Meta-analysis of serum procalcitonin diagnostic test accuracy for osteomyelitis and septic arthritis in children

Hai-Tao Zhang[a,b], Chao Li[a,b], Yi-Zheng Huang[a,b] and Yong Huang[a,b]

The purpose of this study was to evaluate the sensitivity, specificity, and predictive value of serum procalcitonin (PCT) for osteomyelitis and septic arthritis in children. PubMed, EMBase, and Cochrane Library were searched until 10 August 2021, for eligible literature focusing on PCT for the diagnosis of osteomyelitis and septic arthritis. Four articles with six studies were included in the diagnostic meta-analysis, a total of 654 children were examined for bacterial cultures in PCT, osteomyelitis, and septic arthritis. The results of diagnostic meta-analysis showed that the PCT had a sensitivity of 0.72, 95% confidence interval (CI) (0.65–0.79), specificity of 0.90, 95% CI (0.87–0.93), positive likelihood ratio (LR) of 3.87, 95% CI (2.53–5.90), negative LR of 0.39, 95% CI (0.22–0.70), and diagnostic odds ratio was 13.13, 95% CI (6.46–26.66), for the detection of osteomyelitis and septic arthritis using bacterial culture as the gold standard. Based on the summary receiver operating characteristic curve of PCT, it was found that the area under the curve of PCT was 0.88. In the evaluation of publication bias, the result of the regression line test showed that there was not publication bias (bias = 13.72; 95% CI, −1.84 to 29.28; $P = 0.07$). This study provided systematic review of the published literature on the diagnosis of osteomyelitis and septic arthritis in children using PCT, which may serve as a biomarker for diagnosis of osteomyelitis, but it has no direct evidences to support the diagnosis of septic arthritis. However, the specific optimal cutoff value of PCT and specific population still needed to be verified by large sample studies. *J Pediatr Orthop B* 32: 481–489

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[a]Department of Spinal Surgery, Hubei Provincial Hospital of Traditional Chinese Medicine and [b]Department of Spinal Surgery, Hubei Province Academy of Traditional Chinese Medicine, Wuhan, China

Correspondence to Yong Huang, MD, Department of Spinal Surgery, Hubei Provincial Hospital of Traditional Chinese Medicine, Hubei Province Academy of Traditional Chinese Medicine, No.856 Luoyu Road, Wuhan 430074, China
Tel: +86 13871168161; e-mail: huangyong_HPHTCM@163.com

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Introduction

Osteomyelitis in children and adolescents is an inflammation of the bones, usually caused by an acute bacterial infection [1]. In 2016, relevant study showed that the overall prevalence of bone and joint infections was estimated to be at least two per 10 000 children [2], whereas the incidences of developed countries were relatively low [3,4]. Bone and joint infections were common in children under 5 years of age, and it was more common in boys than in girls [5]. Osteomyelitis infection was common in the bones and joints of the lower extremities in children and adolescents and was mainly caused by common bacteria, including staphylococcus aureus, staphylococcus aureus, streptococcus pneumoniae, and streptococcus pyogenes. Bacteria often colonize children's joints and destroy their bones and surrounding tissues [1]. The main clinical manifestations of osteomyelitis were local redness, swelling, suppuration, and other symptoms. In severe cases, systemic inflammation may occur [6].

Clinical studies had shown that procalcitonin (PCT) can be used as a serum inflammatory biomarker, which is more specific for the diagnosis of bacterial infections. In suspected cases of acute bone and joint infections, this biomarker had the characteristics of diagnostic accuracy [7]. Moreover, serum PCT level played a certain role in the diagnosis and treatment of infectious diseases [5,8]. Serum levels of PCT were low in healthy patients (<0.1 ng/ml) and increase rapidly under the action of bacterial endotoxins. Plasma concentrations of PCT were elevated in severe bacterial infections (bacterial meningitis, septic shock, bacteremia, and pyelonephritis) but remain fairly low in viral infections and nonspecific inflammatory diseases (cutoff, 0.5 ng/ml) [9,10]. The purpose of this study was to evaluate the sensitivity, specificity, and predictive value of different cutoff values of PCT for osteomyelitis and septic arthritis in children.

Materials and methods

Data sources

PubMed, EMBase, and the Cochrane Library were searched until 10 August 2021, with the following MeSH terms and free text: osteomyelitis, septic arthritis, infectious arthritis, bacterial arthritis, bone infection, joint infection, PCT, infant, child, adolescent, and

pediatrics, for eligible literature focusing on PCT for diagnoses osteomyelitis and septic arthritis. We manually searched the reference lists of the relevant reviews and meta-analyses.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (a) the purpose of the study was to evaluate the diagnostic value of PCT for osteomyelitis and septic arthritis; (b) included children under 18 years of age; (c) the value, including true positive (TP), false positive (FP), true negative (TN), and false negative (FN), for PCT for the diagnosis of osteomyelitis and septic arthritis, can be obtained directly or indirectly; (d) pathogen isolation and culture were the gold standards for the diagnosis of bone joint infection.

The exclusion criteria were as follows: (a) no control group; (b) no report on the result and the original data of the four-lattice table cannot be obtained by calculation; (c) review, abstracts, case reports, and study with animal experiments.

Literature screening and data extraction

Two evaluators independently conducted literature screening following preestablished inclusion and exclusion criteria, extracted information, and cross-checked. The information extracted mainly included study, year, country, age, sex, sample, region, type of bacteria-infected, cutoff of PCT, gold standards, TP, FP, TN, and FN of PCT. Disagreements were resolved through negotiation or with the assistance of a third researcher. The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies criteria [11].

Criteria of heterogeneity test

In diagnostic tests, the main causes of heterogeneity were the threshold and nonthreshold effects. When the threshold effect was present, sensitivity and specificity were negatively correlated (or the sensitivity was positively correlated with one specificity) and showed a 'shoulder-arm' point distribution on the receiver operating characteristic (ROC) plane graph; otherwise, there was no correlation. If there were multiple critical values in the literature, the data corresponding to the maximum critical value in the four grid tables were selected.

Statistical methods

Meta-disc software, USA, Texas (version 1.4) was used to combine the sensitivity, specificity, positive likelihood ratio (LR), negative LR, and diagnostic odds ratio (OR) of the literature extracted from the four grid table data, draw the summary ROC (SROC) curve, and calculate the area under the curve (AUC) and Q index (Q* value). Spearman correlation analysis was used to detect heterogeneity caused by the threshold effect, and the Chi-square test was used to test the heterogeneity of sensitivity and specificity. The heterogeneity of positive LR, negative LR, and diagnostic OR was determined using the Cochran-Q test and I^2. $I^2 \leq 40\%$ and $P \geq 0.1$ indicated that there was no statistical heterogeneity between the studies, and a fixed-effects model was used. $I^2 > 40\%$ and $P < 0.10$ indicated that there was statistical heterogeneity between the studies. Different populations and different diagnostic cutoff values of PCT were used for the stratification analysis. Statistical significance was set at $P < 0.05$. Deek's funnel plot and regression line test were employed for publication bias in STATA software.

Results

Basic characteristic

Our comprehensive literature search strategy yielded 573 results in Fig. 1. After excluding clearly irrelevant records, we obtained full-text articles from the remaining 58 records for further evaluation. Finally, a total of four articles [8,9,12,13] with six studies enrolling 654 children were included, and the basic characteristics of included studies were shown in Table 1.

Quality evaluation

Two components of the methodological quality summary, including the risk of bias and acceptability of concerns, were shown in Fig. 2. None of the included studies had high risk in either component. Regarding the risk of bias, only one study [12] was described as unclear in the reference standard. In the acceptability content group, only one study [12] was described as unclear in the index tests and reference standard.

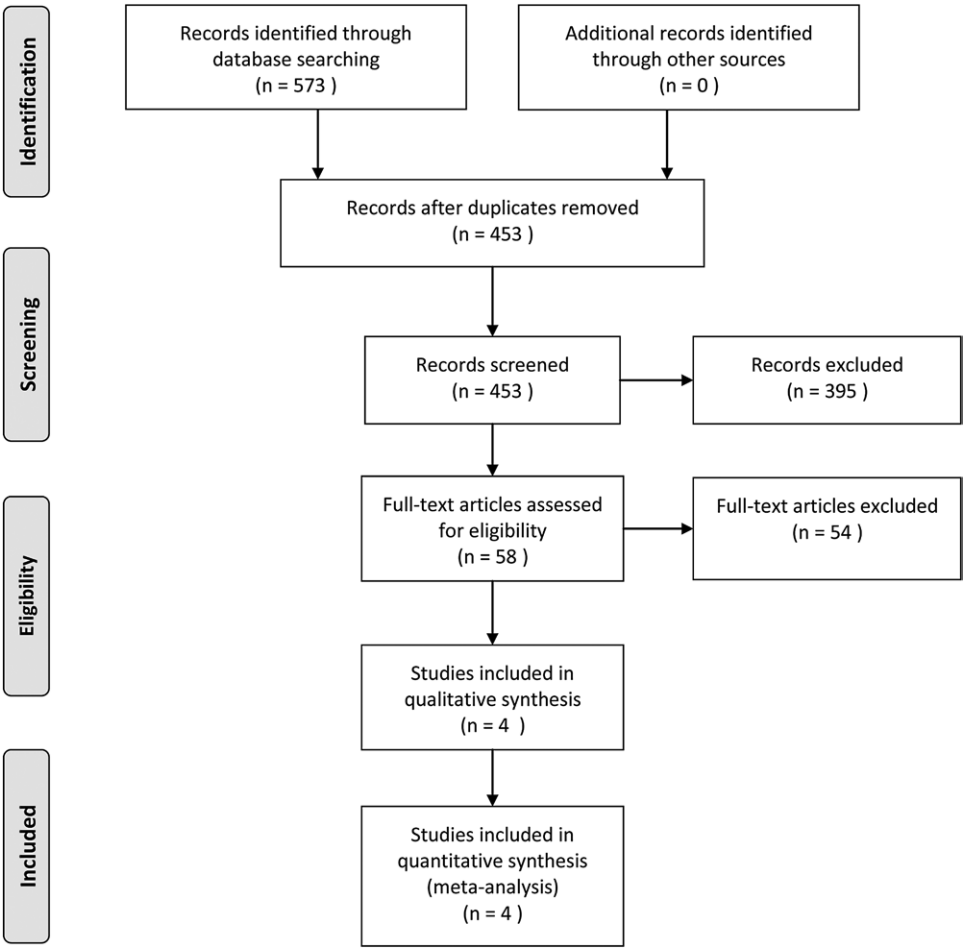
Meta-analysis results

In a diagnostic meta-analysis of four articles [8,9,12,13] with six studies, a total of 654 children were examined for bacterial cultures in PCT and bone joint fluid. The results showed that the PCT had a sensitivity of 0.72, 95% confidence interval (CI) (0.65–0.79) in Fig. 3, specificity of 0.90, 95% CI (0.87–0.93) in Fig. 4, positive LR of 3.87, 95% CI (2.53–5.90) in Fig. 5, negative LR of 0.39, 95% CI (0.22–0.70) in Fig. 6, and diagnostic OR was 13.13, 95% CI (6.46–26.66) in Fig. 7, for the detection of osteomyelitis and septic arthritis using bacterial culture as the gold standard. Based on the SROC curve of PCT in Fig. 8, it was found that the AUC of PCT was 0.88.

Heterogeneity test

The heterogeneity of sensitivity ($I^2 = 82.1\%$), specificity ($I^2 = 90.2\%$), positive LR ($I^2 = 28.3\%$), negative LR ($I^2 = 79.2\%$), and diagnostic OR ($I^2 = 13.3\%$) were large according to the forest results. The Spearman correlation coefficient of PCT was 0.771, with a P-value of 0.07, and the result did not show a significant threshold effect.

Fig. 1



Literature screening of PRISMA 2009 flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Stratification analysis

Different population

Subgroup analyses were developed for different intervention populations in Table 2, and the results of osteomyelitis and septic arthritis from three studies, it showed that the PCT had a sensitivity of 0.65, 95% CI (0.53–0.77), specificity of 0.94, 95% CI (0.92–0.96), positive LR of 5.03, 95% CI (3.11–8.12), negative LR of 0.39, 95% CI (0.18–0.82), and diagnostic OR was 23.06, 95% CI (8.59–61.92), for the detection of osteomyelitis and septic arthritis using bacterial culture as the gold standard. Based on the SROC curve of PCT, it was found that the AUC of PCT was 0.93. However, the only study was involved in osteomyelitis populations, the result showed that the PCT had a sensitivity of 0.77, 95% CI (0.67–0.85) and specificity of 0.70, 95% CI (0.59–0.80), the other results were not available.

Different diagnostic cutoff for procalcitonin

Based on the different diagnostic cutoff for PCT in Table 3, it showed that the cutoff ≥0.1 ng/ml of PCT had a sensitivity of 0.72, 95% CI (0.65–0.79), specificity of 0.90, 95% CI (0.87–0.93), positive LR of 3.87, 95% CI (2.53–5.90), negative LR of 0.39, 95% CI (0.22–0.70), diagnostic OR was 13.13, 95% CI (6.46–26.66), and AUC of 0.88. The cutoff ≥ 0.2 ng/ml of PCT had a sensitivity of 0.70, 95% CI (0.62–0.77), specificity of 0.91, 95% CI (0.88–0.93), positive LR of 4.32, 95% CI (2.39–7.78), negative LR of 0.43, 95% CI (0.25–0.74), diagnostic OR was 10.50, 95% CI (5.87–18.80), and AUC of 0.83. The cutoff ≥ 0.3 ng/ml of PCT had a sensitivity of 0.68, 95% CI (0.60–0.76), specificity of 0.91, 95% CI (0.88–0.94), positive LR of 4.67, 95% CI (2.06–10.62), negative LR of 0.48, 95% CI (0.29–0.79), diagnostic OR was 9.44, 95% CI (5.24–17.03), and AUC of 0.82. The cutoff ≥ 0.4 ng/ml and ≥0.5 ng/ml of PCT had a sensitivity of 0.49, 95% CI (0.33–0.65), specificity of 0.96, 95% CI (0.94–0.98), positive LR of 7.83, 95% CI (3.20–19.14), negative LR of 0.58, 95% CI (0.37–0.91), diagnostic OR was 16.05, 95% CI (4.97–51.86), and AUC of 0.93.

Publication bias

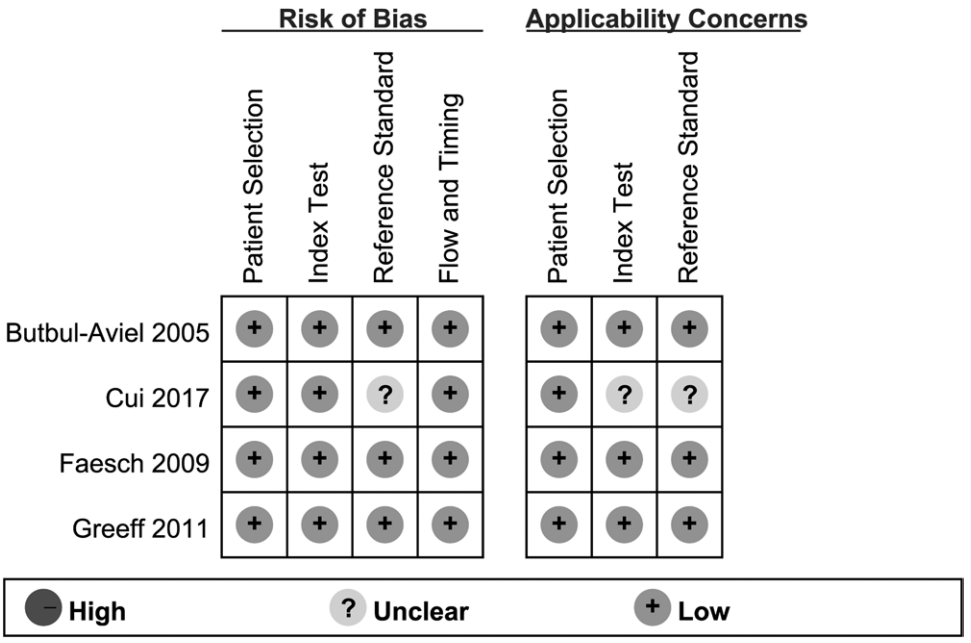
In the evaluation of publication bias, the result of the regression line test showed that there was not publication

Table 1 The basic characteristics of including studies

Study	Year	Country	Age	Sex (female)	Sample	Region	Type of bacteria infected	Cutoff of PCT	Gold standards
Butbul-Aviel	2005	Israel	5.8/5 years	15/15	44	NR	NR	>0.5 ng/ml	The diagnosis of acute osteomyelitis was based on at least two of the following findings: (I) pus on aspiration from the affected bone, (II) positive bacterial culture from bone or blood, (III) presence of classic signs and symptoms of acute osteomyelitis: local pain, swelling, increased skin temperature, or limited mobility of the adjacent joint, and (IV) a positive imaging study, either on radiography, scintigraphy, or magnetic resonance imaging.
Faesch	2009	France	4 (1 month–14 years)	NA	299	NR	Streptococcus: 3, Salmonella: 1, *Kingella Kingae*: 4	>0.5 ng/ml	This confirmed infection group consisted of patients which had one positive bacteriological culture (blood, bone aspiration or joint fluid aspiration).
Greeff	2011	Bloemfontein	<14 years	NA	33	NR	*Staphylococcus aureus*: common	0.1, 0.2, 0.5 ng/ml	The diagnosis was confirmed by clinical signs, the finding of pus at arthrotomy of the involved joint or aspiration and drilling of the bone in theater and microscopy, culture, and sensitivity (MCS) of material (pus, tissue).
Cui	2017	China	6.5/5.31 years	47/33	172	Tibia: 56, Femur: 24, Humerus: 8, Ilium: 2, Phalange: 2	*Staphylococcus aureus*: 44, Streptococcus: 13, Haemophilus: 4, *Escherichia coli*: 3	0.356 ng/ml	Bacterial culture

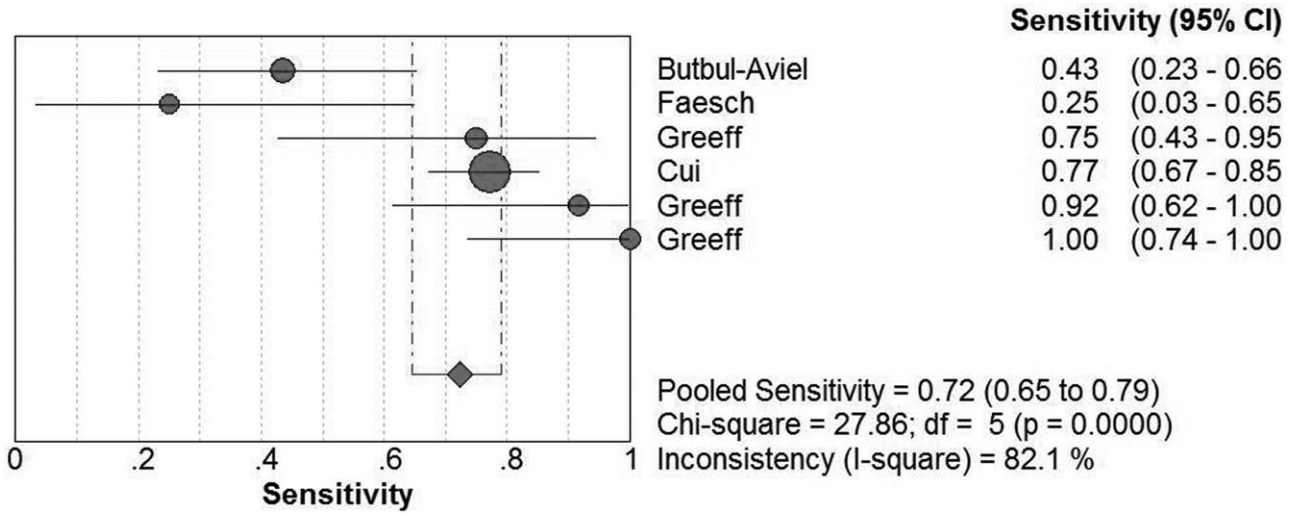
NR, not reported; PCT, procalcitonin.

Fig. 2



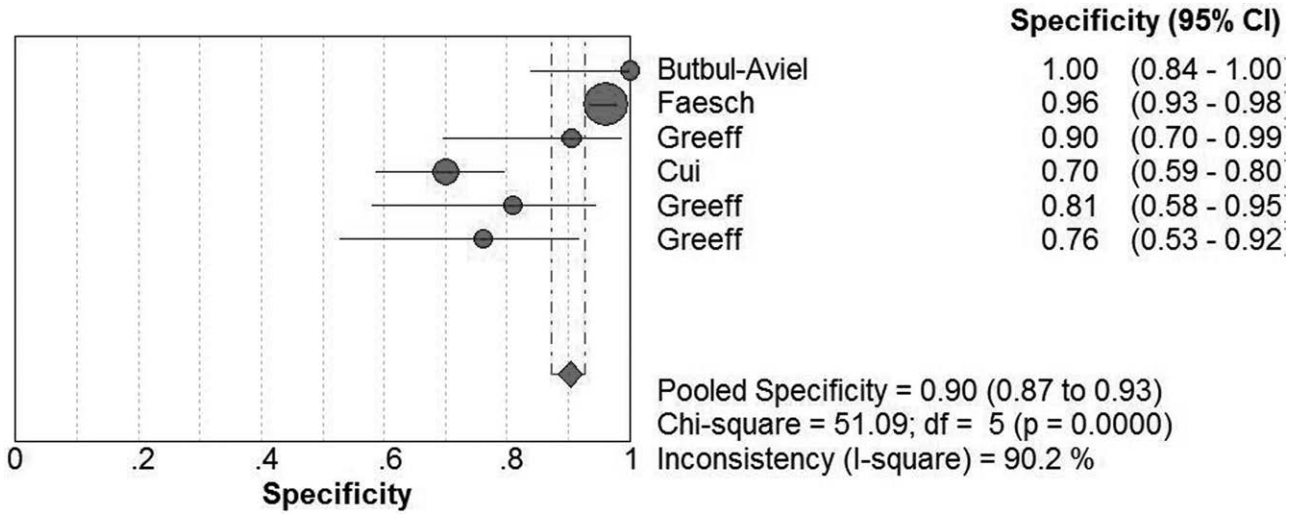
Methodological quality summary.

Fig. 3



Forest of sensitivity for procalcitonin diagnosis of osteomyelitis and septic arthritis.

Fig. 4



Forest of specificity for procalcitonin diagnosis of osteomyelitis and septic arthritis.

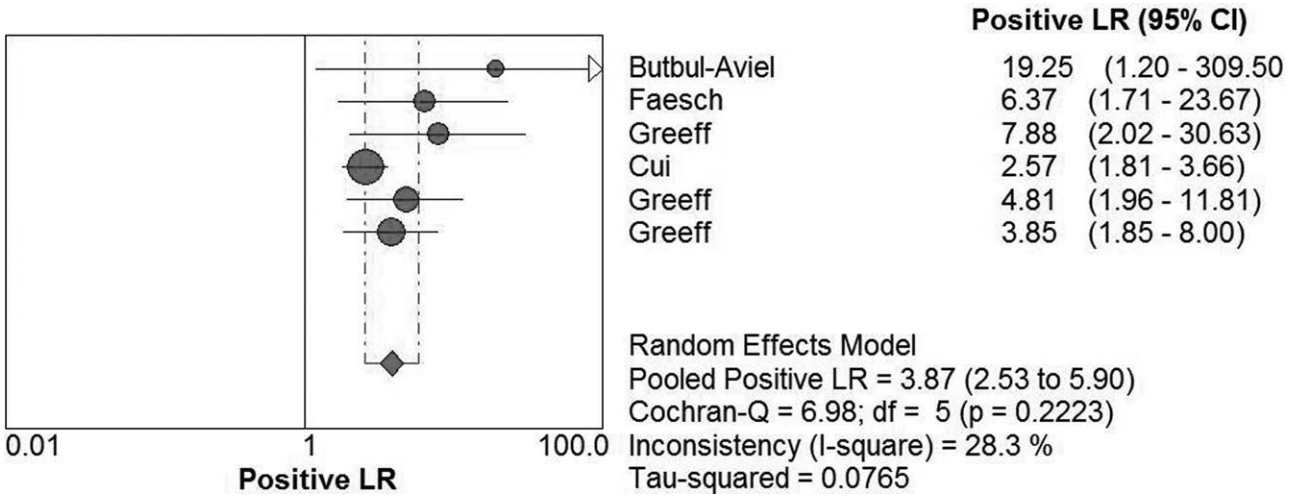
bias (bias = 13.72; 95% CI, –1.84 to 29.28; $P = 0.07$). The results of the Deek's funnel plot were shown in Fig. 9.

Discussion

The cause of suppurative arthritis and osteomyelitis in children was related to the immune age and socioeconomic level of children. Moreover, there were certain differences in pathogen resistance and type. Staphylococcus aureus was a common pathogen that causes skeletal muscle infection in children, accounting for approximately 60% of skeletal infections in children under 4 years of age [14]. To date, there was no unified diagnostic standard for osteoarthrosis worldwide, which was usually judged by microbiological analysis of the clinical manifestations of children [15]. The clinical manifestations of suppurative arthritis in children were mainly local swelling, pain, reduced load-bearing capacity, and limited range of motion, whereas the clinical manifestations of osteomyelitis were mainly pain, fever, and limited range of motion [16,17].

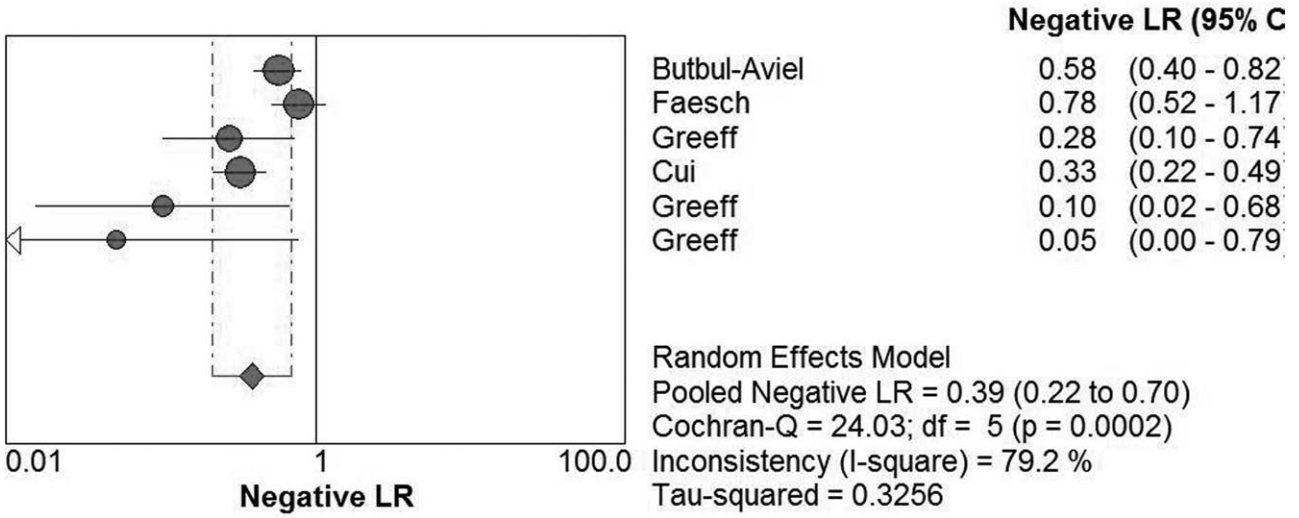
PCT was a precursor peptide of calcitonin, which was stable in the human body. The PCT precursor was

Fig. 5



Forest of positive likelihood ratio for procalcitonin diagnosis of osteomyelitis and septic arthritis.

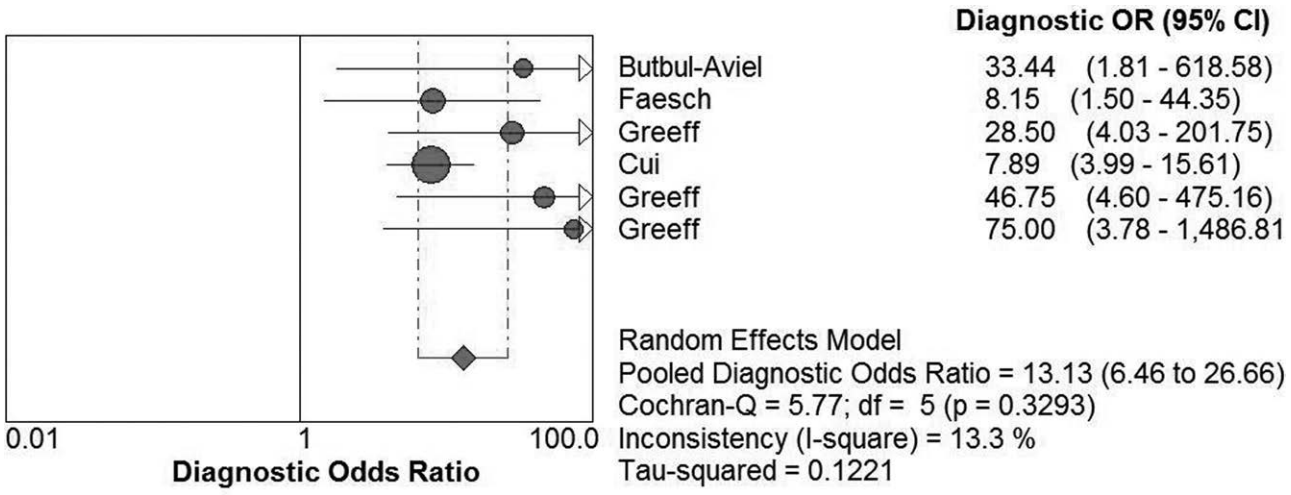
Fig. 6



Forest of negative likelihood ratio for procalcitonin diagnosis of osteomyelitis and septic arthritis.

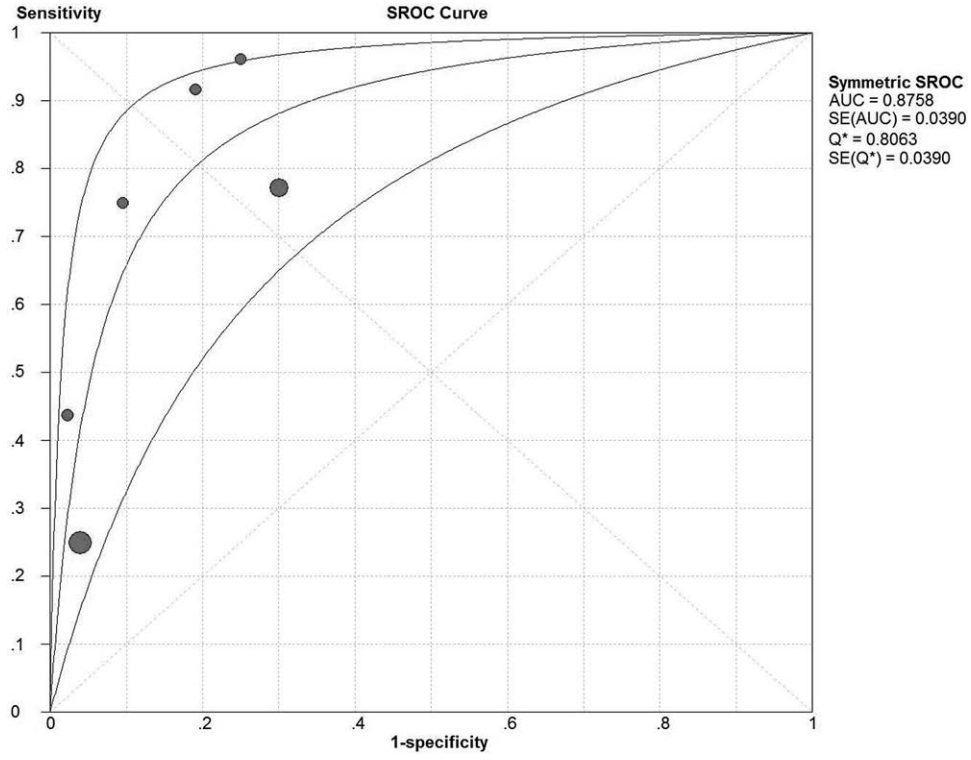
secreted by thyroid cells and then gradually decomposes into PCT calcitonin [10]. Children with low blood levels will release a large amount of interleukins and tumor necrosis factor within a few hours after infection with bacteria to stimulate PCT gene expression [18]. PCT had protease resistance, a significant increase in PCT level can be detected within 2 h after infection, and can slowly return to normal levels after treatment [18]. PCT was a protein composed of 116 amino acids and was a precursor of serum calcitonin without hormonal activity [19]. Generally free in serum, PCT was an immunomodulatory substance derived from chromosome 11. It was a very stable protein *in vivo* and *in vivo*, with a half-life of 20–24 h in the human body and <0.5 μg/l in healthy human plasma when local infection occurs [20]. In a short period of time, the aggregation of monocytes was regulated, and the local release acted as a chemokine to further attract and activate monocytes to pass through the tissue, whereas the feedback was weakened due to the appearance of PCT, so that the cells remain at the infection site. At this time, the PCT level may not increase or the increase was not obvious. In the state of serious systemic bacterial infection, PCT in direct contact with activated monocytes initiated the synthesis of

Fig. 7



Forest of diagnostic odds ratio for procalcitonin diagnosis of osteomyelitis and septic arthritis.

Fig. 8



Summary receiver operating characteristics curve for procalcitonin diagnosis of osteomyelitis and septic arthritis.

PCT and calcitonin gene-related peptide (0.1 ng/ml), which was essentially undetectable; however, when the body was invaded by fungi and bacteria in some cases, causing serious infection, the level of PCT will increase significantly, or when the body organ failure, the level of PCT will increase rapidly. Various clinical tests had proved the presence of PCT in the human body. The content was directly proportional to the degree of infection and was directly related to the type of infection [5,8,12].

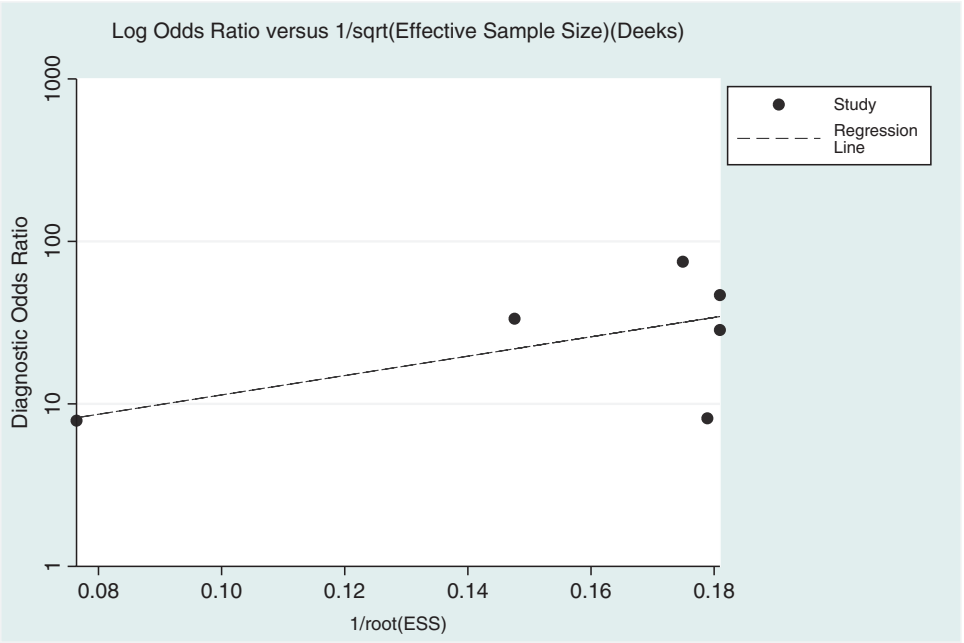
Table 2 **Stratification analysis based on different population**

Different population	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio	Area under curve
Osteomyelitis and septic arthritis	0.65 (0.53–0.77)	0.94 (0.92–0.96)	5.03 (3.11–8.12)	0.39 (0.18–0.82)	23.06 (8.59–61.92)	0.93
Osteomyelitis	0.77 (0.67–0.85)	0.70 (0.59–0.80)	NA	NA	NA	0.77

Table 3 **Stratification analysis based on different diagnostic cutoff of procalcitonin**

Cutoff of procalcitonin (ng/ml)	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio	Area under curve
≥0.1	0.72 (0.65–0.79)	0.90 (0.87–0.93)	3.87 (2.53–5.90)	0.39 (0.22–0.70)	13.13 (6.46–26.66)	0.88
≥0.2	0.70 (0.62–0.77)	0.91 (0.88–0.93)	4.32 (2.39–7.78)	0.43 (0.25–0.74)	10.50 (5.87–18.80)	0.83
≥0.3	0.68 (0.60–0.76)	0.91 (0.88–0.94)	4.67 (2.06–10.62)	0.48 (0.29–0.79)	9.44 (5.24–17.03)	0.82
≥0.4	0.49 (0.33–0.65)	0.96 (0.94–0.98)	7.83 (3.20–19.14)	0.58 (0.37–0.91)	16.05 (4.97–51.86)	0.93
≥0.5	0.49 (0.33–0.65)	0.96 (0.94–0.98)	7.83 (3.20–19.14)	0.58 (0.37–0.91)	16.05 (4.97–51.86)	0.93

Fig. 9



Deek's funnel plot for procalcitonin diagnosis of osteomyelitis and septic arthritis.

Clinical pediatric infectious diseases were common, and early detection and treatment can reduce pain and promote healthy development in children. Serum PCT was an important inflammatory factor in infectious diseases and was a sensitive indicator [21]. It was a precursor of calcitonin without hormone activity. It increased gradually at 3–6 h under bacterial induction and then decreased after the peak at 12–24 h. This was mainly due to the secretion of PCT by macrophages in the liver and by lymphocytes in the intestinal tissues after stimulation. Therefore, the higher the PCT content in infectious diseases, the more serious the infection will be, and the progress of the disease in children can be found early, and the prevention work can be done well. In clinical treatment, appropriate antibiotic treatment can be administered according to the level of serum PCT to improve treatment efficiency, avoid the occurrence of drug resistance, and realize the scientific application of antibiotics.

The differences in serum calcitonin in children are caused by the types of virus and the amount of virus, which is due to the development and developmental process of calcitonin in infectious diseases. Thus, it can be used as an important sensitive index to diagnose bacterial infectious diseases and according to the level of judgment of the degree of bacterial infection. In subgroup analysis with different PCT cutoff values, we found that with the increase of PCT cutoff value, its sensitivity decreased, whereas its specificity increased. This makes the diagnostic accuracy of PCT in osteomyelitis and septic arthritis certain confusion. The

result of AUC showed that the overall diagnostic accuracy of PCT was higher when the cutoff value of PCT was greater than 0.4 and 0.5. However, it remained unknown whether increasing the cutoff of PCT will provide better diagnostic accuracy due to insufficient data. In different populations, we found that PCT was not highly sensitive to osteomyelitis and septic arthritis, but it had high specificity and AUC, which also suggested that PCT still had promising certain diagnostic ability in the diagnosis of osteomyelitis and septic arthritis. However, due to the small number of studies, the evidence of PCT for diagnosis of osteomyelitis was still insufficient, and it was expected to be confirmed by subsequent large sample studies. Therefore, it was often used as an important indicator for the detection of inflammation in the body. In recent years, with the wide application of this indicator in clinical practice, children with severe infection can be detected within 2 h, which guarantees the implementation of effective prevention and treatment measures. Therefore, as a more accurate and timely detection method to reflect the disease situation of children, PCT detection was faster and more timely than other detection methods, so that it can be widely used in the auxiliary and differential diagnosis of bacterial infection, worthy of further promotion in clinical practice.

Conclusion

This study provided a systematic review of the published literature on the diagnosis of osteomyelitis and septic arthritis in children using PCT, which may serve as a biomarker for diagnosis of osteomyelitis, but it has no direct evidences to support the diagnosis of for septic arthritis. However, the specific optimal cutoff value of PCT and specific population still needed to be verified by large sample studies.

Acknowledgements

Y.H. and H.T.Z. conceived and designed the study. H.T.Z., C.L., and Y.Z.H. selected the articles and extracted the data. H.T.Z. and C.L. analyzed the data. H.T.Z. and Y.H. wrote the first draft of the manuscript. H.T.Z., C.L., Y.Z.H., and Y.H. interpreted the data. Y.H. and H.T.Z. contributed to the writing of the final version of the manuscript. All authors agreed with the results and conclusions of this article.

Conflicts of interest

There are no conflicts of interest.

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