European Review for Medical and Pharmacological Sciences 2019; 23: 5904-5911

The predictive value of joint detection of serum amyloid protein A, PCT, and Hs-CRP in the diagnosis and efficacy of neonatal septicemia

F. WU, X.-Q. HOU, R.-R. SUN, X.-J. CUI

New-born ICU, Dongying People's Hospital, Dongying, P.R. China

Fan Wu and *Xiuqing Hou* contributed equally to this study

Abstract. – OBJECTIVE: This study aimed to investigate the predictive value of joint detection of serum amyloid A (SAA), plasma procalcitonin (PCT), and whole blood hypersensitive C-reactive protein (hs-CRP) in the diagnosis and efficacy of neonatal septicemia.

PATIENTS AND METHODS: A total of 195 cases of neonatal septicemia patients admitted to our hospital from March 2013 to May 2017 were selected as observation group, and 100 healthy newborns in the same period were selected as control group. Before treatment, all newborns were detected with enzyme-linked immunosorbent assay (ELISA) for serum SAA, PCT, and hs-CRP three indicators respectively, and differences between expressions of PCT, HS-CRP, SAA in the serum of children (effective group) who improved after treatment and patients in ineffective group were observed.

RESULTS: Three indexes of SAA, PCT, and hs-CRP in study group were significantly higher than those in control group before treatment, while three indexes of SAA, PCT, and hs-CRP in effective group were significantly lower than those in ineffective group after treatment, with statistical significance ($p<0.05$). By drawing the ROC curve, it was found that the AUC area, specificity, and sensitivity of joint detection were better than those of the single item detection.

CONCLUSIONS: Joint detection of SAA, PCT, and hs-CRP has high diagnostic value in neonatal septicemia and is worthy of clinical application.

Key Words:

Serum amyloid A, Plasma procalcitonin, Hypersensitive C-reactive protein, Neonatal septicemia, Diagnostic value, Predictive value of efficacy.

Introduction

Neonatal septicemia refers to a serious disease in the newborn period when germs invade the human body, propagate and produce toxins in the blood circulation, and sometimes produce multiple lesions in the body to form a serious disease[1]. The onset of neonatal septicemia is hidden[2], and symptoms lack of specificity. Therefore, early diagnosis is difficult and the body function of newborns is not well-developed, and their resistance is weak. Once the disease occurs, it develops rapidly and is difficult to control and has a high mortality. Therefore, it is very important to find reliable early bacterial infection markers for early diagnosis and timely and correct treatment of neonatal septicemia.

Serum amyloid A (SAA) protein is an acute phase reaction protein secreted by the liver[3,4]. Secreted in the acute phase of inflammation, it can recruit immune cells to inflammatory sites. Yu et al[5] pointed out that SAA has a certain diagnostic value for the prognosis of sepsis; procalcitonin (PCT) is a precursor peptide of the hormone calcitonin and PCT levels increase significantly in the presence of inflammatory stimuli, particularly bacterial infections; it is also a class of acute phase reactants that have become markers for identifying bacterial infections and guiding the antibiotic treatment[6,7]. Hypersensitive C-reactive protein (hs-crp) is a kind of C-reactive protein in plasma. When the body is exposed to inflammatory stimuli such as microbial invasion or tissue damage, hs-crp increases[8,9]. The degree of increase of hs-crp reflects the size or activity of the inflammatory response. Therefore, hs-crp is also an important indicator to judge whether patients suffer from infection, necrosis of inflammatory tissue, septicemia, and other diseases. In previous studies[10,11], it was found that joint detection is usually more reliable than single detection.

This work observed expression levels of SAA, PCT, and hs-crp in neonatal septicemia, and dis-

Corresponding Author: Xiujie Cui, MD; e-mail: cuixiujie1@163.com

cussed the diagnostic value of their joint detection in neonatal septicemia to provide the basis for early diagnosis of neonatal septicemia.

Patients and Methods

Patients

A total of 195 patients with neonatal septicemia admitted to our hospital from March 2013 to May 2017 were selected as research objects, and 100 healthy newborns in the same period were selected as control group. There were 107 males, 88 females, 26 premature infants, and 169 full-term infants in study group. The average hospital stay was (29±20.42) days; there were 53 males, 47 females, 15 premature infants, and 85 full-term infants in control group.

Inclusion and Exclusion Criteria

Inclusion criteria: all patients were diagnosed according to clinical manifestations, imaging, pathological examination, and laboratory examination. They received treatment in our hospital; the informed consent was signed by the guardian; they had complete medical records. Exclusion criteria: congenital heart disease; combined with severe liver and kidney diseases; combined with genetic and metabolic diseases; not actively cooperating with clinical treatment. This study was approved by the ethics committee of Dongying People's Hospital.

Detection Methods

After newborns in the two groups were admitted to hospital, 2 mL venous blood was taken as a sample before any drug treatment on that day. After centrifugation, SAA, PCT, and hs-CRP were determined within 2 h. The study group received antibiotics clinically and symptomatic treatment for one week, and drew 2 mL venous blood for reexamination before taking any drug treatment in the morning. Levels of SAA (USCNK, SEA-885Bo), PCT (USCNK, SEA689Mu-1), and CRP (IBL International, LD51031) were detected by enzyme-linked immunosorbent assay (ELISA) and operation steps were strictly carried out in accordance with instructions of kits.

Efficacy Evaluation

The specific evaluation criteria refer to the WHO Guidelines for the Use of Antibiotics in Neonates and Children with Sepsis[12], which are as follows: (1) Recovery: after treatment, results of laboratory examination and etiological examination of children returned to normal, and clinical signs and symptoms disappeared; (2) Markedly effective: three items of clinical signs, symptoms, results of laboratory and etiological examination of children recovered to normal after treatment; (3) Effective: after treatment, clinical signs, symptoms, results of laboratory and etiological examination of children were better than before but did not return to normal; (4) Ineffective: after treatment, clinical signs, symptoms, results of laboratory and etiological examination of children have not improved or even worsened. The number of effective group = number of recovery + number of markedly effective + number of effective.

Observation Indicators

Levels of SAA, PCT, and hs-CRP in control group and study group before treatment were observed and compared. The clinical efficacy of neonatal septicemia patients was recorded. Patients were divided into an effective group and ineffective group. Levels of SAA, PCT, and hs-CRP of effective group and ineffective group in study group after treatment were measured and recorded and compared. According to the positive diagnostic threshold, the sensitivity, specificity, and cut-off value of SAA, PCT, and hs-CRP of diagnostic value and efficacy prediction value in joint detection of each group were calculated.

Statistical Analysis

SPSS20.0 (IBM Corp, Armonk, NY, USA) statistical software was used to analyze the data. The counting data were described by [n (%)], the measurement data were described by mean±-standard deviation ($\bar{x} \pm s$), and comparison of measurement data between groups was tested by the t-test. Chi-square test was used to compare the counting data between groups. The ROC curve was used to evaluate the diagnostic efficacy of SAA, PCT, hs-CRP, and joint diagnosis for neonatal septicemia. The receiver operating characteristic (ROC) curve was used to evaluate the diagnostic efficacy of joint diagnosis for neonatal septicemia, with differences being statistically significant when $p<0.05$.

Results

Comparison of General Data

There were no significant differences in age, sex, weight, course of pregnancy, delivery mode,

premature rupture of membranes, nationality, and place of residence between control group and experimental group ($p > 0.050$), proving that patients in the two groups were comparable. See Table I for details.

Comparison of Concentrations of SAA, PCT, and Hs-CRP of Patients Between the Two Groups

Before treatment, SAA in the serum of patients in study group was 71.29±5.28 (mg/L), which was significantly higher than that in control group 65.95±4.17(mg/L), $p < 0.05$. Before treatment, PCT in the serum of patients in study group was 23.77±4.60 (μg/L), significantly higher than that in control group 18.59±4.53 (μg/L), $p < 0.05$. Before treatment, hs-CRP level in serum in study group was 47.36±5.73 (mg/L), which was significantly higher than that in control group 39.95±5.82 (mg/L), $p < 0.05$) (Figure 1).

Diagnostic Value of Serum Amyloid A, PCT, and Hs-CRP in Neonatal Septicemia

The ROC curve analysis showed that when SAA in blood was used to examine neonatal septicemia, the cut-off value was 69.28 (mg/L), the sensitivity and specificity for diagnosing neonatal septicemia were respectively 83.00% and 66.15%. When examining neonatal septicemia with PCT in blood, the cut-off value was 19.94 (μg/L). The sensitivity and specificity for diagnosing neonatal septicemia were respectively 64.00% and 80.51%. When blood hs-CRP was used to examine neonatal septicemia, the cut-off value was 43.42 (mg/L), the sensitivity and specificity for diagnosing neonatal septicemia were respectively 69.00% and 77.44%. When SAA+PCT+hs-CRP was used to jointly examine neonatal septicemia, the cut-off value was 0.331, and the sensitivity and specificity for diagnosing neonatal septicemia were respectively 85.00% and 88.21% (Figure 2 and Table II).

Comparison of Concentrations of SAA, PCT, Hs-CRP before and after Treatment Between Patients in Markedly Effective Group and Ineffective Group in Research Group

Research group was divided into 167 cases in markedly effective group and 28 cases in ineffective group according to a clinical efficacy evaluation. The SAA level in the markedly effective group was 71.64±5.34 (mg/L) before treatment and 67.38±2.14 (mg/L) after treatment. The SAA level before treatment was significantly higher than that after treatment, $p < 0.05$. The SAA level of patients in ineffective group was 71.59±5.17 (mg/L) before treatment and 70.53±4.14 (mg/L) after treatment. There were no significant changes in SAA level before and after treatment, $p > 0.05$. The SAA level

Table I. Comparison of clinical data [n (%)].

	Control group (n = 100)	Research group (n = 195)	χ^2 or t	p
Age (d)	29.42 ± 9.68	28.77 ± 9.24	0.562	0.574
Gender			0.093	0.760
Male	53 (53.00)	107 (54.87)		
Female	47 (47.00)	88 (45.13)		
Weight (Kg)	6.86 ± 2.14	6.67 ± 1.73	0.822	0.411
Premature			0.153	0.695
Yes	15 (15.0)	26 (13.33)		
No	85 (85.00)	169 (86.67)		
Natural childbirth			0.007	0.929
Yes	59 (59.00)	114 (58.46)		
No	41 (41.00)	81 (41.54)		
Premature rupture of membranes			0.477	0.489
Yes	11 (11.00)	27 (13.85)		
No	89 (89.00)	168 (86.15)		
Nationality			0.211	0.646
Han	18 (18.00)	31 (15.90)		
Minority	82 (82.00)	164 (84.10)		
Place of residence			0.014	0.904
City	67 (67.00)	132 (67.69)		
Countryside	33 (33.00)	63 (32.31)		

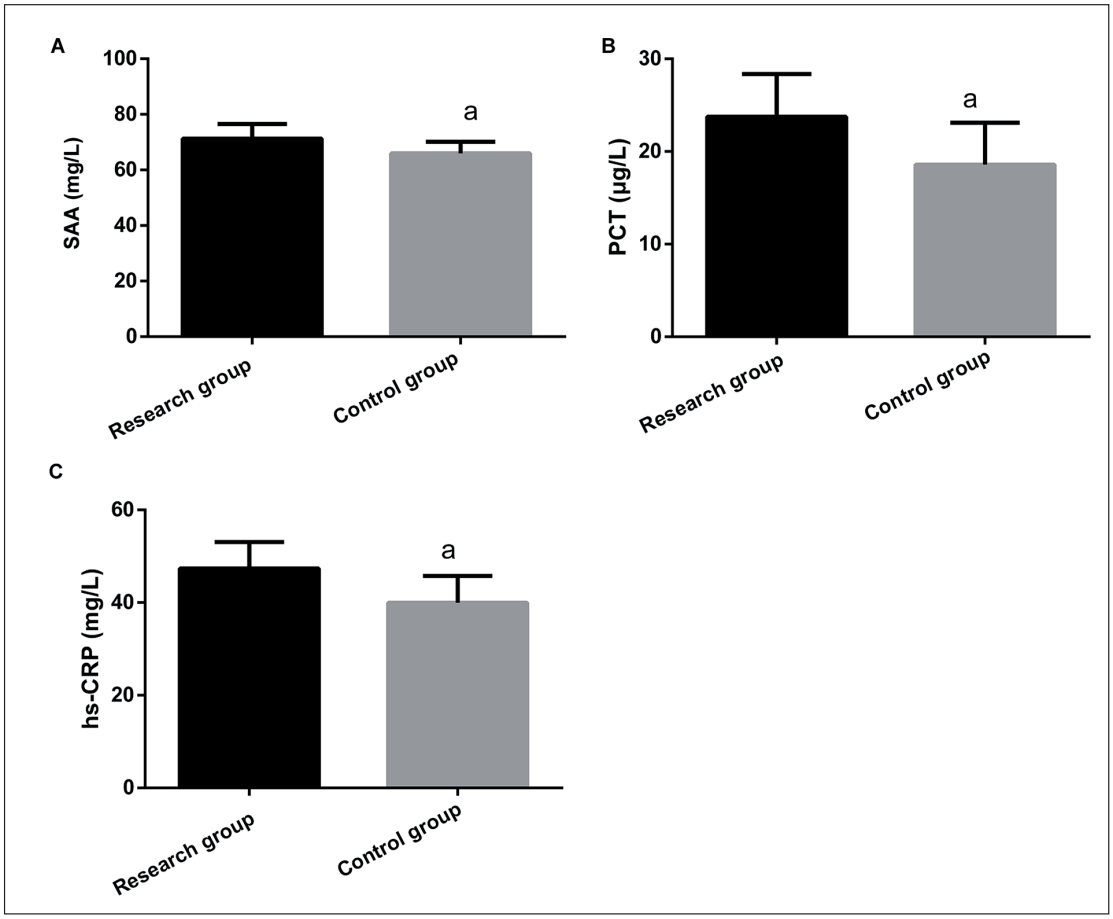

Figure 1. Comparison of concentrations of SAA, PCT and Hs-CRP of patients between the two groups. **A,** SAA expression levels in serum of patients in research group were significantly higher than those in control group before treatment (a:$p< 0.05$). **B,** PCT expression levels in serum of patients in study group were significantly higher than those in control group before treatment (a:$p< 0.05$). **C,** Serum hs-CRP expression levels of patients in study group were significantly higher than those of control group before treatment (a:$p< 0.05$).

in markedly effective group was significantly lower than that in ineffective group after treatment, $p< 0.05$ (Figure 3a for details).

The PCT level in markedly effective group was 23.86±3.58 (μg/L) before treatment and 20.45 ±4.68 (μg/L) after treatment. The PCT level before treatment was significantly higher than that after treatment, $p< 0.05$. The PCT level of patients in ineffective group was 23.49±3.65 (μg/L) before treatment and 24.34±4.89 (μg/L) after treatment. There were no significant changes in PCT level before and after treatment, $p > 0.05$. The PCT level in markedly effective group was significantly lower than that in ineffective group after treatment, $p< 0.05$ (Figure 3b).

The hs-CRP level in markedly effective group was 47.33±3.21 (mg/L) before treatment and 42.13±4.11 (mg/L) after treatment. The hs-CRP level before treatment was significantly higher than that after treatment, $p< 0.05$. The hs-CRP level in ineffective group was 46.91±3.96 (mg/L) before treatment and 48.36±4.63 (mg/L) after treatment. There were no significant changes in hs-CRP level before and after treatment, $p > 0.05$. The Hs-CRP level in markedly effective group was significantly lower than that in ineffective group after treatment, $p< 0.05$ (Figure 3c).

Predictive Value of Joint Detection of Serum Amyloid Protein A, PCT, and Hs-CRP for Effective Treatment

ROC curve analysis showed that when SAA+PCT+hs-CRP was used to jointly examine the efficacy of neonatal septicemia, the cut-off value was 0.313, sensitivity was 60.71%, and specificity was 95.21% (Figure 4).

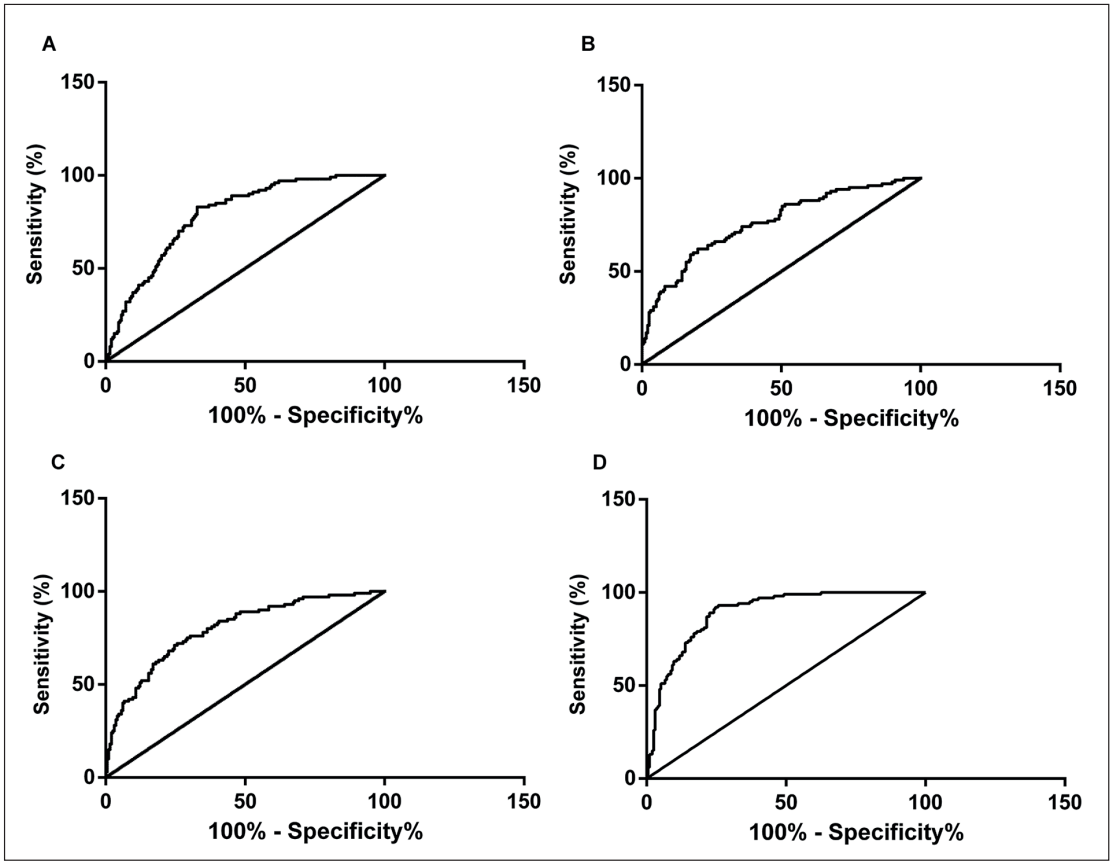

Figure 2. Diagnostic value of serum Amyloid A, PCT, and Hs-CRP in neonatal septicemia. **A,** Diagnostic Value of SAA in Serum. **B,** Diagnostic Value of PCT in Serum. **C,** Diagnostic Value of Hs-CRP in Serum. **D,** Diagnostic Value of Joint Detection of SAA+PCT+Hs-CRP in Serum.

Discussion

Neonatal infection currently causes about 1.6 million deaths in developing countries each year, with sepsis and meningitis being the main causes of neonatal death[13]. Sources of pathogens include intrauterine infection, obtained from maternal flora, or from postpartum hospitals or communities. Exposure time, vaccine dose, and virulence of pathogenic factors affect the process of neonatal septicemia[14]. At present, the diagnosis of neonatal septicemia is considered as the golden standard[15], but this analysis is still too slow and limited. We need to find a faster and more sensitive diagnosis method.

Krishnaveni et al[16] showed that SAA can help diagnose neonatal septicemia to some extent. To predict the early onset of neonatal septicemia, 196 newborn patients suspected of sepsis were measured with quantitative methods. It was found that CRP can be used as a rapid and cheap prediction index through quantitative evaluation, and unnecessary antibiotic use can be prevented[17]. Naher et al[18] by studying the diagnostic

Table II. ROC diagnosis results of neonatal septicemia.

Diagnostic indexes	AUC	95% CI	Cut-off value	Sensitivity (%)	Specificity (%)
SAA	0.785	0.733-0.837	69.28	83.00%	66.15%
PCT	0.760	0.702-0.819	20.14	62.00%	80.00%
Hs-CRP	0.796	0.743-0.849	43.42	71.00%	75.38%
SAA+PCT+hs-CRP	0.891	0.855-0.927	0.194	92.00%	75.38%

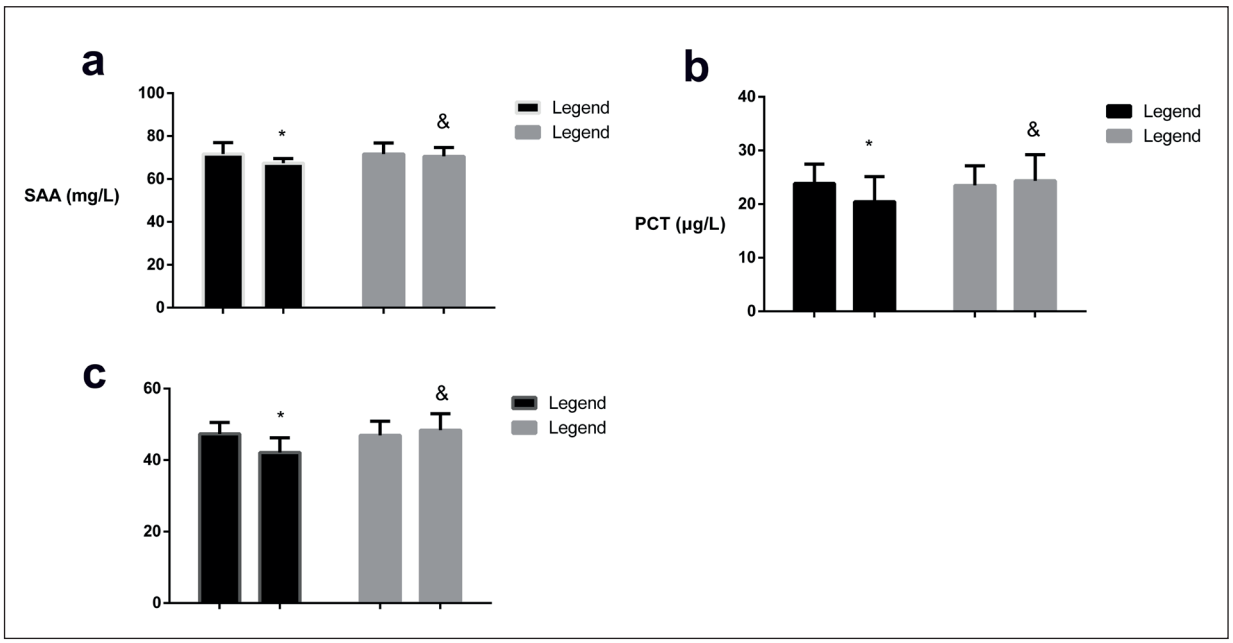

Figure 3. Comparison of concentrations of SAA, PCT, Hs-CRP before and after treatment between patients in markedly effective group and ineffective group in research group. **a,** SAA levels of patients in effective group before treatment were significantly higher than those after treatment (*p< 0.05). After treatment, SAA levels in markedly effective group were significantly lower than those in ineffective group. **b,** PCT levels of patients in markedly effective group before treatment were significantly higher than those after treatment (*p< 0.05). PCT levels in markedly effective group were significantly lower than those in ineffective group after treatment. **c,** Hs-CRP levels before treatment in markedly effective group were significantly higher than hs-CRP levels after treatment (*p< 0.05). Hs-CRP levels in markedly effective group were significantly lower than that in ineffective group after treatment.

value of procalcitonin and C-reactive protein for early onset septicemia of newborns of different ages found that PCT and CRP have age specificity in early end-stage diagnosis without serious complications, and PCT has high sensitivity for early diagnosis. In the past, there have been many researches[19,20] on the diagnostic value of single serum marker in neonatal septicemia, but the detection of single serum marker is easy to cause missed diagnosis and misdiagnosis, delay the treatment opportunity of patients, and joint diagnosis has better detection effect. Therefore, this work observes the expression level of serum amyloid A, PCT, hs-CRP in neonatal septicemia, and discusses the diagnostic value of its joint detection in neonatal septicemia, so as to provide a basis for early diagnosis of neonatal septicemia.

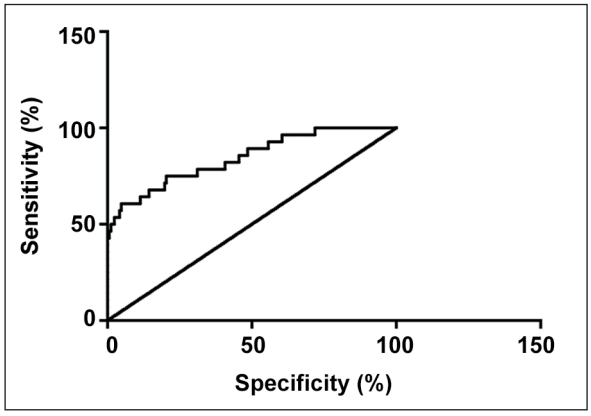

Figure 4. Diagnostic value of SAA+PCT+Hs-CRP in serum for efficacy. When SAA+PCT+hs-CRP was used to jointly examine the efficacy of neonatal septicemia, the cut-off value was 0.313, sensitivity was 60.71%, and specificity was 95.21%.

Results of this study showed that levels of serum SAA, PCT, and hs-CRP in neonatal septicemia patients were significantly higher than those in healthy control group, and levels of SAA, PCT, and hs-CRP in effective group were statistically different from those in ineffective group after treatment, suggesting that SAA, PCT, and hs-crp participated in the development of neonatal septicemia to some extent. Monitoring SAA, PCT, and hs-CRP is helpful for early diagnosis of infectious diseases. Maamouri et al[21] found that PCT

level of clinical sepsis newborns was about twice as high as a normal newborn through analyzing SAA level in the blood of 100 newborns. Rashwan et al[22] detected 168 newborns recruited in the neonatal intensive care unit and found that PCT and hs-CRP serum levels significantly increased in sepsis group and the experimental results are consistent with our investigation. We further analyzed and found that SAA, PCT, and hs-CRP have high clinical value in the diagnosis of neonatal septicemia. When levels of SAA+PCT+hs-CRP were jointly detected, the sensitivity was 92.00% and the specificity was 75.38%. Joint detection can improve the sensitivity of diagnosis of neonatal septicemia and promote the sensitivity and accuracy of diagnosis. Yang et al[23] when studying whether the combination of neutrophil CD64 with PCT, C-reactive protein and white blood cell count can improve the sensitivity and accuracy of neonatal septicemia diagnosis, we found that the combination of these biomarkers can improve the diagnostic sensitivity of suspected delayed neonatal septicemia based on common serum biomarkers Aydin et al[24] observed the effectiveness of flow cytometry detection of inflammatory markers in the early diagnosis of neonatal septicemia. The combination of cell surface antigen and acute reactant can improve the diagnostic accuracy, which is consistent with our conclusion that the combination of multiple markers for detection has higher diagnostic value for neonatal septicemia. The relation between SAA, PCT, and hs-crp and the development of neonatal septicemia treatment was analyzed. It was found that the joint detection of SAA+PCT+hs-CRP with sensitivity of 60.71% and specificity of 95.21% could predict the efficacy to some extent, indicating that it could be used as an examination index for the efficacy of neonatal septicemia in the future, which was consistent with the conclusion proposed by Jia et al[25] that the detection by PCT combined with other markers could predict the severity and prognosis of neonatal septicemia patients.

In this report, although expression levels of SAA, PCT, and hs-crp in blood of patients with neonatal septicemia and healthy newborns were compared and analyzed, the diagnostic value of single detection and joint detection for neonatal septicemia and the diagnostic value of joint detection for efficacy were discussed, but the specific regulatory mechanism of the three in neonatal septicemia has not been discussed yet, and these deficiencies need to be supplemented in the following research.

Conclusions

We found that SAA, PCT, and hs-crp may be involved in the occurrence and development of neonatal septicemia. Joint detection has better sensitivity and specificity in the diagnosis of neonatal septicemia, and may better predict the efficacy of diseases. It has a higher diagnostic value and is worthy of clinical application.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Boskabadi H, Zakerihamidi M. Evaluate the diagnosis of neonatal sepsis by measuring interleukins: a systematic review. Pediatr Neonatol 2018; 59: 329-338.
2) Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet 2017; 390: 1770-1780.
3) Baranova IN, Souza ACP, Bocharov AV, Vishnyakova TG, Hu X, Vaisman BL, Amar MJ, Chen Z, Remaley AT, Patterson AP, Yuen PST, Star RA, Eggerman TL. Human SR-BII mediates SAA uptake and contributes to SAA pro-inflammatory signaling in vitro and in vivo. PLoS One 2017; 12: e0175824.
4) De Buck M, Gouwy M, Struyf S, Opdenakker G, Van Damme J. The ectoenzyme-side of matrix metalloproteinases (MMPs) makes inflammation by serum amyloid A (SAA) and chemokines go round. Immunol Lett 2019; 205: 1-8.
5) Yu MH, Chen MH, Han F, Li Q, Sun RH, Tu YX. Prognostic value of the biomarkers serum amyloid A and nitric oxide in patients with sepsis. Int Immunopharmacol 2018; 62: 287-292.
6) Pérez Solís D, López Sastre JB, Coto Cotallo GD, Diéguez Junquera MA, Deschamps Mosquera EM, Crespo Hernández M. [Procalcitonin for the diagnosis of nosocomial neonatal sepsis]. An Pediatr (Barc) 2006; 64: 349-353.
7) Eschborn S, Weitkamp JH. Procalcitonin versus C-reactive protein: review of kinetics and performance for diagnosis of neonatal sepsis. J Perinatol 2019 Mar 29. doi: 10.1038/s41372-019-0363-4. [Epub ahead of print]
8) Kitagawa K, Hosomi N, Nagai Y, Ohtsuki T, Kagimura T, Minematsu K, Uchiyama S, Matsumoto M. HS-CRP level is an independent predictor for recurrent stroke and vascular events in patients with non-cardiogenic brain infarction. J Neurol Sci 2017; 381: 869-870.
9) Wang J, Wu X, Tian Y, Li X, Zhao X, Zhang M. Dynamic changes and diagnostic and prognostic significance of serum PCT, hs CRP, and s-100 protein in central nervous system infection. Exp Ther Med 2018; 16: 5156-5160.

10) Giacobbe DR, Mikulska M, Tumbarello M, Furfaro E, Spadaro M, Losito AR, Mesini A, De Pascale G, Marchese A, Bruzzone M, Pelosi P, Mussap M, Molin A, Antonelli M, Posteraro B, Sanguinetti M, Viscoli C, Del Bono V; ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva). Combined use of serum (1, 3)-β-D-glucan and procalcitonin for the early differential diagnosis between candidaemia and bacteraemia in intensive care units. Crit Care 2017; 21: 176.

11) Yang X, Yan Z, Yang H, Ni H, Zhang L, Wang Y. Clinical value of combined detection of miR 1202 and miR 195 in early diagnosis of cervical cancer. Oncol Lett 2019; 17: 3387-3391.

12) Fuchs A, Bielicki J, Mathur S, Sharland M, Van Den Anker JN. Reviewing the WHO guidelines for antibiotic use for sepsis in neonates and children. Paediatr Int Child Health 2018; 38: S3-S15.

13) Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal sepsis: an international perspective. Arch Dis Child Fetal Neonatal Ed 2005; 90: F220-F224.

14) Beck R, Malvasi A, Kuczkowski KM, Marinelli E, Zaami S. Intrapartum sonography of fetal head in second stage of labor with neuraxial analgesia: a literature review and possible medicolegal aftermath. Eur Rev Med Pharmacol Sci 2019; 23: 3159-3166.

15) García-Gudiño I, Yllescas-Medrano E, Maida-Claros R, Soriano-Becerril D, Díaz NF, García-López G, Molina-Hernández A, Flores-Herrera O, Zavala-Díaz de la Serna FJ, Del Rosario Peralta-Pérez M, Flores-Herrera H. Microbiological comparison of blood culture and amplification of 16S rDNA methods in combination with DGGE for detection of neonatal sepsis in blood samples. Eur J Pediatr 2018; 177: 85-93.

16) Krishnaveni P, Vanitha GMN, Pradeep GCM. Estimation of serum amyloid A protein in neonatal sepsis: a prospective study. Int J Med Sci Public Health 2016; 5: 1665-1672.

17) Muhammad Z, Ahmed A, Hayat U, Wazir MS, Rafiyatullah, Waqas H. Neonatal sepsis: causative bacteria and their resistance to antibiotics. J Ayub Med Coll Abbottabad 2010; 22: 33-36.

18) Naher BS, Mannan MA, Noor K, Shahiddullah M. Role of serum procalcitonin and C-reactive protein in the diagnosis of neonatal sepsis. Bangladesh Med Res Counc Bull 2011; 37: 40-46.

19) Memar MY, Alizadeh N, Varshochi M, Kafil HS. Immunologic biomarkers for diagnostic of early-onset neonatal sepsis. J Matern Fetal Neonatal Med 2019; 32: 143-153.

20) Zhao FX, Liu GH, Zhang J. Value of IL-6 and IL-8 in the diagnosis of neonatal sepsis. Zhongguo Dang Dai Er Ke Za Zhi 2015; 17: 1311-1315.

21) Maamouri G, Boskabadi H, Azghandi M, Sayedi SJ, Bagheri F, Boskabadi A. The evaluation of serum procalcitonin levels in neonatal infections. Int J Pediatr 2017; 5: 5287-5294.

22) Rashwan NI, Hassan MH, Mohey El-Deen ZM, Ahmed AE. Validity of biomarkers in screening for neonatal sepsis–A single center–hospital based study. Pediatr Neonatol 2019; 60: 149-155.

23) Yang AP, Liu J, Yue LH, Wang HQ, Yang WJ, Yang GH. Neutrophil CD64 combined with PCT, CRP and WBC improves the sensitivity for the early diagnosis of neonatal sepsis. Clin Chem Lab Med 2016; 54: 345-351.

24) Aydin M, Barut S, Akbulut HH, Ucar S, Orman A. Application of flow cytometry in the early diagnosis of neonatal sepsis. Ann Clin Lab Sci 2017; 47: 184-190.

25) Jia Y, Wang Y, Yu X. Relationship between blood lactic acid, blood procalcitonin, C-reactive protein and neonatal sepsis and corresponding prognostic significance in sick children. Exp Ther Med 2017; 14: 2189-2193.