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Nonviral infection-related lymphocytopenia for the prediction of adult sepsis and its persistence indicates a higher mortality

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Abstract

Sepsis is a life-threatening disease that affects 30 million people worldwide each year. Despite the rapid advances in medical technology and organ support systems, it is still difficult to reduce the mortality rate. Early and rapid diagnosis is crucial to improve the treatment outcome. The aim of this study was to investigate the prediction efficiency of lymphopenia and other clinical markers, such as white blood cell (WBC), neutrophil count (N#), procalcitonin (PCT), and arterial lactic acid (Lac) in the diagnosis and prognosis assessment for adult patients with nonviral infection-related sepsis.

A total of 77 sepsis- and 23 non-sepsis adult patients were enrolled in this study from September 2016 to September 2018. Daily lymphocyte count (Lym) of the patients was calculated until discharge or death. The diagnostic performance of the Lym and other biomarkers were compared using the area under the receiver operating characteristic curve (ROC) value.

The level of Lym was decreased significantly in the sepsis group. Lym had a high diagnostic performance for sepsis, with an area under the curve (AUC) value of 0.971 (95% CI = 0.916–0.994). The diagnostic efficacy of Lym was more significant than WBC, N#, and PCT ($P < .001$). The results showed that the 28-day mortality rate of patients with continuous Lym $<0.76 \times 10^9$/L was 39.66%, which significantly higher than patients without persistent lymphocytopenia.

Lym is a promising, low cost, fast, and easily available biomarker for the diagnosis of sepsis. When nonviral infection is suspected and lymphocytopenia level is lower than the optimal cut-off (0.76×10^9/L) value, high vigilance is required for sepsis. The persistence with the lymphocytopenia cut-off value ($<0.76 \times 10^9$/L) >3 days indicates a higher 28-day mortality rate.

Abbreviations: 95% CI = 95% confidence intervals, ACCP = American college of chest physicians, AIDS = acquired immune deficiency syndrome, APACHE II = Acute Physiology and Chronic Health Evaluation II, AUC = area under the curve, CAP = College of American Pathologists, ICU = intensive care unit, Lac = arterial lactic acid , Lym = lymphocyte count, N# = neutrophil count, NLCR = neutrophil–lymphocyte count ratio , NPV = negative predictive value, OR = odds ratio, PCT = procalcitonin, PDW = platelet distribution width, PPV = predictive positive value, Q1 = 1st quartile, Q3 = 3rd quartile, ROC = receiver operating characteristic curve, SCCM = the Society of Critical Care Medicine, SOFA = sequential organ failure assessment, WBC = white blood cell.

Keywords: diagnose, lymphocytopenia, mortality, predict, sepsis

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JJ, HD, YS are co-first authors and have contributed equally to this work.

The authors believe this work is scientifically valid, and all authors have sufficiently contributed to data collection, analysis, and manuscript preparation.

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Key Points

- Lymphocytopenia is an effective predictor of nonviral infection-related sepsis.
- The persistent lymphocytopenia indicates a higher mortality.
- Lymphocytopenia is more effective for the early diagnosis of sepsis compared with white blood cells, neutrophil count, and PCT.

1. Introduction

The incidence of sepsis is increasing over time. According to statistics, in recent years, sepsis has emerged as the major cause of death in the intensive care unit (ICU), with 30 million new cases and >6 million deaths each year.[1,2] Despite the various supportive treatments for sepsis and the most relevant updated guidelines, the mortality rate of sepsis patients is still very high. Early and rapid diagnosis of sepsis may play an important role to

improve the treatment outcome, as the early anti-inflammatory therapy and immunomodulatory treatment are not very effective and cannot benefit patients' survival.[1] Owing to the complexity of the immune dysfunction mechanism, we have investigated other relevant markers for the early diagnosis of sepsis.

According to the pathophysiological characteristics of sepsis, the marker that we choose should primarily reflect the infection and a systemic inflammatory response syndrome state. Also, it should meet the following requirements: rapid detection, globally accepted technology, low economic cost, easy optimization, and easy interpretation. Hence, the lymphocyte count (Lym) was selected as the marker as it meets all these requirements. Lym $<1.0\times10^9$/L was defined as lymphocytopenia. It indicated that the adaptive immune system was impaired, and lymphocyte apoptosis induced by inflammation was responsible for the serious infection, which was associated with a strong inflammatory response and poor results.[3–5] Lymphocytopenia, as an auxiliary examination index of sepsis, was not evaluated in the early diagnosis of adult patients with nonviral infection-related sepsis. The purpose of this study was to compare the efficacy of lymphocytopenia and other clinical markers, such as white blood cell (WBC), neutrophil count (N#), procalcitonin (PCT), and arterial lactic acid (Lac) in the identification of nonviral infection sepsis, and to investigate its diagnostic value in the early diagnosis of adult sepsis and the prediction of 28-day mortality.

2. Materials and methods

2.1. Study population

It was a retrospective study conducted at the Department of Intensive Care Unit (Surgical ICU and Central Medical ICU), the Respiratory Department, and the Infection Department of the First Affiliated Hospital of Chongqing Medical University. The patients with clinically suspected or confirmed infection were enrolled in this study from September 2016 to September 2018. This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing in compliance with the declaration of Helsinki. Written and informed consent was obtained from all enrolled patients.

According to sepsis-3.0 standard, the study subjects were divided into non-sepsis group and sepsis group, and the sepsis group was further divided into 2 sub-groups, general sepsis group and septic shock group. The sex, age, and other basic data of all the included patients were recorded. Acute physiological and chronic health score II (APACHE II) and sequential organ failure score (SOFA) were assessed within 24 hours after admission. Inclusion criteria were the following: age >18 years old and not limited by sex; patients with clinically suspected or confirmed nonviral infection. Exclusion criteria were the following: rejection of relevant inspection due to economic reasons or other problems caused by incomplete data; death within 3 days after admission or gave up treatment; age <18 years old; hematologic system diseases; patients with chronic kidney or liver diseases; malignant tumors, organ transplantation, autoimmune diseases, or acquired immune deficiency syndrome (AIDS); and the patients who had previously undergone long-term treatment with immunosuppressants and glucocorticoid hormone. This study met all the medical ethics requirements and was approved by the hospital ethics committee. The subjects or their family members have given informed consent for the laboratory examination and treatment measures. The samples from peripheral venous blood and arterial blood were collected within 1 hour of admission, and blood routine (including WBC, N#, Lym), procalcitonin (PCT), and blood gas (including Lac) were tested.

2.2. Relevant biomarkers and determination

Peripheral venous blood and arterial blood samples were collected daily for the first 7 days after admission, and other relevant examinations and monitoring shall be conducted according to the needs of the disease. The relevant test results are also collected daily. Routine blood tests (including WBC, N#, Lym) were measured with the Sysmex XN-9000 (Kobe, Japan) by Flow cytometry, PCT were measured with Roche Diagnostics GmbH (Mannheim, Switzerland) by electrochemiluminescence, and plasma Lactate were measured on Gem Premier 3000 (Illinois). All tests are carried out under standardized procedures in the hospital's medical laboratory, and the quality management and testing ability of the medical laboratory department of our hospital has been certified by College of American Pathologists (CAP).

3. Statistical analysis

SPSS 24.0 (IBM Corp.) and MedCalc 18.5 (MedCalc Software, Belgium) software were used for statistical analysis. For continuous variables, paired *t* test was used for the comparison of normally distributed data and Mann–Whitney *U* test for the non-normally distributed data. Kruskal–Wallis H test and chi-square test or Fisher exact probability method were used for the comparison of multiple groups and counting data, respectively. Logistic regression was used to analyze the role of lymphocytopenia in the early identification of sepsis by single-factor and multiple-factor (forward, LR) analysis. The operating characteristic curve (ROC) was drawn, and the early identification value of Lym, WBC, N#, and PCT for sepsis was compared according with the area under the ROC curve (AUC) value. The optimal cut-off value, sensitivity, specificity, positive predictive value, and negative predictive value of each indicator were calculated to measure the diagnostic efficiency. According to the cut-off value determined by Lym ROC curve, patients in the sepsis group were divided into 2 sub-groups (Lym more than the optimal cut-off value and Lym less than the optimal cut-off value), and the mortality of the 2 groups was compared.

4. Results

4.1. Patients enrollment, baseline characteristics, and the comparison of related biomarkers

A total of 130 cases were included in the study, and subsequently, 30 cases were excluded. The exclusion criteria were the following: age <18 years (2 patients), chronic liver, or kidney disease (7 patients), previous treatment with chemotherapy or corticosteroids (8 patients), hematological or immunological disease (5 patients), and death and discharge (3 and 5 patients, respectively) before day 3. A total of 100 cases who met all the criteria were included in the study (Fig. 1). According to sepsis 3.0 criteria, the patients were further divided into non-sepsis group (n = 23) and sepsis group (n = 77). There were 57 men and 43 women in the study, with 6 women in the non-sepsis group and 37 women in the sepsis group. Among the sepsis group, there were 36 cases in the general sepsis group and 41 cases in the septic shock group. The average age was 63 ± 16 years, 57 ± 17 years in the non-sepsis group, and 65 ± 15 years in the sepsis group ($P = .386$) (Table 1).

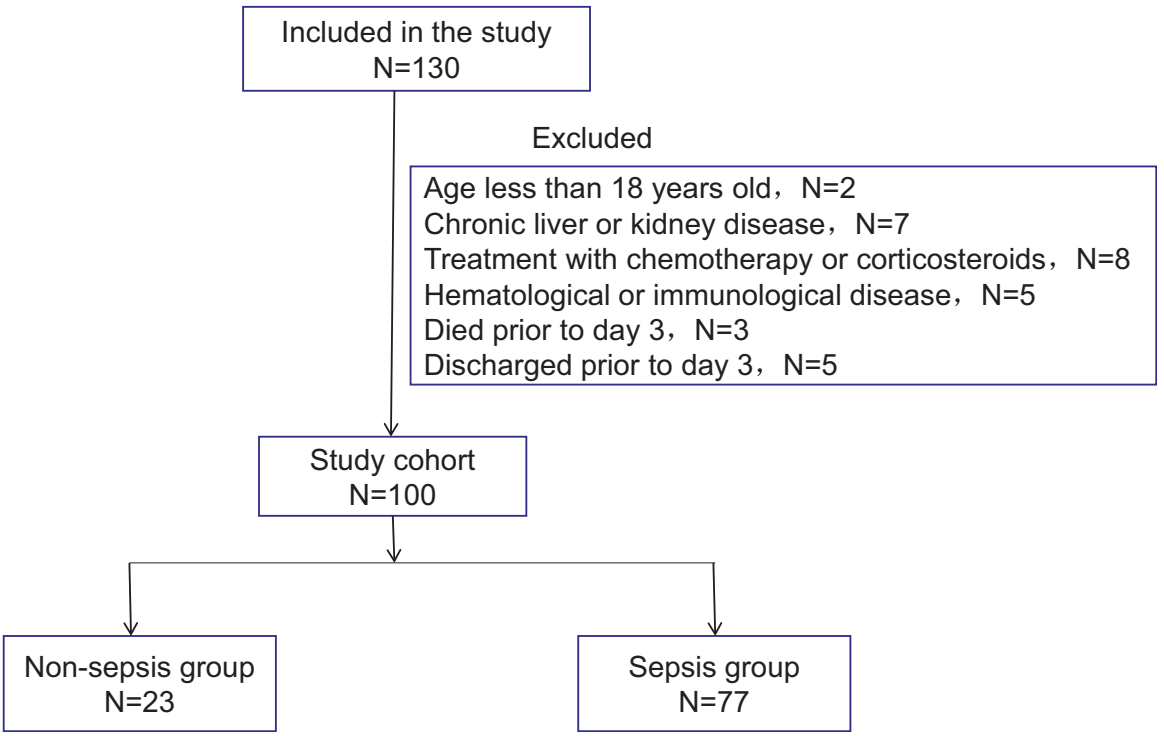

Figure 1. Study population. Details on patient enrollment were presented. Infectious disease department, Pneumology department, and intensive care units were screened daily for collecting information on the age and previous medical history of the infected patients. After identifying the infected patients, they were subjected to further screening and elimination criteria.

There were no statistically significant differences in sex composition, age, infection site between the non-sepsis group and the sepsis group (all $P > .05$), indicating that the baseline data were comparable (Table 1). The comparison of lymphocyte, PCT, lactic acid, disease severity, and other indices levels between the sepsis and non-sepsis group were shown in Table 2, and it could be found that WBC, N#, PCT, Lac, APACHE II score, and SOFA were significantly higher in the sepsis group than in the non-sepsis group, and the Lym was significantly lower in the sepsis compared with non-sepsis group ($P < .001$).

4.2. Value of lymphocytopenia in the early identification of sepsis

4.2.1. Analysis of influencing factors for the prediction of sepsis. Univariate and multivariate analysis for the diagnosis of sepsis showed that WBC, N#, Lym, PCT, Lac, and APACHE II scores were statistically different (OR = 0.845, 95% CI = 0.755–0.947, $P = .004$; OR = 0.748, 95% CI = 0.639–0.876, $P < .001$; OR = 151.699, 95% CI = 18.945–1214.694, $P < .001$; OR = 0.809, 95% CI = 0.681–0.962, $P = .016$; OR = 0.032, 95% CI = 0.005–0.209, $P < .001$; OR = 0.730, 95% CI = 0.619–0.861, $P < .001$, respectively) (Table 3). Logistic regression multivariate analysis was performed on WBC, N#, Lym, PCT, Lac, and APACHE II scores, among which WBC, N#, Lym, and PCT were statistically significant (OR = 0.643, 95% CI = 0.491–0.843, $P = .001$; OR = 1.288, 95% CI = 1.092–1.519, $P = .003$; OR = 2497.102, 95% CI = 38.544–161,777.527, $P < .001$; OR = 1.158, 95% CI = 1.019–1.316, $P = .024$, respectively), that is WBC, N#, Lym, and PCT were associated with the diagnosis of sepsis, but Lac and APACHE II score were not.

4.2.2. ROC curve analysis. ROC curves analysis showed that Lym had the highest AUC for the diagnosis of sepsis: 0.971 (95%

Table 1

Population and baseline characteristics.

	Cases	Non-sepsis	General sepsis	Septic shock	X^2/F	P
Sex Male (n [%])	57(57)	17(29.8)	18(31.6)	22(38.6)	0.103	.749
Female (n [%])	43(43)	6(14.0)	18(41.9)	19(44.2)		
Age, yrs (median)	63 ± 16	57 ± 17	63 ± 15	66 ± 15	0.148	.386
Site of infection (n [%])					3.36	.5
Pulmonary	31(31)	15(48.4)	10(32.3)	6(19.4)		
Urinary	5(5)	1(20)	1(20)	3(60)		
Abdominal	24(24)	2(8.3)	8(33.3)	14(58.3)		
Skin and others	3(3)	1(33.3)	1(33.3)	1(33.3)		
Multiple sites	37(37)	4(10.8)	16(43.2)	17(45.9)		
Death (n [%])	23(23)	0(0)	12(52.2)	11(47.8)	9.3	.09

Table 2

Comparison of lymphocyte, PCT, lactic acid, disease severity, and other indices levels between the sepsis and non-sepsis group.

Group	Case (n [%])	WBC($\times10^9$/L) median (Q_1–Q_3)	N#($\times10^9$/L) median (Q_1–Q_3)	Lym ($\times10^9$/L) median (Q_1–Q_3)	PCT (ng/mL) median (Q_1–Q_3)	Lac (mmol/L) median (Q_1–Q_3)	APACHEII median (Q_1–Q_3)	SOFA median (Q_1–Q_3)
Non-sepsis	23(23)	7.18 (5.41–9.76)	5.02 (3.28–7.02)	1.5 (1.25–1.9)	0.05 (0.04–0.54)	1.0 (0.9–1.1)	10 (9–12)	1 (0–1)
Sepsis	77(77)	11.11 (7.57–15.56)	9.94 (7.00–13.63)	0.5 (0.33–0.70)	11 (1.73–34.43)	2.05 (1.3–3.54)	16 (12.5–22)	7 (4–11)
P		<.001	<.001	<.001	<.001	<.001	<.001	<.001

APACHE II = acute physiological and chronic health score II, Lac = arterial lactic acid, Lym = lymphocyte count, N# = neutrophil, PCT = procalcitonin, Q_1 = 1st quartile; Q_3 = 3rd quartile, SOFA = sequential organ failure assessment, WBC = white blood cell.

Table 3

Analysis of influencing factors for the diagnosis of sepsis.

	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
WBC ($\times10^9$/L)	0.845 (0.755–0.947)	.004	0.643 (0.491–0.843)	.001
N# ($\times10^9$/L)	0.748 (0.639–0.876)	<.001	1.288 (1.092–1.519)	.003
Lym ($\times10^9$/L)	151.699 (18.945–1214.694)	<.001	2497.102 (38.544–161777.527)	<.001
PCT, ng/mL	0.809 (0.681–0.962)	.016	1.158 (1.019–1.316)	.024
Lac, mmol/L	0.032 (0.005–0.209)	<.001		.188
APACHE II	0.730 (0.619–0.861)	<.001		.219

APACHE II = acute physiological and chronic health score II, 95% CI = 95% confidence intervals, Lac = arterial lactic acid, Lym = lymphocyte count, N# = neutrophil, OR = odds ratio; PCT = procalcitonin, WBC = white blood cell.

CI = 0.916–0.994) (Fig. 2, Table 4). The AUC values for the other biomarkers were as follows: WBC 0.726 (95% CI = 0.628–0.811), N# 0.807 (95% CI = 0.716–0.879), and PCT 0.894 (95% CI = 0.817–0.947).

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for Lym, WBC, N#, and PCT are depicted in Table 4. The sensitivity and NPV were 87.01% and 69.7%, respectively, when the Lym cut-off value was 0.76×10^9/L.

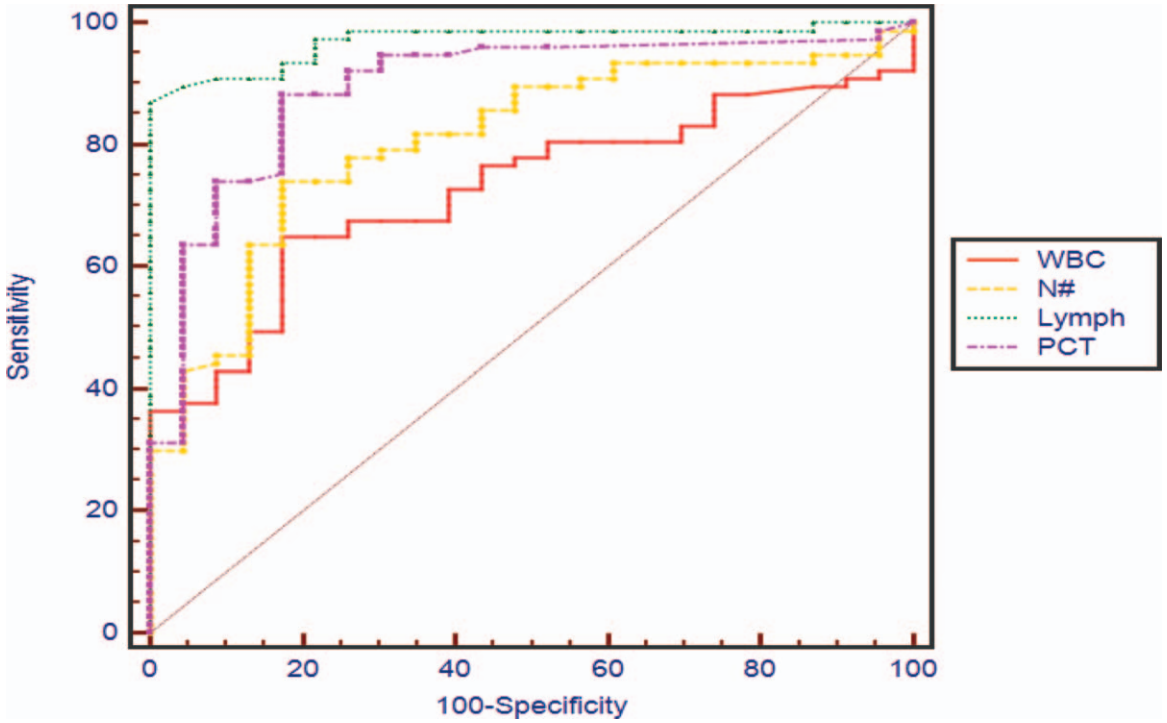

Figure 2. Receiver operating characteristic curve (ROC) of WBC, N#, Lym, and PCT on day 1 for differentiating sepsis from non-sepsis. The results showed that the AUCs of lymphocytopenia, WBC, N#, and PCT in the diagnosis of sepsis were 0.971, 0.726, 0.807, and 0.894, respectively, and were statistically significant ($P < .0001$). The study indicated that lymphocytopenia could be a helpful diagnostic biomarker for sepsis. AUC = area under the curve, Lac = arterial lactic acid, Lym = lymphocyte count, N# = neutrophil count, PCT = procalcitonin, WBC = white blood cell.

Table 4

Performance characteristics of the single biomarker for diagnosing sepsis.

Markers	AUC	95% CI	*P*	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
WBC	0.726	0.628–0.811	<.001	9.87	64.94	82.61	92.6	41.3
N#	0.807	0.716–0.879	<.001	7.08	74.03	83.12	93.4	48.7
Lym	0.971	0.916–0.994	<.001	0.76	87.01	82.57	95.1	69.7
PCT	0.894	0.817–0.947	<.001	0.71	88.31	84.39	94.4	67.9

Lym = lymphocyte count; N# = neutrophil; NPV = negative predictive value; PCT = procalcitonin; PPV = predictive positive value; WBC = white blood cell.

4.2.3. Relationship between persistent lymphocytopenia and 28-day mortality in patients with sepsis. According to the optimal cut-off value obtained by the Lym ROC curve, patients in the sepsis group on day 3 were divided into 2 groups for comparison (Lym $>0.76\times10^9$/L and Lym $<0.76\times10^9$/L) (Table 5). The results showed that the 28-day mortality rate of patients with Lym $<0.76\times10^9$/L sustained for >3 days was 39.66%, which was significantly increased ($P=.001$), compared with the patients without persistent lymphocytopenia.

5. Discussion

Early identification of sepsis can lead to early initiation of treatment, which can improve the treatment outcome and lower the mortality rate.[6] Although sepsis was redefined in 2016, the clear diagnostic criteria for sepsis were not proposed.[7] In clinical practice, microbial culture, though time-consuming, was considered as the golden criterion for the diagnosis of sepsis. In addition, the previously received antibiotics may cause false negatives, and contamination during specimen submission may cause false positives. Therefore, recent researches were focused on the development of new and effective markers with better diagnosis and prognosis for sepsis. This study preliminarily discussed the diagnostic value of lymphocytopenia in the identification of nonviral infection-related sepsis, and the results showed that lymphocytopenia had a significant advantage in the diagnosis of sepsis compared with WBC, N#, PCT, and Lac. In addition, the study showed that the 28-day mortality rate was significantly increased in the group with continuous lymphopenia, which was consistent with the study of Drewry et al.[5] In this study, we chose day 3 as the cut-off point to express continuous lymphocytopenia, as the major cause of early death (<3 days) of sepsis patients is excessive inflammatory reaction, while the cause of late death (>3 days) is continuous immunosuppression, Lym depletion, and Lym reduction.[8]

Sepsis was first defined in 1991 by the American college of chest physicians (ACCP) and the Society of Critical Care Medicine (SCCM).[9] To date, sepsis definition has undergone 2 updates, namely sepsis-2 in 2001 and sepsis-3 in 2016. Sepsis-1 is simple, easy to operate, and highly sensitive, it has a specificity of 90% in the ICU ward and 50% in the general ward,[10,11] and false positive diagnosis increased significantly. Sepsis-2 contains 6 general parameters, 5 inflammatory parameters, 11 hemodynamic parameters, and 2 tissue perfusion parameters, and it was so complex that it could not be widely used in clinics. Sepsis-3 is defined as a sequential organ failure based on suspected infection, and SOFA score is >2 points.[12] The indices of organ function in the SOFA score were difficult to rapidly carry out and widely implement in the outpatient and emergency departments. However, for the qSOFA, most of these were used for screening and have a low specificity.[13] It was reported that in the early stage of the infection, with a delay in the use of antibiotics in every 1 hour, 72 hours of survival were significantly reduced by 7.7%, and it emphasizes the necessity of early diagnosis of sepsis.[14]

Early-stage sepsis is associated with obvious systemic inflammatory response, and a strong inflammatory response stimulates the increase of anti-inflammatory response in the body. Nonviral infection triggers a cascade of inflammation in vivo, with increased secretion of interleukin 1, 2, 6, and tumor necrosis factor (TNF)-α, chemokines, and the mobilization of neutrophil proliferation to eliminate pathogens. To avoid the pathogens cleared by the immune system and control the significantly strong inflammatory response, the body increases the anti-inflammatory response through various ways and starts the negative regulation of lymphocytes. The most significant feature is the inhibition of lymphocyte function, increase of apoptosis, and even depletion.[2,8,15] Therefore, lymphopenia is considered as an effective clinical marker for the early diagnosis of sepsis. According to clinical studies, the level of Lym in circulation declined at the early stage of sepsis and up to 28 days.[5]

Because of the presence of increased neutrophils and reduced lymphocytes caused by excessive inflammation after infection, many clinicians use lymphopenia[5,16] and the neutrophil–lymphocyte count ratio (NLCR) as predictors of sepsis.[17–21] Previous studies have found that infective lymphocytopenia can be used as an indicator of the postoperative prediction of sepsis, and its predictive efficacy was better than WBC, N#, etc.[16] Ljungström et al[17] found that although NLCR can be used as a predictive indicator of sepsis, it should be combined with other indicators such as PCT, CRP, and platelet distribution width

Table 5

Comparison of the relevant characteristics of the subgroup of persistent lymphocytopenia and their 28-day mortality.

Group	Cases	Gender (n)		Age, y	APACHE II	Died (n [%])	Lym ($\times10^9$/L)	
		M	F				1st day	3rd day
Lym ≥0.76 ($\times10^9$/L)	19	13	6	58 ± 18	15 ± 6	0 (0)	0.51 (0.32–0.9)	1.06 (0.9–1.49)
Lym<0.76 ($\times10^9$/L)	58	27	31	67 ± 14	18 ± 6	23 (39.66)	0.49 (0.33–0.68)	0.51 (0.34–0.60)
P		.098		.023	.138	<.001	.257	<.001

APACHE II = acute physiological and chronic health score II; Lym = lymphocyte count.

(PDW) to achieve higher predictive efficacy.[20] Generally, lymphocytopenia is present in most severe bacterial infections, but neutrophils are not necessarily increased.[22] The increased number of neutrophils is not positively correlated with the degree of infection, so NLCR maybe not specific for infection.

Previous studies have investigated PCT as an effective indicator of sepsis, and found that it was not specific for infection, because PCT is generally increased in many other inflammatory states, such as surgery, trauma, paraneoplastic, and autoimmune disease[23] and also in less than half of the patients with fungal infection. So, PCT is less effective for the diagnosis of fungal infection,[24] and its clinical application is limited because of the higher cost (self-funded project). Our study showed that lymphopenia was more effective for the diagnosis of sepsis compared with PCT.

Lactic acid is generally considered as an indicator of tissue perfusion, and according to Sepsis 3.0, Lac should be performed within 3 hours of patients' admission. Hyperlactic acid (blood Lac concentration >4 mmol/L) is one of the criteria for the diagnosis of severe sepsis..[12] However, other factors, such as respiratory insufficiency, increase in anaerobic glycolysis, reduction in liver clearance of Lac, and some hematologic system diseases,[25,26] may also contribute to the increase of Lac. Therefore, hyper lactic acidemia did not fully respond to hypoperfusion. Ranzani et al[27] found that despite the continuous low perfusion, 72% of the patients did not have hyperlactic acidemia, and only 14% of the patients with severe sepsis had hyperlactic acidemia. Our results also indicated that Lac was not an effective predictor (earlier or rapid) of sepsis.

Our study has the following advantages and contributions: first, in the pathophysiological mechanism of sepsis, the inflammatory reaction aggravates lymphocyte apoptosis, and therefore lymphocytopenia may be a better diagnostic indicator. Also, as Lym was rapid, simple, and easy to obtain, it was more clinically favored. Second, our study was more reliable as we ruled out other diseases that might cause lymphopenia. Third, the optimized cutoff value of Lym was obtained by ROC curve. In addition, this is a simple evaluation method that could easily stratify the patient to determine the prognosis and potential future intervention. Moreover, it is likely that an evidence-based threshold in the future can improve the diagnostic veracity.

This study has the following limitations: it is only a single-center, small sample size, and retrospective study and hence is not the representative of other hospitals (large sample size). As an academic tertiary care medical center, sepsis patients admitted to our hospital were more serious cases than the general hospitals, which may affect the case composition of sepsis. Therefore, larger studies based on the multicenter data of sepsis are required to estimate the true prevalence of lymphocytopenia. Lymphocyte count $<1.0 \times 10^9$/L was selected as the definition of lymphocytopenia. It is likely that choosing different cutoff values for lymphocytopenia could have different findings; our study did not consider the underlying diseases, nutritional status, and other factors; although lymphocyte count alone screening for sepsis has a high specificity, its specificity has not exceeded 90%, which needs to be further improved. Our future studies will be aimed at combining infective lymphopenia with other rapid detection indicators to further improve the specificity and sensitivity of the rapid recognition of sepsis, and hence the majority of the outpatient or emergency patients with sepsis can get early treatment and improve their prognosis.

6. Conclusion

Lymphocyte count is a promising, low cost, fast, and easily available biomarker for the diagnosis of sepsis. When nonviral infection is suspected and lymphocytopenia level is lower than the optimal cut-off (0.76×10^9/L) value, high vigilance is required for sepsis. The persistence with the lymphocytopenia cut-off value ($<0.76 \times 10^9$/L) >3 days indicates a higher 28-day mortality rate.

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