Erythrocyte Sedimentation Rate for Assisted Diagnosis of Pediatric Osteomyelitis: A Meta-Analysis

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Objective: For the diagnosis of pediatric osteomyelitis, the sensitivity, specificity, and predictive value of erythrocyte sedimentation rate (ESR) were evaluated in this study.

Methods: A systematic computer-based search was performed for relevant articles focusing on the ESR diagnosis of pediatric osteomyelitis in PubMed, Embase, and the Cochrane Library with an inclusion criteria: 1) the diagnostic utility of ESR for diagnosing osteomyelitis patients under the age of 18;2) two-by-two contingency tables can be obtained. Case reports, review papers, and animal experiments were excluded.

Results: The diagnostic meta-analysis included 8 studies involving 348 children with osteomyelitis, all of whom were tested for ESR. Diagnostic meta-analysis revealed a sensitivity and specificity of 0.90, 95% confidence interval (CI) (0.86–0.93), and 0.50 (95% CI,0.47–0.54) for ESR in pediatric osteomyelitis diagnosis, respectively. The positive likelihood ratio (LR), negative LR, and diagnostic odds ratio were 1.38,(95% CI,1.08–1.78), 0.46, (95% CI,0.26–0.73), and 3.20, (95% CI,1.33–7.69), respectively. The area under the curve (AUC) was determined to be 0.80 based on the summary receiver operating characteristic curve (SROC).

Conclusion: The literature on the use of ESR in pediatric osteomyelitis diagnosis was thoroughly reviewed in this study. It was also found that ESR may be useful as a biomarker for pediatric osteomyelitis diagnosis. Due to its low specificity, it should be used in combination with other markers such as C-reactive protein, neutrophil percentage, and white blood cell count.

Keywords: osteomyelitis, pediatric, ESR, diagnosis, meta-analysis

Introduction

Osteomyelitis is an inflammation of the bones that is brought on by an acute bacterial infection.[1] Osteomyelitis is more common in boys, younger children, with incidence rates ranging from 2 to 13 per 10,000 young people.[2] In clinical practice, the skin, oral cavity, or respiratory mucous membranes may all be the source of infection, as the bacteria responsible for the illness are sometimes difficult to identify, with Staphylococcus aureus being the most common cause of osteomyelitis, being implicated in more than 75% of cases.[3] The main clinical signs of osteomyelitis are localized redness, swelling, suppuration, and pain, however the specificity is weak and the early characteristics of osteomyelitis are also unclear.[4] Early diagnosis of acute osteomyelitis is often challenging, but timely treatment to minimize bone destruction is critical.[5] Failure to diagnose and treat such infections can lead to chronic osteomyelitis, bone destruction or septicemia.[6] After an infection has taken root, a rapid chain reaction of local and systemic inflammatory reactions, with the creation of various inflammatory mediators, ensues, and in severe cases, systemic inflammation may occur. Therefore, early diagnosis and timely treatment of osteomyelitis is of critical importance. Inflammatory markers in blood taken from the lab were reported to accurately identify infants with probable acute bone infections.[7,8] The most common diagnostic auxiliary examination signs of

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osteomyelitis in pediatric patients at this time are the erythrocyte sedimentation rate (ESR), C-reactive protein, neutrophil percentage, and white blood cell count.[5,8] ESR is a sensitive indicator of inflammation in the blood that can be used to predict the probability of bone infection.[9] There have been several reports in the literature suggesting that ESR is useful in identifying acute osteomyelitis in children.[10–12] In light of the expanding use of ESR in this sector, we conducted a thorough analysis of significant literature reports in order to provide a scientific basis for the clinical application of ESR in the diagnosis of pediatric osteomyelitis.

Materials and Methods
Search Strategy
For the meta-analysis, we searched PubMed, Embase, and the Cochrane Library for publications with the following subject terms: "osteomyelitis" or "bone infection" and "erythrocyte sedimentation rate" or "ESR" and "adolescent" or "children" or "pediatrics" (last search: April 01, 2023). Search time: April 15, 2023. Only English literatures were included. We also looked over the list of references for earlier systematic reviews. In conducting and reporting this systematic review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.

Inclusion and Exclusion Criteria
The following topics were included in this study: (a) diagnostic utility of ESR for the diagnosis of osteomyelitis; (b) the clinical gold standard for the determination of osteomyelitis was bacterial culture of bone aspirates; (c) feasibility of the two-by-two contingency table; and (d) children under the age of 18. Case reports, review papers, and animal experiments were among the types of research not included in the analysis.

Quality Assessment
The technique was validated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2); the methodological quality of the included studies was assessed.

Literature Screening and Data Extraction
The inclusion and exclusion criteria were independently evaluated by two reviewers. The third reviewer settled the disagreement. The following information was taken from the literature: study, year, country, age, sample size, ESR threshold, values of true positives (TP), false negatives (FN), false positives (FP), and true negatives (TN) per study.

Criteria of Heterogeneity Test
First, there were variations in diagnostic tests due to threshold and non-threshold effects. The receiver operating characteristic (ROC) plane graph would have a "shoulder-arm" point distribution when the threshold effect was present. If threshold effects were present, it was best to calculate the area and Q-index using the Summary ROC (SROC) curve method. Individual evaluation measures, such as sensitivity and specificity, can be immediately incorporated when there were no threshold effects.

Statistical Methods
Software such as Review Manager 5.3, Meta-disc 1.4, STATA 12.0, and R 3.4 were used for statistical analysis. Threshold effects were found using Spearman correlation analysis. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were calculated. I^2 values were used to gauge the heterogeneity between trials. I^2 values more than 50% indicated the presence of considerable heterogeneity. Potential publication bias was ruled out by using a Deeks' regression test for funnel plot asymmetry.
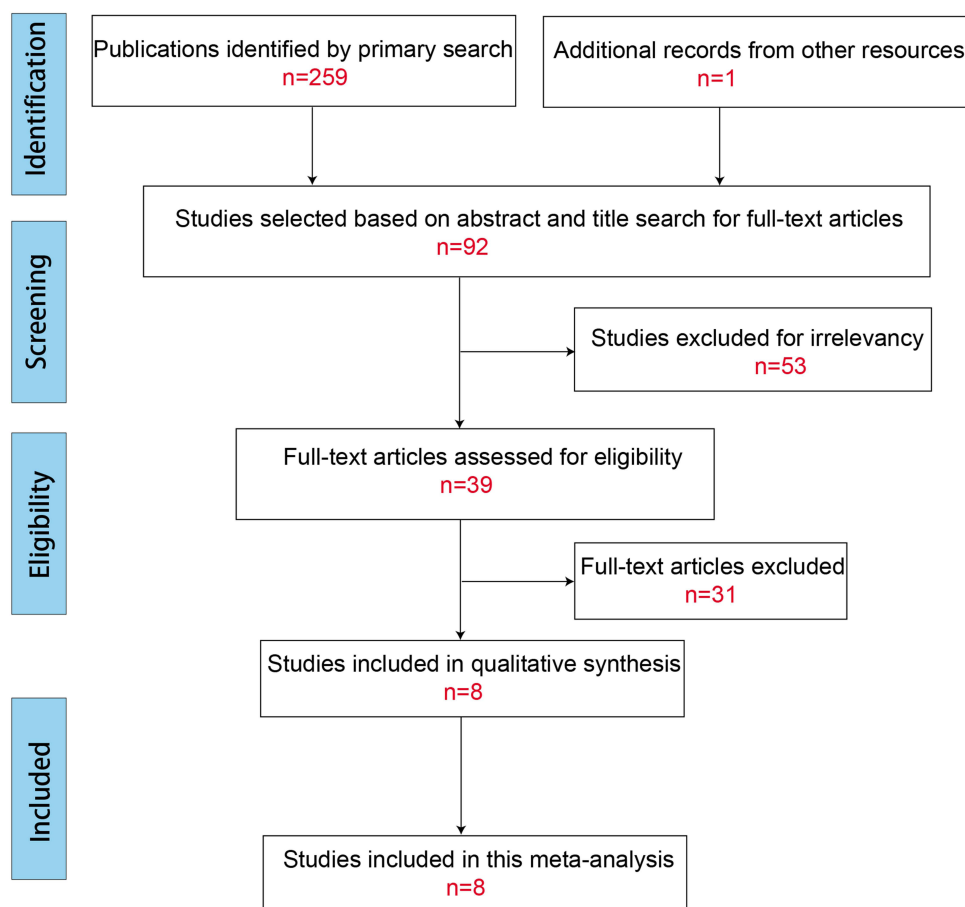
Figure 1 Diagram of workflow in the systematic review and meta-analysis.

Results

Basic Characteristic

The aforementioned search approach resulted in 260 papers, of which 8 were eventually included in the qualitative analysis. (Figure 1): Butbul-Aviel et al,[12] Riise et al,[11] Paakkonen et al,[10] Reitzenstein et al,[8] Nduaguba et al,[13] Maciej K et al,[14] Zulian et al,[15] Chen et al.[16] Of this, 2 were from USA, 1 each from Finland, Israel, Norway, China, Switzerland, and Italy. A total of 1016 patients were enrolled from 2005 until 2021. (Table 1 and Table 2).

Table 1 Basic Characteristic of the Included Studies

Author	Year	Nation	Age(Year)	Study Design	ESR Detection Method	Instrument company
Butbul-Aviel[12]	2005	Israel	7.9 (7.6 ± 5.5)	Prospective	NA	NA
Riise[11]	2008	Norway	<16	Retrospective	NA	NA
Paakkonen[10]	2009	Finland	8.4 (4.0–11.3)	Prospective	NA	NA
Reitzenstein[8]	2010	USA	8.5±4.5	Retrospective	NA	NA
Nduaguba[13]	2016	USA	6.5 (0.2–14)	Retrospective	NA	NA
Maciej K[14]	2018	Switzerland	12 (2–15)	Retrospective	NA	NA
Zulian[15]	2021	Italy	0.3–18	Retrospective	NA	NA
Chen[16]	2021	China	6.4 (0.9 ± 11.6)	Retrospective	NA	NA

Table 2 Basic Data of the Included Studies

Author	Year	Sample	Osteomyelitis	True Positive	False Positive	False Negative	True Negative	Sensitivity	Specificity	Cut-Off
Butbul-Aviel[12]	2005	31	7	7	4	0	20	100%	83.33%	20 mm/h
Riise[11]	2008	429	37	27	110	10	282	73.5%	72%	20 mm/h
Paakkonen[10]	2009	265	131	123	125	8	9	94.00%	6.82%	20 mm/h
Reitzenstein[8]	2010	114	84	71	28	9	2	89%	6.67%	20 mm/h
Nduaguba[13]	2016	12	7	7	4	0	1	100%	25%	20 mm/h
Maciej K[14]	2018	7	4	4	3	0	0	100%	0%	20 mm/h
Zulian[15]	2021	92	44	38	29	6	19	86.36%	39.58%	30 mm/h
Chen[16]	2021	66	34	33	29	1	3	97.06%	9.38%	20 mm/h

Quality Evaluation

The QUADAS-2 criteria, which encompass patient selection, index test, reference standard, and patient flow, were used to assess the quality of the included studies. Figure 2 presented the outcome of the quality assessment criteria.

Threshold Effect Detection

The initial stage in this study was to determine whether a threshold effect exists, as several important factors could give rise to a threshold effect. When the ROC plane graph was examined, it was discovered that there is no "shoulder-arm" point distribution, and the Spearman correlation coefficient was 0.38, P=0.34, indicating that no threshold effect has occurred. (Figure 3).

The Value of ESR in Diagnosing Osteomyelitis in Children

Data for 8 studies were collected and these articles were included in the final meta-analysis. Based on these results, it was found that the pooled sensitivity of CRP for the diagnosis of osteomyelitis in children was 0.90 (95% Confidence interval (CI), 0.86–0.93) (Figure 4A), the pooled specificity was 0.50 (95% CI, 0.47–0.54) (Figure 4B), and pooled positive LR, negative LR, diagnostic OR, were 1.38 (95% CI, 1.08–1.78)(Figure 5A), 0.46 (95% CI, 0.29–0.73)(Figure 5B), 3.20, 95% CI (1.33−7.69)(Figure 5C), respectively. After meta-analysis, ESR's positive predictive capacity in the diagnosis of pediatric osteomyelitis increased by 10% (from 0.2 to 0.22), while it's negative predictive ability increased by 50% (from 0.2 to 0.1). This was demonstrated using Fagan's nomogram (Figure 6A). Due to pooled positive LR 10 and pooled negative LR >0.1, the predictive practicality, however, was not very good. (Figure 6B). The area under the sROC curve was 0.80 (Figure 7).

Publication Bias

According to Deeks' regression test, there was no discernible publication bias. (P=0.33) (Figure 8).

Discussion

Osteomyelitis is an inflammatory bone disease, which translates from the Greek as "inflammation of the bone marrow".[17] Osteomyelitis is brought on by a bacterial infection. The most common route for infection to migrate into bone tissue is through the bloodstream, although other routes of infection include trauma, local diffusion and surgery.[1] Staphylococcus aureus is the most frequent pathogen and accounts for the majority of cases of hematologic osteomyelitis cases in children.[3] Currently, bacterial culture of bone aspirates is the gold standard for osteomyelitis diagnosis.[12] However, children sometimes refuse to participate in bone aspirates, and bacterial cultures typically take several days, making it difficult to diagnose osteomyelitis in children at an early stage.
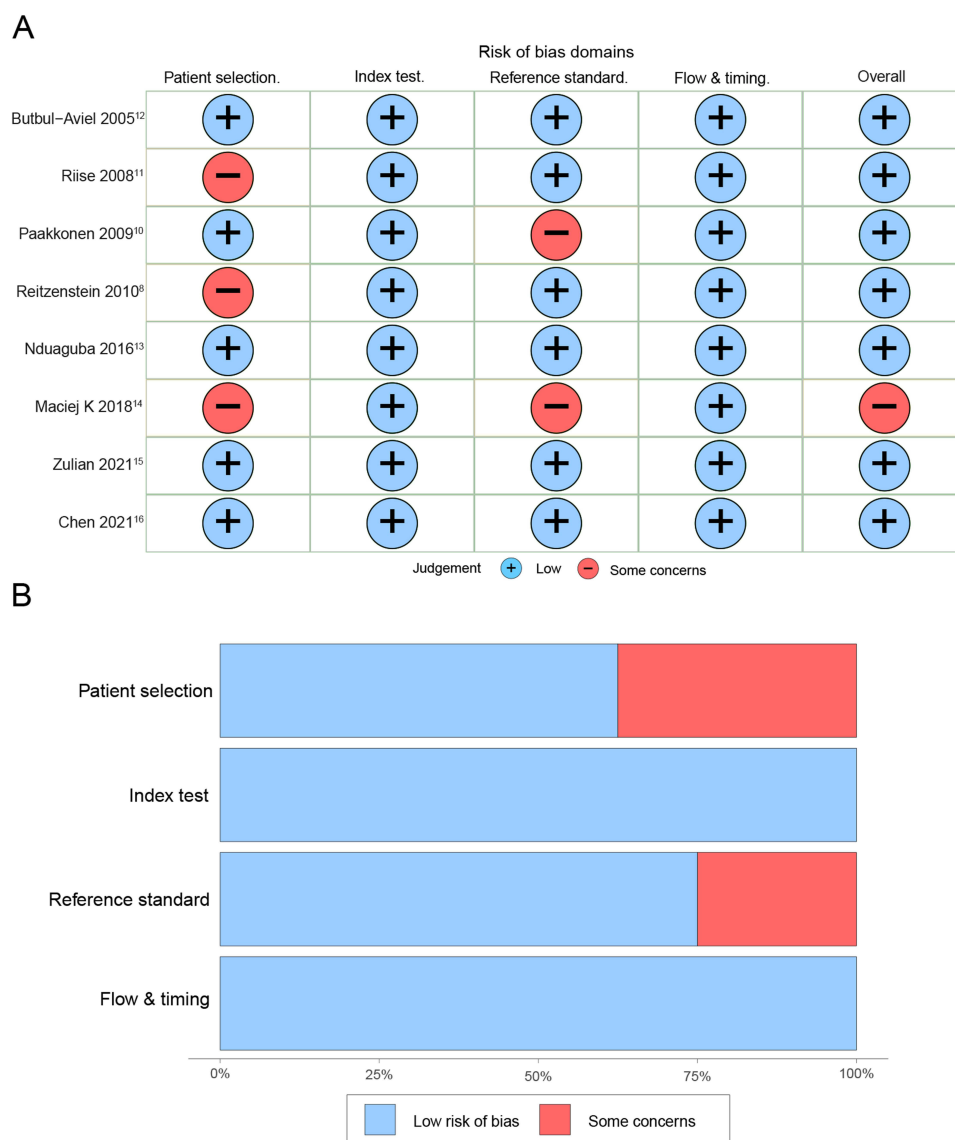
A

Risk of bias domains

	Patient selection.	Index test.	Reference standard.	Flow & timing.	Overall
Butbul–Aviel 2005[12]	+	+	+	+	+
Riise 2008[11]	−	+	+	+	+
Paakkonen 2009[10]	+	+	−	+	+
Reitzenstein 2010[8]	−	+	+	+	+
Nduaguba 2016[13]	+	+	+	+	+
Maciej K 2018[14]	−	+	−	+	−
Zulian 2021[15]	+	+	+	+	+
Chen 2021[16]	+	+	+	+	+

Judgement   + Low   − Some concerns

B

Figure 2 Methodological quality summaries.(**A**)Risk of bias summary; (**B**)Risk of bias graph.

The ESR calculates the rate in millimeters (mm)/hour, at which erythrocytes fall or settle in the plasma of a randomly collected anticoagulated blood specimen over a given period of time (often 60 minutes).[18] Dr. Edmund Faustyn Biernacki made the first observations of this phenomena in 1897, finding that blood settled at different rates in different people and that red blood cells settled more quickly in the presence of more fibrinogen.[19] The ESR can also be significantly affected by changes in multiple plasma proteins and their interactions with each other, such as cytokine-induced elevations in acute phase proteins in response to infection, inflammation or trauma.[20] ESR is currently frequently used in the diagnosis of acute bone inflammatory diseases such as septic arthritis, osteomyelitis and acute rheumatic fever.[12] Since ESR is a sensitive biomarker of an essential inflammatory component of infections, it is now commonly used as a marker of infection. Despite our best efforts, we were unable to find any meta-analyses using ESR to identify pediatric osteomyelitis. So, we conducted a meta-analysis to examine the utility of ESR as a diagnostic indicator for pediatric osteomyelitis, and eventually included 8 studies. 6 retrospective studies and 2 prospective trials with a total of 1106 children were included in our analysis, which pooled data from 8 studies with excellent overall quality. Of those, 348 children developed osteomyelitis. Our meta-analysis revealed a joint sensitivity and specificity of 90% and 50% for
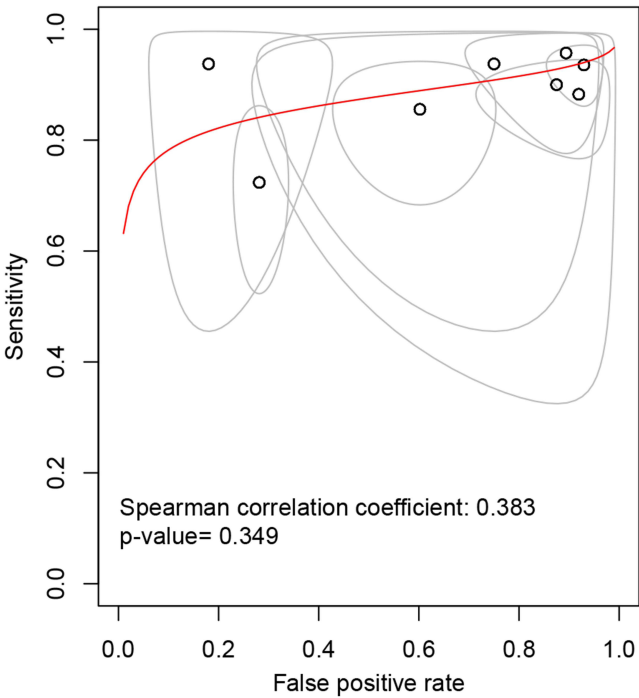
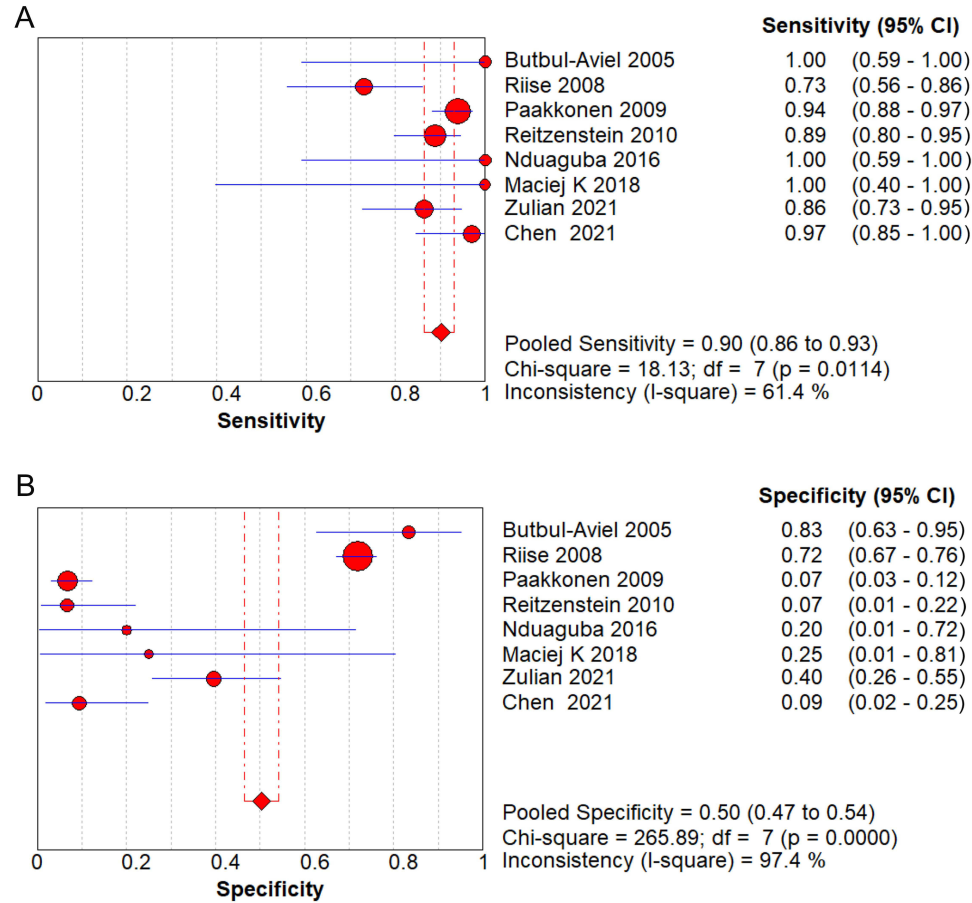**Figure 3** ROC plane diagram for threshold effect detection.

Figure 4 (**A**) Sensitivity of the forest to the ESR diagnosis of osteomyelitis in children; (**B**) Specificity of the forest to the ESR diagnosis of osteomyelitis in children.
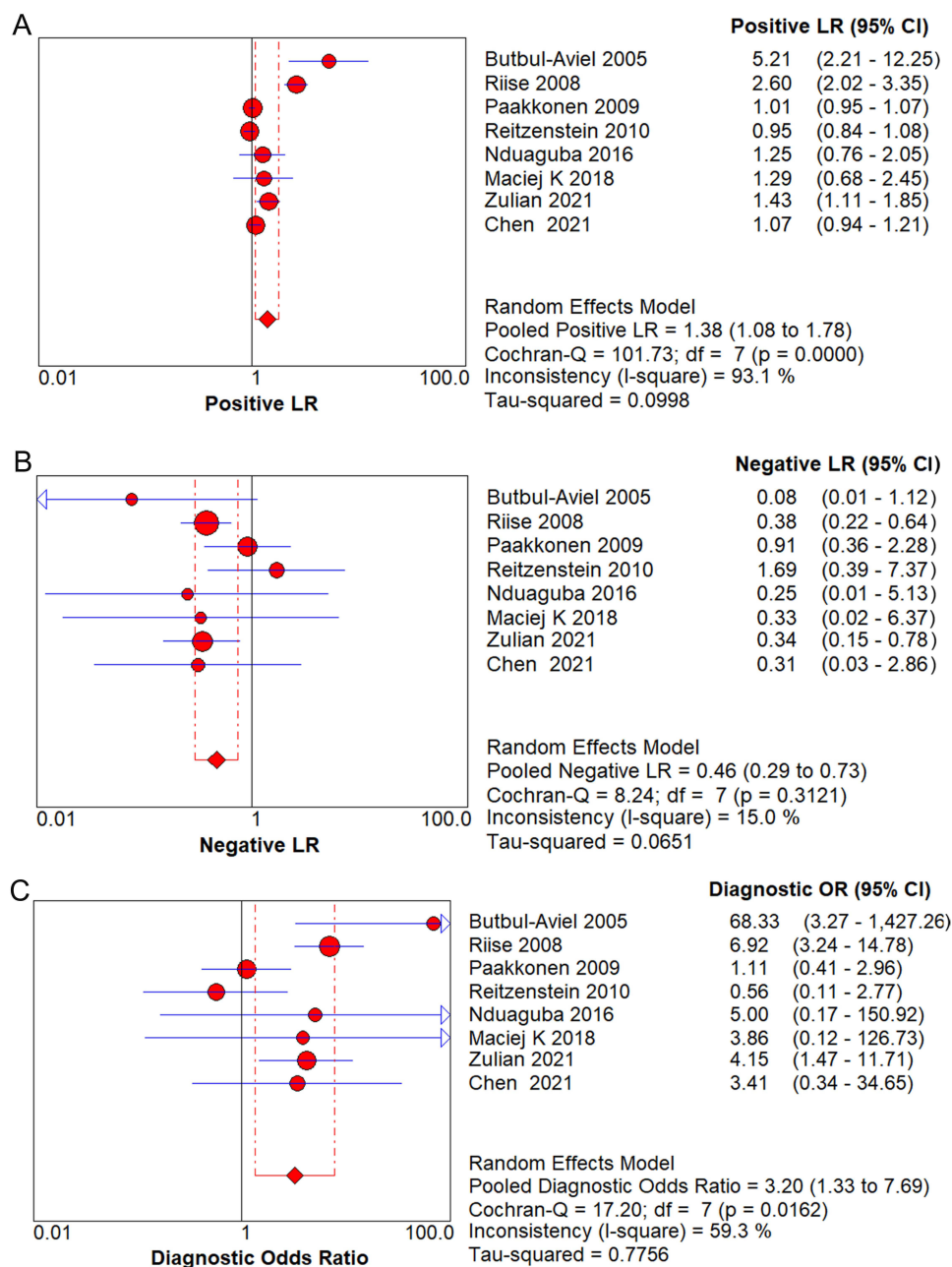
Figure 5 (**A**) Forest of positive likelihood ratio for ESR diagnosis in children with osteomyelitis; (**B**) Forest of negative likelihood ratio for ESR diagnosis in children with osteomyelitis; (**C**) Forest of diagnostic odds ratio for ESR diagnosis in children with osteomyelitis.

pediatric osteomyelitis, respectively. These findings suggested that while pediatric osteomyelitis has a significant rate of missed diagnoses; there are few cases of misdiagnosis.

Both positive and negative LR are clinically significant indicators of efficacy in diagnostic trials and are relatively independent. They are frequently employed to calculate post-test probabilities in order to improve the therapeutic relevance of the findings. The meta-analysis revealed a pooled positive LR of 1.38 and a pooled negative LR of 0.46. In addition, the Fagan's nomogram revealed that a pooled negative LR of 0.46, and reduced the post-test probability from 20% to 10%. However, prior studies have demonstrated that the likelihood of diagnosing or eliminating a certain ailment increases considerably when pooled positive LR >10 and pooled negative LR < 0.1.[21] This suggested that ESR still has some limitations when used to diagnose pediatric osteomyelitis.
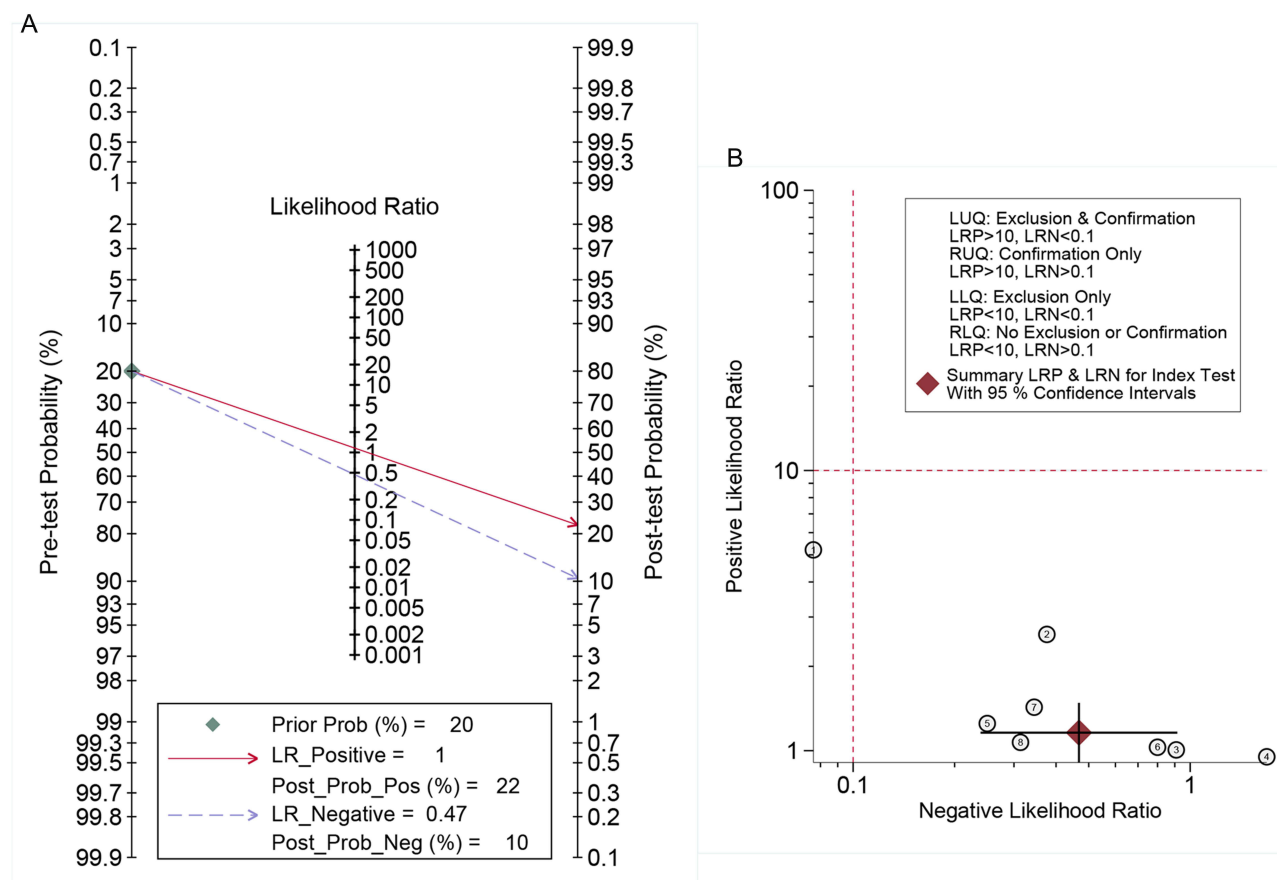
Figure 6 (**A**) Fagan nomogram of ESR for diagnosis in children with osteomyelitis; (**B**) The value gram of positive likelihood ratio and negative likelihood ratio for ESR diagnosis in children with osteomyelitis.
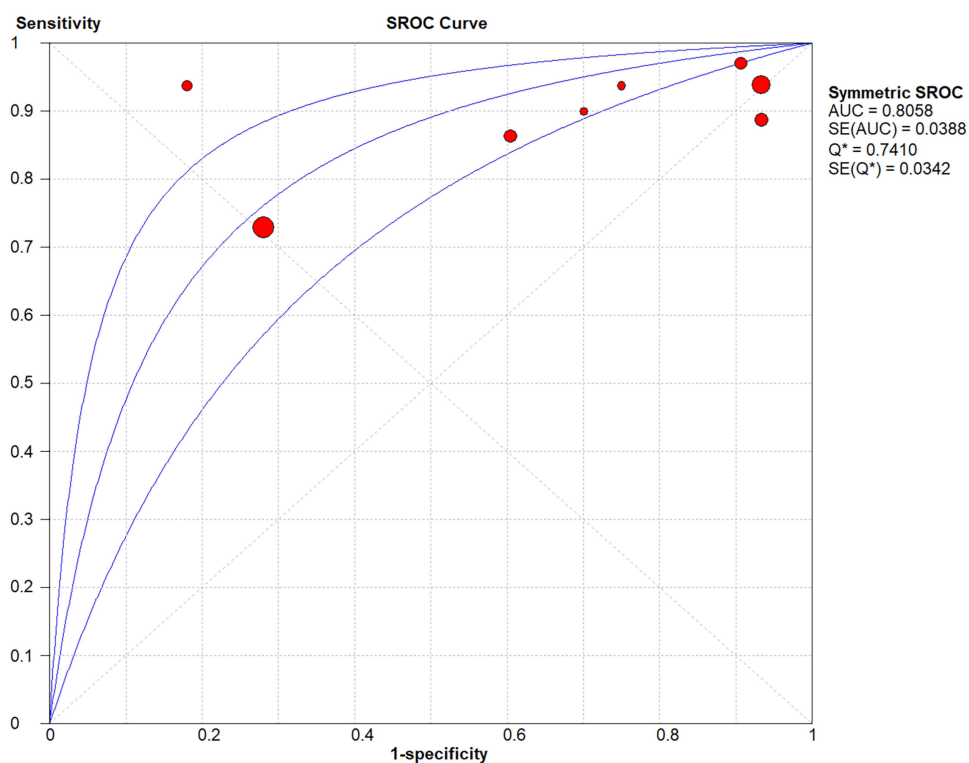

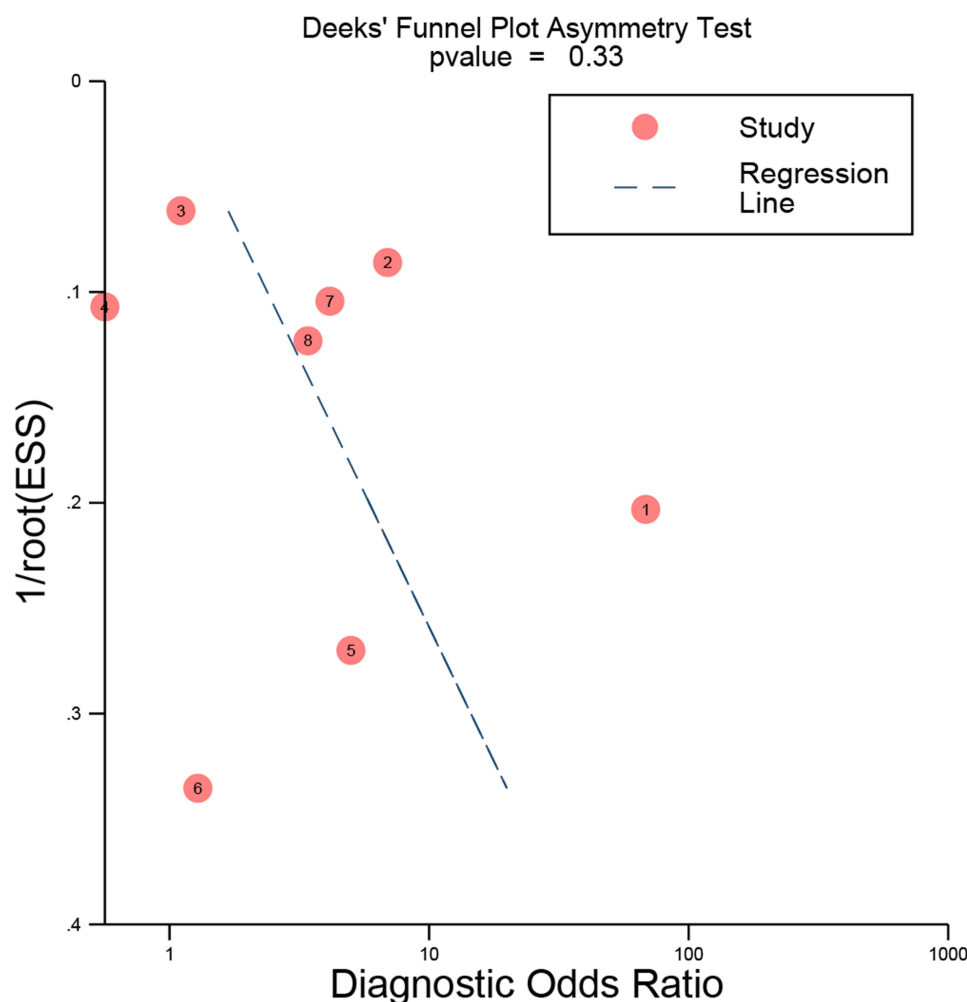**Figure 7** Summary receiver operating characteristics curve for ESR diagnosis in children with osteomyelitis.

Figure 8 Deeks' funnel plot for ESR diagnosis of osteomyelitis in children.

When AUC is less than 0.5, it shows no diagnostic value; it signals a low diagnostic value when it is between 0.5 and 0.7; a value between 0.7 and 0.9 indicates a high diagnostic value; moreover, when it exceeds 0.9, it represents the best diagnostic accuracy.[22] The results showed a good level of diagnostic precision with an AUC for this research of 0.80.

This study also had a number of other shortcomings, including: 1) This meta-analysis included both prospective and perspective studies, which may have had some bearing on the results; 2) The diagnostic value of serological biomarkers for osteomyelitis is influenced by multiple factors, such as infection stage, site of infection, previous treatment, and many confounding factors were not well controlled; 3) Some information were not provided about the clinical characteristics of the patients, such as infection site, stage of infection, pathogen type; 4) There may have been a linguistic bias as only English literature was looked at in this study.

Conclusion

To diagnose osteomyelitis in pediatric patients, this study set out to thoroughly evaluate the literature on the use of ESR as a biomarker. The specificity of ESR for the diagnosis of pediatric osteomyelitis is low, though. To diagnose pediatric osteomyelitis, it should therefore be used in conjunction with other tests rather than as a single biomarker. Due to the limitation of this study, much more high-quality studies will be required in the future to evaluate the applicability value of their combined diagnosis.

Abbreviations

ESR, erythrocyte sedimentation rate; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; TP, true positive; FP, false positive; TN, true negative; FN, false negative; ROC, receiver operating characteristic; SROC, summary receiver operating characteristic; LR, likelihood ratio; DOR, diagnostic odds ratio; CI, Confidence interval.

Data Sharing Statement

They may get from correspondence author.

Ethical Approval

This study was approved by the ethics committee of The Second People's Hospital of Lianyungang.

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Disclosure

The authors declare that they have no competing interest in this work.

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