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Emerging Problems in Infectious Diseases

Diagnostic and prognostic values of immunocyte ratios in patients with sepsis in the intensive care unit

Dan Wu[1], Haidong Qin[1]

[1] *Department of Emergency Medicine, Nanjing First Hospital, Nanjing Medical University, Nanjing 200001, China*

Abstract

Introduction: The aim of this study was to evaluate the diagnostic and prognostic values of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelet-to-neutrophil ratio (PNR), monocyte-to-lymphocyte ratio (MLR), neutrophils-to-lymphocytes and platelets ratio (N/LPR), mean platelet volume-to-platelet count ratio (MPV/PC), red blood cell distribution width-to-platelet count ratio (RDW/PC), and platelet volume distribution width-to-platelet count ratio (PDW/PC) in patients with sepsis.

Methodology: A total of 203 patients with sepsis admitted to an emergent intensive care unit (EICU) were enrolled in this retrospective study. Basic data, inflammatory factors, NLR, PLR, PNR, MLR, N/LPR, MPV/PC, RDW/PC, PDW/PC were compared between survival and non-survival groups. Receiver operating characteristic (ROC) curve was used to assess the diagnostic values. The univariate and multivariate regression analyses were used for constructing a prognostic model for sepsis.

Results: There were significant differences in acute physiology and chronic health evaluation (APACHEII) score, mechanical ventilation, use of vasopressors, acute kidney injury (AKI), continuous renal replacement therapy (CRRT), long-term antiplatelet drug use, lymphocyte, monocyte, hemoglobin, procalcitonin (PCT), interleukin-6 (IL-6), C-reactive protein (CRP)*PCT, and N/LPR. APACHE II had the highest diagnostic value [Area Under Curve (AUC) = 0.999], followed by CRP*PCT (AUC = 0.718). The prognoses were different between patients stratified according to CRP, IL-6, lactic acid (Lac), PNR, PLR, PDW/PC, and APACHEII. Lac, CRP*PCT, PDW/PC, MPV/PC and APACHE II were independent prognostic factors of sepsis.

Conclusions: Both N/LPR and CRP*PCT had high values to predict mortality in sepsis patients. CRP*PCT, PDW/PC and MPV/PC were independent factors to predict the prognosis of sepsis.

Key words: sepsis, immunocyte, diagnosis, prognosis, ICU.

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Introduction

Sepsis, caused by a dysregulated host response to infection, has substantially high morbidity (about 19 million annual severe sepsis cases occur) and mortality (16.7-33.3%) worldwide [1,2]. Early diagnosis and treatment are critical for the outcome of sepsis [3]. Currently, numerous biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) are being used for diagnosing sepsis [4]. However, despite its high specificity in detecting bacterial infection, PCT is expensive and time-consuming, which limits its wide use [5]. CRP is used to detect acute infection, but its specificity is relatively low, especially for non-infectious diseases, such as acute myocardial infarction, surgical trauma, malignant tumors, and rheumatic immune diseases [6]. Ratios between blood cells have been used to diagnose sepsis, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), neutrophils-to-lymphocytes and platelets ratio (N/LP), and mean platelet volume-to-platelet count ratio (MPV/PC) [7-8]. However, NLR, PLR, MLR, N/LP and MPV/PC have achieved conflicting results [9]. Therefore, we designed this prospective observational study to assess the prognostic values of NLR, PLR, MLR and MPV/PC ratios as well as platelet-to-neutrophil ratio (PNR), red blood cell distribution width-to-platelet count ratio (RDW/PC) and platelet volume distribution width-to-platelet count ratio (PDW/PC) in predicting the outcome of critical sepsis.

Methodology

Patient selection and study design

A total of 203 patients suspected of sepsis or septic shock admitted to the emergent intensive care unit (EICU) in Nanjing First Hospital were enrolled from January 1, 2019 to December 31, 2021. Inclusion criteria were: (1) age ≥ 18 years; (2) diagnosed by the third international consensus definitions for sepsis and septic shock 2016 (Sepsis 3.0) [10] and the sequential

organ failure assessment (SOFA) score ≥ 2. Exclusion criteria were: (1) pregnancy and lactation; (2) intensive care unit (ICU) length of stay (LOS) < 72 h and incomplete clinical data; (3) chronic kidney diseases (CKD) under renal replacement therapy, or hematological diseases. This study was approved by the Ethics Committee of Nanjing Hospital affiliated to Nanjing Medical University (approval number: KY20201102-03). Due to the retrospective and non-interventional nature of the study, the requirement for informed consent was waived by the Ethical Committee. All the patients were categorized into survival and non-survival groups. Outcomes were measured within 28 days after admission.

Data collection

Baseline variables were analyzed: demographic information (gender, age); time from onset to admission; comorbidities (cardiovascular disease [CVD], diabetes mellitus, hypertension, chronic obstructive pulmonary disease [COPD], cerebral infarction, autoimmune rheumatic disease, malignancy); disease severity according to the SOFA at admission and the acute physiology and chronic health evaluation (APACHE II) as determined by the worst variables throughout the first 24 h after ICU admission; mechanical ventilation, vasopressor use and renal replacement therapy; laboratory indexes at admission: partial arterial oxygen pressure (PaO_2) / fraction of inspired oxygen (FiO_2) (P/F), lactic acid (Lac), triiodothyronine (T3), tetraiodothyronine (T4), thyroid stimulating hormone (TSH), albumin (Alb), blood urea (BUN), creatinine (Cr), blood glucose (Glu), N-terminal pro brain natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP), D-dimer (D-D); and use of antiplatelet agents.

Blood sampling and analysis

2 mL blood was collected into an EDTA-K2 tube from each patient at admission, and sent for laboratory testing within 2 hours. If the testing could not be performed immediately, the samples were stored at -20 °C. A complete blood count (CBC) was determined by the BC-5390 automatic blood cell analyzer (Mindray, Shenzhen, China), including white blood cells, neutrophils, lymphocytes, monocytes, hemoglobin and platelets. Mean platelet volume (MPV) was measured for platelet volume histogram, red blood cell distribution width (RDW) for red blood cell volume, and platelet volume distribution width (PDW) for platelet volume. Ratios between immunocytes were calculated, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-neutrophil ratio (PNR), neutrophils-to-lymphocytes and platelets ratio (N/LP), mean platelet volume-to-platelet count ratio (MPV/PC), red blood cell distribution width-to-platelet count ratio (RDW/PC) and platelet volume distribution width-to-platelet count ratio (PDW/PC).

$$\frac{N}{LPR} = (NEU * 10^9 * 100)/(LYM * 10^9 * PLT * 10^9)$$

CRP was measured by the turbidimetric method with a reference range from 0 to 10 mg/L. The expression levels of PCT and interleukin-6 (IL-6) were measured by fluorescence immunochromatography using Vazyme automatic fluorescence immunoassay analyzer (Vazyme, Nanjing, China), with reference ranges < 0.1 ng/mL and < 0.007 ng/mL, respectively. PaO_2 and lactate were obtained from GEM-3500 automatic arterial blood gas analyzer (IL, Texas, USA). T3, T4, TSH were measured using Abbott i2000SR automatic chemiluminescence analyzer (Abbott, Chicago, USA).

Alb, BUN, Cr, and Glu were measured using Au5821 automatic biochemical analyzer (Beckman, Pasadena, USA). NT-proBNP was measured by NT-proBNP II STAT detection kit using a Cobase 601 electrochemical luminescence automatic immunoanalyzer (Roche, Basel, Switzerland), with a reference range of < 148 pg/mL. D-D was measured using Sysmex's CS-2000i automatic blood coagulation analyzer (Sysmex, Kobe, Japan). Blood specimens were collected in BACTEC bottles containing anaerobic or aerobic broth and resins before antibiotics administration. Blood culture bottles were incubated in Bact/Alert 3D 120 automatic blood culture instrument (Meylan, Grenoble, France) for a maximum of 5 days or until they were positive.

Statistical methods

Data were analyzed using statistical software SPSS 25.0 (IBM). Normally distributed data were expressed in mean ± standard deviation, and non-normally distributed data were presented in median and interquartile range. A Student's t-test was performed to compare data between two groups, and an ANOVA or Kruskal-Wallis test for data among multiple groups. Numerical data were tested using the Chi-square test. The relationship between two variables was established using Spearman correlation analysis. The Receiver operating characteristic (ROC) curve was drawn to analyze sensitivity, specificity, cut-off values, the Youden index and the area under the ROC curve. A cut-off value was defined as that with the strongest

discriminative ability. The Kaplan-Meier was used for estimating survival. The univariate and multivariate regression analyses were carried out to analyze the diagnostic values of indicators in survival and non-survival groups. Statistical significance was defined as $p < 0.05$.

Results

Baseline data

A total of 203 patients with sepsis were enrolled (116 males [57.14%], mean age 72.23 ± 15.71 years). No difference was observed in the incidences of underlying diseases between survival and non-survival groups: hypertension (52.14% vs. 56.98%, $p = 0.494$), heart disease (33.33% vs. 44.18%, $p = 0.115$), diabetes (41.17% vs. 31.39%, $p = 0.199$), cancer (16.24% vs. 20.93%, $p = 0.001$), nervous system disease (35.89% vs. 39.53%, $p = 0.597$), lung disease (1.71% vs. 6.98%, $p = 0.001$). Among the patients, 86 died during the 28 days after admission, with a mortality rate of 42.36%. There was no difference in mortality between male and female patients ($p = 0.563$). Non-survivors were older (77.15 ± 12.70 vs 69.26 ± 16.25) ($p < 0.001$). The mean LOS in ICU was 8.80 ± 7.97 days in all patients, 7.73 ± 5.52 days in the survival group and 11.01 ± 6.81 days in the non-survival group, without difference between the two groups ($p = 0.439$).

The sepsis was caused by abdominal infection (92/203, 45.32%, including biliary tract infection, liver abscess, intestinal infection and abdominal postoperative, etc.), lung infection (91/203, 44.83%), urinary tract infection (54/203, 26.60%), skin soft-tissue infection (8/203, 3.94%), and bloodstream infection of unknown origin (4/203, 1.97%). The non-survival group demonstrated higher incidences of abdominal infection ($p < 0.001$) and lung infection ($p = 0.003$) than the survival group. The percentages of patients receiving mechanical ventilation, vasopressors, acute kidney injury (AKI) and continuous renal replacement therapy (CRRT) for AKI, long-term antiplatelet drugs (including aspirin, clopidogrel, etc.) (41.89% vs 97.67%, $p < 0.001$; 76.92% vs 98.84%, $p <$

Table 1. Patients' baseline characteristics.

Characteristics	All patients	Survival group	No-survival group	*p* value
Number of patients (%)	203 (100%)	117 (57.64%)	86 (42.36%)	
Male gender, n (%)	116 (57.14%)	66 (56.41%)	52 (60.47%)	0.563
Age (years)	72.23 ± 15.71	69.26 ± 16.25	77.15 ± 12.70	< 0.001*
Underlying diseases, n (%)				
Hypertension	110 (54.19%)	61 (52.14%)	49 (56.98%)	0.494
Heart disease	77 (37.93%)	39 (33.33%)	38 (44.18%)	0.115
Diabetes	74 (36.45%)	47 (41.17%)	27 (31.39%)	0.199
Cancer	37 (18.23%)	19 (16.24%)	18 (20.93%)	0.001*
Nerve system disease	76 (37.44%)	42 (35.89%)	34 (39.53%)	0.597
Lung disease	8 (3.94%)	2 (1.71%)	6 (6.98%)	0.001*
Infection source, n (%)				
Abdominal	92 (45.32%)	33 (28.21%)	59 (68.60%)	< 0.001*
Lung	91 (44.83%)	42 (35.90%)	49 (56.98%)	0.003*
Urinary tract	54 (26.60%)	29 (24.79%)	25 (29.07%)	0.495
Skin soft-tissue	8 (3.94%)	4 (3.42%)	4 (4.65%)	0.656
Unknown	4 (1.97%)	2 (1.71%)	2 (2.33%)	0.755
Blood culture number (%)				
Gram-positive pathogens	17 (8.37%)	8 (6.83%)	9 (10.46%)	0.357
Gram-negative pathogens	90 (44.33%)	41(35.04%)	49 (56.98%)	0.002*
Polymicrobial	6 (2.95%)	2 (1.71%)	4 (4.65%)	0.221
Fungal	3 (1.48%)	1 (0.08%)	2 (2.32%)	0.391
Negative	87 (42.86%)	65 (55.56%)	22 (25.58%)	< 0.001*
APACHE II	28.04 ± 8.39	26.08 ± 7.83	30.72 ± 8.44	< 0.001*
SOFA	10.35 ± 2.63	9.80 ± 2.51	11.08 ± 2.64	0.552
Mechanical ventilation, n (%)	133 (65.52%)	49 (41.89%)	84 (97.67%)	< 0.001*
Vasopressors, n (%)	175 (86.31%)	90 (76.92%)	85 (98.84%)	< 0.001*
AKI, n (%)	133 (65.52%)	62 (52.99%)	71(82.56%)	< 0.001*
CRRT, n (%)	37 (27.8%)	13 (11.11%)	24 (27.91%)	0.002*
Antiplatelet drugs, n (%)	89 (43.84%)	69 (58.97%)	20 (23.25%)	0.01*
LOS in ICU (days)	8.80 ± 7.97	7.73 ± 5.52	11.01 ± 6.81	0.439
28-day mortality, n (%)	86 (42.64%)			

Data are shown as number (%), mean (standard deviation, SD). Significant differences are marked by ∗ ($p < 0$ 05) and in bold. APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; AKI: acute kidney injury; CRRT: continuous renal replacement therapy; LOS in ICU: length of stay in intensive care unit.

0.001; 52.99% vs 82.56%, $p < 0.001$; 11.11% vs 27.91%, $p = 0.002$; 58.97% vs 23.25%, $p = 0.01$, respectively) were different between groups.

Laboratory testing showed higher incidences of Gram-negative culture in the non-survival group (35.04% vs 56.98%, $p = 0.002$) and negative blood culture in the survival group (55.56% vs 25.58%, $p < 0.001$). However, there were no significant differences in Gram-positive culture, polymicrobial culture and fungal culture between the two groups. APACHE II and SOFA scores were lower in the survival group than in the non-survival group (26.08 ± 7.83 vs 30.72 ± 8.44, $p < 0.001$; 9.80 ± 2.51 vs 11.08 ± 2.64, $p = 0.552$) (Table 1).

Laboratory blood indexes and inflammatory biomarkers

The survival group showed higher P/F, T3, T4, Alb, but lower Lac, BUN, Cr, NT-proBNP, BNP, D-D levels than the non-survival group (all $p < 0.05$); while the levels of TSH and Glu were not statistically different between the two groups. The survival group showed lower PCT, IL-6 and CRP*PCT than the non-survival group. CRP was not statistically different between the two groups. The detailed results are shown in Table 2.

Diagnostic values of routine blood indexes

Lymphocyte, monocyte, and hemoglobin counts were significantly higher in the survival group ($p = 0.045$, 0.003, and 0.001, respectively), while leukocyte,

Table 2. Laboratory blood indexes and inflammatory indicators in two groups.

Characteristics	Survival (n = 117)	Non-survival (n = 86)	*p* value
P/F	250.0 (190.5,332.5)	160.0 (100.0, 256.25)	< 0.001*
Lac (mmol/L)	3.37 ± 2.64	5.93 ± 4.89	< 0.001*
T3 (nmol/L)	0.63 ± 0.13	0.59 ± 0.10	0.011*
T4 (nmol/L)	67.70 ± 19.46	54.17 ± 16.23	< 0.001*
TSH (m IU/L)	1.05 ± 1.26	0.98 ± 1.04	0.665
Alb (g/L)	29.07 ± 4.48	27.00 ± 4.91	0.003*
BUN (mmol/L)	10.38 (6.82, 16.89)	15.78 (10.74, 21.88)	< 0.001*
Cr (umol/L)	121.7 (75.35, 223.65)	197.85 (110.93, 319.00)	< 0.001*
Glu (mmol/L)	7.66 (6.16, 10.22)	7.65 (5.19, 11.02)	0.394
NT-proBNP (pg/ml)	2724.00 (908.55, 8268.20)	8917.50 (1783.25, 17383.75)	< 0.001*
BNP (pg/ml)	230.00 (110.00, 799.50)	795.50 (230.00, 2300.00)	< 0.001*
D-D (ug/ml)	4.42 (1.75, 8.84)	5.77 (3.13, 11.80)	0.02*
CRP (mg/L)	112.00 (64.44, 156.59)	114.55 (85.94, 182.54)	0.262
PCT (ng/ml)	17.26 (3.14, 44.28)	30.29 (13.27, 65.23)	0.002*
CRP*PCT $(mg/L)^2$	1.72 (0.19, 4.67)	3.95 (1.57, 9.81)	< 0.001*
IL-6 (ng/ml)	0.31 (0.10, 1.23)	0.92 (0.17, 3.90)	0.006*

Data are shown as mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate. Significant differences are marked by ∗($p < 0$ 05) and in bold. P/F: partial arterial oxygen pressure (PaO2)/fraction of inspired oxygen (FiO2); Lac: lactic acid; T3: triiodothyronine; T4: tetraiodothyronine; TSH: thyroid stimulating hormone; Alb: albumin; BUN: blood urea; Cr: creatinine; Glu: blood glucose; NT-proBNP: N-terminal pro brain natriuretic peptide; BNP: brain natriuretic peptide; D-D: D-dimer; CRP: C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6.

Table 3. Indexes of routine blood test.

Indexes	Survival (n = 117)	Non-survival (n = 86)	*p* value
WBC (10^9 /L)	14.84 (10.57, 20.54)	13.09 (8.01, 19.03)	0.057
N (10^9/L)	13.04 (9.37, 18.64)	11.70 (7.02, 17.75)	0.076
L (10^9 /L)	0.68 (0.47, 0.93)	0.56 (0.32, 0.83)	0.045*
M (10^9 /L)	0.60 (0.30,0.92)	0.43 (0.21, 0.71)	0.003*
Hb (g/L)	115.36 ± 21.61	104.50 ± 25.85	0.001*
PLT (10^9 /L)	139.00 (79.50, 211.50)	119.00 (64.75, 220.50)	0.376
NLR	20.69 (12.04, 32.55)	18.59 (11.00, 36.17)	0.930
PLR	205.36 (113.15, 384.66)	222.85 (117.82, 499.09)	0.467
PNR	10.82 (6.72, 17.33)	10.17 (5.16, 21.38)	0.786
MLR	0.78 (0.47, 1.36)	0.65 (0.42, 1.18)	0.138
N/LPR	12.74 (6.33, 30.32)	15.51 (8.86, 57.81)	0.027*
PDW/PC	0.11(0.07, 0.19)	0.14 (0.07, 0.25)	0.134
RDW/PC	0.10 (0.07, 0.17)	0.12 (0.05, 0.18)	0.113
MPV/PC (fl 10^{-9} L)	0.08 (0.05, 0.14)	0.09 (0.05, 0.14)	0.332

Data are shown as mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate. Significant differences are marked by ∗ ($p < 0$ 05) and in bold. WBC: white blood cell; N: neutrophil; L: lymphocyte; M: monocyte; Hb: hemoglobin; PLT: platelet; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNR: platelet-to-neutrophil ratio; MLR: monocyte-to-lymphocyte ratio; N/LPR: neutrophils-to-lymphocytes and platelets ratio; PDW/PC: platelet volume distribution width-to-platelet count ratio; RDW/PC: red blood cell distribution width-to-platelet count ratio; MPV/PC: mean platelet volume-to-platelet count ratio.

neutrophil, and platelet counts did not differ significantly between groups. The N/LPR in the non-survival group was significantly higher in the survival group (p = 0.027), while NLR, PLR, PNR and MLR values did not differ significantly between groups. The PDW/PC, RDW/PC and MPV/PC ratios were not statistically different between groups (p = 0.134, 0.113, 0.332 respectively). The detailed results are shown in Table 3.

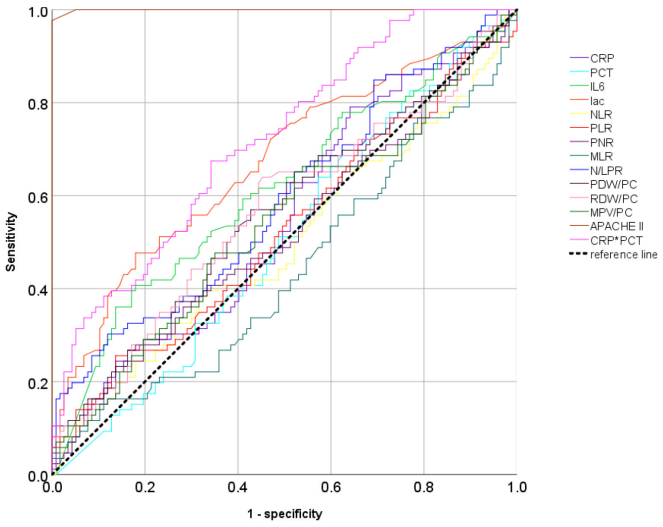
Diagnostic values of inflammatory biomarkers

The ROC curve analysis showed that APACHE II had the high diagnostic value (sensitivity 97.7%, specificity 100%, $p < 0.001$), with an Area Under Curve (AUC) of 0.999 and a Youden index of 0.977. The diagnostic value of CRP*PCT was just next to APACHE II (sensitivity 67.4%, specificity 65.8%, $p < 0.001$), with an AUC area of 0.718 and a Youden index of 0.333. The diagnostic value of IL-6, Lac, N/LPR were also favorable (Table 4 and Figure 1). The cut-off values of CRP, PCT, CRP*PCT, IL-6, Lac, NLR, PLR, PNR, MLR, N/LPR, PDW/PC, RDW/PC, MPV/PC and APACHE II were 81.93 mg/L, 14.28 ng/mL, 2.52 $(mg/L)^2$, 1.78 ng/mL, 4.81 mmol/L, 49.190, 490.830, 23.520, 1.680, 45.810, 0.120, 0.098, 0.068, and 29.500, respectively.

Prognoses in both groups

According to the cut-off value of inflammatory indicators, the patients were divided into high and low value groups. CRP, IL-6, Lac, PLR, PNR, PDW/PC, APACHEII were statistically significant independent predictors of mortality (log-rank: all $p < 0.05$) (Figure 2). However, the prognosis showed no statistical difference between patients stratified according to PCT (p = 0.503), NLR (p = 0.291), MLR (p = 0.276), N/LPR (p = 0.14), RDW/PC (p = 0.089), MPV/PC (p = 0.202) and CRP*PCT (p = 0.204) (Figure 3).

Figure 1. The ROC curves of CRP, PCT, CRP*PCT, IL-6, Lac, APACHE II and ratios between immunocytes.



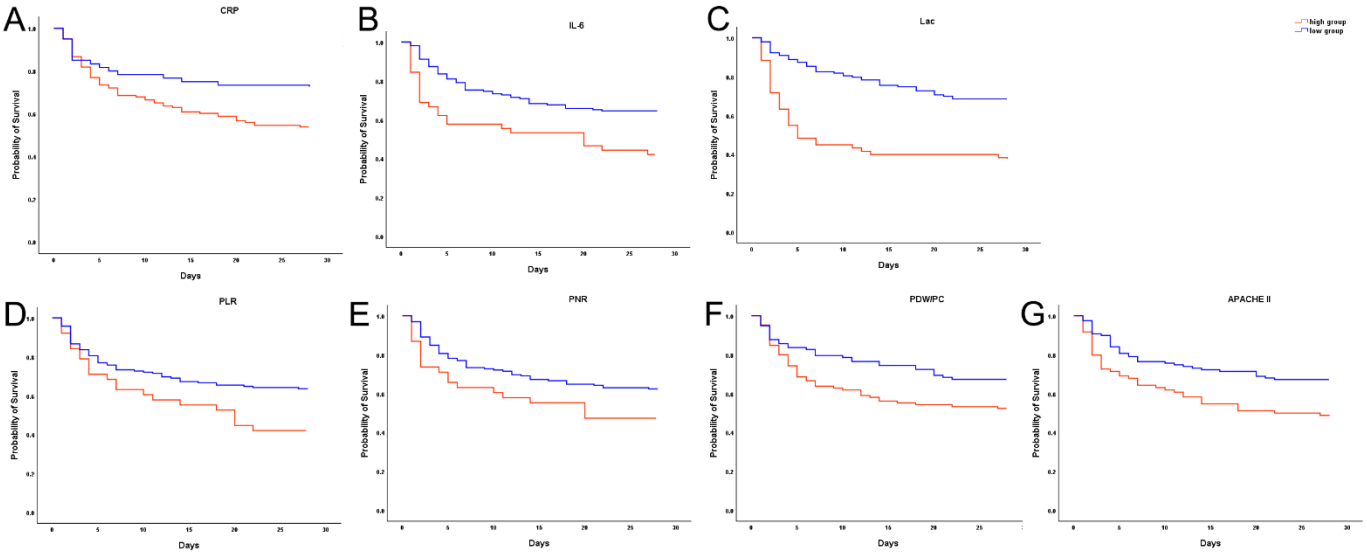
Data are shown as number (%), mean (standard deviation, SD). Significant differences are marked by *($p < 0$ 05) and in bold. APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; AKI: acute kidney injury; CRRT: continuous renal replacement therapy; LOS in ICU: length of stay in intensive care unit.

Table 4. Diagnostic values of inflammatory biomarkers.

Variable	AUC	95% CI	Sensitivity (%)	Specificity (%)	Yuden Index (%)	Cut-off	*p* value
CRP	0.546	0.466-0.626	79.1	35.9	0.150	81.93 mg/L	0.262
PCT	0.503	0.424-0.538	64.0	42.7	0.067	14.28 ng/ml	0.933
CRP*PCT	0.718	0.649-0.787	67.4	65.8	0.333	2.52 $(mg/L)^2$	< 0.001*
IL-6	0.612	0.532-0.692	40.7	82.1	0.227	1.78 ng/ml	0.006*
Lac	0.671	0.594-0.747	47.7	82.1	0.297	4.81 mmol/L	< 0.001*
NLR	0.496	0.414-0.579	16.3	91.5	0.077	49.190	0.930
PLR	0.524	0.442-0.606	25.6	86.3	0.119	490.830	0.562
PNR	0.520	0.438-0.602	24.4	84.6	0.090	23.520	0.624
MLR	0.439	0.358-0.520	16.3	88.0	0.043	1.680	0.138
N/LPR	0.591	0.511-0.671	30.2	88.0	0.183	45.810	0.027*
PDW/PC	0.562	0.481-0.643	57.0	57.3	0.142	0.120	0.134
RDW/PC	0.565	0.484-0.646	64.0	54.7	0.187	0.098	0.113
MPV/PC	0.540	0.458-0.622	65.1	47.9	0.130	0.068	0.332
APACHE II	0.999	0.998-1.000	97.7	100.0	0.977	29.500	< 0.001*

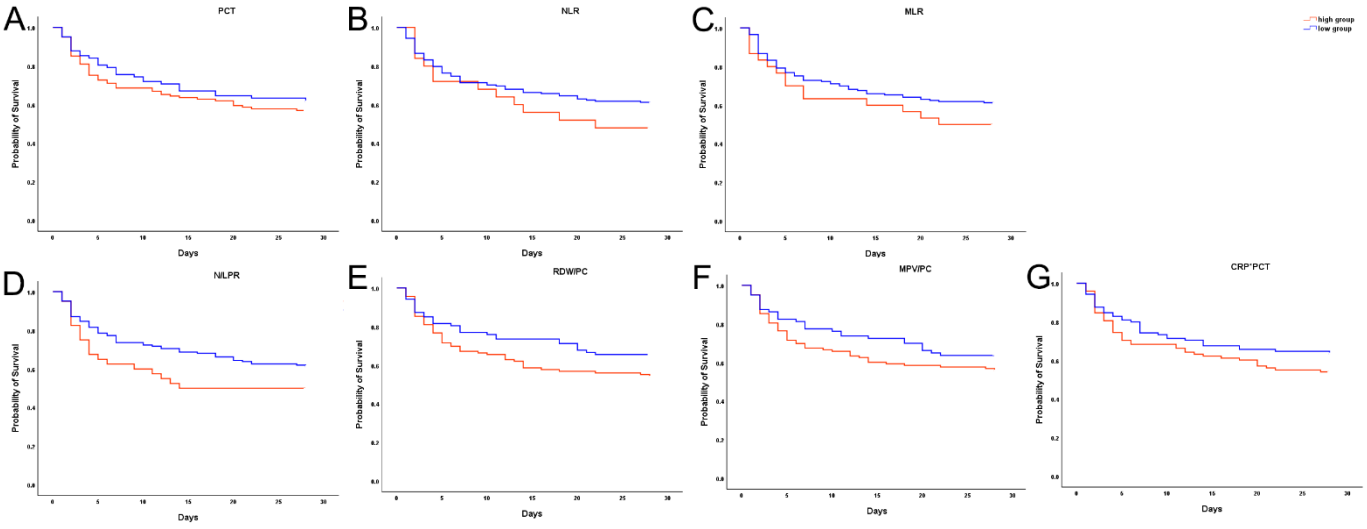
Significant differences are marked by ∗($p < 0$ 05) and in bold . CRP: C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6; Lac: lactic acid;NLR: neutrophil-to-lymphocyte ratio;PLR: platelet-to-lymphocyte ratio;PNR: platelet-to-neutrophil ratio;MLR: monocyte-to-lymphocyte ratio; N/LPR: neutrophils-to-lymphocytes and platelets ratio; PDW/PC: platelet volume distribution width-to-platelet count ratio; RDW/PC: red blood cell distribution width-to-platelet count ratio; MPV/PC: mean platelet volume-to-platelet count ratio; APACHE II: acute physiology and chronic health evaluation II.

Figure 2. The prognosis of each factor (stratified by diagnostic cut-off value).



Data are shown as mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate. Significant differences are marked by *($p < 0$ 05) and in bold. P/F: partial arterial oxygen pressure (PaO2)/fraction of inspired oxygen (FiO2); Lac: lactic acid; T3: triiodothyronine; T4: tetraiodothyronine; TSH: thyroid stimulating hormone; Alb: albumin; BUN: blood urea; Cr: creatinine; Glu: blood glucose; NT-proBNP: N-terminal pro brain natriuretic peptide; BNP: brain natriuretic peptide; D-D: D-dimer; CRP: C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6.

Figure 3. The prognosis of each factor (stratified by diagnostic cut-off value).



Data are shown as mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate. Significant differences are marked by *($p < 0$ 05) and in bold. WBC: white blood cell; N: neutrophil; L: lymphocyte; M: monocyte; Hb: hemoglobin; PLT: platelet; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNR: platelet-to-neutrophil ratio; MLR: monocyte-to-lymphocyte ratio; N/LPR: neutrophils-to-lymphocytes and platelets ratio; PDW/PC: platelet volume distribution width-to-platelet count ratio; RDW/PC: red blood cell distribution width-to-platelet count ratio; MPV/PC: mean platelet volume-to-platelet count ratio.

Table 5. Results of univariate regression analysis.

Variable	B	SE	DW	DF	F	r	p
Sex	-0.017	0.070	1.896	1	0.060	0.017	0.807
Age	0.008	0.002	0.155	1	14.398	0.259	< 0.001*
Lac	0.040	0.008	0.190	1	22.974	0.320	< 0.001*
CRP	0.001	0.000	0.046	1	2.064	0.101	0.152
PCT	0.000	0.001	0.019	1	0.134	0.026	0.715
IL-6	0.003	0.008	0.021	1	0.131	0.025	0.718
CRP*PCT	0.000033	0.000	0.244	1	28.825	0.354	< 0.001*
NLR	0.001	0.002	0.023	1	0.360	0.042	0.549
PLR	0.000	0.000	0.033	1	2.658	0.114	0.105
PNR	0.002	0.002	0.028	1	1.526	0.087	0.218
MLR	-0.027	0.047	0.023	1	0.332	0.041	0.565
N/LPR	0.002	0.001	0.102	1	11.636	0.234	0.001*
PDW/PC	0.379	0.134	0.098	1	7.982	0.195	0.005*
RDW/PC	0.372	0.143	0.087	1	6.773	0.181	0.010*
MPV/PC	0.373	0.171	0.068	1	4.770	0.152	0.030*
APACHE II	0.049	0.002	1.378	1	435.837	0.827	< 0.001*

Variable: Sex, age, Lac, CRP, PCT, IL-6, CRP*PCT, NLR, PLR, PNR, MLR, N/LPR, PDW/PC, RDW/PC, MPV/PC, and APACHE II.SE: Standard error; DW: Durbin-Watson; DF: degree of freedom. Significant differences are marked by ∗ (p < 0 05) and in bold. Lac: lactic acid;CRP: C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6; NLR: neutrophil-to-lymphocyte ratio;PLR: platelet-to-lymphocyte ratio;PNR: platelet-to-neutrophil ratio;MLR: monocyte-to-lymphocyte ratio; N/LPR: neutrophils-to-lymphocytes and platelets ratio; PDW/PC: platelet volume distribution width-to-platelet count ratio; RDW/PC: red blood cell distribution width-to-platelet count ratio; MPV/PC: mean platelet volume-to-platelet count ratio; APACHE II: acute physiology and chronic health evaluation II.

Regression analysis results

The univariate regression analysis showed that age, Lac level, CRP*PCT, N/LPR, PDW/PC, RDW/PC, MPV/PC, and APACHE II were inversely associated with the patient's survival (Table 5). The multivariate regression analysis showed that Lac value, CRP*PCT, PDW/PC, MPV/PC and APACHE II were independent prognostic factors of sepsis if confounding factors were ruled out (Table 6).

Discussion

Sepsis and septic shock attack millions of people around the world each year, and kill as many as one in four (and often more) [1]. Therefore, an efficient and accurate method is needed to predict the prognosis of sepsis. In the present study, we found that the Lac, CRP*PCT, PDW/PC, MPV/PC and APACHE II were all independent prognostic factors of sepsis, all expected to be used in the construction of prediction tools.

A total of 203 patients with sepsis were included in this retrospective study. The patients with an older age, cancer and respiratory diseases had a higher mortality. Besides, the mortality also increased in those with sepsis caused by abdominal and lung infection, which is different from a previous study finding that urinary

Table 6. Results of multivariate regression analysis.

Variable	B	SE	t	p
Gender	-0.063	0.038	-1.671	0.096
Age	0.002	0.001	1.385	0.168
Lac	0.011	0.005	2.047	0.042*
CRP	0.000	0.000	0.542	0.589
PCT	-0.001	0.000	-1.300	0.195
IL-6	-0.002	0.004	-0.695	0.621
CRP*PCT	0.000014	0.000	3.888	< 0.001*
NLR	0.000	0.001	0.215	0.830
PLR	0.000087	0.000	1.014	0.312
PNR	0.000	0.001	0.499	0.618
MLR	0.000	0.029	-0.017	0.986
N/LPR	0.001	0.000	1.412	0.160
PDW/PC	0.474	0.162	2.932	0.004*
RDW/PC	0.023	0.085	0.270	0.788
MPV/PC	-0.449	0.221	-2.032	0.044*
APACHE II	0.044	0.002	18.327	<0.001*

Variable: Gender, age, Lac, CRP, PCT, IL-6, CRP*PCT, NLR, PLR, PNR, MLR, N/LPR, PDW/PC, RDW/PC, MPV/PC, and APACHE II. Significant differences are marked by ∗ (p < 0 05) and in bold. Lac: lactic acid;CRP: C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6; NLR: neutrophil-to-lymphocyte ratio;PLR: platelet-to-lymphocyte ratio;PNR: platelet-to-neutrophil ratio;MLR: monocyte-to-lymphocyte ratio; N/LPR: neutrophils-to-lymphocytes and platelets ratio; PDW/PC: platelet volume distribution width-to-platelet count ratio; RDW/PC: red blood cell distribution width-to-platelet count ratio; MPV/PC: mean platelet volume-to-platelet count ratio; APACHE II: acute physiology and chronic health evaluation II.

tract infections kill more people with sepsis [8]. Interestingly, we noticed that the survival group was more likely to use antiplatelet drugs (p = 0.01). As shown in many observational studies, long-term low-dose aspirin can reduce mortality in patients with sepsis, which may be related to the suppression of tumor necrosis factor, inhibition of platelet activation and resolution of lipid mediators of inflammation [11-12]. While another trial showed that low-dose aspirin in individuals aged over 70 years did not reduce the mortality associated with sepsis [13]. We need more prospective randomized trials to verify the association between antiplatelet drugs and sepsis-related mortality.

PCT and CRP, two inflammatory markers, could effectively assist in diagnosing sepsis [14-15]. However, CRP has a high sensitivity but a low specificity, while PCT has a high specificity but an average sensitivity in previous studies [16-18]. The combination of CRP with PCT can achieve higher specificity and sensitivity in diagnosing sepsis, which allows early treatment. In this study, this combination exhibited the best diagnostic performance for sepsis among all indicators (sensitivity 67.4%, specificity 65.8%), especially in the non-survival group (p < 0.001), which agrees with the findings in previous studies [19-20]. Neutrophils, monocytes, lymphocytes and platelets modulate both innate and adaptive immune responses, as shown by their critical roles in the recruitment, activation and migration of leukocytes in inflammation [21-22]. Red blood cells (RBCS) are responsible for transporting oxygen to all cells and tissues, and carbon dioxide back to the lungs. Additionally, they are involved in phagocytic functions and immune adhesion functions [23].

NLR, PLR, PNR and MLR can reflect the inflammation and immune status of the host [24-25]. NLR serves as an independent prognostic factor for patients with sepsis [26]. However, we found in this study that NLR did not differ significantly between survivors and non-survivors (p = 0.930), with a low sensitivity (16.3%) and a high specificity (91.5%) in the diagnosis of sepsis. Previous studies have found that PLR was significantly associated with the prediction and prognosis of sepsis [27-28]. Besides, non-survivors with negative blood cultures have shown a significantly higher PLR value in traumatized patients [29]. In this study, PLR showed no difference between survivors and non-survivors (p = 0.467), with a low sensitivity (25.6%) and a relatively high specificity (86.3%). PNR can mark the status of inflammation and thrombosis [30]. MLR can predict the survival in patients with various malignant diseases, including endometrial cancer [31-32]. However, MLR was not different between survivors and non-survivors, with a low sensitivity (16.3%). Furthermore, both univariate and multivariate logistic regression analyses confirmed that MLR had no independent prognostic significance.

The incorporation of platelets into NLR increases its sensitivity in predicting the outcome of sepsis [22]. The N/LPR has shown close association with mortality in patients with severe sepsis and septic shock [33-34]. A recent study confirms a significant correlation between N/LPR and mortality in septic-AKI patients [8]. In the present study, the N/LPR was significantly higher in the non-survival group than in the survival group (p = 0.027), with a low sensitivity (30.2%) and a relatively high specificity (88.0%) in the diagnosis of sepsis, and the cut-off value was 45.810. More importantly, the univariate regression analysis showed that N/LPR was inversely associated with the patient's survival. Thus, the N/LPR can be introduced to evaluate systemic inflammatory response at admission to ICU.

A platelet with a higher MPV may have more granules and a larger surface area that is associated with its activation. A high MPV/PC ratio may induce coagulation activation and increase platelet consumption, indicating the involvement of platelet dysfunction in inflammatory responses. MPV/PC has recently been considered as a predictor for mortality in critical sepsis patients [35]. Interestingly, Djordjevic *et al*. found that patients with Gram-positive blood culture had significantly a lower MPV/PC ratio than those with Gram-negative and polymicrobial blood cultures [29]. In the present study, we found that the MPV/PC ratio was not statistically different between survivors and non-survivors (p = 0.332). However, our univariate and multivariate logistic regression analyses confirmed that the MPV/PC ratio was inversely associated with the patient's survival, as an independent predictor, which is in accordance with some reported in other studies [36].

Oh *et al*. reported that PC alone was not statistically different between sepsis survivors and non-survivors, and could not predict mortality [35]. PDW, as an indicator of platelet hyperactivation, reflects the distribution of naive and mature platelets in the blood. A high PDW indicates an increase in large naive platelets. Few studies have reported the relationship between PDW/PC and sepsis mortality. A prospective study suggested that a PDW/PC > 0.07 in the first sample after admission was an independent predictor of mortality in pediatric ICUs, with sensitivity and specificity of 77.1% and 77.5%, respectively [37]. In our study, the PDW/PC was not statistically different

between the sepsis survivors and non-survivors (p = 0.134).

However, in patients stratified by its cut-off value of 0.120, PDW/PC became an independent predictor of mortality ($p < 0.05$). Furthermore, our univariate and multivariate logistic regression analyses furthered that PDW/PC was associated with the patient's survival as an independent prognostic factor. RDW is the coefficient of variation in erythrocyte volume. Studies have found that some inflammatory factors can inhibit the maturation of erythrocytes during infection, and make immature erythrocytes become larger and enter the peripheral blood, thus increasing the level of RDW in the peripheral blood [38]. Multiple studies have confirmed that RDW is an independent prognostic factor for sepsis, and a high RDW at admission may be associated with short and long-term adverse outcomes in adults [39]. Some studies showed that RDW obtained an AUC of 0.61 in predicting sepsis, much lower than 0.8 of PCT, suggesting the limited diagnostic value of RDW [40]. In patients with sepsis, the dysregulated inflammatory response also inhibits the growth of or injures bone marrow megakaryocytes, thus decreasing the production of platelets [41]. However, the value of RDW/PC ratio in predicting the prognosis of adult patients with sepsis is still unclear. In our study, the RDW/PC ratio was not statistically different between the sepsis survivors and non-survivors (p = 0.113). The univariate logistic regression analysis showed that RDW/PC ratio was associated with the patient's survival (p = 0.010); however, this association was not significant in the multivariate regression analysis (p = 0.788).

However, this study has certain limitations. First, it is a retrospective study, which makes it difficult to exclude confounding factors that affect the results. Second, the results may be compromised by the single center with a small cohort. Third, the time point in our study might not always coincide with that of the worst status in the first 24 hours, and we cannot claim that the measurements could completely represent the final prognosis of the patients. Fourth, some parameters such as MDW could not be compared, because of the limitations of reagents in our hospital.

Conclusions

N/LPR differs significantly between sepsis survivors and non-survivors. Both N/LPR and CRP*PCT have high values in predicting the mortality of sepsis patients. PNR, PLR and PDW/PC were independent predictors of mortality. CRP*PCT, PDW/PC and MPV/PC were independent prognostic factors of sepsis.

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Corresponding author

Haidong Qin, MD
Department of Emergency Medicine, Nanjing First Hospital, Nanjing Medical University, Nanjing, China
Tel: +86-15205162912
Fax: +8602552271264
Email: qhd1234567890@126.com

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