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Research Article

Correlation between CD3+, CD4+, CD8+ T Lymphocytes and CRP, IL-6, and PCT in Children with Sepsis and their Value in Disease Assessment

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Abstract

Objective: To analyze the relationship between CD3+, CD4+, CD8+ T lymphocyte percentages in peripheral blood lymphocytes and CRP, IL-6, and PCT in children with sepsis and its value in evaluating the severity of the disease. **Methods:** 91 children diagnosed with sepsis who were hospitalized at the First Affiliated Hospital of Xinxiang Medical College from December 2019 to April 2021 were retrospectively included. Among them, 60 were male (65.9%) and 31 were female (34.1%), aged 3 (1.00, 7.00) years old. Group according to severity of illness. Data were collected within 24 hours of admission. Spearman correlation was used to analyze the relationship between the percentages of CD3+T, CD4+T, CD8+T lymphocytes and CRP, IL-6, and PCT. The non-parametric rank sum test was used to compare differences between mild and severe groups. Logistic regression was used to analyze the relationship between CD3+T, CD4+T, CD8+T lymphocytes and sepsis. Build predictive models to evaluate conditions. Use the Receiver-Operating Curve (ROC) to evaluate the model effect. **Results:** CD3+T lymphocytes were negatively correlated with PCT, IL-6, and CRP (r=-0.450, P=<0.001; r=-0.378, P=<0.001; r=-0.378). CD8+T lymphocytes were negatively correlated with PCT and CRP (r=-0.215, P=0.041, r=-0.310, P=0.003). There was a negative correlation between the percentage of CD4+T lymphocytes and PCT (r=-0.224, P=0.033). The fever peak, CT3+T (%), CD8+T (%), PCT, CRP, and IL-6 in the mild group were lower than those in the severe group. CD3+T lymphocyte percentage, CRP, and fever peak are risk factors for severe sepsis. **Conclusion:** The increases in CRP, IL-6, and PCT are negatively correlated with CD3+T, CD8+T, and CD4+T lymphocytes. CD3+T lymphocytes combined with CRP and fever peak can improve the performance of predicting the occurrence of severe sepsis.

Keywords: Sepsis; Children; T lymphocytes; Severity of illness

Abbreviations: SAA: Serum Amyloid A; IL-6: Interleukin-6; PCT: Procalcitonin; CRP: C-Reactive Protein; ROC, Receiver Operating Characteristic; AUC: Area under the Curve; CD3+T (%): CD3+T Lymphocyte Percentage; CD8+T (%): CD8+T Lymphocyte Percentage; CD4+T (%): CD8+T Lymphocyte Percentage

Introduction

Sepsis is a life-threatening systemic inflammatory response syndrome often caused by infection and is a common condition in pediatric intensive care units. Its incidence and fatality rates vary greatly in different regions and age groups, but overall they are still very high [1]. The occurrence and development of sepsis involve complex interactions of multiple cytokines, immune cells, coagulation factors, etc. The body will have two opposite inflammatory responses, pro-inflammatory and anti-inflammatory,

leading to immune suppression and organ dysfunction [2]. At present, the treatment of sepsis still focuses on early identification, anti-infection, fluid resuscitation, organ support, etc., and there is a lack of effective intervention methods for immune dysfunction. One important reason is that the clinical factors involved in the development of immunosuppression are not fully understood [3]. In the immune response to sepsis, T lymphocytes are an important adaptive immune cell. T lymphocytes can be divided into various subpopulations according to their surface markers, such as CD3+, CD4+, CD8+ T lymphocytes, etc. [4]. The number and function of these T lymphocyte subsets will change significantly in sepsis, reflecting the body's ability to respond to and recover from infection [5]. Therefore, exploring the relationship between T lymphocytes, inflammatory indicators, and the severity of sepsis in children will help understand the immune factors that aggravate sepsis.

Materials and Methods

Normal information

A retrospective study was used. Inclusion subjects: 91 children with sepsis who were hospitalized at the First Affiliated Hospital of Xinxiang Medical College from December 2019 to April 2021 were selected. According to the diagnostic criteria, they were divided into mild group and severe group. Inclusion criteria: (1) Meet the diagnostic criteria in the 2015 edition of the Chinese Expert Consensus on the Diagnosis and Treatment of Septic Shock in Children [6]. (2) The detection of T lymphocyte subgroups has been improved and has complete clinical data. (3) Aged more than 28 days and less than or equal to 18 years old. (4) Sign the informed consent form for this study. Exclusion criteria: Age less than or equal to 28 days. Patients were automatically discharged from the hospital less than 24 hours after admission or had incomplete clinical data. Clinical indicators did not detect lymphocyte subpopulations. Presence of autoimmune diseases, immunodeficiency diseases, diabetes, chronic renal failure, tumors and recent use of immunosuppressive therapy.

In this study, 60 (65.9%) children with sepsis were male and 31 (34.1%) female, with an age of 3 (1.00, 7.00) years. It has been reviewed by the Ethics Committee of the First Affiliated Hospital of Xinxiang Medical College (Ethics number: EC-018-111). All research subjects or family members gave informed consent and signed the informed consent form. All clinical indicators were collected from the hospital information system. All clinical indicators are within 24 hours after admission. Among them, the detection of T lymphocyte subpopulations uses flow cytometry method.

Statistical method

SPSS27.0 statistical software was used for statistical analysis of the research data. The measurement data were described using the median and interquartile range, and the non-parametric rank sum test was used for comparison between groups. Percentages were used to describe count data, and chi-square tests were used to compare between groups. Correlation analysis adopts Spearman correlation analysis method. Use stepwise regression to build a logistic regression analysis model. Use the ROC curve to evaluate the diagnostic performance of the model and calculate the area under the curve. Two-sided test, the test level is $\alpha=0.05$.

Results

There were no statistically significant differences in age, gender, weight, and prehospital disease course between the mild sepsis group and the severe sepsis group. Basic information is comparable. The fever peak, CT3+T (%), CD8+T (%), PCT, CRP, and IL-6 in the mild group were lower than those in the severe group, and the difference was statistically significant (Table 1).

Variable		All(n=91)	Mild group(n=62)	Severe group(n=29)	Z/□²	P
Age (years old)		3.00(1.00,7.00)	3.27(1.82,7.00)	2.00(1.00,8.00)	-1.469	0.142
Gender	Male (%)	65.9	67.7	62.1	0.283	0.595
	Female (%)	34.1	32.3	37.9		
Weight (kg)		16.00(11.00,26.00)	16.75(11.88,24.88)	13.00(9.75,29.50)	-0.912	0.362
Pre-hospital course (days)		4.00(2.00,7.00)	4.00(2.00,8.25)	3.00(1.50,6.00)	-1.106	0.269

Fever peak (°C)	39.00(38.70,39.40)	39.00(38.60,39.10)	39.30(39.00,40.00)	-3.433	0.001
WBC ($\times 10^9$/L)	11.60(7.30,17.60)	10.70(7.30,15.90)	15.73(6.05,24.10)	-1.367	0.172
Plt ($\times 10^9$/L)	280.00(210.00,369.00)	294.50(222.00,368.00)	240.00(175.50,394.00)	-1.342	0.180
Total protein (g/L)	65.50(61.50,70.00)	66.20(63.70,69.92)	64.00(58.50,70.15)	-1.883	0.060
CD3+T (%)	65.83(58.38,70.02)	68.13(64.55,71.08)	55.04(44.99,62.05)	-5.813	<0.001
CD8+T (%)	20.97(18.08,28.73)	23.06(19.77,30.83)	18.19(12.51,25.89)	-3.092	0.002
CD4+T (%)	34.84(27.89,40.26)	35.73(30.33,40.31)	28.05(24.39,40.88)	-1.610	0.107
PCT(ng/ml)	0.46(0.20,1.92)	0.25(0.13,0.51)	2.50(1.23,16.58)	-6.449	<0.001
IL-6(pg/ml)	21.28(9.05,60.39)	11.56(6.11,27.05)	67.71(25.70,149.90)	-5.259	<0.001
CRP(mg/L)	21.76(8.77,59.79)	15.35(3.59,28.05)	59.90(28.59,124.70)	-5.017	<0.001

SAA: Serum Amyloidase A (mg/L); CRP: C-Reactive Protein (mg /L); PCT: Procalcitonin (ng/ml); IL-6: Interleukin-6 (pg/ml); WBC: White Blood Cell count ($\times 10^9$/L); CD3+T(%): CD3+T lymphocyte percentage; CD8+T(%): CD8+T lymphocyte percentage; CD4+T(%): CD4+T lymphocyte percentage; WBC ($\times 10^9$/L): White blood cell count ($\times 10^9$/L)

Table 1: Comparison of clinical indicators between mild group and severe group.

Indicators with statistically significant comparisons between groups were included in the multi-factor logistic regression analysis of severe sepsis, and a multi-factor regression equation was established using the stepwise regression method. CD3+T percentage, CRP, and fever peak are risk factors for severe sepsis. ROC was used to evaluate the quality of the model, and it was found that the AUC (area under the curve) of the model prediction (i.e., CD3+ T lymphocyte percentage, CRP combined with fever peak) in predicting severe sepsis was the largest at 0.925. (Tables 2 and 3, Figure 1).

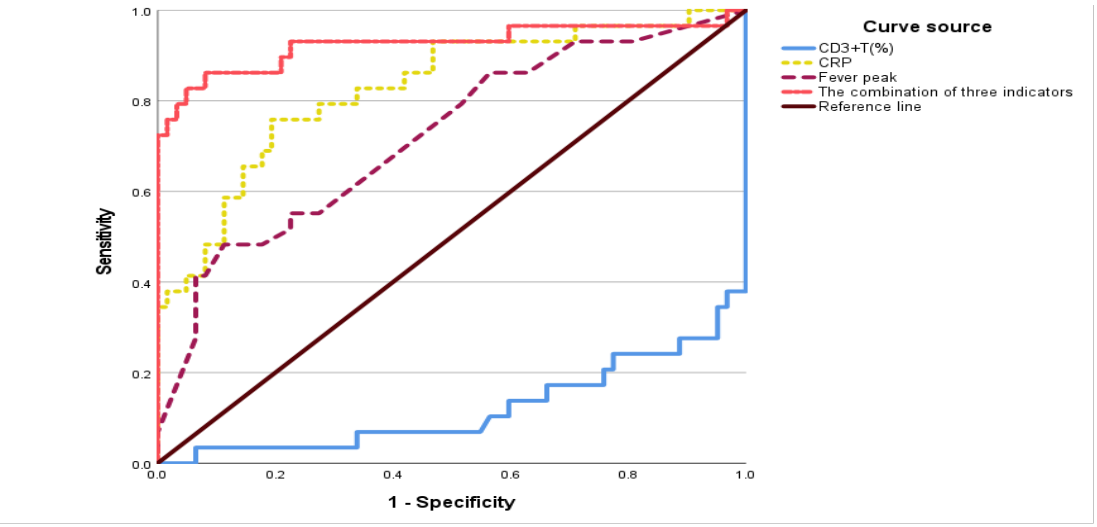

Figure 1: ROC of the predictive value of CD3+T, CRP, fever peak and their combined indicators for severe sepsis.

Variable	B	SD	Wald	P	OR (95%CI)
CD3+T	-0.202	0.051	15.507	<0.001	0.817(0.739, 0.904)
CRP	0.032	0.011	8.147	0.004	1.033(1.010, 1.056)
Fever peak	0.266	0.081	10.765	<0.001	1.305(1.113, 1.530)
CRP: C-Reactive Protein (mg /L); CD3+T (%): CD3+T lymphocyte percentage					

Table 2: Multifactor logistic regression analysis of severe sepsis.

Variable	AUC	SD	P	95%CI
Combination of three indicators#	0.925	0.039	<0.001	(0.848, 1.002)
CD3+T*	0.12(0.88)	0.044	<0.001	(0.034, 0.207)
CRP	0.828	0.048	<0.001	(0.734, 0.921)
Fever peak	0.722	0.059	<0.001	(0.607, 0.837)
#That is, CD3+T lymphocyte percentage, CRP combined with fever peak; *CD3+T percentage is an obstructive factor in the occurrence of severe sepsis; CRP: C-Reactive Protein (mg /L); CD3+T(%): CD3+T lymphocyte percentage				

Table 3: ROC analysis of CD3+T, CRP, fever peak and their combined indicators in severe sepsis.

The percentage of CD3+T lymphocytes is related to PCT (r=-0.450**, P=<0.001), IL-6 (r=-0.378***, P=<0.001), CRP (r=-0.378**, P =<0.001). The percentage of CD8+T lymphocytes was negatively correlated with PCT (r=-0.215*, P=0.041) and CRP (r=-0.310**, P=0.003). Positive correlation with age (r=0.296**, P=0.004) and weight (r=0.297**, P=0.004). There was a negative correlation between the percentage of CD4+T lymphocytes and PCT (r=-0.224*, P=0.033) (Figures 2 and 3, Table 4).

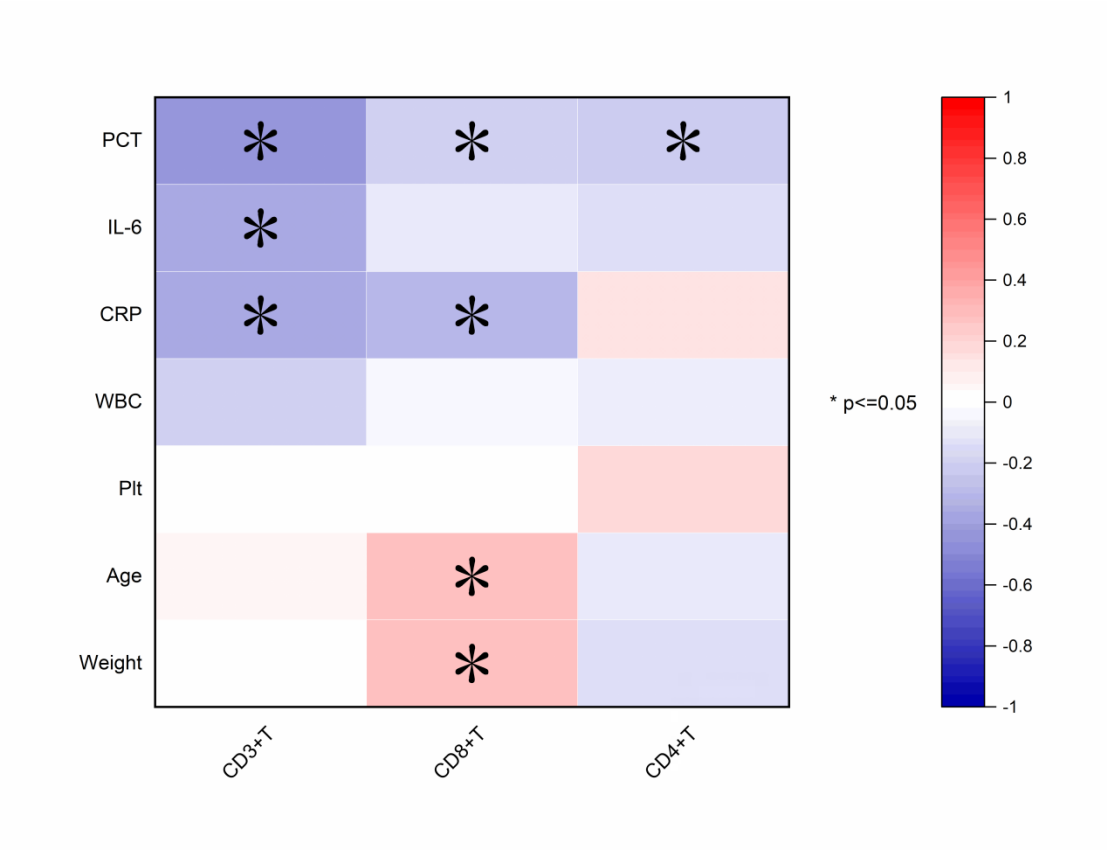

Figure 2: Correlation analysis between CD3+T, CD4+T, CD8+T lymphocyte percentages and inflammatory indicators. SAA: Serum Amyloidase A (mg/L); CRP: C-Reactive Protein (mg /L); PCT: Procalcitonin (ng/ml); IL-6: Interleukin-6 (pg/ml); WBC: White Blood Cell count ($\times 10^9$/L); CD3+T (%): CD3+T lymphocyte percentage; CD8+T(%): CD8+T lymphocyte percentage; CD4+T(%): CD4+T lymphocyte percentage; WBC($\times 10^9$/L): White Blood Cell count ($\times 10^9$/L).

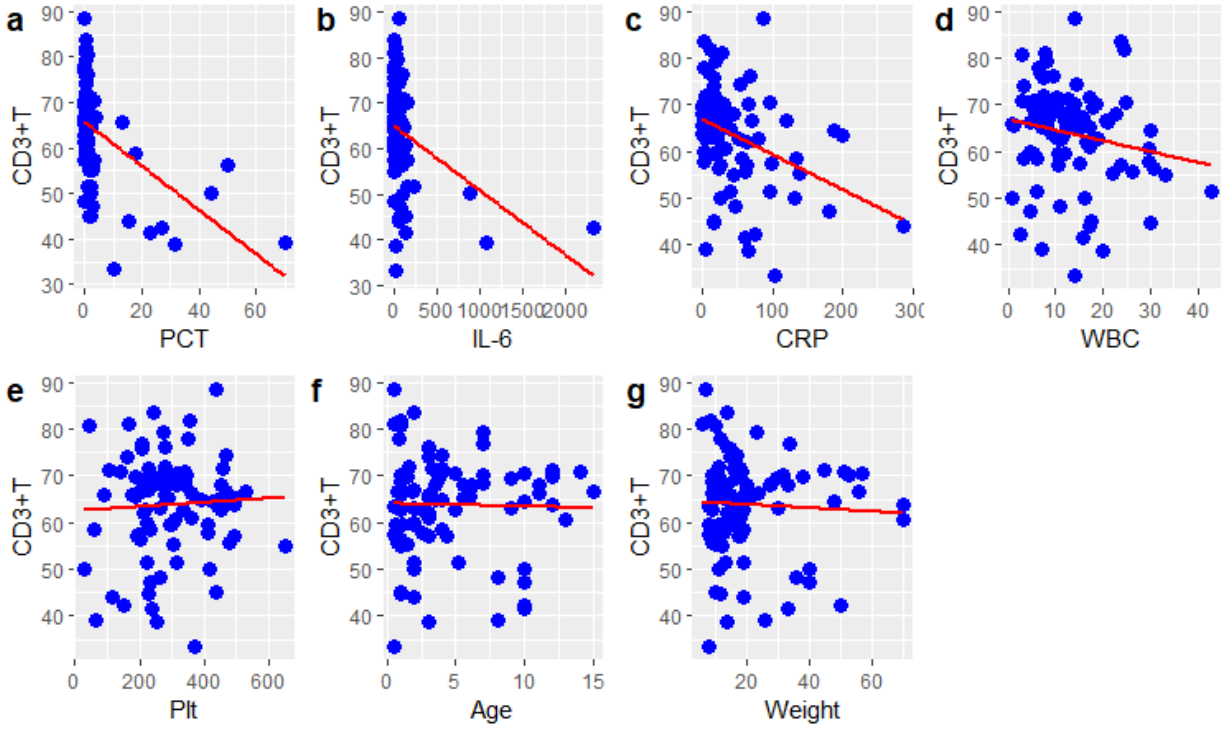

Figure 3A

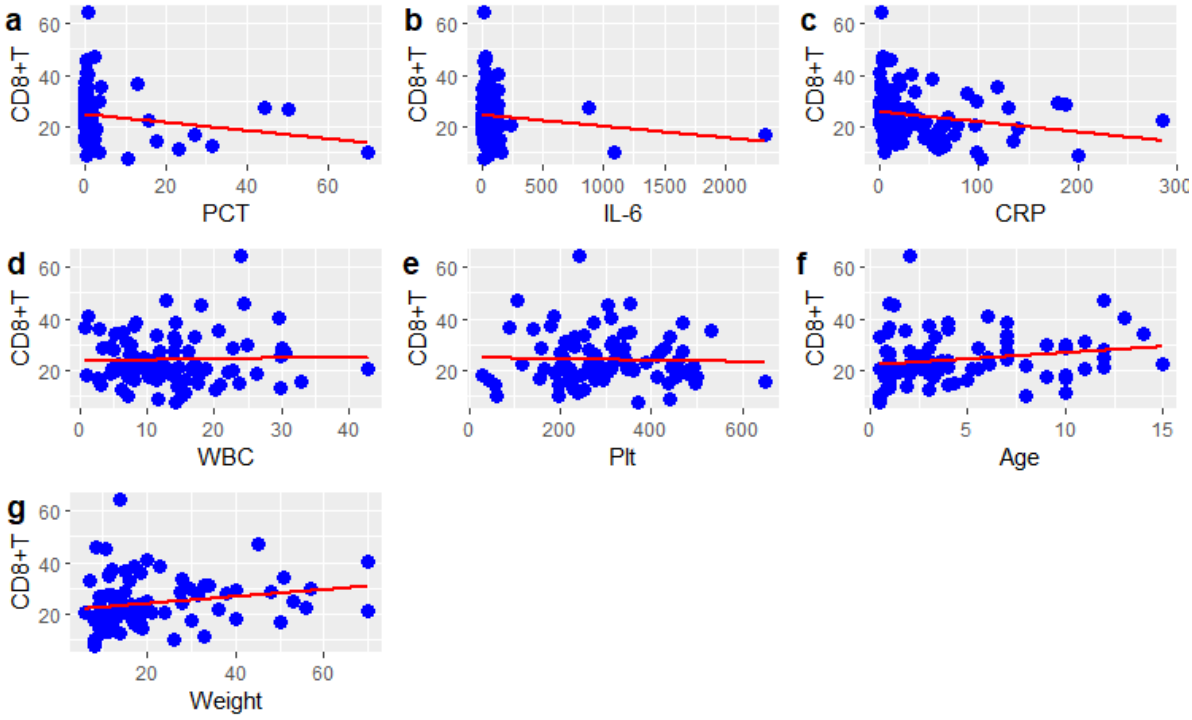

Figure 3B

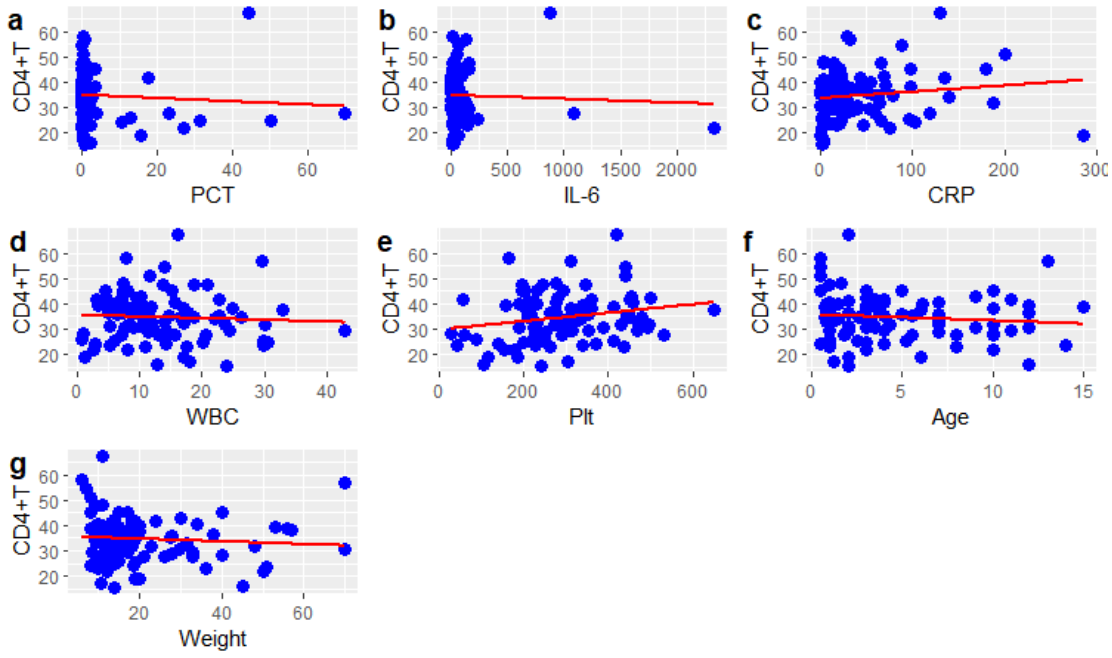

Figure 3C

Figure 3 (A, B, C): Scatter plot of correlation between CD3+T, CD4+T, CD8+T lymphocyte percentages and inflammatory indicators.

Variable	CD3+		CD8+		CD4+	
	r	*P*	r	*P*	r	*P*
Age(years old)	0.063	0.556	0.296**	0.004	-0.120	0.258
Weight(kg)	0.009	0.932	0.297**	0.004	-0.159	0.131
PCT(ng/ml)	-0.450***	<0.001	-0.215*	0.041	-.224*	0.033
CRP(mg/L)	-0.378***	<0.001	-0.310***	0.003	0.149	0.158
IL-6(pg/ml)	-0.378***	<0.001	-0.109	0.306	-0.141	0.182
WBC($\times 10^9$/L)	-0.203	0.053	-0.045	0.670	-0.097	0.361
Plt($\times 10^9$/L)	-0.006	0.958	0.019	0.856	0.186	0.078
*Represents P<0.05, **Represents P<0.01, ***Represents P<0.001						

Table 4: Correlation analysis between CD3+T, CD4+T, CD8+T lymphocyte percentages and inflammatory indicators.

Discussion

Sepsis is a serious systemic infectious disease in children, which can lead to immune dysfunction and organ dysfunction. Although research in recent years has further understood the pathogenesis of sepsis, the mortality or sequelae rate in critically ill children is still high, especially when they enter the immunosuppressive period of sepsis and it is more difficult to correct [7].Currently, there are many clinical biomarkers for early identification of sepsis, such as PCT, CRP, etc. But a single indicator lacks specificity. Should lymphocyte subpopulations, which are indicators of immune function status in children with sepsis, be included in disease assessment and prognosis

assessment? The jury is still out. This study explores whether T lymphocytes combined with inflammatory indicators can improve the assessment of severe sepsis in children.

CRP is an acute phase response protein produced by the liver during inflammation or tissue damage, and plays an important role in the body's infection response and innate immunity. However, it is easily interfered by infection, stress, autoimmunity and other factors, so it lacks specificity [8]. PCT can better reflect bacterial infection, but it poorly reflects the severity of the disease when infected with a virus [9]. IL-6 is a pro-inflammatory cytokine, mainly derived from immune cells and macrophages, and is the most sensitive cytokine to body damage and infection [10].

T lymphocytes are important immune response cells in sepsis and can be divided into CD3+T, CD8+T and CD4+T lymphocytes according to their surface antigens. It participates in the regulation of cellular immunity and humoral immunity, and also reflects the body's ability to eliminate pathogens. The decrease in its level can effectively reflect the immunosuppressive state. Studies have shown that this indicator is of great value in the assessment and prognosis of sepsis [11].

This study found that compared with the mild group, the fever peak, PCT, IL-6, and CRP in the severe group were significantly increased, and the percentages of CD3+T, CD8+T, and CD4+T lymphocytes were significantly decreased. The elevated inflammatory indexes in children with severe sepsis reflect the severe inflammatory response of the body. A higher fever peak also indicates that there are more pyrogenic sources in the body. The decrease in T lymphocytes suggests the possibility of immunosuppression. Qian Li et al. compared the differences in T lymphocyte subpopulations in different sepsis patients, and the results support the above conclusion [12].

This study incorporated meaningful indicators in univariate analysis into multivariate logistic regression analysis and found that the decrease in CD3+ T cells, the increase in CRP and fever peak are independent risk factors for the occurrence of severe sepsis. A disease assessment model was established based on this and compared with a single indicator. It was found that the model had good predictive ability. Whether CD3+T cells are used as a single indicator or combined with inflammatory indicators, they are of great significance in assessing sepsis. This may be because the development and progression of sepsis involves the interaction of multiple cytokines and immune cells.

This study further analyzed the correlation between CD3+T, CD4+T, CD8+T lymphocytes and some commonly used clinical indicators. There is a negative correlation between CD3+T, CD4+T, and CD8+T lymphocytes and inflammatory indicators. This shows that changes in T cells not only reflect one's own immune status, but are also closely related to the body's inflammatory response status.

Limitations of this Study

First, age stratification was not possible due to the relatively small sample size. Secondly, the data span of this study is long, and there is continued understanding and optimization of the identification and management of pediatric patients with sepsis. Finally, whether there is a causal relationship between the increase in inflammatory indicators and the decrease in CD3+T lymphocytes requires further study.

Conclusion

Therefore, in addition to reflecting immune function status, CD3+, CD4+, and CD8+ T lymphocytes can also reflect the condition of sepsis, and combined with clinical inflammation indicators can improve the prediction of severe sepsis. The results of this study can provide certain evidence support for clinical assessment of sepsis in children.

Authors' Contributions

Conception and design of the work: LX; Data collection: LX, SP; Supervision: LX; Analysis and interpretation of the data: LX, SP, WZY; Statistical analysis: LX, WZY; Drafting the manuscript: LX; Critical revision of the manuscript: LX, LSJ; Approval of the final manuscript: all authors.

Data Availability

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate. This study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the First Affiliated Hospital of Xinxiang Medical College (EC-018-111), and with informed consent from the guardians.

Competing Interests

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

References

1. Fleischmann-Struzek C, Mellhammar L, Rose N, Cassini A, Rudd KE, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. Intensive Care Med 46: 1552-1562.
2. Zhang YY, Ning BT (2021) Signaling pathways and intervention therapies in sepsis. Signal Transduct Target Ther 6: 407.
3. Jarczak D, Kluge S, Nierhaus A (2021) Sepsis-Pathophysiology and Therapeutic Concepts. Front Med 8: 628302.

4. Schultze-Florey CR, Chukhno E, Goudeva L, Blasczyk R, Ganser A, et al. (2021) Distribution of major lymphocyte subsets and memory T-cell subpopulations in healthy adults employing GLP-conforming multicolor flow cytometry. Leukemia 35: 3021-3025.

5. De Pablo R, Monserrat J, Prieto A, Alvarez-Mon M(2014) Role of circulating lymphocytes in patients with sepsis. Biomed Res Int 2014: 671087.

6. Subspecialty Group of Emergency Medicine, the Society of Pediatrics, Chinese Medical Association (2015) Expert consensus for the diagnosis and management of septic shock (infectious shock) in children. Zhonghua Er Ke Za Zhi 53: 576-580.

7. Genga KR, Russell JA (2017) Update of Sepsis in the Intensive Care Unit. J Innate Immun 9: 441-455.

8. Opal SM, Wittebole X (2020) Biomarkers of Infection and Sepsis. Crit Care Clin 36: 11-22.

9. Gregoriano C, Heilmann E, Molitor A, Schuetz P (2020) Role of procalcitonin use in the management of sepsis. J Thorac Dis 12: S5-S15.

10. Shao WX, Yu DJ, Zhang WY, Wang XJ (2018) Clinical Significance of Interleukin-6 in the Diagnosis of Sepsis and Discriminating Sepsis Induced by Gram-negative Bacteria. Pediatr Infect Dis J 37: 801-805.

11. Luperto M, Zafrani L (2022) T cell dysregulation in inflammatory diseases in ICU. Intensive Care Med Exp 10: 43.

12. Li Q, Yan W, Liu S, Li H (2023) Study on the correlation and clinical significance of T-lymphocyte Subsets, IL-6 and PCT in the severity of patients with sepsis. Pak J Med Sci 39: 227-231.