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ORIGINAL ARTICLE

Diagnostic value of serum procalcitonin for acute pyelonephritis in infants and children with urinary tract infections: an updated meta-analysis

Huhai Zhang[1] · Jurong Yang[1] · Lirong Lin[1] · Bengang Huo[1] · Huanzi Dai[1] · Yani He[1]

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Abstract
Purpose The aims were to assess (1) the diagnostic value of serum procalcitonin (PCT) for acute pyelonephritis (APN) in infants and children with urinary tract infections (UTIs) and (2) to compare the performance of two commonly used cutoff values.
Methods A meta-analysis of serum PCT in the diagnosis of APN among pediatrics with lower UTIs was conducted. The process of search strategy, publications selection and data analysis was in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines.
Results Eighteen high-quality studies with a total of 831 APN patients and 651 individuals with lower UTIs were analyzed. The overall performance of serum PCT ≥ 0.5 ng/mL was as follows: pooled sensitivity of 0.86 (95 % CI 0.73–0.93), pooled specificity of 0.76 (95 % CI 0.66–0.83), DOR of 18.90 (95 % CI 6.78–52.71) and AUROC of 0.86 (95 % CI 0.83–0.89), with significant heterogeneity. However, use of 1.0 ng/mL as a cutoff value produced an improved specificity of 0.91 (95 % CI 0.86–0.94), a DOR of 55.06 (95 % CI 22.57–115.48) and an AUROC of 0.94 (95 % CI 0.92–0.96), without obvious heterogeneity.
Conclusion In pediatrics with UTIs, the cutoff value of serum PCT, 1.0 ng/mL, has a preferable diagnostic performance compared with 0.5 ng/mL for APN. Additional prospective studies that propose an appropriate cutoff value and validate the performance of PCT for young with APN are needed in the future.

Keywords Procalcitonin · Urinary tract infections · Acute pyelonephritis · Diagnosis

Introduction

Urinary tract infections (UTIs) frequently occur in infants and children. Before reaching 6 years of age, nearly 1.8 % of boys and 6.6 % of girls have suffered from at least one UTI [1]. In clinical practice, acute pyelonephritis (APN) and lower UTIs are two common forms of UTI that occur during infancy and childhood. Lower UTIs do not normally have complications, while APN is severe form of UTI that may result in renal scarring and subsequent complications, such as hypertension, hyposthenuria and chronic renal failure [2, 3]. The nonspecific signs and symptoms, including fever, flank pain or dysuria, make the clinical differentiation between APN and lower UTIs difficult, even for the experienced clinician [4, 5]. Commonly used laboratory parameters or other novel markers, such as erythrocyte sedimentation rate (ESR), serum leukocyte counts, neutrophil counts, C-reactive protein (CRP), interleukin (IL)-6 and IL-8, have low specificity and cannot reliably differentiate APN from lower UTIs, particularly in young children [6–8].

Differentiating APN from lower UTIs is important because the accurate diagnosis and prompt treatment of APN can prevent renal scarring and subsequent complications. Renal ^{99m}Tc-dimercaptosuccinic acid (DMSA) scintigraphy is considered the gold standard imaging method

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✉ Yani He
heyani1966@163.com

[1] Department of Nephrology, Institute of Surgery Research, Daping Hospital, Third Military Medical University, Chongqing, China

for APN diagnosis. However, there are factors that limit wide application of early DMSA scintigraphy in clinical practice, including the cost, availability and risk of exposing young patients to attendant radiation and sedation [9, 10]. Therefore, it is necessary to develop a reliable, specific and alternative biological marker that could be widely used by clinicians to differentiate APN from lower UTI in infants and children.

Procalcitonin (PCT), a 116-amino acid propeptide of calcitonin, is an early, reliable diagnostic marker of serious bacterial infections and sepsis that has several advantages compared with other potential biomarkers, including a wide biological range, short time of induction after bacterial stimulus and long half-life [11]. Recent studies have reported a correlation between serum PCT levels and renal parenchymal damage in UTIs [12, 13]. Increasing evidence indicates that serum PCT is a potential marker for differentiating APN from lower UTIs in children; however, the different studies that have evaluated the clinical utility of this test are controversial. This controversy has arisen due to the single study design of the previous studies and the fact that the various diagnostic threshold values used to perform sensitivity and specificity analyses disagreed among the studies [14–21]. Additionally, new studies have been performed since the publication of the previous meta-analyses, and our understanding of PCT is still developing [22, 23]. Based on the above, we conducted an updated meta-analysis to comprehensively investigate the performance of serum PCT for the differentiation of APN and lower UTI in infants and children.

Methods

We performed this systematic review and meta-analysis in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [24].

Data sources and search strategy

Systematic literature searches of Medline (via PubMed), Embase (via Elsevier), Web of Science and Cochrane Library were performed to identify relevant studies that assessed the accuracy of PCT for APN diagnosis until November 30, 2014, using the following search terms without language restrictions: (procalcitonin or PCT) and (acute pyelonephritis or APN). Manual searches were completed following a review of the reference lists of selected articles to identify any missing articles.

Study selection

Eligible studies were identified based on the following inclusion criteria: (1) enrolled infants and children who were diagnosed as UTIs and underwent serum PCT detection and subsequent renal ^{99m}Tc-DMSA scintigraphy; (2) evaluated the efficacy of PCT for diagnosing APN based on DMSA scintigraphy as a reference standard; (3) data were available to obtain true-positive (TP), false-positive (FP), true-negative (TN) and false-negative (FN) diagnostic results of APN and lower UTI; and (4) the sensitivity, specificity, positive predictive values (PPVs) or negative predictive values (NPVs) for the diagnosis of APN based on certain cutoff PCT values could be calculated in each study. Conference abstracts were excluded. Studies involving patients with renal dysplasia and renal scarring on DMSA scan, which were often associated with previous APN, were excluded.

Date extraction and quality assessment

The characteristics of each included study were extracted using a standardized form: first author, year of publication, study design, country of origin, sample size in each group, demographic characteristic of the study population (age, sex), PCT levels, referred cutoff values of PCT, time for DMSA scan and whether first episode. The Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Review (QUADAS) assessment tool, which contains 14 items, was applied for the quality assessment of the included studies. Each question was assigned a response of yes, no or unclear for each study [25]. We graded them as 1 score to yes, 0 score to no or unclear for each of the 14 items. Because the quality assessment related strongly to the reporting of results, a well-conducted study could score poorly if the methods and results were not reported in sufficient detail. Two reviewers screened the studies and performed the study selection, data extraction and quality assessment independently. Any disagreements were resolved through discussion or a third reviewer.

Data synthesis and analysis

All synthesis and analysis were performed with the use of STATA 12.0 (StataCorp, College Station, TX). We used the bivariate mixed-effect model to estimate the pooled sensitivity, specificity, diagnostic odds ratio (DOR), area under the receiver operating characteristic curve (AUROC) and positive and negative likelihood ratios (LRs) of included studies by the MIDAS module [26]. In order to propose the potential optimal cutoff value, we conducted the data synthesis on two common threshold values of PCT (0.5 vs. 1.0 ng/mL) used in the literature. We used the derived logit estimates of sensitivity, specificity and respective variances to construct a hierarchical summary receiver operating curve (HSROC) by the METANDI module. The closer the AUROC was to 1, the better the test performance. Based

on the summary sensitivity and specificity, we calculated the pretest probabilities of 25 % versus the corresponding posttest probabilities with the detection of serum PCT after admission. Graphs were produced with STATA 12.0 program. The I^2 test was used to assess heterogeneity of pooled statistical variables, with $I^2 > 50$ % indicating significant heterogeneity and $I^2 < 25$ % indicating no obvious heterogeneity. To explore the potential source of heterogeneity, we stratified the studies into several subgroups according to the characteristics of studies. Specificity, sensitivity, DOR, AUROC, I^2, PLR, NLR and 95 % confidence intervals (95 % CI) were calculated for each subgroup to quantitatively estimate the proportion of total variation. We investigated publication bias by Deeks' test. Publication bias was considered to be present if there was a nonzero slope coefficient ($p < 0.05$) [27].

Results

Search results and study characteristics

As shown in Fig. 1, our systematic search initially yielded 239 publications in total, with 127 duplicates removed. Another 33 articles, including reviews, case reports and commentaries, were excluded after screening the titles and/or abstracts. A total of 79 studies remained for evaluation via detailed reading. Several studies did not meet our inclusion criteria because they were focused on therapy, risk evaluation or adults. Thirty studies did not include patients with lower UTIs. Additionally, we could not extract data for a 2 × 2 quadrant table in two studies. An additional manual search of the reference lists of the included studies and relevant reviews did not identify any other articles. Finally, 18 studies were included in this meta-analysis. The main characteristics of the included studies are listed in Table 1. These studies were performed in ten countries throughout Europe, America and Asia from 1998 to 2014, representing an international experience. A total of 1482 patients with UTIs were enrolled, and all the studies were conducted in infants and children. Only four of the 18 included studies had sample sizes greater than 100 subjects. The serum PCT levels were provided in most studies, and they were significantly different between patients with APN and those with lower UTIs. Ten of the included studies evaluated the performance of serum PCT using more than two cutoff values. Eleven of the 18 studies were conducted in patients experiencing their first UTI. Only one study did not report the time between admission to the hospital and performance of a DMSA scan, whereas the other studies reported performance of a DMSA scan within 7 days.

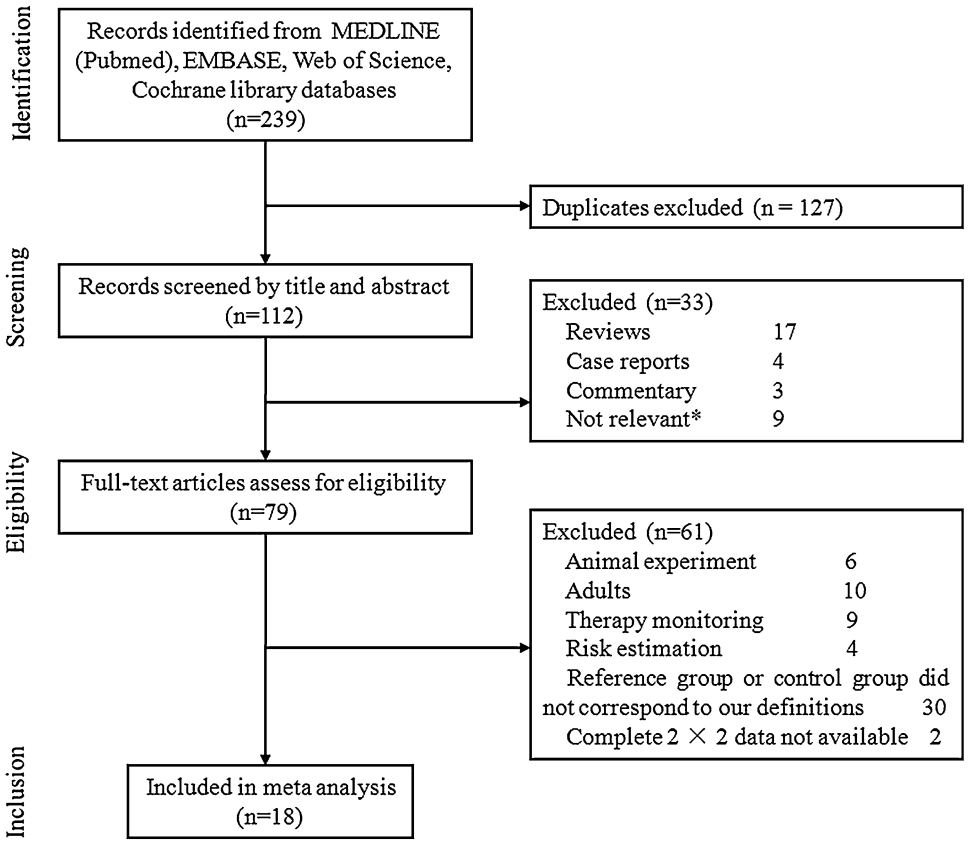

Fig. 1 Flow chart of study selection

Table 1 Characteristics of included studies evaluating the performance of serum PCT in the diagnosis of APN among infants and children

References	Study design	Country	Included sample size (APN/lower UTI, *n*)	Age (mo.)*	Sex (M/F)	PCT levels (ng/mL)*		Referred PCT cutoff values (ng/mL)	First episode	Time for DMSA scan
						APN	Lower UTI			
Benador et al. [28]	Prospective	France	37/23	3.0 ± 0.8	17/43	0.38 ± 0.19	5.37 ± 1.90	>0.6	NR	≤5 days
Gervaix et al. [29]	Prospective	Switzerland	34/20	NR	18/36	NR	NR	≥0.5	NR	3–5 days
Smolkin et al. [15]	Prospective	Israel	18/42	14 (1–5)	17/43	0.13 (0.02–2.15)	3.41 (0.36–12.4)	≥0.5	NR	≤7 days
Pecile et al. [30]	Prospective	Italy	53/47	19 (1–156)	31/69	0.44 ± 0.30	4.48 ± 5.84	≥0.5, ≥0.8, ≥1.0	1st	≤5 days
Tuerlinckx et al. [31]	Prospective	Belgium	50/13	44 (2–168)	13/49	1.1 (0.1–7.3)	1.5 (0.12–30.5)	≥0.5, ≥1.7	1st	≤72 h
Gurgoze et al. [16]	Prospective	Turkey	34/42	39.6 ± 33.8	28/48	0.1 (0.1–3.2)	1.68 (0.14–5.4)	>0.5	NR	≤7 days
Bigot et al. [32]	Prospective	France	19/23	29.5 ± 32.5 and 43.3 ± 57.3	13/29	0.4 ± 1.1	5.4 ± 9.6	≥0.5	NR	≤72 h
Guven et al. [33]	Prospective	Turkey	21/12	53 (12–132)	2/31	0.766 ± 0.644	1.232 ± 1.172	≥0.5, ≥0.96, ≥1.0, ≥2.	1st	≤72 h
Karavanaki et al. [34]	Prospective	Greece	18/34	7.2 (1–114)	19/32	0.3 (0.1–0.98)	4.8 (0.4–28.7)	≥0.5, ≥0.8, ≥1.0	1st	≤7 days
Kotoula et al. [35]	Prospective	Greece	27/30	12 (2–108)	13/43	0.3 (0.1–0.9)	4.8 (0.5–13.2)	≥0.5, ≥0.85, ≥1.2	1st	≤7 days
Nikfar et al. [17]	Prospective	Iran	62/38	15 (1–168)	19/81	NR	NR	≥0.5	NR	≤5 days
Sheu et al. [18]	Prospective	China	76/36	5 (0.8–24)	66/46	0.35 (0.25–0.44)	2.95 (1.37–8.37)*	≥0.5, ≥1.0, ≥1.5, ≥2.0	1st	≤3 days
Chen et al. [19]	Prospective	China	87/49	3.0 (7.0–44.9)	56/80	0.39 (0.29–0.82)	3.29 (1.63–5.71)*	≥0.5, ≥1.3, ≥2.0	1st	≤3 days
Sun et al. [36]	Prospective	China	169/103	5 (0.5–24)	168/104	NR	NR	≥1.0	1st	≤5 days
Zhang et al. [20]	Prospective	China	39/26	NR	33/42	0.37 (0.07–0.68)	3.08 (1.09–5.21)*	≥0.11, ≥0.33, ≥1.03	1st	NR
Bouguila et al. [37]	Prospective	Tunisia	33/42	14.7 (1–180)	25/50	1.7 ± 5.3	8.81 ± 14.53	≥0.5, ≥0.76, ≥0.8	1st	≤7 days
Mahyar et al. [21]	Prospective	Iran	33/46	(1–144)	5/74	0.026 (0.02–7.79)	0.245 (0.2–77.6)	≥0.5, ≥0.6	1st	≤7 days
Xu et al. [38]	Retrospective	China	21/25	2–168	18/28	0.48 ± 0.39	3.90 ± 3.51	≥1.0	Part	≤5 days

PCT procalcitonin, *APN* acute pyelonephritis, *UTI* urinary tract infection, *M* male, *F* female, *DMSA* ^{99m}Tc-dimercaptosuccinic acid, *NR* not reported, *Mo* month

* Data were expressed as an statistic range or mean ± standard deviation

Quality assessment

As summarized in Figure S1, the methodological quality of each included study was moderate to high according to the QUADAS standard. Seventeen of the studies were designed as prospective research and contained sufficient clinical information. In most studies, the index test results were not interpreted with knowledge of the blinded reference tests to eliminate bias, and uninterpretable, indeterminate or intermediate results were not reported.

Data analysis and calculations

Because some studies used different cutoff values for serum PCT, the 18 included studies were stratified into two groups according to two commonly used cutoff values in the literature (0.5 and 1.0 ng/mL) to investigate the diagnostic value of serum PCT for differentiating between APN and lower UTI. Because the numbers of TP, FP, TN and FN results were not directly provided by some studies, we calculated these indexes from the provided sample size, sensitivity and specificity values. Fourteen studies provided data for a cutoff value of 0.5 ng/mL, with a total of 1049 patients (55 % had APN), and seven studies (680 patients in total, 58 % had APN) used a cutoff value of 1.0 ng/mL. The relevant data from the individual studies of the two groups are listed in Table S1 and S2. The sensitivity of serum PCT with a cutoff value of 0.5 ng/mL ranged from 0.31 to 1.00, and the specificity ranged from 0.23 to 0.90. The sensitivity of serum PCT with a cutoff value of 1.0 ng/mL ranged from 0.52 to 0.94, and the specificity ranged from 0.83 to 1.00. Figures 2 and 3 present forest plots of the pooled analysis. As summarized in Table 2, the pooled sensitivity of serum PCT (≥0.5 ng/mL) for the diagnosis of APN in infants and children with UTIs was 0.86 [95 % confidence interval (CI), 0.73–0.93] and the specificity was 0.76 (95 % CI 0.66–0.83) with a DOR of 18.90 (95 % CI 6.78–52.71). The heterogeneity across studies was significant, as evidenced by the I^2 statistic of 95.78 %, and it was not derived from the threshold effect ($r = -0.26$, $p = 0.38 > 0.05$) because of the identical cutoff values used in these studies. However, serum PCT ≥ 1.0 ng/mL had a similar sensitivity of 0.84 (95 % CI 0.78–0.89) but a higher DOR of 55.06 (95 % CI 22.57–115.48) and specificity of 0.91 (95 % CI 0.86–0.94) without noticeable heterogeneity ($I^2 = 0.00$ %). The areas under the receiver operating characteristic curve (AUROC) of the two cutoff values were 0.86 (95 % CI 0.83–0.89; Fig. 4a) and 0.94 (95 % CI 0.92–0.96; Fig. 4b). The threshold effect was evaluated using the Spearman correlation coefficient of sensitivity and specificity ($r = -0.32$, $p = 0.48 > 0.05$), which suggested that there is no heterogeneity from the threshold effect when using 1.0 ng/mL as a cutoff value within the studies.

No potential publication biases were identified in the studies using cutoff values of 0.5 ng/mL ($t = -0.66$, $p = 0.52$, Figure S2A) and 1.0 ng/mL ($t = 0.06$, $p = 0.95$, Figure S2B), as evidenced by the symmetric plots.

Subgroup analysis

To identify the sources of significant heterogeneity when using a cutoff of 0.5 ng/mL, the area of origin, ratio of males/females, first episode reported and timing of DMSA scan after admission were chosen as potential variables. Table 3 summarizes the results of the subgroup analysis.

Area of origin

Because the incidence of UTIs differs across countries, different races and ethnicities may be important factors that could affect the performance of PCT. Based on the origin of the subjects enrolled in this meta-analysis, we classified the 14 publications into two subgroups: Europe or America and Asia. Mild differences were evident in the statistical variables of each subgroup. The six studies from Asia had a relatively higher specificity (0.80; 95 % CI 0.68–0.89), DOR (22.19; 95 % CI 7.09–69.45) and AUROC (0.88; 95 % CI 0.85–0.91), while the specificity, DOR and AUROC of the eight studies in Europe or America were 0.72, 16.09 and 0.84, respectively. The difference between the subgroups was not statistically significant ($p = 0.60$).

Ratio of male/female

Physiologically, females are more susceptible to UTIs than males. Therefore, we divided the patients into two subgroups based on the sex ratio (males/females ≥0.5 and <0.5). The DOR was 17.63 for males/females ≥0.5 and 20.87 for males/females <0.5. The difference in DOR between the subgroups was not statistically significant ($p = 0.23$). The heterogeneity observed in each subgroup was still quite large because $I^2 > 50$ %.

First episode

Five studies did not report whether the subjects were experiencing their first UTI; therefore, we separated these studies. The DOR and AUROC of these five studies were 13.45 and 0.81, respectively. However, the nine remaining studies in which all included subjects were experiencing their first UTI showed improved serum PCT performance (DOR 30.50; AUROC 0.90) without obvious heterogeneity ($I^2 = 0.00$ %).

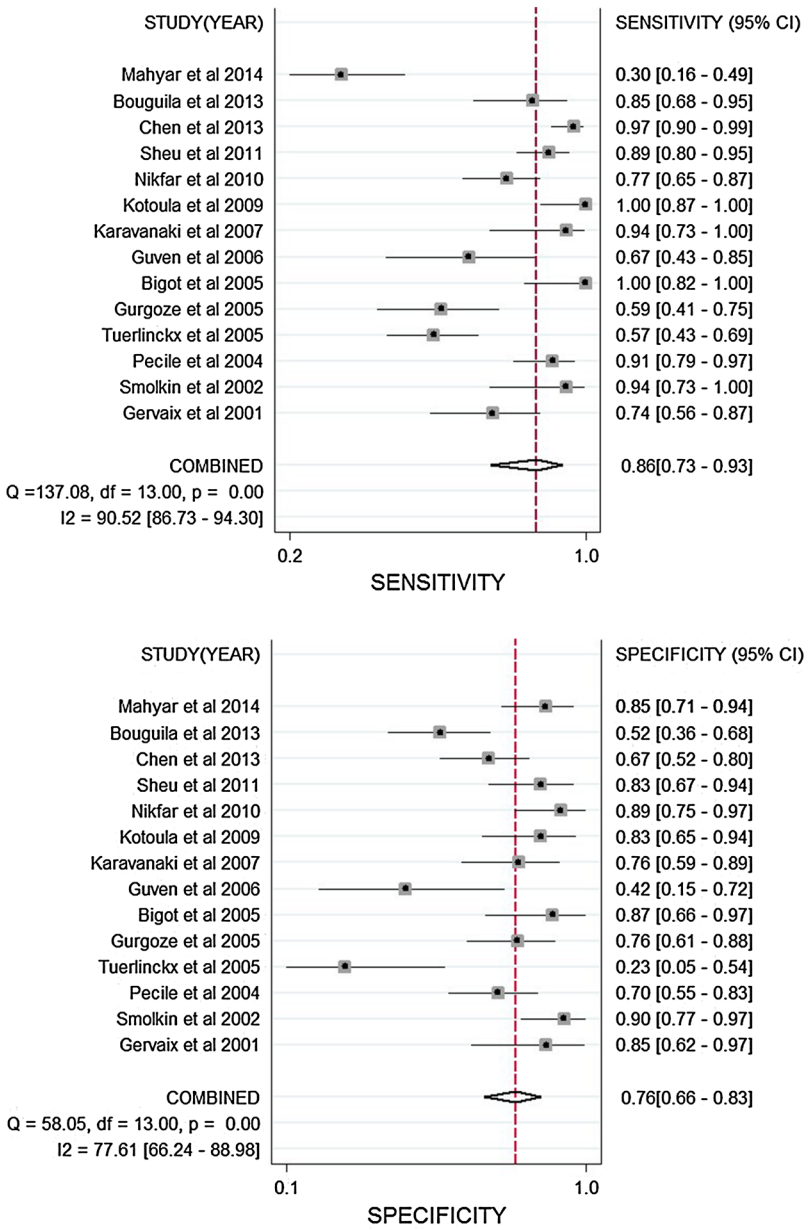

Fig. 2 Forest plots of the pooled sensitivity and specificity of serum PCT (cutoff value, 0.5 ng/mL) for differentiation APN from lower UTIs. The *black squares* in the *gray squares* and the *horizontal lines* represent the point estimate and 95 % confidence interval (CI), respectively. The *dotted line* represents the pooled estimate, and the *diamond shape* represents the 95 % CI of the pooled estimate

Timing of DMSA scans after admission

Of the 14 studies, five studies conducted a DMSA scan less than or equal to 72 h after admission, while the patients of the other studies may have received a DMSA scan less than or equal to 7 days after admission. The DOR and AUROC of the former subgroup (timing of DMSA scan $\leq$72 h) were 13.12 and 0.84, respectively, without heterogeneity across studies ($I^2 = 0.00$ %). However, the DOR and AUROC of the studies in which the timing of the DMSA scan was $\leq$7 days were 20.29 and 0.87, although it is difficult to reach a definitive conclusion due to the significant heterogeneity ($I^2 = 94.24$ %).

Discussion

PCT has been recognized as a marker for APN since 1998 [28]. However, the reported diagnostic value in children varies worldwide. A previous meta-analysis conducted by Mantadakis et al. [22] was published on a similar subject in 2009; however, some deficiencies in their design and data analysis may have affected the accuracy of their conclusions. First, only ten studies that used a serum PCT cutoff value of 0.5–0.6 ng/mL were used to calculate the estimated pooled statistics, which had obvious heterogeneity. Second, there were some errors in the data extraction from the included articles. Additionally, no further

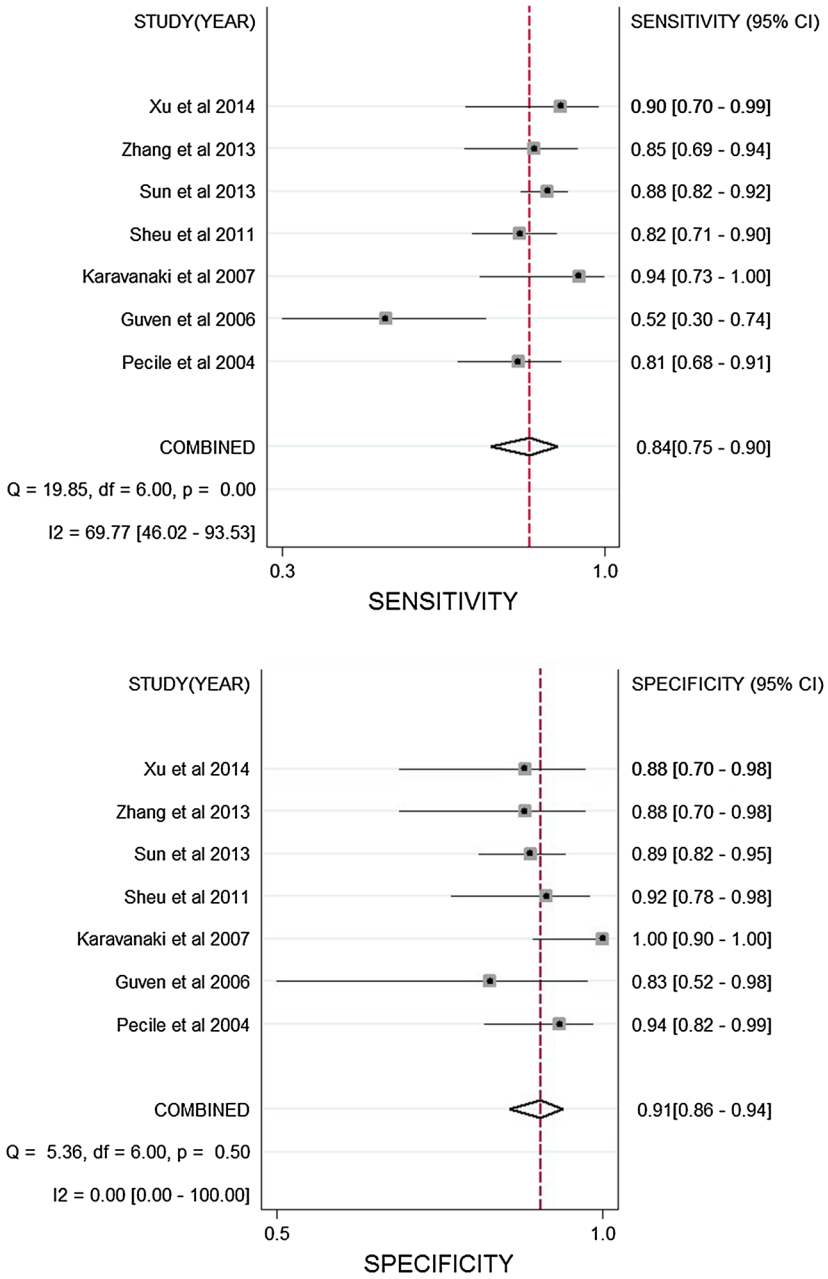

Fig. 3 Forest plots of the pooled sensitivity and specificity of serum PCT (cutoff value, 1.0 ng/mL) for differentiation APN from lower UTIs in infants and children. The *black squares* in the *gray squares* and the *horizontal lines* represent the point estimate and 95 % confidence interval (CI), respectively. *The dotted line* represents the pooled estimate, and the *diamond shape* represents the 95 % CI of the pooled estimates

analyses were performed to identify the source of heterogeneity. In another meta-analysis from 2013, which included 18 studies from January 1993 (when PCT was first described in relation to bacterial infection) to September 2011, Leroy et al. [23] studied procalcitonin as a predictor of both APN and scarring in children with UTIs. The diagnostic accuracy of serum PCT was low: The pooled sensitivity and specificity were 0.71 (95 % CI 0.67–0.74) and 0.72 (95 % CI 0.67–0.76), respectively, for the cutoff value 0.5 ng/mL and 0.65 (95 % CI 0.61–0.69) and 0.87 (95 % CI 0.83–0.90), respectively, for the cutoff value 1.0 ng/mL. When examining studies included in that meta-analysis individually, we determined that some publications did not perform the current gold standard, DMSA renal scintigraphy, which was not strictly in accordance with the inclusion criteria. Furthermore, the authors did not provide the extracted data used for the analysis in detail. Despite considering three PCT cutoff values, the number of publications used to evaluate the performance of each cutoff value was unknown, and the authors did not offer any novel viewpoints. Moreover, in the last three years (from September 2011 to September 2014), at least six additional publications that assessed the suitability of PCT in pediatric UTIs have been performed; therefore, it is appropriate to re-evaluate the diagnostic value of PCT.

Table 2 Pooled diagnostic accuracy for differentiation APN from low UTIs

Cutoff value of PCT (ng/mL)	No. of studies	Total sample size (APN/lower UTI)	Pooled sensitivity (95 % CI)	Pooled specificity (95 % CI)	DOR (95 % CI)	AUROC (95 % CI)	I^2 (%)	Likelihood ratio (95 % CI)		Pretest	Posttest (+)	Posttest (−)
								Positive	Negative			
0.5	14	575/474	0.86 (0.73–0.93)	0.76 (0.66–0.83)	18.90 (6.78–52.71)	0.86 (0.83–0.89)	95.78	3.53 (2.36–5.29)	0.19 (0.09–0.39)	0.55	0.81	0.19
1.0	7	397/283	0.84 (0.75–0.90)	0.91 (0.86–0.94)	55.06 (22.57–115.48)	0.94 (0.92–0.96)	0.00	9.17 (5.81–14.47)	0.18 (0.11–0.29)	0.58	0.93	0.20

PCT procalcitonin, *CI* confidence interval, *DOR* diagnostic odds ratio, *AUROC* area under the receiver operating characteristic curve, I^2 Chi square

In this systematic review and meta-analysis, we summarized the results of all published studies that assessed the performance characteristics of serum PCT for the differential diagnosis of APN and lower UTIs in infants and children in detail. Our findings are consistent with previous studies; however, we add more evidence and novel views that support the utilization of serum PCT as a marker of APN in clinical practice. We enrolled 1482 pediatric patients with UTIs in total and applied two commonly used cutoff values for serum PCT (0.5 or 1.0 ng/mL) in the analysis.

The results revealed that a serum PCT cutoff value of 0.5 ng/mL had a DOR of 18.90 (95 % CI 6.78–52.71) and an AUROC of 0.86 with significant heterogeneity across studies. Notably, according to the subgroup analysis, we determined that lack of information about the number of episodes and timing of the DMSA scan after admission, rather than the area of origin or ratio of males/females, may be the major sources of heterogeneity in the studies with this cutoff value. Nine of the 14 included studies reported that all subjects were experiencing their first episode and exhibited good performance for pooled specificity, DOR and AUROC and lacked heterogeneity (Table 3), indicating that well-controlled studies may provide more reliable information for selection. Therefore, several pediatric patients in the other studies may have previously suffered APN, and these patients were responsible for the observed heterogeneity. Patients in five studies had a DMSA scan within 72 h after admission, and it appears that this group had a higher pooled sensitivity (0.88; 95 % CI 0.68–0.97) and AUROC (0.84; 95 % CI 0.80–0.87) compared with patients who had a DMSA scan within 7 days. Some possible explanations for this observation are that some patients may not have arrived at the hospital in time or may have used antibiotics before admission; therefore, a DMSA performed within 72 h may be more accurate. There was a potential skewing of the reference standard test in the studies that performed DMSA within 5 or 7 days because of the different positive results caused by time point selection, specifically for patients with mild renal parenchymal involvement, which could directly contribute to the observed heterogeneity. To our knowledge, the incidence of APN in different genders and races may differ; however, we failed to further stratify the patients enrolled in our study due to the limited valid data.

Conversely, our analysis determined that 1.0 ng/mL may be an optimal serum PCT value for APN diagnosis, with a DOR of 2.60, high sensitivity (0.84; 95 % CI 0.75–0.90), high specificity (0.91; 95 % CI 0.86–0.94) and an AUROC of 0.94, which further suggested that its overall predictive accuracy was high. The likelihood ratios and posttest probabilities are also relevant for clinicians. The overall positive

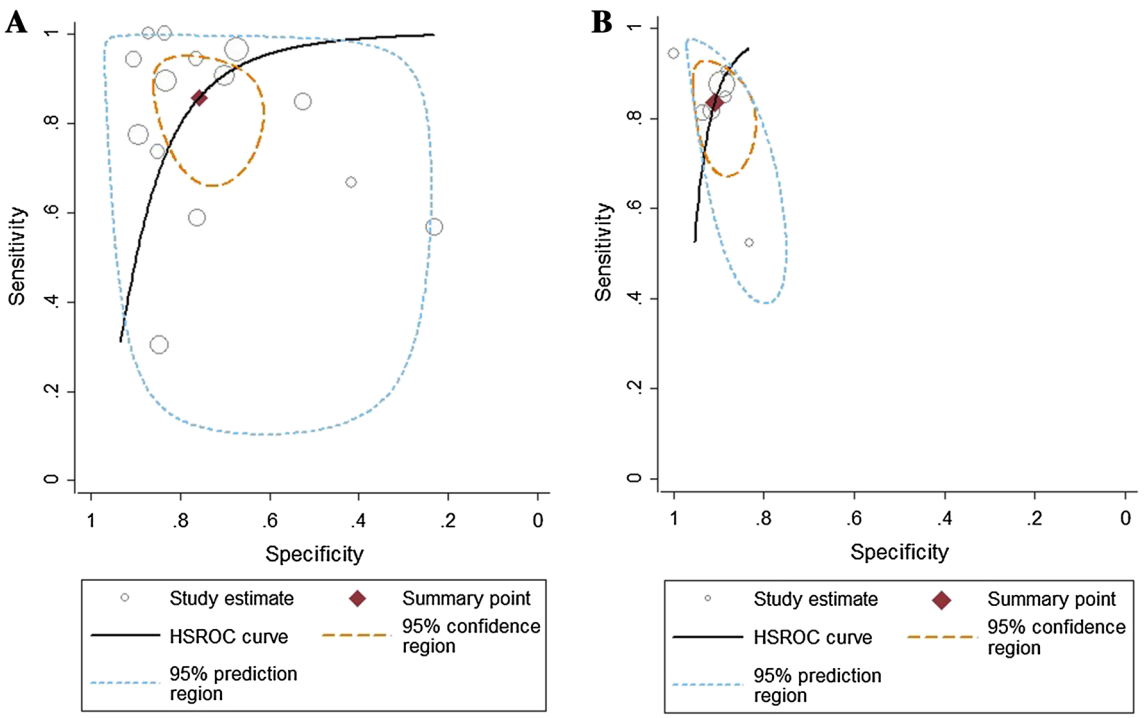

Fig. 4 Hierarchical summary receiver operating characteristic (HSROC) plots of serum PCT for the diagnosis of APN in young. **a** Derived from studies using cutoff value of 0.5 ng/mL. **b** Derived from studies using cutoff value of 1.0 ng/mL. The *summary point* represents the summary sensitivity and specificity, the 95 % confidence region represents the 95 % confidence intervals of the summary sensitivity and specificity, and the 95 % *prediction region* represents the 95 % confidence interval of sensitivity and specificity of each individual study included in the analysis. The plot also includes study estimates indicating the sensitivity and specificity estimated using the data from each study separately

LR (9.17; 95 % CI 5.81–14.47) of this cutoff value was relatively reliable compared with 0.5 ng/mL; for example, an infant or child with APN is almost nine times more likely to have a positive test result than a patient with a lower UTI. With a pretest probability of 58 %, the posttest probability of a positive test result increased to 93 %, which was much higher than the posttest probability of 81 % calculated using 0.5 ng/mL as a cutoff value. Furthermore, the negative LR of 0.19 reduced the posttest probability of a negative test result to 20 %. The main strength of the present study compared with previous studies is that the data synthesis and analysis were conducted using a commonly used cutoff value (0.5 ng/mL) and a possible optimal cutoff value 1.0 ng/mL. In addition to conventional DOR, sensitivity, specificity and AUROC, we also provided the LR to ensure that the results can be better understood by clinicians. On the basis of our results, we consider 1.0 ng/mL to be an effective cutoff value for serum PCT to distinguish APN from lower UTIs.

There are some limitations to our study. First, the age of the included patients ranged from 3 weeks to 12 years. The sensitivity of serum PCT may vary at different life stages; however, due to the nature of the data extracted from the research studies, we were not able to stratify the subjects according to age. Second, we were unable to formally assess the related clinical signs and symptoms or the coexistence of infections at other sites, which may influence serum PCT levels. Third, the sample sizes in a majority of the included studies were less than 100, and only seven studies evaluated the diagnostic value of a cutoff of 1.0 ng/mL for serum PCT. More than half of the studies were performed in Asian populations, which may have led to selection bias. Moreover, the LRs were calculated from dichotomized data. The results of the serum PCT test were artificially classified as either positive or negative. Therefore, it is possible that some useful intermediate information was lost.

In conclusion, this meta-analysis demonstrates that a serum PCT cutoff value of 1.0 ng/mL provided good diagnostic value for discriminating between APN and lower UTIs in infants and children. Moreover, several published studies have suggested that serum PCT is also a predictive marker of renal scarring or vesicoureteral reflux in patients with UTIs. Further studies are needed to validate the diagnostic and potential prognostic value of this cutoff value of serum PCT in large multicenter cohorts.

Table 3 Diagnostic accuracy of serum PCT (cutoff value, 0.5 ng/mL) in various analyzed subgroups

Subgroup	No. of studies	Pooled sensitivity (95 % CI)	Pooled specificity (95 % CI)	DOR (95 % CI)	AUROC (95 % CI)	I^2 (%)	Likelihood ratio (95 % CI)		Pretest	Posttest (+)	Posttest (−)
							Positive	Negative			
Area of origin											
Europe or America	8	0.86 (0.67–0.95)	0.72 (0.57–0.83)	16.09 (3.36–77.13)	0.84 (0.81–0.87)	67.93	3.05 (1.74–5.35)	0.19 (0.06–0.56)	0.25	0.50	0.06
Asia	6	0.85 (0.64–0.94)	0.80 (0.68–0.89)	22.19 (7.09–69.45)	0.88 (0.85–0.91)	95.38	4.24 (2.55–7.04)	0.19 (0.08–0.48)	0.25	0.58	0.06
Ratio of male/female											
≥0.5	6	0.87 (0.74–0.94)	0.73 (0.64–0.81)	17.63 (7.40–42.00)	0.84 (0.80–0.87)	86.34	3.25 (2.33–4.53)	0.18 (0.09–0.38)	0.25	0.52	0.06
<0.5	8	0.86 (0.62–0.96)	0.77 (0.60–0.88)	20.87 (3.35–129.87)	0.87 (0.84–0.90)	93.17	3.72 (1.83–7.57)	0.18 (0.05–0.63)	0.25	0.55	0.06
First episode											
Yes	9	0.83 (0.64–0.93)	0.86 (0.78–0.92)	30.50 (7.90–117.71)	0.90 (0.87–0.93)	0.00	6.00 (3.42–10.57)	0.20 (0.08–0.48)	0.25	0.67	0.06
NR or Not all	5	0.86 (0.69–0.95)	0.68 (0.55–0.79)	13.45 (3.57–50.72)	0.81 (0.78–0.85)	95.00	2.71 (1.73–4.25)	0.20 (0.08–0.53)	0.25	0.47	0.06
Timing of DMSA scan after admission											
≤3 days	5	0.88 (0.68–0.97)	0.64 (0.38–0.83)	13.12 (1.46–118.11)	0.84 (0.80–0.87)	0.00	2.42 (1.11–5.28)	0.18 (0.04–0.79)	0.25	0.45	0.06
≤5 days or 7 days	9	0.84 (0.67–0.93)	0.80 (0.71–0.86)	20.29 (7.26–56.72)	0.87 (0.83–0.89)	94.24	4.13 (2.82–6.07)	0.20 (0.09–0.45)	0.25	0.58	0.06

CI confidence interval, *DOR* diagnostic odds ratio, *AUROC* area under the receiver operating characteristic curve, I^2 Chi square, *NR* not report

Compliance with Ethical Standards

Conflict of interest No conflict of interest was declared.

Ethical statement The manuscript does not contain original clinical studies.

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