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Procalcitonin and Pancreatic Stone Protein Function as Biomarkers in Early Diagnosis of Pediatric Acute Osteomyelitis

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Statistical Analysis C
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Manuscript Preparation E
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Background: High plasma levels of procalcitonin (PCT) are typically seen in children with severe bacterial infection, particularly in cases of septic shock or bacteremia. Similarly, pancreatic stone protein (PSP) is associated with inflammation, infection, and other disease-related stimuli. However, the prognostic value of PSP in critically ill pediatric patients is unknown. This study investigated the early diagnostic value of PCT and PSP in pediatric acute osteomyelitis.

Material/Methods: A total of 187 patients with suspected acute osteomyelitis and 80 healthy control children were enrolled. The serum expression of PTC and PSP was measured. Pearson correlation analysis was conducted to correlate PTC with PSP. ROC analysis was used to test the value of PTC and PSP in early diagnosis of pediatric acute osteomyelitis.

Results: Acute osteomyelitis was diagnosed in 49.2% of the patients (n=92) based on the layered bone puncture. The serum levels of PTC and PSP in pediatric acute osteomyelitis were higher than in the non-acute osteomyelitis group ($P<0.01$). Serum PTC concentrations showed a significantly positive correlation with PSP levels ($P<0.001$). ROC analysis showed that the AUC values of PTC and PSP were 0.767 (95% CI, 0.700–0.826), and 0.796 (95% CI, 0.731–0.855), respectively. The AUC value of PTC & PSP was 0.903 (95% CI: 0.851–0.941), which was markedly increased compared with PTC or PSP ($P<0.01$).

Conclusions: Serum levels of PCT and PSP are promising biomarkers for early diagnosis of pediatric acute osteomyelitis.

MeSH Keywords: Calcitonin • Diagnosis • Lithostathine • Osteomyelitis

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Background

Acute osteomyelitis, a serious disease that affects bone, concomitant with septic arthritis, is characterized by rapid onset and progression [1]. Unfortunately, its incidence of approximately 8 cases per 100 000 children annually, and is highly prevalent in those aged ≤7 years [2]. Acute osteomyelitis usually occurs in 3 types: osteomyelitis secondary to a contiguous focus of infection (after trauma, surgery, or insertion of a joint prosthesis); osteomyelitis secondary to vascular insufficiency (in diabetic foot infections); and osteomyelitis of hematogenous origin [3]. Despite advances in living standards and antibiotic management, the small group of patients who subsequently develop chronic osteomyelitis require prolonged hospitalization, extensive intravenous antibiotic intervention, and repeat surgery and management of long-term functional sequelae [4]. The signs and symptoms of disease onset warrant prompt diagnostic and therapeutic intervention. Current diagnosis based on detection of pus cells or bacterial culture during bone biopsy causes severe trauma and prolonged diagnostic monitoring [5]. White-cell count, erythrocyte sedimentation rate, and serum C-reactive protein levels do not facilitate differential diagnosis of septic arthritis from other forms of acute arthritis, while serum procalcitonin (PCT) levels are useful for differentiation [6–8]. Aviel et al. regarded PCT as a diagnostic marker for the initiation of treatment and management of acute osteomyelitis [8]. Several studies have demonstrated that pancreatic stone protein (PSP), a newly discovered and sensitive indicator of infection, may represent a potential biomarker of sepsis-related inflammation [9–11]. However, its role in the diagnosis of pediatric acute osteomyelitis is still unknown. Our study was designed to detect the serum concentrations of PCT and PSP in children suspected of acute osteomyelitis, with the clinical signs of abrupt high fever, sepsis and bone tenderness. We evaluated the role of PCT and PSP in early diagnosis of pediatric acute osteomyelitis.

Material and Methods

Study population

As shown in Figure 1, The study enrolled 187 children with suspected osteomyelitis admitted to Department of integrated traditional Chinese and Western Medicine from 2012 to 2015. All the cases satisfied the inclusion criteria: a) abrupt high fever or sepsis; b) predisposition to severe pain in the metaphysis; c) tenderness in the metaphysis; and d) white blood cell count greater than 10×10^9/L. In addition, 80 healthy volunteers were adopted. The 187 children suspected with acute osteomyelitis were divided into groups of acute osteomyelitis (n=92) and non-acute osteomyelitis (n=95), according to the layered bone structure. Patients signed informed consent, which was approved by the ethics committee of the hospital.

Data collection

Age, sex, height, weight, body mass index (BMI), blood pressure and surgical history were recorded by an orthopedist. Medical examination was conducted by an orthopedist and bone tenderness was recorded as well.

Serum samples

Fasting blood samples were extracted from each subject. Supernatants were obtained after centrifugation (4°C, 3000 r/min, 10 min) and stored at –80°C. Routine blood testing was conducted by laboratory physicians at our hospital. Microparticle enzyme immunoassay was used to test the serum levels of PCT and DakoCytomation immunoturbidimetric assay was used for PSP analysis.

Statistical analysis

Data were statistically analyzed using SPSS, MedCalc and GraphPad Prism. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were displayed as counts or percentages. Median test was conducted to compare median values. Differences between the groups were analyzed using Student's t-test and χ^2-test for categorical variables. Spearman correlation was used to analyze the relationship between PCT and PSP. Receiver operating characteristic (ROC) analysis was used to compare the prognostic value of PCT and PSP in pediatric acute osteomyelitis. Multivariate analysis of markers was performed by constructing a logistic regression model, and a new score, named (PCT & PSP), was generated. Differences were considered significant at $P<0.05$.

Results

Baseline patient demographics

A total of 187 suspected cases of acute osteomyelitis were collected, with an average age of 12.4±4.5 years, including 104 males and 83 females. Finally, 92 children were diagnosed with acute osteomyelitis, accounting for 49.2%. 80 healthy volunteers were recruited, with an average age of 11.3±3.2 years. No significant differences were found in patients' age, sex, and weight between patients with acute and non-acute osteomyelitis. The location of different lesions in 92 children with acute osteomyelitis was identified. Tibia was the most common site accounting for 60.8%, followed by femur (26.1%), humerus (8.7%), and ilium and phalanges (each 2.2%). The bacterial culture results revealed that methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus* were the most common bacteria causing acute osteomyelitis. Further, the serum PCT, hs-CRP and PSP levels were higher than in the non-acute osteomyelitis group of patients ($P<0.05$; Table 1).

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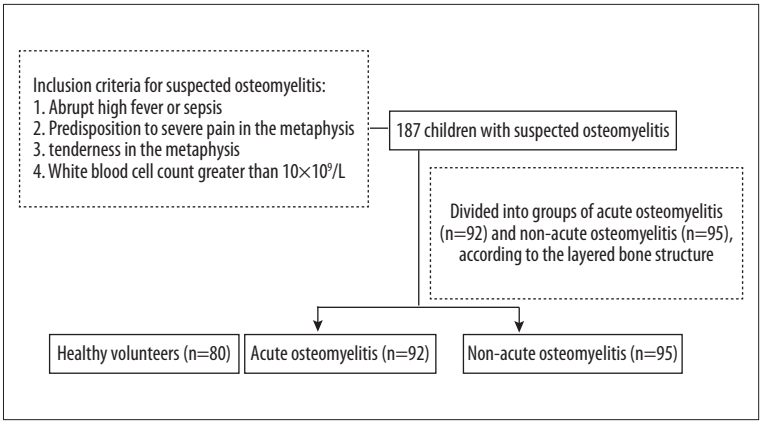

Figure 1. A flow diagram of study participants.

Table 1. Baseline characteristics of 187 patients (x±s).

	Volunteers (n=80)	Non-acute osteomyelitis (n=95)	Acute osteomyelitis (n=92)	*P**
Age (year)	5.31±3.20	6.17±2.74	6.50±3.44	0.678
Sex				
Male	47 (58.7%)	63 (66.3%)	45 (48.9%)	0.546
Female	33 (41.3%)	32 (33.7%)	47 (51.1%)	0.546
Weight (Kg)	37.12±3.91	35.62±4.84	36.47±4.21	0.531
Lesion site				
Tibia		51 (53.7%)	56 (60.8%)	0.241
Femur		24 (25.3%)	24 (26.1%)	0.241
Humerus		10 (10.5%)	8 (8.7%)	0.241
Ilium		5 (5.3%)	2 (2.2%)	0.241
Phalange		5 (5.3%)	2 (2.2%)	0.241
Layered Bone stab culture				
Staphylococcus aureus			44 (47.8%)	
Streptococcus			13 (14.1%)	
Haemophilus			4 (4.3%)	
Escherichia coli			3 (3.3%)	
WBC (×10⁹/L)	3.64±1.25	12.84±2.72	13.64±3.92	0.135
hs-CRP (mg/mL)	6.11±0.45	63.64±12.36	77.71±23.84	0.048
PCT (ng/mL)	0.06±0.05	2.73±2.17	5.20±4.27	<0.01
PSP (ng/mL)	5.12±2.70	23.63±9.86	36.80±12.05	<0.01

hs-CRP – high-sensitivity C-reactive protein; PCT – procalcitonin; PSP – pancreatic stone protein. **P* value – compared between non-acute osteomyelitis and acute osteomyelitis.

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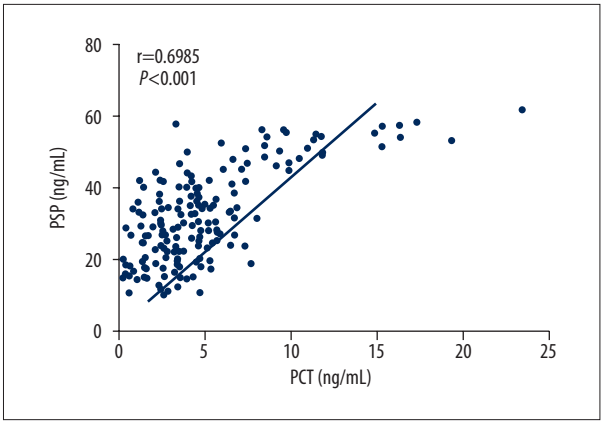

Figure 2. Correlation analysis of Procalcitonin with Pancreatic Stone Protein.

Correlation of PCT with PSP

As illustrated in Figure 2, PCT was positively correlated with PSP (r=0.6985, P<0.001) using Spearman correlation analysis of all patients suspected with acute osteomyelitis.

Diagnostic value of PCT and PSP: ROC curves

The serum concentrations of PCT and PSP were higher in the group of suspected patients (P<0.05; Table 1) compared with volunteers, as shown in Figure 3. To further determine the diagnostic value of the 2 biomarkers, receiver operating characteristic (ROC) curves were obtained. The results shown in Figure 4 indicated that the area under the curve (AUC) values of PCT and PSP were 0.767 (95% CI, 0.700–0.826) and 0.796 (95% CI, 0.731–0.851), respectively. The sensitivity and specificity of cutoff values were calculated according to ROC curve analysis (Table 2). Subsequently, the ROC curve comparison revealed no significant differences between PCT and PSP (P=0.5320) as shown in Figure 5. As shown in Table2, multivariate logistic regression analysis revealed that PCT (OR=1.19, 95% CI=0.69–2.55) and PSP (OR=1.39, 95% CI=0.54–2.41) as risk factors for children with acute osteomyelitis (P<0.05). Then we used these 2 biomarkers to conduct a new score: (PCT & PSP)=–0.2195+0.03724*PCT+0.01684*PSP. ROC analysis of PCT, PSP and PCT & PSP are presented in Table 3. The diagnostic value of the combined PCT and PSP levels in acute osteomyelitis was superior to that of the individual levels (P<0.01; Figure 5), with a high AUC value of 0.903 (95%CI, 0.851–0.941).

Discussion

Acute osteomyelitis is usually caused by pyogenic bacteria through hematogenous infection, and MRSA [12–14]. Acute osteomyelitis can easily turn chronic if the onset is not recognized early, and may be complicated with sepsis, bone abnormalities, pain from repeated surgeries, and associated medical treatment costs [15]. Hence, early diagnosis of pediatric acute osteomyelitis is critically important.

PCT is a peptide hormone released by non-neuroendocrine parenchymal cells in the body [16]. It is rarely released into vascular circulation under normal circumstances and its serum levels are as high as 50-800 ng/mL in patients with severe sepsis [17]. Simon, L., et al. argued that PCT was useful marker to differentiate bacterial infections from viral infections and to differentiate bacterial infections from other non-infective causes of systemic inflammation [18]. Recently, the diagnostic and predictive value of PCT in acute osteomyelitis was validated in several studies. Karthikeyan et al. detected serum PCT levels in 82 suspected acute osteomyelitis patients

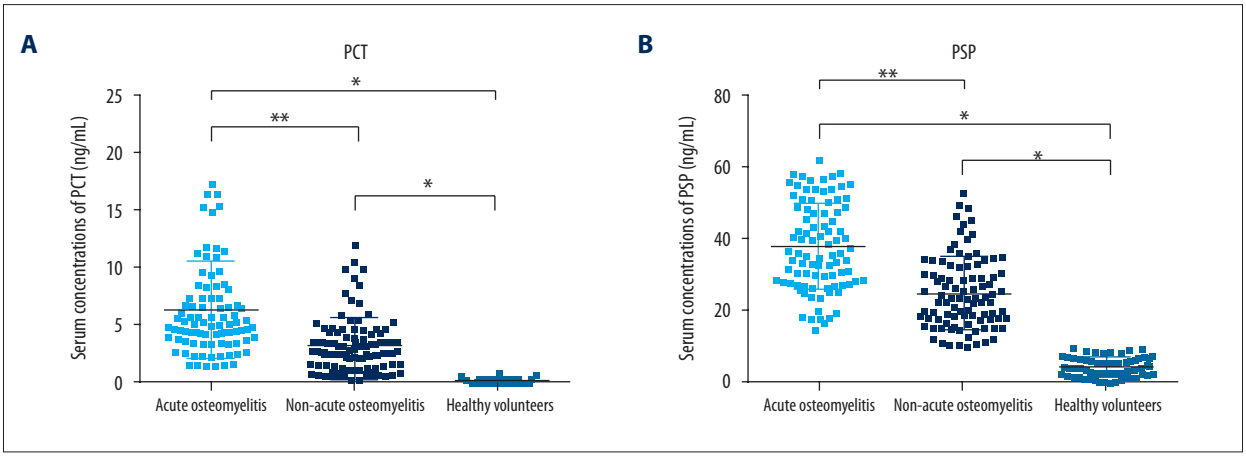

Figure 3. The serum level of Procalcitonin and pancreatic stone protein (**A**) The serum concentration of Procalcitonin (PCT) in acute osteomyelitis group, non-acute osteomyelitis group and healthy volunteers group. (**B**) The serum concentration of Pancreatic Stone Protein (PSP) in acute osteomyelitis group, non-acute osteomyelitis group and healthy volunteers group. * P<0.01 *vs.* healthy volunteers group; ** P<0.01 *vs.* non-acute osteomyelitis group.

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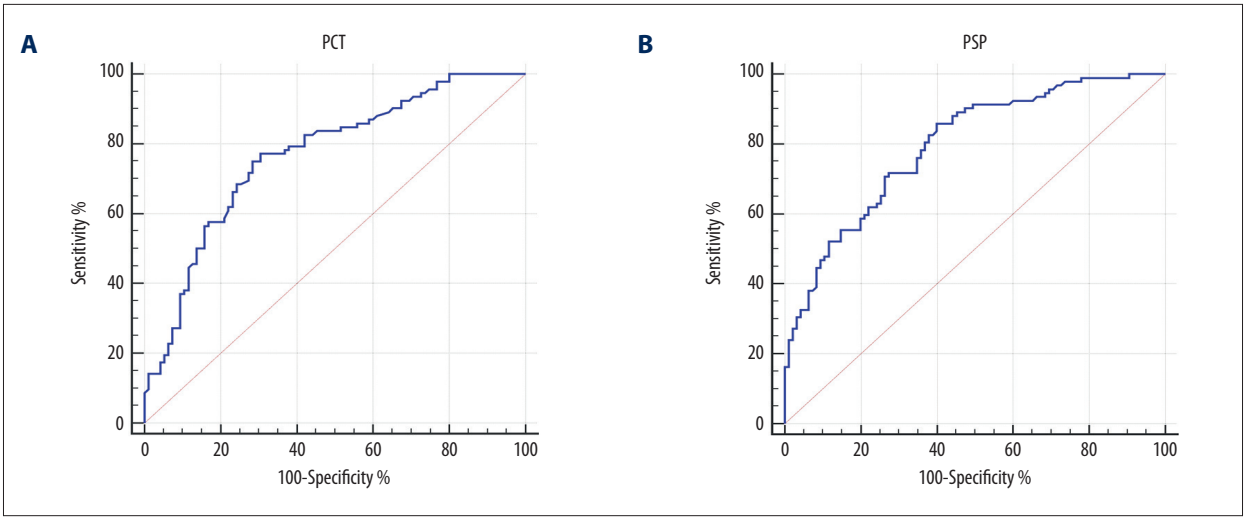

Figure 4. ROC analysis of Procalcitonin and Pancreatic Stone Protein on early diagnosis of acute osteomyelitis. (**A**) ROC analysis of Procalcitonin. AUC value: 0.767 (95% CI, 0.700–0.826), and its sensitivity and specificity was 77.17% and 69.47%, respectively. Cutoff value is 3.56 mg/ml. (**B**) ROC analysis of Pancreatic Stone Protein, AUC value: 0.796 (95% CI, 0.731–0.851), and its sensitivity and specificity was 85.87% and 60.00%, respectively. Cutoff value is 26.49 mg/ml.

Table 2. Multivariable Logistic regression analysis for patients with acute osteomyelitis.

Parameter	B	Wald	OR (95% CI)	*P* values
WBC(<5.80=0, ≥5.80=1)	0.041	0.724	1.04 (0.30–1.81)	0.354
hs-CRP(<2.55=0, ≥2.55=1)	0.101	0.963	1.09 (0.38–1.95)	0.096
PCT (<3.56=0, ≥3.56=1)	0.182	1.998	1.19 (0.69–2.55)	0.015
PSP (<26.49=0, ≥26.49=1)	0.334	2.114	1.39 (0.54–2.41)	0.008

hs-CRP – high-sensitivity C-reactive protein; PCT – procalcitonin; PSP – pancreatic stone protein; B – partial regression coefficient; CI – confidence interval.

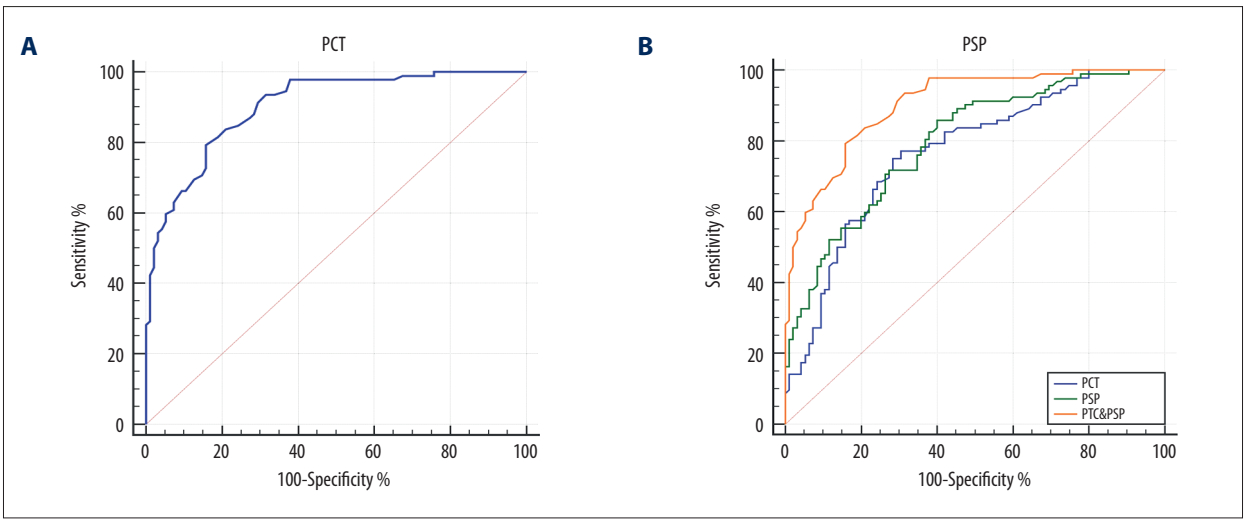

Figure 5. ROC analysis of combination of Procalcitonin with Pancreatic Stone Protein on early diagnosis of acute osteomyelitis. (**A**) ROC analysis of PTC & PSP, AUC value: 0.903 (95%CI,0.851–0.941), and its sensitivity and specificity was 85.87% and 84.21%, respectively. Cutoff value is 0.23 mg/ml. (**B**) comparison of AUC of Procalcitonin, Pancreatic Stone Protein and PTC & PSP.

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Table 3. ROC analysis of Procalcitonin and Pancreatic Stone Protein on early diagnosis of acute osteomyelitis.

Values	auROC	95%CI	P	Youden	Cut-off	Sensitivity	Specificity
PTC	0.767	0.700–0.826	<0.001	0.4665	3.56	77.17%	69.47%
PSP	0.796	0.731–0.851	<0.001	0.459	26.49	85.87%	60.00%
PTC & PSP	0.903	0.851–0.941	<0.001	0.6356	0.23	85.87%	84.21%

Value of (PTC & PSP)=–0.2195+0.03724*PCT+0.01684*PSP; AUC – area under ROC curve; PCT – Procalcitonin; PSP – Pancreatic Stone Protein.

and found that PCT showed appropriate sensitivity and specificity, at a cutoff value of 0.4 ng/mL for the early diagnosis of acute osteomyelitis [19]. By contrast, Maharajan et al. regarded plasma PCT as a diagnostic marker in acute osteomyelitis, with a single standard of cutoff values and larger studies with better design using newer-generation, quantitative, and more sensitive kits [19]. In our study, we tested the PCT levels in 187 suspected cases of acute osteomyelitis and discovered higher values compared with healthy volunteers, which suggested an increase in PCT under infection. We further compared PCT levels of patients with acute osteomyelitis and septic arthritis after diagnosis using a layered double hydroxide nanocomposite and found that serum PCT levels were high in acute osteomyelitis patients. Further, AUC value of PCT was 0.767 (95% CI, 0.700–0.826) and PCT showed sufficient sensitivity and specificity at a cutoff value of 3.56 ng/mL in the differential diagnosis. Based on the foregoing data, we conclude that PCT is a potential diagnostic aid in pediatric acute osteomyelitis.

PSP, also known as regenerating protein, is constitutively secreted by pancreatic acinar cells and subsets of intestinal and gastric cells. Graf R et al. found that PSP exhibited protective function by promoting cellular proliferation during beta-cell regenerative processes and epithelial repair [20]. PSP was upregulated in blood after trauma, and was bound to activate neutrophils. Thus, PSP might serve as an acute-phase protein [21]. Recent focus is on the role of PSP in infectious diseases, such as sepsis. Palmiere et al. investigated PSP in postmortem serum in a series of sepsis-related and non-septic fatalities and found that PSP was positively correlated with PCT, whose serum concentrations were markedly lower in non-sepsis patients [22]. Furthermore, Jiri et al. conducted a prospective observational study and found higher levels of PSP in patients with organ dysfunction indicating that PSP was a potential marker of severity or high risk of death in a few patients in pediatric ICU [23]. Besides, Schlapbach et al. found increased PSP levels were strongly associated with early-onset sepsis and its cutoff value was 9 ng/ml and revealed that combining PSP and PCT improved the diagnosis [24]. A recent study revealed by Wu et al. showed the similar findings that PSP was an independent risk factor for pediatric sepsis and was a promising biomarker for risk stratification of pediatric sepsis [25]. Based on the prognostic value of PSP in infectious diseases, we detected serum PCT and PSP levels in 187 children with suspected acute osteomyelitis and found that PSP, which was positively correlated with PCT, was a similar diagnostic marker of early-stage acute osteomyelitis. The AUC value of PSP was 0.796 (95% CI, 0.731–0.851) and its sensitivity and specificity were 85.87% and 60.00%, respectively. Therefore, it appears that PSP can be used as a biomarker to identify the onset of pediatric acute osteomyelitis.

It is unlikely that any single biomarker is perfect in the diagnosis of pediatric diseases. Detection of multiple biomarkers and statistical analysis markedly enhance the diagnostic sensitivity and specificity [26,27]. In this study, we used multivariate logistic regression analysis to calculate each coefficient: PTC & PSP=–0.2195+0.03724*PCT+0.01684*PSP, and the AUC value of (PCT & PSP) was up to 0.903, which was notably superior to PCT or PSP alone. Therefore, the joint detection of PCT and PSP improves the sensitivity and specificity of early diagnosis in pediatric acute osteomyelitis.

Conclusions

In conclusion, this study shows that serum PCT and PSP levels are promising diagnostic biomarkers of early-stage pediatric acute osteomyelitis. Furthermore, the combination of serum PCT and PSP improves the early diagnosis of the disease.

Conflict of interest

None.

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