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ARTICLE

The use of procalcitonin in the diagnosis of bone and joint infection: a systemic review and meta-analysis

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Abstract Only a few studies have investigated the use of PCT in the diagnosis of bone and joint infection, and these studies have had relatively small sample sizes. We performed a systematic review and meta-analysis of the diagnostic performance of serum procalcitonin (PCT) in the identification of osteomyelitis and septic arthritis in patients who present with fever and orthopedic symptoms. EMBASE, MEDLINE, and Cochrane databases and the reference lists of relevant articles were searched, with no language restrictions, through February 2012. All original studies that reported the use of serum PCT alone or in comparison with other biomarkers for diagnosis of osteomyelitis and septic arthritis were included. Seven studies qualified for inclusion. These studies enrolled a total of 583 patients with suspected bone or joint infection, 131 of whom had confirmed osteomyelitis or septic arthritis. Analysis of the PCT data indicated a bivariate pooled sensitivity of 0.67 (95 % CI: 0.37–0.88), specificity of 0.90 (95 % CI: 0.78–0.96), a positive likelihood ratio (LR+) of 6.48 (95 % CI: 2.28–14.6), and a negative likelihood ratio (LR−) of 0.37 (95 % CI: 0.16–0.84). Use of a lower PCT cut-off value (0.2–0.3 ng/mL) improved the LR + to 6.66 and the LR− to 0.15. Analysis of the three studies that also measured serum C-reactive protein (CRP) indicated that CRP had an LR + of 1.39 (95 % CI: 1.17–1.65) and an LR− of 0.40 (95 % CI: 0.12–1.36). Our results indicate that PCT may be more suitable as an aid for rule-in diagnosis rather than for exclusion of septic arthritis or osteomyelitis and that use of a lower cut-off value for serum PCT may improve its diagnostic performance.

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Introduction

The diagnosis of patients who present with signs of infection and limping or arthralgia can be difficult. In particular, bacterial infection, viral infection, and non-infectious disorders can all lead to fever with inflammation, so a serial laboratory and imaging work-up may be necessary [1, 2]. Clinical signs and conventional laboratory markers, such as elevated white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), cannot differentiate infectious from non-infectious inflammation. Isolation and culturing of pathogenic microorganisms from bone or synovial fluid is considered the gold standard for the diagnosis of etiology, but this can be time-consuming and aspirated fluid cultures are

positive in only 66 % of patients with osteomyelitis and 75 % of patients with septic arthritis [1–3].

Procalcitonin (PCT) is the 116-amino acid precursor of calcitonin, a 32-amino acid hormone that regulates serum calcium. Serum PCT concentration is less than 1 ng/mL in healthy patients, but increases rapidly following systemic bacterial infections such as those responsible for bacterial meningitis, septic shock, bacteremia, and pyelonephritis [4, 5]. Unlike other markers, serum PCT is usually not elevated in patients with inflammation because of viral infection or non-infectious disorders [4], although previous studies have observed that non-infectious triggers, such as surgical trauma [6], Kawasaki disease [7], and adult onset Still's disease [8] can induce PCT elevation. Thus, serum PCT is potentially useful for the differential diagnosis of patients with clinical symptoms of joint and bone infections. Measurement of serum PCT may allow the more judicious use of empirical antibiotic treatment in patients with lower respiratory tract infections.

Only a few studies have investigated the use of PCT in the diagnosis of bone and joint infection, and these studies have had relatively small sample sizes [9–15]. We reviewed the current evidence regarding the use of PCT for the identification of bone and joint infections by performing a systematic review and meta-analysis.

Materials and methods

Search strategy and selection criteria

We searched three electronic databases (Medline, Embase, and Cochrane) for clinical studies published through February 2012 with the following MeSH terms and free text: "osteomyelitis," "septic arthritis," "arthritis," "joint fluid," "bone infection," "joint infection,", "orthopedic infection" in combination with "biomarker" or "procalcitonin." There were no publication date or language restrictions. We also checked the reference lists of all relevant review articles. Selection was performed independently by two reviewers and discrepancies between reviewers were resolved by a consensus meeting with a third reviewer.

Figure 1 summarizes the study inclusion and exclusion process. All studies were screened for title and abstract in the first round, and potentially relevant articles were retrieved for full-text review in the second round. We included original studies that evaluated the diagnostic accuracy of PCT alone or compared PCT with other laboratory markers such as CRP for the identification of osteomyelitis or septic arthritis. The type of PCT tests used included Kryptor (Brahms, Berlin, Germany), LUMItest (Brahms), and the PCT-Q assay systems (Brahms). The Kryptor PCT assay has the highest precision with a detection limit of 0.02 ng/mL and a functional sensitivity of 0.06 ng/mL. The PCT-Q assay system is a semi-quantitative bedside assay and the LUMItest PCT test uses an immunoluminometric method with a functional sensitivity of 0.5 ng/mL. Each study included had sufficient data for construction of a 2×2 contingency table and patients of all ages were considered. We excluded case reports, case series, review articles, editorials, and clinical guidelines. The primary endpoint was osteomyelitis or septic arthritis and studies without these endpoints were excluded.

Two authors independently reviewed all titles and abstracts to determine whether the inclusion criteria were satisfied. Full-text articles were retrieved if any of the reviewers considered the abstract suitable.

Quality assessment

The quality of the selected studies was assessed by Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria [16]. The spectrum of patients included in a study was considered to be representative of the target population if they had clinical manifestation of suspected septic arthritis. The reference standard is positive culture from joint fluid with compatible clinical symptoms. Partial and differential verification bias was considered if all the patients included were not assessed with the same reference standard. Incorporation bias was considered to be avoided if the diagnosis of septic arthritis was established strictly based on the reference standard regardless of the value of serum PCT levels.

Data synthesis and analysis

We calculated the sensitivity and specificity of each dataset included. There is generally a negative correlation between sensitivity and specificity, so we estimated the pooled sensitivity and specificity of PCT with a bivariate model, assuming a bivariate distribution for the log-transformed sensitivity and specificity. The bivariate model accounts for study size and also adjusts for the negative correlation between sensitivity and specificity of the index test that may arise because of the use of different thresholds in different studies. For comparison of the diagnostic performance of two biomarkers, we calculated the area under the summary receiver operating characteristic (AUROC) curve and the diagnostic odds ratio (OR) to summarize the true- and false-positive rates of different diagnostic studies, irrespective of the use of different cut-off points in different studies. When there was no observation in one of the cells of the 2×2 contingency table, we performed continuity correction by adding 0.5 to the empty cell, reducing the bias from exclusion of small studies. Overall sensitivity and specificity and 95 % confidence intervals (CIs) were calculated

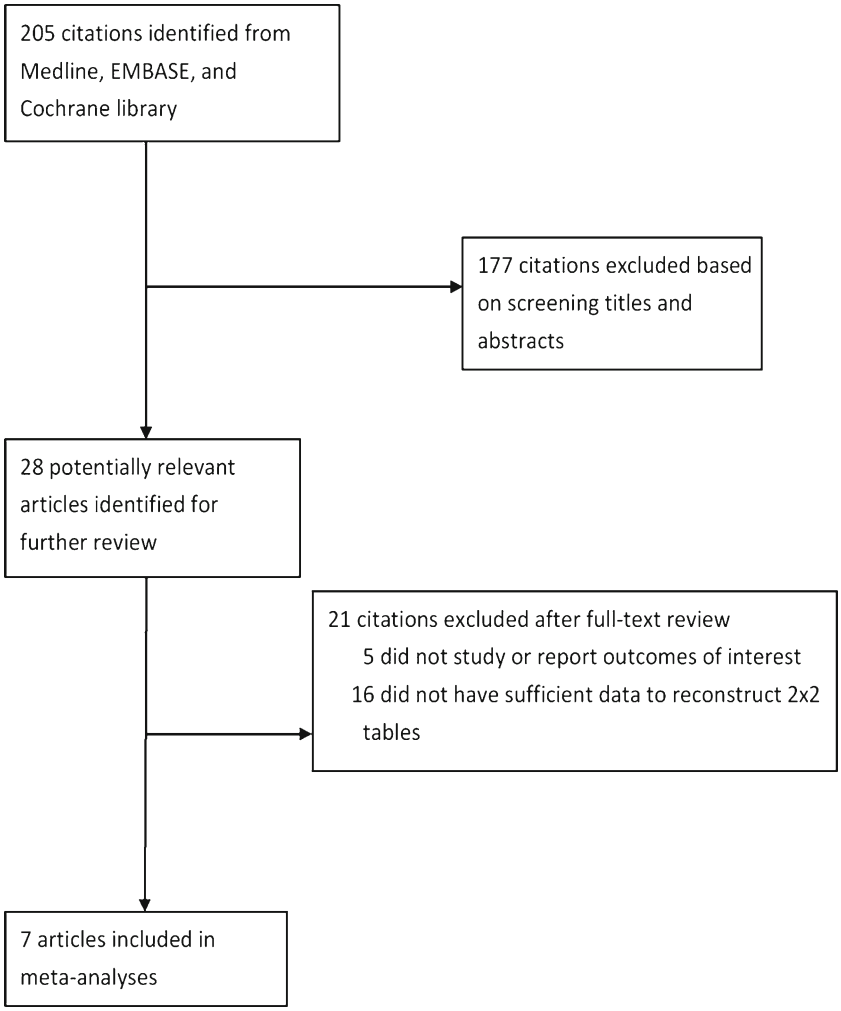

Fig. 1 Flow chart of study identification and inclusion

based on the binominal distributions of the true positives and true negatives.

We formally quantified the extent of between-study variation (heterogeneity) by calculation of the inconsistency index (I^2), which represents the proportion of heterogeneity not explained by random variation. Statistically significant heterogeneity was considered present if I^2 was greater than 50 %. Summary diagnostic ORs were estimated by random (DerSimonian–Laird) or fixed (Mantel–Haenszel) effect models depending on whether I^2 was greater or less than 50 %. We defined a priori the following clinical and design characteristics of a study as potentially relevant covariates: cut-off value, adult or pediatric population, and testing systems used for PCT measurement. We tested the publication bias by using Egger's test. Egger's test uses regression methods to test the asymmetry of funnel plots. Skewed and asymmetrical funnel plots indicate the presence of publication bias. All statistical analyses were conducted using STATA 11.0 (Stata Corp, College Station, TX, USA). All statistical tests were two-sided and a p value less than 0.05 was considered significant.

Results

Identification of studies and assessment of quality

Our initial search yielded 205 citations. We retrieved 28 studies for full-text review and identified 7 studies that met our inclusion criteria (Fig. 1).

Tables 1 and 2 summarize the characteristics of the 7 studies included. These studies enrolled patients from 6 countries, were published between 1998 and 2012, and included a total of 583 patients (median: 42; range: 23–291). Bone and joint infection were confirmed in 127 patients overall (prevalence: 22.4 %; range: 3.0–61 %). Four studies used prospective cross-sectional designs and 3 used retrospective designs. Five studies were undertaken in hospital wards and 2 were performed in an emergency department or out-patient clinic. Five studies used microbiological criteria to define bone and joint infection, and 2 used clinical or microbiological criteria to define bone and joint infection. Three studies also reported serum CRP values.

Table 1 Summary of the characteristics of the 7 studies included part 1

Country, reference	Age range	Prevalence (number of participants)	Biomarkers tested	Cut-off (PCT, ng/mL CRP, mg/L)	Outcomes definition	Setting	PCT sensitivity, specificity (%)	CRP sensitivity, specificity (%)
Sweden [11]	Adult	0.61 (77)	PCT	0.5	MDI	Inpatient	42.0 67.0	NA
France [10]	Adult	0.26 (42)	PCT	0.3, 0.5, 0.7	MDI	Inpatient	73.0	100
			CRP	50			93.5	40.0
Israel [6]	Children	0.48 (23)	PCT	0.5	MDI and CDI	Inpatient	27.0	56.0
			CRP	50			100	61.0
Germany [8]	Adult	0.45 (33)	PCT	0.2	MDI	ED and outpatient	100 94.0	NA
Switzerland [9]	Adult	0.33 (42)	PCT	0.25, 0.1	MDI and CDI	Inpatient	93.0 75.0	NA
France [7]	Children	0.1 (291)	PCT	0.5	MDI	ED	7.1 96.9	NA
Iran [12]	Adult	0.33 (75)	PCT	0.5	MDI	ED	68.0	92.0
			CRP	18			80.0	30.0

PCT procalcitonin, *CRP* C-reactive protein, *MDI* microbiologically documented infection, *CDI* clinically documented infection, *ED* emergency department, *NA* not available

The overall quality of the studies included, based on the QUADAS criteria, was modest (Fig. 2). Only two studies reported masking of the biomarker results in the determination of outcome by the reference standard; thus, incorporation bias was likely. In addition, none of the studies reported uninterpretable or indeterminate results, and none provided information on patient withdrawal or drop-out.

Diagnostic accuracy indices

The diagnostic accuracy of PCT for the identification of bone and joint infection from other etiologies is suboptimal (Figs. 3, 4). The pooled sensitivity and specificity were 0.67 (95 % CI: 0.37–0.88) and 0.90 (95 % CI: 0.78–0.96) respectively (Table 3). The high positive likelihood ratio (LR+: 6.48; 95 % CI: 2.88–14.6) indicates that the PCT test is suitable for a rule-in diagnosis, but its poor negative likelihood ratio (LR−: 0.37; 95 % CI: 0.16–0.84) makes it less useful as a rule-out tool.

The pooled sensitivity for CRP was 0.85 (95 % CI: 0.72–0.94), higher than PCT, and the specificity was 0.37 (95 % CI: 0.27–0.47), lower than PCT (Table 3). CRP has a poorer LR+ (1.39; 95 % CI: 1.17–1.65) and LR− (0.40; 95 % CI: 0.12–1.36); thus, it has little value for the diagnosis of bone and joint infection. Two global measures, AUROC (PCT: 0.89, CRP: 0.59) and diagnostic OR (PCT: 12.1, CRP: 3.56), indicate that the discriminative capability of PCT is superior to that of CRP. There was substantial heterogeneity for PCT (I^2=75.6 %; 95 % CI: 40.8–87.3 %), but not for CRP (I^2=0.0 %; 95 % CI: 0.0–89.6 %).

Subgroup analysis

We performed subgroup analysis of the 6 studies that reported diagnostic parameters on serum PCT levels based

Table 2 Summary of the characteristics of the 7 studies included part 2

Reference	Population	Outcome	PCT testing system
[11]	Patients with symptoms of acute arthritis (septic and crystal)	Septic arthritis	BRAHMS, LUMItest
[10]	Patients with symptoms of acute arthritis (septic, crystal, and rheumatoid)	Septic arthritis	BRAHMS, LUMItest
[6]	Patients with symptoms of osteomyelitis and septic arthritis	Osteomyelitis and septic arthritis	BRAHMS, PCT-Q
[8]	Patients with symptoms of acute arthritis (septic and nonseptic)	Septic arthritis	BRAHMS, LUMItest
[9]	Patients with symptoms of acute arthritis (septic and nonseptic)	Septic arthritis	BRAHMS, LUMItest
[7]	Patients having febrile or afebrile joint symptoms	Osteomyelitis and/or septic arthritis	BRAHMS, Krypto PCT
[12]	Patients with symptoms of arthritis (septic and inflammatory)	Septic arthritis	BRAHMS, LUMItest

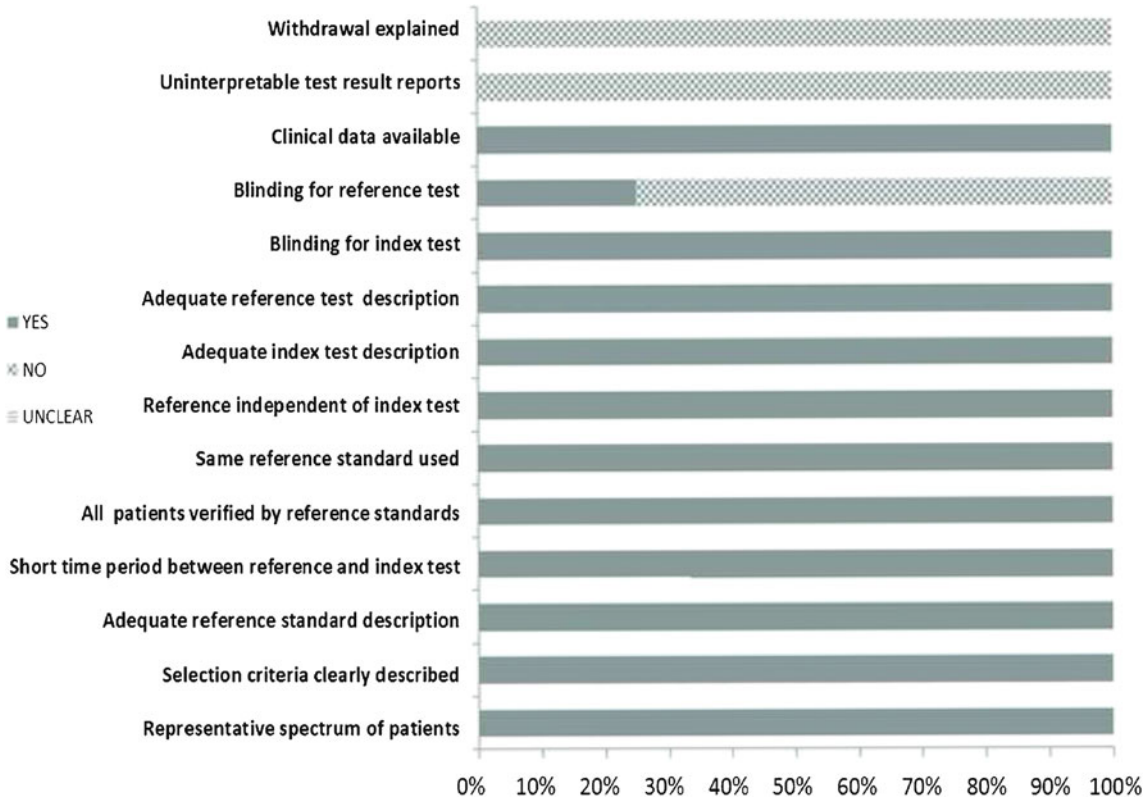

Fig. 2 Assessment of study quality using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) criteria for the studies included

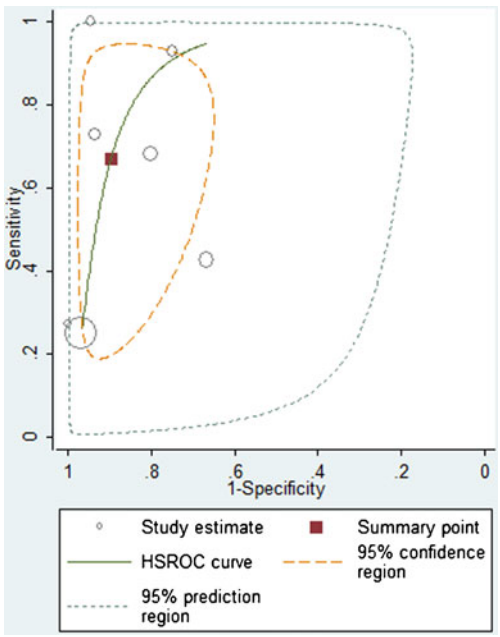

Fig. 3 Hierarchical summary receiver operating characteristic (HSROC) curve (*solid line*) and the bivariate summary estimate (*solid square*), together with the corresponding 95 % confidence ellipse (*inner dashed line*) and 95 % prediction ellipse (*outer dotted line*). The symbol size for each study is proportional to the study size

on the standard cut-off value of 0.5 ng/mL. The pooled sensitivity and specificity were 0.46 (95 % CI: 0.62–0.70) and 0.91 (95 % CI: 0.80–0.96) respectively. Three studies that used a lower PCT cut-off value (0.2–0.3 ng/mL) had greatly enhanced performance. In these studies, the pooled sensitivity was 0.90 (95 % CI: 0.76–0.97) and pooled specificity was 0.87 (95 % CI: 0.77–0.94). The five studies that used older test kits had inferior specificity (0.83; 95 % CI: 0.72–0.90). The pooled results from the 5 studies on adults had improved sensitivity (0.76; 95 % CI: 0.54–0.90) and specificity (0.83; 95 % CI: 0.72–0.90). There was substantial heterogeneity (I^2=54.7 %; 95 % CI: 0.0–81.8 %) in all subgroups except for the pooled results of the 3 studies that used lower cut-off values.

Discussion

We used pooled data from seven studies on serum PCT that enrolled a total of 583 patients who presented with clinical symptoms of joint and bone infections. Our meta-analysis indicated that the pooled sensitivity was 67 % and the specificity was 90 % for the diagnosis of osteomyelitis and septic arthritis. Subgroup analysis in which a lower cut-off value was used (0.2–0.3 ng/mL) improved the sensitivity to 90 %, but had no significant

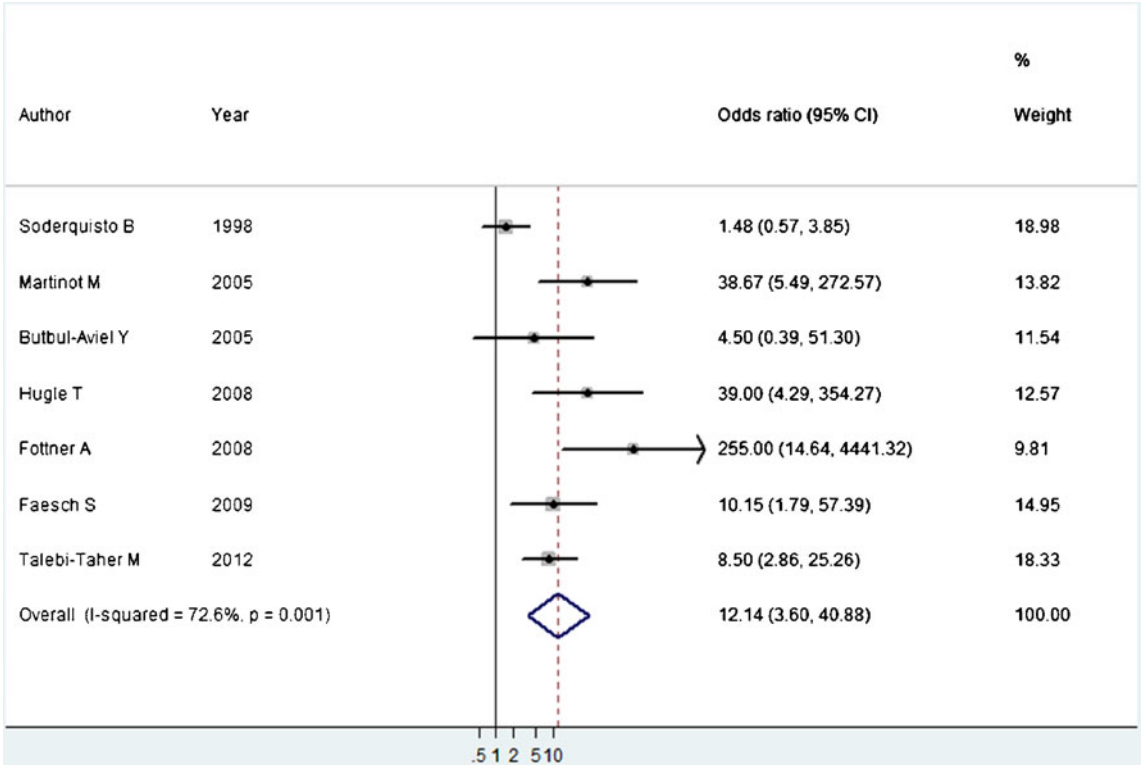

Fig. 4 Forest plot of the diagnostic odds ratio showing good accuracy for the use of PCT in the diagnosis of osteomyelitis and septic arthritis. OR was defined by "(odds of sensitivity)/(odds of 1-specificity)"

effect on specificity (0.87; 95 % CI: 0.77–0.94). In addition, our results indicate that the PCT test was more sensitive in adult patients and that the newer generation kits had better diagnostic accuracy. We cannot draw firm conclusions regarding the diagnostic utility of serum CRP owing to the small number of studies. However, pooled results from 3 of the 7 studies included that measured CRP indicated that serum CRP is not sensitive or specific enough for the diagnosis of osteomyelitis and septic arthritis.

We used pooled likelihood ratio estimates (LR+ and LR−) to calculate post-test probabilities in order to make our results more clinically informative [17, 18]. Thus, in a virtual population with a prevalence of osteomyelitis or septic arthritis of 20 % (the actual pooled prevalence in this study was 22.4 %), use of a serum PCT test with an LR+ of 6.48 would increase the post-test probability (positive predictive value) to 62 %. Likewise, in the same population, application of a serum PCT test with a negative likelihood ratio of 0.37 would reduce the post-test probability to 8 %. Use of data from the subgroup with a lower PCT cut-off value, a similar calculation indicated a positive post-test probability of 63 % and a negative post-test probability of 4 %. These results show that the use of a lower cut-off point makes serum PCT a more useful indicator for the diagnosis of orthopedic infection. A previous meta-analysis indicated that the PCT test had a sensitivity of 88 % (95 % CI: 80–93 %) and a specificity of 81 % (95 % CI: 67–90 %) for the identification of systemic infection [19]. Our results indicate that PCT appears to be less sensitive in the identification of local infection using the standard cut-off value of 0.5 ng/mL and corroborates the findings of Assicot et al.'s seminal paper on use of the PCT test for pediatric febrile disease [4]. This previous study reported low PCT levels (0.3–1.5 ng/mL) in patients with localized infections. Several other studies attempted to measure PCT levels in patients with localized infections, such as pyelonephritis [20], pneumonia [21], pancreatitis [22], and sinusitis, and also reported suboptimal diagnostic performance of serum PCT.

It is possible that the PCT assay of the synovial fluid might be more sensitive than serum PCT for the early identification of septic arthritis, because bacterial infection can cause inflammatory cells (monocytes, lymphocytes, and neutrophils) to produce PCT, which then accumulates in the synovial fluid. At present, only two studies investigated the role of synovial fluid PCT in diagnosis. Martinot et al. and Streit et al. both reported

Table 3 Summary of subgroup analysis of the studies included by different study characteristics

Variables	Number of studies	Sensitivity (95 % CI)	Specificity (95 % CI)	Likelihood ratio+	Likelihood ratio-	AUROC (95 % CI)	Diagnostic OR (95 % CI)	I^2 (95 % CI)	Publication bias (Egger's test p)
Procalcitonin overall analysis [6–12]	7	0.67 (0.37–0.88)	0.90 (0.78–0.96)	6.48 (2.88–14.6)	0.37 (0.16–0.84)	0.89 (0.86–0.92)	12.1 (3.60–40.9)	72.6 (40.8–87.3)	0.039
Septic arthritis [7–12]	6	0.65 (0.30–0.89)	0.88 (0.75–0.94)	5.25 (2.52–10.95)	0.40 (0.16–1.02)	0.88 (0.85–0.89)	11.1 (2.83–43.7)	77.9 (51.1–90.0)	0.045
Cut-off = 0.5 [6, 7, 10–12]	6	0.46 (0.62–0.70)	0.91 (0.80–0.96)	4.84 (2.19–10.68)	0.60 (0.47–0.76)	0.66 (0.62–0.70)	6.53 (2.52–16.9)	54.7 (0.0–81.8)	0.169
Low cut-off value [8–10]	3	0.90 (0.76–0.97)	0.87 (0.77–0.94)	6.66 (2.59–17.1)	0.15 (0.04–0.53)	0.94 (0.89–0.99)	57.4 (15.6–210)	0.0 (0.0–89.6)	0.210
LUMItest [8–12]	5	0.76 (0.54–0.90)	0.83 (0.72–0.90)	4.50 (2.20–9.19)	0.29 (0.12–0.66)	0.87 (0.84–0.90)	16.1 (3.12–83.2)	81.4 (56.8–92.0)	0.034
Adult [7–12]	5	0.76 (0.54–0.90)	0.83 (0.72–0.90)	4.50 (2.20–9.19)	0.29 (0.12–0.66)	0.87 (0.84–0.90)	16.1 (3.12–83.2)	81.4(56.8–92.0)	0.034
CRP overall analysis [6, 10, 12]	3	0.85 (0.72–0.94)	0.37 (0.27–0.47)	1.39 (1.17–1.65)	0.40 (0.12–1.36)	0.59 (0.34–0.85)	3.56 (1.30–9.73)	0.0 (0.0–89.6)	0.698

CRP C-reactive protein

that patients with septic arthritis had significantly higher synovial fluid PCT than patients with rheumatoid arthritis, osteoarthritis, or crystal-induced arthritis [13, 23], but Martinot et al. reported worse sensitivity (63.6 %) and specificity (61.3 %) than for serum PCT. Several studies attempted to measure PCT in other body fluids, such as cerebrospinal fluid, amniotic fluid, or ascites, but all the results indicated worse diagnostic performance than for serum PCT [13]. It is likely that PCT is secreted at much lower levels in body fluids other than serum [24–26].

The main strength of this meta-analysis is that it employed standard guidelines for the diagnostic meta-analysis and a rigorous bivariate model for the calculation of results. We calculated sensitivities and specificities and also presented likelihood ratios and calculated the corresponding post-test probability to make our results more clinically meaningful. The most obvious limitations of our study are the paucity of studies on this topic, the lack of a gold standard reference test, and the heterogeneous etiology of the reference comparison groups. Another limitation may be the PCT testing system used in the older studies that were included. Four of the seven studies used the PCT LIA test (LUMItest PCT; Brahms Diagnostica, Berlin, Germany) with a reported functional sensitivity of 0.5 ng/mL. However, values less than 0.5 ng/mL lack precision [27], and these may be of great importance in this patient population [27]. Only two studies used the Kryptor PCT assay (Brahms Diagnostica), which has a functional sensitivity of 0.06 ng/mL [10, 15, 27]. Further studies employing this or other sensitive PCT assays may improve the performance of the serum PCT test in the identification of osteomyelitis or septic arthritis in patients with symptoms suggestive of skeletal infection.

In conclusion, published studies that have examined the diagnostic accuracy of serum PCT indicate that it may be a useful predictor of osteomyelitis or septic arthritis. We recommend that PCT can be used as a rule-in test at the cut-off value of 0.5 ng/mL and can be used as a rule-out test at the cut-off value of 0.3 ng/mL. In contrast, CRP appears to have limited value in the diagnosis of osteomyelitis and septic arthritis. Our meta-analysis also indicates that use of a lower cut-off point in the PCT test (0.2–0.3 ng/mL) may improve its rule-out diagnostic value. Most previous studies used older generation assay kits that lack precision for serum levels below 0.5 ng/mL. Thus, further studies are needed to confirm the value of newer generation PCT assay kits for the diagnosis of osteomyelitis or septic arthritis in patients who present with undifferentiated skeletal symptoms.

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Conflict of interest None declared.

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