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The clinical value of high mobility group box-1 and CRP/Alb ratio in the diagnosis and evaluation of sepsis in children

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Abstract. – OBJECTIVE: To explore the clinical value of high mobility group box-1 (HMGB-1), C-reactive protein (CRP), procalcitonin (PCT), and CRP to albumin (Alb) ratio in the diagnosis and evaluation of the severity of sepsis in children.

PATIENTS AND METHODS: A total of 90 children, 50 with sepsis and 40 with general infection, whose symptoms did not meet the criteria for diagnosis of sepsis, were admitted to the Pediatrics Department of Jingzhou Central Hospital in Hubei Province between November 2021 and December 2022, were enrolled and selected as experimental and control group, respectively. The serum of two groups was collected within 24 hours after admission, the levels of HMGB-1 were detected by enzyme-linked immunosorbent assay (ELISA), and CRP, PCT, Alb, and hospitalization days were recorded. The differences in indicators between the two groups were compared, and correlation analysis was performed between hospitalization days and various indicators. The receiver operating characteristic (ROC) curve was drawn to evaluate the independent or combined value of CRP, PCT, HMGB-1, and CRP/Alb ratio in the early diagnosis of sepsis in children.

RESULTS: These four indicators of children with sepsis were significantly higher than those in the general infection group (all p=0.000). The levels of CRP, PCT and CRP/Alb ratio were significantly positively correlated with the hospitalization days (r=0.329, 0.333, 0.329; p=0.02, 0.01, 0.002). The area under curve (AUC) of CRP, PCT, HMGB-1, and CRP/Alb ratio for the diagnosis of sepsis in children was 0.798, 0.817, 0.838, 0.809, respectively, and that of the combination of four indicators was 0.952.

CONCLUSIONS: CRP, PCT, HMGB-1, and CRP/Alb ratio resulted as effective indicators for early diagnosis and evaluation of childhood sepsis, having a higher value in combined diagnosis.

Key Words:
Sepsis, HMGB-1, CRP/Alb ratio, Children.

Introduction

Sepsis is dysregulated host immune response to infection that results in life-threatening organ dysfunction[1]. Approximately 1.2 million children and 3 million newborns are diagnosed with sepsis every year worldwide[2]. Sepsis is one of the important diseases encountered in children's Intensive Care Units (ICUs). Early diagnosis and assessment of the severity of children's sepsis are crucial for subsequent treatment and improving children's prognosis. CRP and PCT are commonly used for diagnosis and evaluation in a clinical setting. Previous studies have shown that HMGB-1 is an important late-stage inflammatory mediator, which has an important role in the occurrence and development of sepsis[3,4]. Both CRP and Alb are acute-phase proteins produced by the liver. When sepsis occurs, CRP is often increased and is positively correlated with the degree of infection[5], while Alb is often decreased[6]. Consequently, some scholars combined the two indicators, finding that they had a good inverse correlation, thus more effectively reflecting the degree of inflammation and nutritional status in patients[7]. However, there are few studies on the HMGB-1 and CRP/Alb ratio in pediatric sepsis. The purpose of this study was to explore the clinical application value of HMGB-1 and CRP/Alb ratio in the early diagnosis and evaluation of sepsis in children so as to provide a certain basis for the clinical diagnosis and treatment of childhood sepsis.

Patients and Methods

Patients

A total of 90 children, 50 with sepsis and 40 with a general infection that did not meet the cri-

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teria for diagnosis of sepsis, admitted to the Pediatrics Department of Jingzhou Central Hospital in Hubei Province between November 2021 and December 2022, were selected as the research subjects, and assigned to experimental and control groups, respectively.

Inclusion and Exclusion Criteria

Inclusion criteria were the following: (1) birth age > 28 days, corrected gestational age > 41 weeks, and age ≤ 18 years old; (2) meeting the 2005 International Guidelines for Diagnosis of Sepsis in Children. Exclusion criteria were: (1) complicated with congenital heart disease, autoimmune disease, hematological disease, malignant tumor; (2) children with high doses of catecholamines; (3) children with incomplete clinical data; (4) children who died within 24 hours after admission.

Ethics

This study was approved by the Ethics Committee of Jingzhou Central Hospital in Hubei Province. In this study, the secondary use of biological specimens related to the subjects was used, and the requirement for patient's informed consent was waived. The research fully adhered to the basic ethical principles of benefit and harmlessness, protecting the privacy of research subjects, and avoiding physical or psychological damage to children.

Methods

We recorded the basic information, including (gender and age), CRP, PCT, Alb, and hospitalization days of these children, and collected their venous blood within 24 hours after admission before using any medication. After centrifugation, HMGB-1 was determined within 2 h. The HMGB-1 was tested by ELISA (test kit: Shanghai Yize Biotechnology), strictly following the instructions of the kit. The CRP/Alb ratio of the children was calculated.

Statistical Analysis

SPSS 25.0 statistical software was used for statistical analysis (SPSS Corp., Armonk, NY, USA). First, a normality test was performed on the measurement data in each group. If with normal distribution, they were represented by "mean ± standard deviation" (X±s), and the independent sample *t*-test was used for comparisons between the two groups. The data with non-normal distribution was represented by median (25th percentile, 75th percentile), and an independent sample non-parametric test was applied. The Chi-square test of four tables or chi-square test of contingency table was used for counting data. If not stated otherwise, all *p*-values represented bilateral probability, and $p<0.05$ was considered statistically significant. Pearson or Spearman correlation analysis was used to analyze the correlation between observation indexes and hospitalization days. The receiver operating characteristic curve (ROC) was drawn to evaluate individual and a combined value of CRP, PCT, HMGB-1, and CRP/Alb for early diagnosis of sepsis in children.

Results

Comparison of Related Indicators Between the Two Groups

A total of 90 children were included in this study, including 40 males (44.44%) and 50 females (55.56%), with an average age of 51.06±32.30 months. Among them, there were 50 children with sepsis (19 males and 31 females, with a mean age of 56.30±35.70 months) and 40 controls (21 males and 19 females, with a mean age of 44.50±26.47) months in the general infection group. There was no significant difference in age and gender between the two groups ($p=0.066$, $p=0.169$), while the CRP, PCT, HMGB-1, CRP/Alb ratio, and hospitalization days in the sepsis group were higher than those in the general infection group (Table I).

Correlation Analysis of Crp, Pct, Hmgb-1, Crp/Alb Ratio, and Hospitalization Days

As shown in Table II, CRP, PCT and CRP/Alb ratios were positively correlated with hospitalization days ($r=0.329, 0.333, 0.329$; $p=0.02, 0.01, 0.02$).

The Value of Crp, Pct, Hmgb-1, Crp/Alb Ratio and Their Combination in the Diagnosis Of Sepsis

The AUC of CRP, PCT, HMGB-1, CRP/Alb ratio, and their combination in the diagnosis of sepsis in children were 0.798, 0.817, 0.838, 0.809, and 0.952, respectively (Figure 1, Table III).

Discussion

The pathogenesis of sepsis in children is complex, as it involves a series of problems, such as immune system disorders, tissue damage, coagulation disorders, and metabolic abnormalities. As

Table I. Comparison of clinical data.

Indicator	Experimental group (n=50)	Control group (n=40)	Z or t or χ^2	*p*
Age (month)	56.30±35.70	44.50±26.47	-1.84	0.066
Gender			1.892	0.169
Male [n(%)]	19 (38%)	21 (52.5%)		
Female [n(%)]	31 (62%)	19 (47.5%)		
CRP (mg/l)	55.39±46.46	7.57±8.14	-4.840	0.000
PCT (ng/ml)	5.49±19.71	0.15±0.12	-5.205	0.000
HMGB-1 (ng/ml)	32.87±4.08	24.43±7.66	-6.289	0.000
CRP/Alb	1.38±1.49	0.18±0.19	-5.022	0.000
Hospitalization days (day)	6.65±3.72	4.85±1.21	-2.072	0.038

a result, a series of changes occur in biochemical blood indicators. The expression and changes in blood-related indicators can be used for early diagnosis of sepsis and assessment of the severity of the disease, which in turn could help to determine a timely, accurate, reasonable, and effective treatment plan, thus effectively improving the prognosis of children and reducing the mortality rate.

CRP and PCT are the most commonly used serological indicators of sepsis in clinic. Numerous studies have shown their value in the early diagnosis and disease assessment of sepsis. Na et al[8] and Cui et al[9] found that the concentrations of CRP and PCT in the sepsis survival group and the sepsis group were lower than those in the sepsis non-survival group and the septic shock group, respectively, thus indicating that PCT and CRP have good clinical value in the early diagnosis and prognosis of sepsis. In their study, Gai et al[10] found that serum PCT in patients with sepsis was significantly increased in the early stage of infection, having the ability to effectively identify different pathogenic bacteria, reflect the severity of the disease and predict the prognosis of patients with sepsis. Our results also showed that the levels of CRP and PCT in children with sepsis were significantly higher than in children with general infection ($p<0.05$) and were significantly correlated with hospitalization days in children with sepsis (r=0.329, r=0.333; $p=0.02$, $p=0.01$). This was consistent with the above results, suggesting that CRP and PCT can be used for early diagnosis and disease assessment of childhood sepsis to a certain extent.

HMGB-1 is a non-histone chromatin-binding protein in the nucleus. When trauma, hypoxia, or infection occurs, immune cells are stimulated and activated to release HMGB-1 out of the cell, while the nucleus of necrotic cells can also passively release HMGB-1. Furthermore, HMGB-1 released into the extracellular is considered a key factor in initiating and maintaining a cascade of inflammatory responses[11], which can stimulate immune cells to overexpress and release a variety of pro-inflammatory cytokines, thus stimulating the secretion of HMGB-1. Through this positive feedback effect, the body is encouraged to initiate, maintain and amplify the inflammatory cascade reaction[12], thereby aggravating the degree of inflammation and prolonging its duration. Milić et al[13] found that serum HMGB-1 levels in patients with sepsis were significantly higher. In their study, Chen et al[14] compared patients with sepsis, patients with septic shock, healthy subjects, patients who died after 28 days, and patients who survived, finding that the concentration of HMGB-1 in peripheral blood of patients with sepsis was significantly increased and the more serious the disease, the higher the level. Chen et al[14] also found that HMGB-1 was positively correlated with acute physiology and chronic health score II (APACHEII) and sequential organ failure score (SOFA), thus further proving the effectiveness of HMGB-1 as a clinical monitoring indicator. In this study, the level of HMGB-1 in children with sepsis was significantly higher than in the general infection group ($p<0.05$), but the correlation analysis revealed no correlation between the level of HMGB-1 within 24 hours of admission and hospitalization days of children (r=0.186, $p=0.079$). Fangzheng et al[15] also found no significant correlation between the

Table II. Correlation analysis between serological indexes and hospitalization days of children.

Indicator	r	*p*
CRP	0.329	0.002
PCT	0.333	0.001
HMGB-1	0.186	0.079
CRP/Alb	0.329	0.002

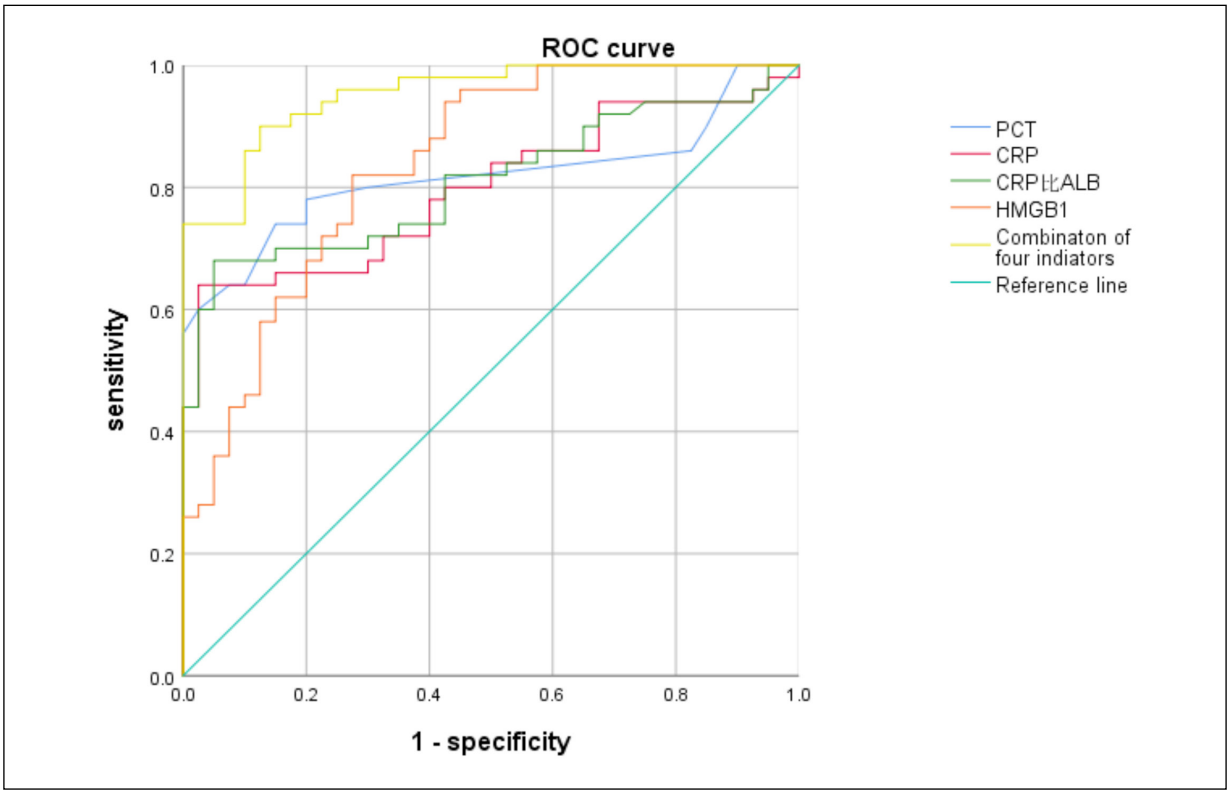

Figure 1. The ROC curve of CRP, PCT, HMGB-1, CRP/Alb ratio and their combined diagnosis of sepsis in children.

serum HMGB-1 level of patients and APACHE II and SOFA on the first day ($p>0.05$), which was consistent with our study. However, they also found no significant change in HMBG-1 level between the sepsis and non-sepsis groups. There was no significant change in the level of HMGB-1 on day 1 ($p>0.05$), but the HMGB-1 level was significantly increased on day 3, 5, and 7 ($p<0.05$) and was significantly positively correlated with APACHE II and SOFA ($p<0.05$). This was also found between the multiple organ dysfunction syndrome (MODS) group and the non-MODS group. The reason may be that HMGB-1 is a late-stage inflammatory mediator. Although it can be increased in the early stage of sepsis, the time course of its increase is still unclear. Therefore, continuous dynamic monitoring may have a higher value in assessing the severity and prognosis of the disease in children.

When sepsis occurs, the Alb of patients is often reduced, which may be due to the following three aspects: first, the expression of Alb mRNA in hepatocytes is inhibited by inflammatory mediators. Second, inflammatory mediators increase the permeability of capillary endothelium, and then Alb leaks from the vascular to the interstitial space. Finally, when the stress response occurs, Alb consumption increases, but synthesis decreases, so CRP changes inversely with Alb during sepsis. Kim et al[16] found that CRP/Alb ratio is an inde-

Table III. The diagnostic efficacy of CRP, PCT, HMGB-1, CRP/Alb ratio and their combination in children with sepsis.

Indicator	AUC	95% CI	Cut-off value	Sensitivity (%)	Specificity (%)	Youden index
CRP	0.798	0.706-0.89	22.825	64%	97.5%	0.615
PCT	0.817	0.725-0.909	0.295	74%	85%	0.59
HMGB-1	0.838	0.756-0.920	29.26	82%	72.5%	0.545
CRP/Alb	0.809	0.719-0.900	0.497	68%	95%	0.63
Combination of four indicators	0.952	0.915-0.990	52.11	90%	87.5%	0.775

pendent predictor of 180-day mortality in sepsis patients and was more effective than CRP alone in predicting 180-day mortality in sepsis patients. Kai et al[17] also reported that the CRP/Alb ratio of the 28-day sepsis survival group was lower than that of the death group ($p<0.05$). Also, CRP/Alb ratio was positively correlated with APACHE II, suggesting that the CRP/Alb ratio is closely related to the severity of the disease and has a good predictive value of prognosis. Our study also showed that the CRP/Alb ratio of children with sepsis was significantly higher than that of the general infection group ($p<0.05$), and the CRP/Alb ratio was significantly positively correlated with the hospitalization days (r=0.329, $p=0.002$), which is consistent with the conclusion that the CRP/Alb ratio could be used as an effective indicator for evaluating the severity and prognosis of patients. The CRP/Alb ratio combined with the two effective indicators was more conducive to understanding inflammatory process, as it could more sensitively reflect more subtle changes in patients.

In this study, the ROC curve showed that the AUC of CRP, PCT, HMGB-1, and CRP/Alb ratio for the diagnosis of sepsis in children were 0.798, 0.817, 0.838, and 0.809, respectively, all of which had certain diagnostic significance. Nonetheless, the AUC of the combined diagnosis of the four-parameter was 0.952, which was higher than any single parameter, and suggested that the combination of multiple indicators could effectively improve the diagnostic value in clinic work.

The present study has the following limitations: first, as this was a cross-sectional survey, there might be some selection bias. Second, the area of this study was relatively limited, and the research subjects may not represent the whole population, so further multi-center and large-sample research is needed to verify the reported results. Finally, continuous and dynamic monitoring of the above indicators may have more clinical value.

Conclusions

The levels of CRP, PCT, HMGB-1, and CRP/Alb ratio in children with sepsis within 24 hours of admission are helpful for the early diagnosis of childhood sepsis and can be used to evaluate the severity of the disease to a certain extent. Joint detection is an effective means for improving the accuracy of early diagnosis and disease assessment. Monitoring these indicators is worthy of promotion for clinical diagnosis and treatment of children with sepsis and deserves further exploration.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Authors' Contributions

Q.-Y. Wang: conception and design of the research, and manuscript writing. Q.-Y. Wang and F. Lu: acquisition of data, analysis, and interpretation. A.-M. Li: statistical analysis, obtaining financing, and critical revision of the manuscript for intellectual content. The article's final version has been read and approved by all authors.

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Ethics Committee Approval

This study was approved by the Ethics Committee of Jingzhou Central Hospital in Hubei Province.

Informed Consent

In this study, the secondary use of biological specimens related to the subjects was used, and the requirement for patient's informed consent was waived. The research fully adhered to the basic ethical principles of benefit and harmlessness, protecting the privacy of research subjects, and avoiding physical or psychological damage to children.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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