/00325481.2022.2140535.

[34] S.K. Hou, H.A. Lin, S.C. Chen, C.F. Lin, S.F. Lin, Monocyte distribution width, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio improves early prediction for sepsis at the emergency, J. Personalized Med. 11 (8) (2021), https://doi.org/10.3390/jpm11080732.

[35] D. Djordjevic, G. Rondovic, M. Surbatovic, I. Stanojevic, I. Udovicic, T. Andjelic, et al., Neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume-to-platelet count ratio as biomarkers in critically ill and injured patients: which ratio to choose to predict outcome and nature of bacteremia? Mediat. Inflamm. 2018 (2018) 3758068 https://doi.org/10.1155/2018/3758068.

[36] C. Cao, M. Yu, Y. Chai, Pathological alteration and therapeutic implications of sepsis-induced immune cell apoptosis, Cell Death Dis. 10 (10) (2019) 782, https://doi.org/10.1038/s41419-019-2015-1.

[37] T. Rimmele, D. Payen, V. Cantaluppi, J. Marshall, H. Gomez, A. Gomez, et al., Immune cell phenotype and function in sepsis, Shock 45 (3) (2016) 282–291, https://doi.org/10.1097/SHK.0000000000000495.

[38] F. Venet, G. Monneret, Advances in the understanding and treatment of sepsis-induced immunosuppression, Nat. Rev. Nephrol. 14 (2) (2018) 121–137, https://doi.org/10.1038/nrneph.2017.165.

[39] J. Zhang, D. Xu, B. Xie, Y. Zhang, H. Huang, H. Liu, et al., Poor-sleep is associated with slow recovery from lymphopenia and an increased need for icu care in hospitalized patients with covid-19: a retrospective cohort study, Brain Behav. Immun. 88 (2020) 50–58, https://doi.org/10.1016/j.bbi.2020.05.075.