

The Value of NLR Combined SOFA in Assessing the Prognosis of Sepsis Patients

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Research Article

Keywords: sepsis, risk factor, neutrophil to lymphocyte ratio, SOFA, APACHE II

Posted Date: July 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-671911/v1>

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Abstract

Background: In order to evaluate the risk factors and its assessment values in patients with sepsis, and to explore a method to improve the prognosis prediction efficiency of patients with sepsis.

Methods: Patients with sepsis admitted to Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University from January 2020 to December 2020 were enrolled, and they were divided into survival group and death group according to the prognosis at 28 days. Demographic data of patients and laboratory values at admission were collected. In terms of the first time data within 24h of patients admitted to hospital, the sequential organ failure assessment (SOFA) score and acute physiology and chronic health evaluation (APACHE II) score were calculated, and compared the difference between the two groups, the logistic regression was used to analysis the risk factors for death within 28 days, as well as the calculated combined predictor of SOFA and neutrophil to lymphocyte ratio (NLR). Predicted values of various indicators for 28 days' mortality in sepsis patients were analyzed by receiver operating characteristic (ROC) curve.

Results: 302 patients in total were included in this study, including 238 patients in survival group and 64 patients in death group. The age (78.36±9.8 years old vs. 71.6±14.1 years old), procalcitonin (PCT) (1.00 ng/ml vs. 0.05 ng/ml), C-reactive protein (CRP) (93 mg/l vs 14 mg/l), lactic acid (Lac) (1.20 mmol/l vs. 2.20 mmol/l), NLR (11.7 vs. 6.20), SOFA score (8 vs. 4) and APACHE II score (20.5 vs. 11.0) of death group were significantly higher than those of survival group (all $P<0.001$). Age (OR=1.046, 95%CI 1.020-1.074, $P=0.001$), PCT (OR=1.115, 95%CI 1.055-1.177, $P<0.001$), CRP (OR=1.016, 95%CI 1.011-1.021, $P<0.001$), Lac (OR=1.887, 95%CI 1.518-2.346, $P<0.001$), NLR (OR=1.038, 95%CI 1.016-1.060, $P=0.001$), APACHE II score (OR=1.231, 95%CI 1.166-1.300, $P<0.001$), SOFA score (OR=1.499, 95%CI 1.344-1.671, $P<0.001$), NLR combined SOFA (SOFA+NLR×0.085) (OR=1.492, 95%CI 1.341-1.660, $P<0.001$) were risk factors of 28 days' mortality in sepsis patients, and the area under the curve (AUC) of APACHE II, NLR combined SOFA were 0.853 and 0.855, higher than Lac (0.767, $P<0.05$), CRP (0.746, $P<0.05$) and PCT (0.761, $P<0.05$), the AUC of APACHE II was similar with NLR combine SOFA ($P>0.05$). The sensitivity and specificity of APACHE II and NLR combined SOFA to predict the 28 days' prognosis of sepsis patients were better than the other indicators.

Conclusion: NLR combined SOFA was a risk factor for the death of sepsis patients, and its predictive efficacy was similar with that of APACHE II score, which is superior to other predictive indexes.

1 Background

Sepsis is a life-threatening organ dysfunction syndrome due to the disordered response of the body to infection^[1]. Approximately 31.5 million patients with sepsis and 19.4 million patients with septic shock worldwide each year, in which 5.3 million patients died, and the in-hospital mortality rate of sepsis patients was 17%-31%^[2,3]. Beside it, the in-hospital mortality rate of septic shock patients was higher, which made sepsis becomes one of the most severe problems faced by medical workers in clinical work globally. In order to effectively improve the prognosis of patients with sepsis and the survival rate in China, determining the severity and prognosis of patients with sepsis quickly and correctly becomes very more important. The aim of this study was focused on investigating the risk factors for death within 28 days in patients with sepsis and their assessment values to prognosis.

2 Methods

2.1 Participants: A retrospective study was conducted on sepsis patients admitted to the Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University from January 2020 to December 2020.

Inclusion criteria: Patients who were older than 18 years, non-surgical trauma, survival time in the emergency room ≥ 24 hours, and met the definition and diagnostic criteria of sepsis-3 published by the American Society for Critical Care Medicine and the European Society for Critical Care Medicine in 2016 were involved in this investigation.^[1]

Exclusion criteria: The patients who had survival time less than 24 hours in emergency room, cardiac or respiratory arrest, incomplete data within 24 hours of admission, did not meet sepsis-3 diagnostic criteria, pregnancy, presence of immune system diseases, malignant tumor, hematological diseases and usage of glucocorticoids were included. Data on the first time at admission were obtained for patients who visited the hospital repeatedly during the inclusion period.

2.2 Data collection: The age and gender of sepsis patients were collected, as well as the levels of C-reactive protein (CRP), procalcitonin (PCT), white blood cells (WBC), absolute neutrophil count, absolute lymphocyte count, absolute platelet count, creatinine, urea nitrogen, lactic acid (Lac) at admission. According to the first data of the admitted patients within 24 hours, the sequential organ failure assessment (SOFA) score, acute physiology and chronic health assessment II (APACHE II) score, and neutrophil to lymphocyte ratio (NLR) were calculated. Death or survival within 28 days was recorded.

2.3 Statistical analysis: SPSS 22.0 statistical software (IBM) was used for data analysis. The measurement data conforming to normal distribution was represented by mean \pm standard (\pm s), the non-normal distribution was represented by quartile, and the counting data was represented by percentage. The t test was used for the parameters that fit the normal distribution, the non-parameter test was used for the non-normal distribution parameters, and the chi-square test was used for the comparison of rates. Logistic regression was used to analyze the risk factors for death within 28 days. The predictors of NLR combined SOFA were calculated via formula predictor = Mark1 + Mark2 \times (B2/B1), where B1 and B2 were the constants of Logistic regression of Mark1 and Mark2, respectively. Receiver operating characteristic (ROC) curve was plotted and the corresponding 95% confidence interval (95% CI), area under the curve (AUC), sensitivity, specificity and optimal cut-off were calculated. The Z test was used to compare the AUC between the indicators $[Z = (A1 - A2) / \sqrt{SE_1^2 + SE_2^2}, Z_{0.05} = 1.96, Z_{0.01} = 2.58, Z > Z_{0.05}$ means $P < 0.05$]. $\alpha = 0.05$

was used as the test level, and $P < 0.05$ was considered to be difference statistically, $P < 0.001$ was difference significantly.

3 Results

3.1 General information: A total of 302 patients involved in this study, which were divided into survival group (238 cases) and death group (64 cases) according to the prognosis within 28 days, with a fatality rate of 21.2%. The demographic data and laboratory values of the two groups were compared in Table 1. Age (78.36 ± 9.8 years old vs. 71.6 ± 14.1 years old), PCT (1.00 ng/ml vs. 0.05 ng/ml), CRP (93 mg/l vs. 14 mg/l), WBC ($11.25 \times 10^9/L$ vs. $8.9 \times 10^9/L$), neutrophils ($9.69 \times 10^9/L$ vs. $6.86 \times 10^9/L$), creatinine ($126.65 \mu\text{mol}/L$ vs. $81.05 \mu\text{mol}/L$), urea nitrogen ($15.09 \text{mmol}/L$ vs. $7.17 \text{mmol}/L$), Lac (2.20 mmol/L vs. 1.20 mmol/L), NLR (11.7 vs. 6.20), SOFA score (8 vs. 4), APACHE II score (20.5 vs. 11.0) in death group were significantly higher than the ones in survival group, which indicated a significant difference in statistics from the two groups comparison ($P < 0.001$). Similarly, lymphocytes in the death group were much lower than survival group ($0.96 \times 10^9/L$ vs. $1.16 \times 10^9/L$, $P = 0.042$). In addition, there were no significant statistical differences in gender and platelet among groups ($P > 0.05$).

Table 1
General information of survival group and death group

General information	Survival group (n = 238)	Death group (n = 64)	P value
Age (years old)	71.6 ± 14.1	78.36 ± 9.8	< 0.001
Gender (male)	133(55.9%)	42(65.6%)	0.161
PCT (ng/ml)	0.05(0.5,0.27)	1.00(0.09,5.95)	< 0.001
CRP(mg/l)	14.0(8.0,65.8)	93.0(43.3,120.0)	< 0.001
WBC($\times 10^9$ /L)	8.90(6.48,11.70)	11.25(8.03,16.60)	< 0.001
Neutrophils ($\times 10^9$ /L)	6.86(4.70,9.48)	9.69(6.43,14.58)	< 0.001
Lymphocytes ($\times 10^9$ /L)	1.16(0.73,1.70)	0.96(0.58,1.37)	0.042
Platelets ($\times 10^9$ /L)	185.0(142.3,256.3)	202.5(129.3,282.3)	0.409
Creatinine (μ mol/L)	81.05(61.93,119.28)	126.65(85.60,253.33)	< 0.001
Urea nitrogen (mmol/L)	7.17(5.05,10.87)	15.09(8.70,23.75)	< 0.001
Lac (mmol/L)	1.20(0.80,1.80)	2.20(1.50,4.35)	< 0.001
NLR	6.20(3.10,11.09)	11.70(5.82,22.39)	< 0.001
SOFA score	4(3,6)	8(6,12)	< 0.001
APACHE II score	11.0(8.0,15.3)	20.5(16,25)	< 0.001

3.2 Risk factors for 28 days' death in patients with sepsis

The 28 days' survival status of patients with sepsis was used as the dependent variable, and age, PCT, CRP, Lac, NLR, SOFA score, and APACHE II score were used as independent variables to perform logistic regression analysis (Table 2), and found age (OR = 1.046, 95%CI 1.020–1.074, $P = 0.001$), PCT (OR = 1.115, 95%CI 1.055–1.177, $P < 0.001$), CRP (OR = 1.016, 95%CI 1.011–1.021, $P < 0.001$), Lac (OR = 1.887, 95%CI 1.518–2.346, $P < 0.001$), NLR (OR = 1.038, 95%CI 1.016–1.060, $P = 0.001$), SOFA score (OR = 1.499, 95%CI 1.344–1.671, $P < 0.001$), APACHE II score (OR = 1.231, 95%CI 1.166–1.300, $P < 0.001$) were played the roles as risk factors for 28 days' mortality in sepsis patients. Combined with SOFA and NLR, it was indicated that the predictor was SOFA + NLR \times (0.034/0.400), namely, SOFA + NLR \times 0.085 (Table 3). The comparison of SOFA with NLR in the death group and the survival group showed that the SOFA combined with NLR in the death group was significantly higher than the one in the survival group [8.76 (7.04,12.74) vs. 4.85 (3.19,6.52)], which had a statistically significant difference between these two groups ($P < 0.001$). Using the predictor mentioned above for logistic regression analysis, it was found that SOFA combined NLR was a risk factor for death within 28 days in sepsis patients (OR = 1.492, 95%CI 1.341–1.660, $P < 0.001$).

Table 2
Logistics regression analysis of 28 days' death in sepsis patients

Predictor	OR	95% CI	P value
Age	1.046	1.020–1.074	0.001
PCT	1.115	1.055–1.177	< 0.001
CRP	1.016	1.011–1.021	< 0.001
Lac	1.887	1.518–2.346	< 0.001
NLR	1.038	1.016–1.060	0.001
SOFA score	1.499	1.344–1.671	< 0.001
APACHE II score	1.231	1.166–1.300	< 0.001

Table 3
Logistics regression analysis of SOFA combined NLR for 28 days' death in sepsis patients

Predictor	β coefficient	Standard error	Wald statistic	P value	OR
SOFA	0.400	0.057	49.603	< 0.001	1.492
NLR	0.034	0.013	6.860	0.009	1.035
constant	-4.163	0.447	86.898	< 0.001	0.016

3.3 Predictive value of risk factors for 28 days' mortality in patients with sepsis

According to the result of ROC analysis (Table 4 and Fig. 1), age, PCT, CRP, Lac, NLR, SOFA, APACHE II, NLR combined SOFA could be used to predict the prognosis of sepsis patients within 28 days. The AUC of NLR combination SOFA (AUC = 0.855, 95%CI 0.807–0.903, $P < 0.001$), APACHE II (AUC = 0.853, 95%CI 0.807–0.899, $P < 0.001$) were higher than Lac (0.767, $Z = 2.11 > Z_{0.05} = 1.96$, $P < 0.05$), CRP (0.746, $Z = 2.51 > Z_{0.05} = 1.96$, $P < 0.05$) and PCT (0.761, $Z = 2.17 > Z_{0.05} = 1.96$, $P < 0.05$), and the AUC of NLR combined SOFA was the largest. The sensitivity and specificity of APACHE II and NLR combined SOFA to predict the 28 days' outcomes for patients with sepsis were better than other indicators based on the Youden index. The Z test was used to compare the AUC of APACHE II and NLR combined SOFA, but did not find any significant difference between them ($Z = 0.06 < Z_{0.05} = 1.96$, $P > 0.05$).

Table 4
 Predictive value of risk factors for 28 days mortality in patients with sepsis

Predictor	AUC	95%CI	P value	SE	Cut-off	Sensitivity(%)	Specificity(%)	Youden index	Positive likelihood ratio	Negative likelihood ratio
Age	0.645	0.573–0.717	< 0.001	0.037	74.5	73.4	50.0	0.234	1.468	0.532
PCT	0.761	0.691–0.831	< 0.001	0.036	0.405	67.2	78.6	0.458	3.140	0.417
CRP	0.746	0.677–0.816	< 0.001	0.036	55.5	75.0	73.5	0.485	2.830	0.340
Lac	0.767	0.700–0.834	< 0.001	0.034	2.05	56.3	80.3	0.366	2.858	0.544
NLR	0.680	0.609–0.750	< 0.001	0.036	4.885	89.1	42.4	0.315	1.547	0.257
SOFA	0.827	0.770–0.884	< 0.001	0.029	5.5	79.7	73.9	0.536	3.054	0.275
APACHE II	0.853	0.807–0.899	< 0.001	0.023	14.5	84.4	73.1	0.575	3.138	0.213
NLR combined SOFA	0.855	0.807–0.903	< 0.001	0.024	6.898	78.1	78.6	0.567	3.650	0.280

4 Discussion

Our study retrospectively analyzed the patients with sepsis admitted to Emergency Medicine Clinical Research Center, and it was found that APACHE II score, SOFA score and NLR combined SOFA (NLR + NLR×0.085) could be used to predict the prognosis of sepsis patients within 28 days well, of which NLR combined SOFA is optimal.

PCT and CRP are commonly used to evaluate sepsis. The study results indicated that both PCT (OR = 1.115, 95%CI 1.055–1.177, $P < 0.001$) and CRP (OR = 1.016, 95%CI 1.011–1.021, $P < 0.001$) could predict 28 days mortality in sepsis patients. Consistent with the results of our finding, Castelli et al [4] found that 150 ICU patients in PCT and CRP levels were associated with the severity of organ dysfunction in sepsis patients. A study conducted by Rosanova et al [5] on children with burns complicated infection showed that PCT level had a sensitivity of 100% to predict the mortality within 30 days. Wang et al [3] found that PCT was an independent risk factor that may affect the prognosis of patients with sepsis. Ganesan et al [6] found that when compared with high-sensitivity CRP, CRP was a better predictor of neonatal sepsis because CRP has a higher diagnostic specificity.

Lac is an anaerobic metabolite of cells, and the increase of Lac indicates tissue hypoperfusion and increased anaerobic metabolism in patients with sepsis. Besides that, it is also one of the prognostic indicators for patients with sepsis [7, 8], and plays a role of independent risk factor for death in patients with septic shock [9]. In this study, Lac was a risk factor for the death of sepsis patients (OR = 1.887, 95%CI 1.518–2.346, $P < 0.001$), which indicated the same result the one in most studies. However, Lac was affected by many factors and needed to be evaluated in combination with other indicators.

NLR is an important inflammatory marker for the diagnosis and prognosis of sepsis patients in recent years. Zahorec et al [10] conducted a prospective study of 90 ICU patients and found NLR could predict the severity and prognosis of sepsis patients. Lorente et al [11] found that the NLR within 7 days after the diagnosis of sepsis was associated with the severity and mortality of sepsis. Jie C et al [12] studied 226 sepsis patients and found that the AUC of NLR in predicting the 28 days death of sepsis patients was 0.642 [95%CI (0.556, 0.728)]. Liu et al [13] also found that NLR was significantly correlated with the 28 days death rate of sepsis patients, which was similar with the results of our study.

In the Sepsis and Sepsis Treatment International Guidelines (Sepsis-3) developed in 2016, SOFA score has become an important diagnostic criteria for the diagnosis of sepsis^[14], and SOFA score can predict the mortality of patients with sepsis (AUC = 0.753, 99% CI 0.750–0.757)^[15]. In addition, Karakike et al^[16] demonstrated in 448 study cohorts and 199 validation cohorts that a decrease in SOFA score of < 25% within 7 days of admission was associated with the increased mortality. Therefore, our study was the first to combine NLR with SOFA score, and found that NLR combined SOFA (SOFA + NLR×0.085) could predict the 28 days mortality of sepsis patients (OR = 1.492, 95%CI 1.341–1.660, $P < 0.001$), and its AUC was 0.855, which was higher than the AUC of SOFA (0.827) and NLR (0.680). It could be seen from the Youden index that NLR combined SOFA had a high sensitivity and specificity.

APACHE II score, which involved multiple factors, such as age, chronic health conditions, acute physiology score, can fully clarify the overall situation and predict the prognosis of patients^[17], higher APACHE II score means higher mortality^[18]. Our study concluded that APACHE II score could well predict the prognosis of patients (AUC = 0.853), while APACHE II scored at 14.5 or more, the sensitivity and specificity of predict the 28 days mortality of sepsis patients was 84.4% and 73.1%. However, APACHE II grading is based on 12 physiological indexes (the worst value admitted to hospital within 24 hours), age and chronic health conditions to assess the severity of disease, needs lots of clinical data and laboratory test index, which is too complicated to get specific rating at the first time, and limited clinical application. Our study showed that the AUC of NLR combined SOFA (SOFA + NLR×0.085) in evaluating the 28 days mortality of sepsis patients was similar than that of APACHE II scoring. According to the Z test, there was no significant difference between the AUC of NLR combined SOFA and APACHE II score, suggesting that the role of NLR combined SOFA in evaluating the disease status and outcome of sepsis patients was consistent with the role of APACHE II score. The assessment process of NLR combined SOFA was simpler than that of APACHE II score, which may provide a basis for early rapid and effective guidance of treatment and also may be popularized in clinical work.

There are still some limitations in our study. Firstly, it was a single-center retrospective study with a medium sample size, which may be biased to some extent. Secondly, our study mainly focused on the influence of baseline data on prognosis, and lacked of the correlation analysis of the influence of dynamic changes in post-treatment indicators on prognosis.

5 Conclusion

This study was the first one to combine NLR with SOFA score to identify a risk factor for sepsis patients. NLR combined SOFA (SOFA + NLR×0.085) was used to predict the prognosis of patients with sepsis within 28 day, which could not only maintain high sensitivity and specificity, but maintain the speed and practicability of the scoring process, and the predictive efficiency was consistent with the APACHE II score and was better than other predictive indexes.

Abbreviations

SOFA=sequential organ failure assessment

APACHE II=acute physiology and chronic health evaluation II

NLR= neutrophil to lymphocyte ratio

ROC= receiver operating characteristic

PCT=procalcitonin

CRP=C-reactive protein

Lac=lactic acid

AUC=area under the curve

WBC=white blood cells

Declarations

-Ethics approval and consent to participate

This study protocols was in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of Beijing Chao-Yang Hospital (2016-7-4-1).

-Consent for publication

Not applicable.

-Availability of data and material

The datasets used and analyzed in the current study are available from the corresponding authors on reasonable request.

-Funding

Shijingshan District medical key support specialty construction, Beijing Municipal Administration of Hospitals Incubating Program

-Authors' contributions

YXL, BW, JYW designed this study; YXL carried out the collection, analysis, and interpretation of data; and drafted the manuscript. TT, XHY, XQZ, LH helped in the collection of data of patients. BW and JYW revised the manuscript. JYW read and approved the final manuscript.

-Acknowledgements

We sincerely thank the patients who participated in this study and thanks to the leadership and all staff of the Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospita.

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Figures

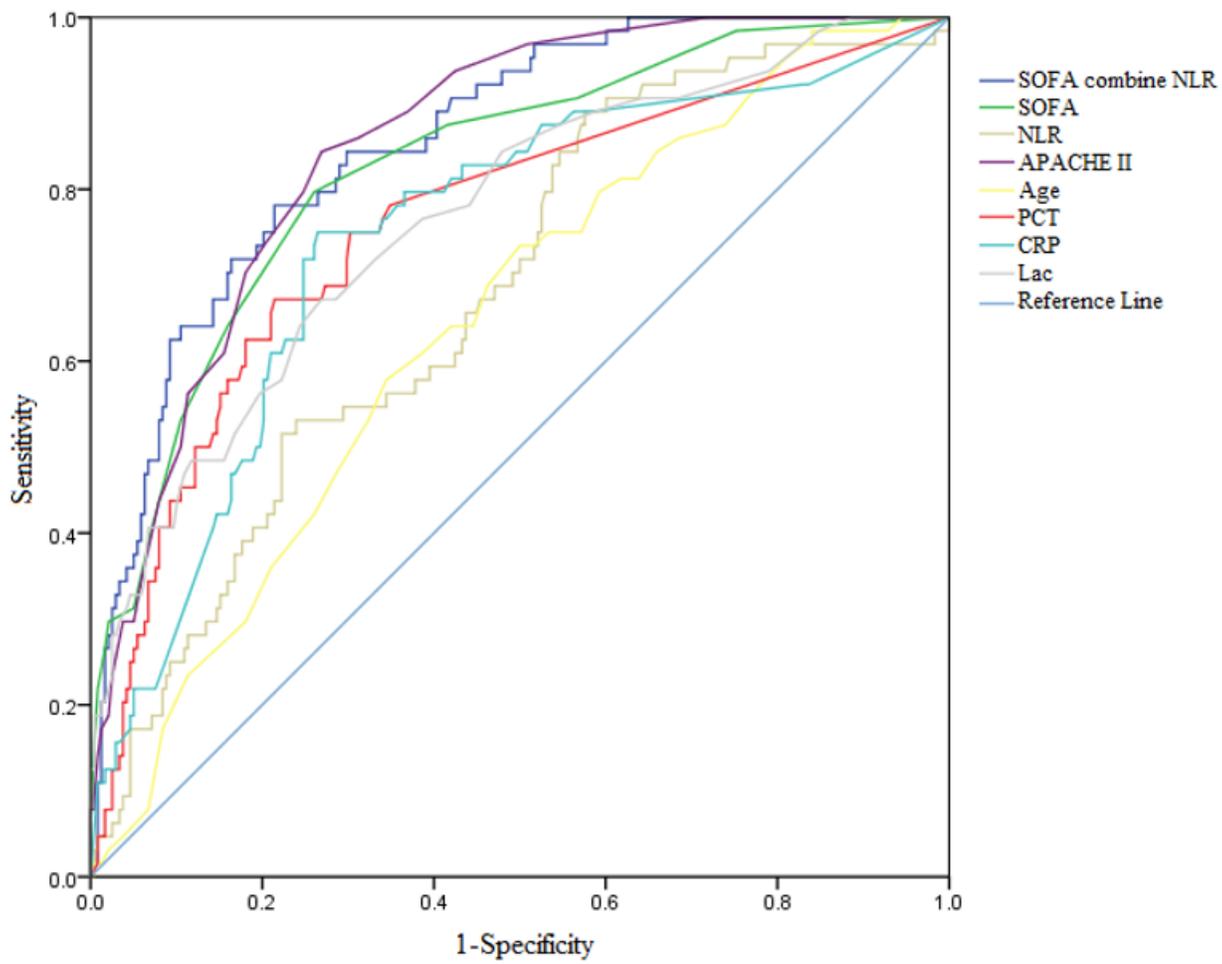


Figure 1

ROC for predicting 28 days mortality in sepsis patients