Int J Clin Exp Med 2018;11(4):2988-2999
www.ijcem.com /ISSN:1940-5901/IJCEM0063245

Review Article

Prediction of acute pyelonephritis from urinary tract infection in children with fever using detection of CRP level: a diagnostic meta-analysis

Wenhua Zhang, Yuyu Zhang, Lin Xu, Jing Zhao

Department of Obstetrics and Gynecology, Qilu Hospital of Shandong University, Jinan, Shandong, China

Received June 19, 2017; Accepted March 28, 2018; Epub April 15, 2018; Published April 30, 2018

Abstract: C-reactive protein (CRP) is usually used to assess the degree of disease and the therapeutic effect by measuring serum CRP level. Many studies also performed the differential diagnosis of urinary tract infection (UTI) and acute pyelonephritis (APN) through CRP level, but the results were different. Our objective was to assess whether serum CRP level can be used to discriminate between UTI and APN using a diagnostic meta-analysis. MeSH terms and free terms were used at the same time and searched in the Web of science, PubMed, EmBase and OVID databases according to presupposed inclusion and exclusion criteria. Research information were extracted and sensitivity, specificity, diagnostic score, diagnostic odds ratio (DOR) with the corresponding 95% confidence interval (CI) from each study were combined under a random effect model and area under the summary receiver operating curve (AUSROC) was also calculated. There were 21 studies included in this meta-analysis, and the pooled results suggested that sensitivity and specificity of the CRP level used for diagnosis of APN from UTI in children with fever were 0.826 (95% CI, 0.744 to 0.886) and 0.669 (95% CI, 0.582 to 0.747), corresponding AUROC and DOR were 0.81 (95% CI, 0.77 to 0.84) and 9.605 (95% CI, 6.855 to 13.458), respectively. In conclusion, the results showed a moderate accuracy of CRP used for diagnosing APN from UTI though there was heterogeneity. So, more studies with a unified detection method and strict quality control measures are needed.

Keywords: APN, UTI, CRP, diagnostic meta-analysis

Introduction

Urinary tract infection (UTI) is a common clinical and frequently-occurring disease. Patients often possess the characteristics of frequent urination, urgency, dysuria and other symptoms, severe case can occur systemic infection symptoms. Women, the elderly, and children are frequent people infected with UTI [1]. UTI can usually be divided into upper UTI and lower UTI. Upper UTI mainly refers to acute and chronic pyelonephritis and ureteritis. Lower UTI includes cystitis and urethritis. UTI is a common acute disease in infants and children, which can be limited to the lower urinary tract, or can be involved in the kidneys and lead to persistent kidney damage and scarring, especially in patients with the vesicoureteral reflux (VUR) and other urinary system development deformity [2].

Acute pyelonephritis (APN) is a common childhood serious bacterial infectious disease, also known as upper UTI, the incidence is higher in infants under 3 years of age [3]. If not treated promptly, APN often leads to persistent kidney damage and scarring, and then causes hypertension and chronic renal failure [4]. However, it is not easy to distinguish APN from lower UTI from common clinical symptoms and laboratory indicators. Clinical treatment and the prognosis of APN and bladder, urethral inflammation exist different degrees of difference. UTI early detection and accurate identification can help to reduce renal damage and scar formation, shorten the course of disease, and improve the prognosis [5]. However, clinical manifestations of children (especially infants under 3 years old) often are atypical, the diagnosis and differential diagnosis of APN and lower UTI mainly depend on vesicoureteral imaging and 99mTc-DMSA (dimercaptosuccinic acid). The former one in the clinical application still exists a lot of controversy [6], the latter one with special equipment and professional operation techniques is not suitable for clinical wide develop-

Table 1. Characteristics of studies include in this meta-analysis and patient's baseline demographics

Study (publish years)	Country	Delivery time	UTI	Years old	No. of UTI	Gold standard	A DMSA renal scintigraphy was performed following admission	Cut off value
Abolfazl Mahyar (2013)	Iran	2012	First episode of febrile UTI	< 12 y	79	Tc-99m dimercaptosuccinic acid renal scan	7 days	4, 10, 20 mg/dl
Alberto Biggi (2001)	Italy	-	First episode of febrile UTI	< 13.5 y	101	Tc-99m dimercaptosuccinic acid renal scan	No later than 15 days	88 mg/dl
Andrew Fretzayas (2000)	Greece	-	First episode of febrile UTI	< 14 y	83	Tc-99m dimercaptosuccinic acid renal scan	3 days	20 mg/dl
Banuelos-Andrío, L (2017)	Spain	2009.1-2011.12	First episode of febrile UTI	< 16 y	101	Tc-99m dimercaptosuccinic acid renal scan	3 days	39.4 mg/dl
Byung Kwan Kim (2017)	Korea	2014.10-2015.9	First episode of febrile UTI	< 13 y	138	Tc-99m dimercaptosuccinic acid renal scan	3 days	2.78 mg/dl
Eduardo H. Garin (2007)	Chile and the USA	1999-2004	First episode of febrile UTI	3 month to 2 years	185	Tc-99m dimercaptosuccinic acid renal scan	Between 48 h and 5 days	> 0.5 μg/ml
Hai-Lun Sun (2014)	China	-	First episode of febrile UTI	< 2 y	272	Tc-99m dimercaptosuccinic acid renal scan	96 hours	6.2 mg/dl
I Re Lee (2015)	Korea	2012.1-2013.12	First episode of febrile UTI	< 2 y	118	Tc-99m dimercaptosuccinic acid renal scan	5 days	-
Jen-Hsi Wu (2012)	China	2001.1-2009.12	First episode of febrile UTI	< 4 months	116	Tc-99m dimercaptosuccinic acid renal scan	As soon as possible	5,10 mg/dl
Ji Hyun Sim (2015)	Korea	2013.10-2014.9	First episode of febrile UTI	< 5 y	123	Tc-99m dimercaptosuccinic acid renal scan	-	3.68 mg/dl'
Ji-Nan Sheu (2003)	China	2009-2011	First episode of febrile UTI	< 2 y	112	Tc-99m dimercaptosuccinic acid renal scan	3 days	2, 3.5, 6, 10 mg/dl
Ji-Nan Sheu (2006)	China	2004-2006	First episode of febrile UTI	< 10 y	78	Tc-99m dimercaptosuccinic acid renal scan	7 day	2.5 mg/dl
Jung Won Lee (2013)	Korea	2010.1-2014.12	First episode of febrile UTI	< 12 months old	288	Tc-99m dimercaptosuccinic acid renal scan	5 days	-
Kianoush Ansari Gilani (2010)	Iran	2006-2007	First episode of febrile UTI	< 10 y	119	Tc-99m dimercaptosuccinic acid renal scan	7 day	30 mg/dl
Paolo Pecile (2005)	Italy	2000.1-2002.1	First episode of febrile UTI	< 13 months old	100	Tc-99m dimercaptosuccinic acid renal scan	3 days	20, 50 mg/dl
Parviz AyAzi (2013)	Iran	2005-2006	First episode of febrile UTI	< 12 months old	127	Tc-99m dimercaptosuccinic acid renal scan	-	10 mg/dl
Sandrine Leroy (2013)	United Kingdom	1993.1-2011.9	First episode of febrile UTI	< 32.3 months old	1101	Tc-99m dimercaptosuccinic acid renal scan	7 days	20 mg/dl
Song Yi Han (2016)	Korea	2010.1-2014.12	First episode of febrile UTI	< 3 y	298	Tc-99m dimercaptosuccinic acid renal scan	5 days	-
Su Jin Jung (2016)	Korea	2010.1-2012.12	First episode of febrile UTI	< 1 y	150	Tc-99m dimercaptosuccinic acid renal scan	As soon as possible	1,3,8 mg/dl
Won Hee Seo (2014)	Korea	2011.4-2012.3	First episode of febrile UTI	1-12 months	47	Tc-99m dimercaptosuccinic acid renal scan	-	5.1 mg/dl
Yuan-Yow Chiou (2010)	China	2005.1-2006.12	First episode of febrile UTI	< 180 months old	125	Tc-99m dimercaptosuccinic acid renal scan	7 days	39.4 mg/dl

UTI, urinary tract infection; DMSA, dimercaptosuccinic acid.

ment because of the radiation risk for children and high cost [5].

C-reactive protein (CRP) is one of the acute phase-responsive proteins, mainly produced by the liver [7]. CRP participates in a variety of physiological and pathophysiological processes. CRP can not only participate in the body's defense function, but also can limit the potential damage caused by the inflammatory response after the complement activation [8]. In addition, CRP has a similar conditioning and agglutination effect with IgG and complement, enhancing macrophage phagocytosis of various bacteria and foreign bodies [9, 10], thereby reducing the abnormalities due to foreign antigens immune response [11]. CRP also plays an anti-inflammatory role [7]. Serum CRP level is a sensitive and objective indicator of bacterial infection. When bacterial infection happens, serum CRP level can be significantly increased, with positive rate of over 90%. CRP level also has a certain relationship with the extent and the severity of infection, with concentration of 10-99 mg/L suggesting focal or superficial infection and 100 mg/L prompting sepsis or invasive infection and other serious cases [12]. The half-life of serum CRP is approximately 19 h, and serum CRP level is dependent on the rate of liver synthesis, whereas serum CRP level doesn't affect removal speed of CRP [13]. Thus, disease state and curative effect can be evaluated by monitoring CRP level [14].

At present, a large number of domestic and foreign scholars discuss the predictive value of bacterial infection marker CRP for APN, bladder ureter reflux and other UTIs in children and adults, but the results are still controversial. This study was performed to analyze the studies of CRP level in children with UTI developed into APN using diagnostic meta-analysis method. Then it was evaluated if APN developed from UTI in children with fever could be predicted from CRP level, which could play a guiding role for the clinical treatment of upper and lower UTI and acute pyelonephritis.

Materials and methods

Document retrieval

In order to ensure the recall ratio, increasing the sensitivity and reducing the miss rate, MeSH terms and free terms were used at the same time for the search strategy. (urinary tract infection OR urinary tract infections OR UTI) AND (C-reactive protein OR CRP) AND (Child OR infant OR children OR infants) AND (febrile OR fever OR temperature OR pyrexia) AND (acute pyelonephritis or APN) were searched in the web of science, PubMed, EmBase and OVID databases. And secondary retrieval was also performed through reviewing references from retrieved articles to prevent the miss detection. The deadline of search time was April 12, 2017.

Document screening

These retrieved articles were gradually screened from title, abstract and full text according to the pre-set inclusion/exclusion criteria. Inclusion criteria: 1) Articles about prediction of UTI in children with fever developed into APN through CRP level; 2) Articles with exact sensitivity and specificity according to the cut-off value, or the best sensitivity and specificity can be obtained from ROC curve; 3) UTI is clearly defined as first episode of febrile UTI; 4) The Tc-99m dimercaptosuccinic acid renal scan method was used as the gold standard for APN diagnosis; 5) Detection of CRP was performed before UTI treatment; 6) The most recently published or most detailed literature was selected among repeated articles. Exclusion criteria: 1) Review, case report, handbook, letter; 2) Cell, animal or simulation experiments; and 3) Data cannot be harvested. This work was independently executed by two researchers at the same time, and consensus was gained from inconsistent views after discussion with the third author.

Data extraction

Data extraction was also conducted by two researchers independently, and when the opinion was inconsistent, the third researcher was asked to discuss the solution. The extracted data included information such as research information, clinical case information, laboratory information, and diagnostic analysis information (as shown in **Table 1**), and true positive (TP), true negative (TN), false positive (FP), false negative (FN) for each cut-off value. Acute pyelonephritic lesions were diagnosed when scintiscan revealed focal (single or multiple) or diffuse areas of diminished 99mTc-DMSA uptake with an intact or slightly bulging contour according to criteria. Optimum cut off value was obtained from the best cut off value in the text or the given ROC curve. For the latter one,

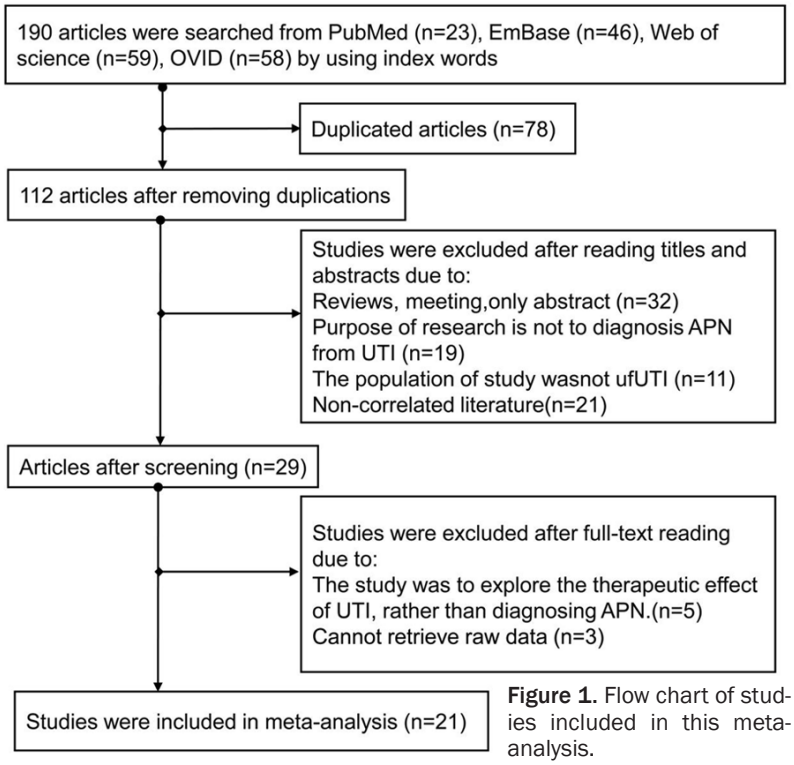

Figure 1. Flow chart of studies included in this meta-analysis.

the corresponding sensitivity and specificity of point in the ROC curve were outputted using Engauge Digitizer 4.1, then those sensitivity and specificity were used to calculate the Youden index, and the sensitivity and specificity according to the maximum value of Youden index was the one corresponding to the best cut off value. Youden index = sensitivity - (1-specificity).

Diagnostic threshold effects and heterogeneity

Firstly, diagnostic threshold effect was detected in this meta-analysis for checking the heterogeneity from different cut-off values in those included studies [15]. And this detection of diagnostic threshold effects was performed through Spearman correlation analysis using Meta-Disc software. Tests for heterogeneity from other sources except for diagnostic threshold effect were performed using Cochrane-Q test. When $I^2 > 50\%$, heterogeneity was existed and P value < 0.05 indicated statistical significance [15].

Diagnostic accuracy assessment

Data of sensitivity, specificity, diagnostic score, and diagnostic odds ratio (DOR) with the corresponding 95% confidence interval (CI) from each study were combined under a random effect model, and area under the summary receiver operating curve (AUSROC) was also calculated. Positive likelihood ratio (PLR), negative likelihood ratio (NLR), and pre-test probability, post-test probability were determined and performed using forest plot and Fagan's nomogram [16, 17]. Furthermore, distribution of sensitivity and specificity was also evaluated using bivariate box plot [18].

Publication bias

To identify the publication bias, Deeks' funnel plot asymmetry analysis was carried out. In short, the Deeks' funnel plot was a scatter plot obtained by linear regression of the diagnostic log odds ratio (ie, lnDOR) against the square root of effective sample size (1/root (ESS)) [19]. The criteria of the publication bias or significant asymmetric funnel map was that the P value for slope coefficient was less than 0.05.

Statistical analysis

All statistical analysis were undertaken by STATA software version 12.0 (College Station, TX, USA) and Meta-Disc V.1.4 (Unit of Clinical Biostatistics, Ramon y Cajal Hospital, Madrid, Spain). The following guidelines have been suggested for interpretation of intermediate AUROC values: low ($0.5 \leq AUC \leq 0.7$), moderate ($0.7 \leq AUC \leq 0.9$), or high ($0.9 \leq AUC \leq 1$) accuracy [20]. The value of a DOR ranged from 0 to infinity, with higher values indicating better discriminatory test performance. A value of 1 meant that a test did not discriminate between patients with the disorder and those without. Values lower than 1 pointed to improper test interpretation (more negative tests among the diseased). The diagnostic odds ratio (DOR) may be used as a single summary measure with the caveat that the same odds ratio may be obtained with different combinations of sensitivity and specificity. The LRs indicate by how much a given test would raise or lower the prob-

Table 2. Diagnostic accuracy under different cut off values in included studies

Author	Year	Cut off value (mg/dl)	APN	UTI	Se	Sp
Eduardo H. Garin	2007	0.5	91	94	100%	8%
Sandrine Leroy	2013	1	613	488	87%	41%
Su Jin Jung	2016	1	54	96	100%	27%
Ji-Nan Sheu	2011	2	76	36	100%	39%
Ji-Nan Sheu	2006	2.5	42	36	93%	81%
Byung Kwan Kim	2017	2.78	59	79	83%	81%
Su Jin Jung	2016	3	54	96	93%	59%
Ji-Nan Sheu	2011	3.5	76	36	91%	58%
Ji Hyun Sim	2015	3.86	53	70	87%	73%
Jen-Hsi Wu	2012	5	40	76	53%	79%
Won Hee Seo	2014	5.1	24	23	53%	78%
Abolfazl Mahyar	2013	6	33	46	97%	67%
Ji-Nan Sheu	2011	6	76	36	74%	81%
Hai-Lun Sun	2014	6.2	169	103	70%	82%
Su Jin Jung	2016	8	54	96	41%	92%
Abolfazl Mahyar	2013	10	33	46	97%	74%
Jen-Hsi Wu	2012	10	40	76	20%	93%
Ji-Nan Sheu	2011	10	76	36	47%	94%
Parviz AyAzi	2013	10	54	42	98%	7%
Sandrine Leroy	2013	10	613	488	74%	54%
Abolfazl Mahyar	2013	20	33	46	85%	83%
Andrew Fretzayas	2000	20	30	53	69%	57%
Paolo Pecile	2005	20	47	53	94%	32%
Sandrine Leroy	2013	20	613	488	63%	55%
Kianoush Ansari Gilani	2010	30	66	42	52%	77%
Yuan-Yow Chiou	2010	34.9	89	36	80%	67%
Banuelos-Andrío, L	2017	39.4	64	37	76%	89%
Paolo Pecile	2005	50	47	53	74%	77%
Alberto Biggi	2001	88	70	31	64%	68%
Abolfazl Mahyar	2013	-	33	46	91%	83%
I Re Lee	2015	-	62	56	71%	73%
Jung Won Lee	2013	-	155	133	68%	69%
Sandrine Leroy	2013	-	613	488	80%	54%
Song Yi Han	2016	-	163	135	66%	71%
Su Jin Jung	2016	-	54	96	87%	68%

APN, acute pyelonephritis; UTI, urinary tract infection; Se, sensitivity; Sp, specificity; -, no exact cut off value in included studies, and optimum sensitivity and specificity were calculated using Youden index.

ability of having disease. In order for the high diagnostic informativeness, an LR of > 10 or < 0.1 would be required for a positive and negative test result, respectively. Moderate informational value can be achieved with LR values of 5-10 and 0.1-0.2; LRs of 2-5 and 0.2-0.5 have very small informational value.

Results

Document retrieval

A total of 190 studies were preliminary retrieved for the meta-analysis. After screening through the subject and summary, 29 English studies were selected. The final 21 studies were included after further screening by reading in full [21-41]. The retrieval process was shown in **Figure 1**, the included studies and the baseline demographic characteristics of patients were shown in **Table 1**.

Diagnostic accuracy assessment

A total of 3861 first episode of febrile UTI patients and 35 cut-off values from 21 experiments were included in the system evaluation and meta-analysis. The sensitivity and specificity and associated cut off value were shown in **Table 2**. Spearman correlation coefficient was -0.804, and *P* value was 0.65, so there was no threshold effect and those results could be combined. Sensitivity and specificity of the CRP level used for diagnosis of APN from UTI in children with fever were 0.826 (95% CI: 0.744 to 0.886) and 0.669 (95% CI: 0.582 to 0.747), respectively (**Figure 2A**). And the AUROC was 0.81 (95% CI: 0.77 to 0.84) (**Figure 2B**), diagnostic score and DOR were 2.262 (95% CI: 1.925 to 2.6) and 9.605 (95% CI: 6.855 to 13.458) (**Figure 2C**), respectively. Pre-test probability of the CRP level used for diagnosis of APN from UTI in children with fever was 53%, positive likelyhood ratio (PLR) and negative likelyhood ratio (NLR) were 2.498 (95% CI: 2.048 to 3.047) and 0.26 (95% CI: 0.188 to 0.36), respectively. Furthermore, the result of Fagan's nomogram analysis showed that post-test probability of PLR increased to 74% and post-test probability of NLR decreased to 23% compared to the 53% of pre-test probability, respectively (**Figure 2D**).

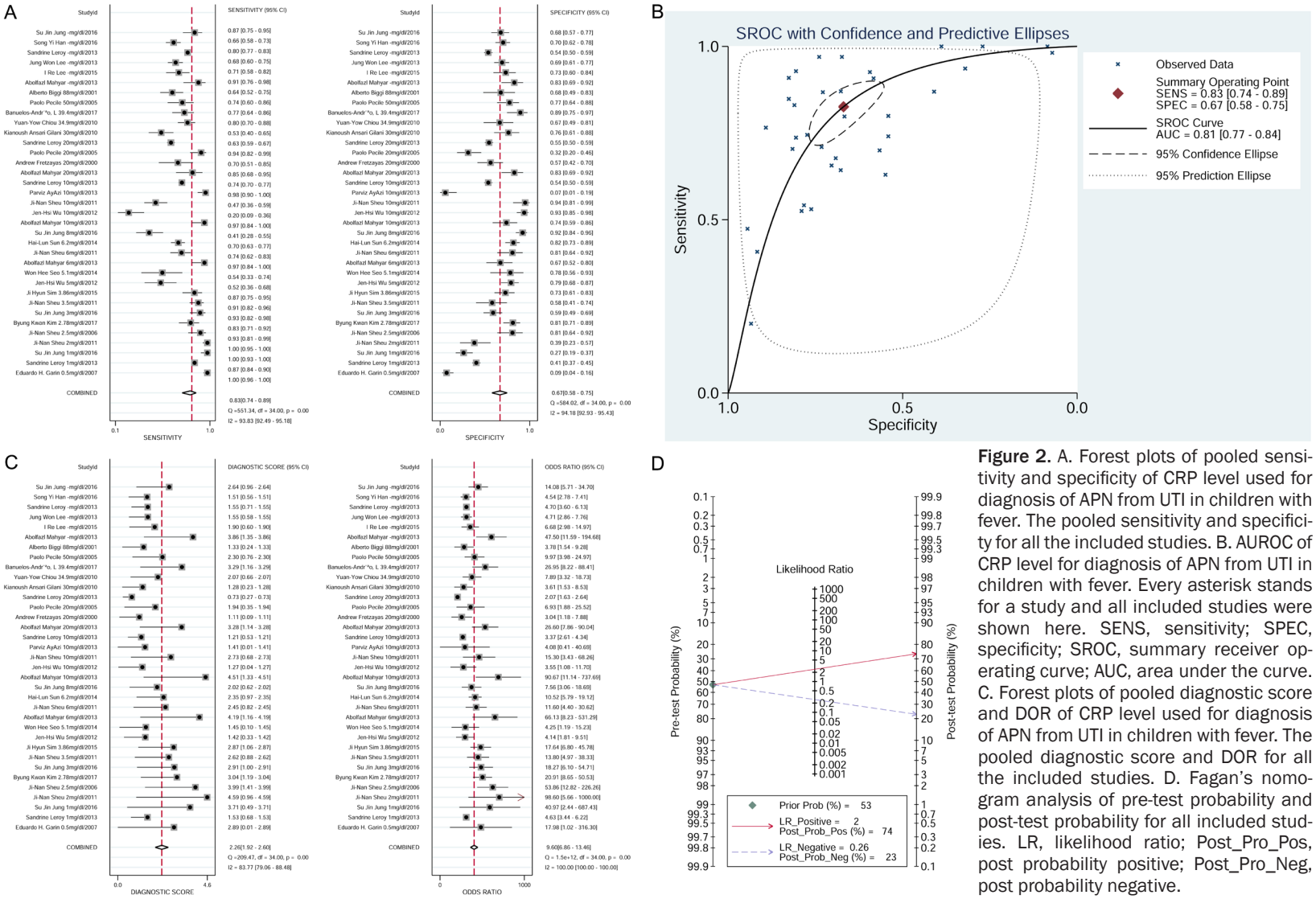

Figure 2. A. Forest plots of pooled sensitivity and specificity of CRP level used for diagnosis of APN from UTI in children with fever. The pooled sensitivity and specificity for all the included studies. B. AUROC of CRP level for diagnosis of APN from UTI in children with fever. Every asterisk stands for a study and all included studies were shown here. SENS, sensitivity; SPEC, specificity; SROC, summary receiver operating curve; AUC, area under the curve. C. Forest plots of pooled diagnostic score and DOR of CRP level used for diagnosis of APN from UTI in children with fever. The pooled diagnostic score and DOR for all the included studies. D. Fagan's nomogram analysis of pre-test probability and post-test probability for all included studies. LR, likelihood ratio; Post_Pro_Pos, post probability positive; Post_Pro_Neg, post probability negative.

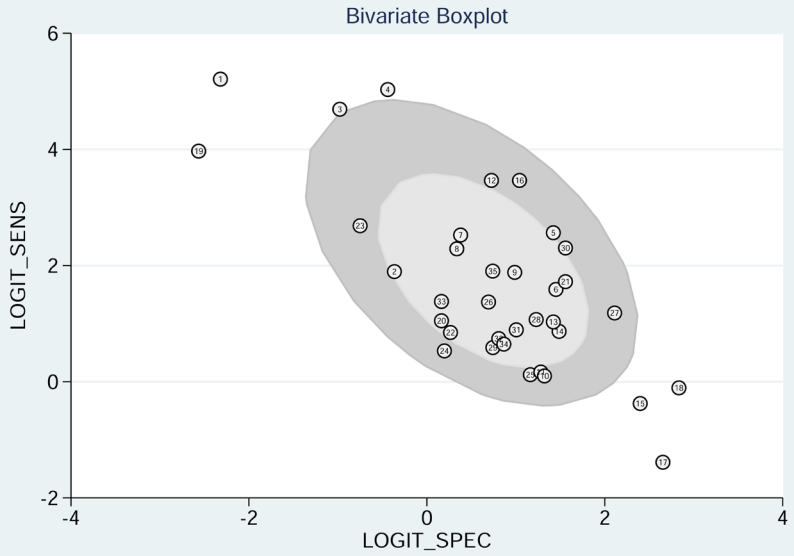

Figure 3. Bivariate Boxplot used to estimate outliers for all included studies.

Bivariate box plot used to estimate outliers

In order to assess the distribution of sensitivity and specificity and determine the possible outliers of the diagnostic results, the bivariate box plot was used in this analysis. In all included studies, seven cut-off values were abnormal, including Eduardo H. Garin 0.5 mg/dl (2007), Su Jin Jung 1 mg/dl (2016), Ji-Nan Sheu 2 mg/dl (2011), Su Jin Jung Jinc-Hsi Wu 10 mg/dl (2012), Ji-Nan Sheu 10 mg/dl (2011), Parviz AyAzi 10 mg/dl (2013), (**Figure 3**). And we found that those seven cut-off values just corresponded to the best sensitivity or specificity, which caused a greater distress for the correct evaluation of the diagnostic value of CRP.

Subgroup analysis

Because sensitivities and specificities with different cut-off values were different, subgroup analysis based on different cut off values was performed in this study. In all the incorporated literature, six of the optimal cut-off values were calculated by the ROC curve, including Byung Kwan Kim 2.78 mg/dl (2017), Ji-Nan Sheu 3.5 mg/dl (2011), Ji Hyun Sim 3.86 mg/dl (2015), Won Hee Seo 5.1 mg/dl (2014), Hai-Lun Sun 6.2 mg/dl (2014), Banuelos-Andrío, L 39.4 mg/dl (2017). But the best cut-off value was not obtained from another six studies, including Aboulazl Mahyar (2013), I Re Lee (2015), Jung Won Lee (2013), Sandrine Leroy (2013), Song Yi Han (2016), Su Jin Jung (2016). And most of the literatures showed that the best cut-off values were mainly between 2.5 and 7, so we chose the right literatures to perform the subgroup analysis. Spearman correlation coefficient was -1.00, and *P* value was 1, so there was no threshold effect and those results could be combined. And the combined results showed that sensitivity and specificity of the CRP level used for diagnosis of APN from UTI in children with fever were 0.83 (95% CI: 0.73 to 0.90) and 0.74 (95% CI: 0.69 to 0.80) (**Figure 4A**), DOR was 14.16 (95% CI: 8.97 to 22.37) (**Figure 4B**); and the corresponding AUROC was 0.82 (95% CI: 0.79 to 0.86) (**Figure 4C**). PLR and NLR were 3.2 (95% CI: 2.8 to 3.8) and 0.23 (95% CI: 0.15 to 0.36), and pre-test probability of the CRP level used for diagnosis of APN from UTI in children with fever was 54%. The results of Fagan's nomogram analysis showed that post-test probability of PLR increased to 79% and post-test probability of NLR decreased to 21% compared to the 54% of pre-test probability, respectively (**Figure 4D**). Furthermore, the analysis result of the bivariate box plot showed that the entire shape of the bivariate box was symmetrical, indicating that the data within the normal distribution was tight and had no outlier (**Figure 4E**).

Heterogeneity source analysis

A large heterogeneity was found between the pooled results from all studies with 35 cut off values (sensitivity: $P = 0.000$, $I^2 = 93.83$; specificity: $P = 0.000$, $I^2 = 94.18$; DOR: $P = 0.000$, $I^2 = 100.00$) and studies with cut-off values distributed between 2.5 and 7 (sensitivity: $P = 0.000$, $I^2 = 85.33$; specificity: $P = 0.000$, $I^2 = 63.13$; DOR: $P = 0.000$, $I^2 = 97.45$). But the combined heterogeneity from latter ones was reduced, indicating that cut-off value was one of heterogeneity sources.

Publication bias analysis

The Deeks' chart was used to assess the publication bias. Midas performs linear regression

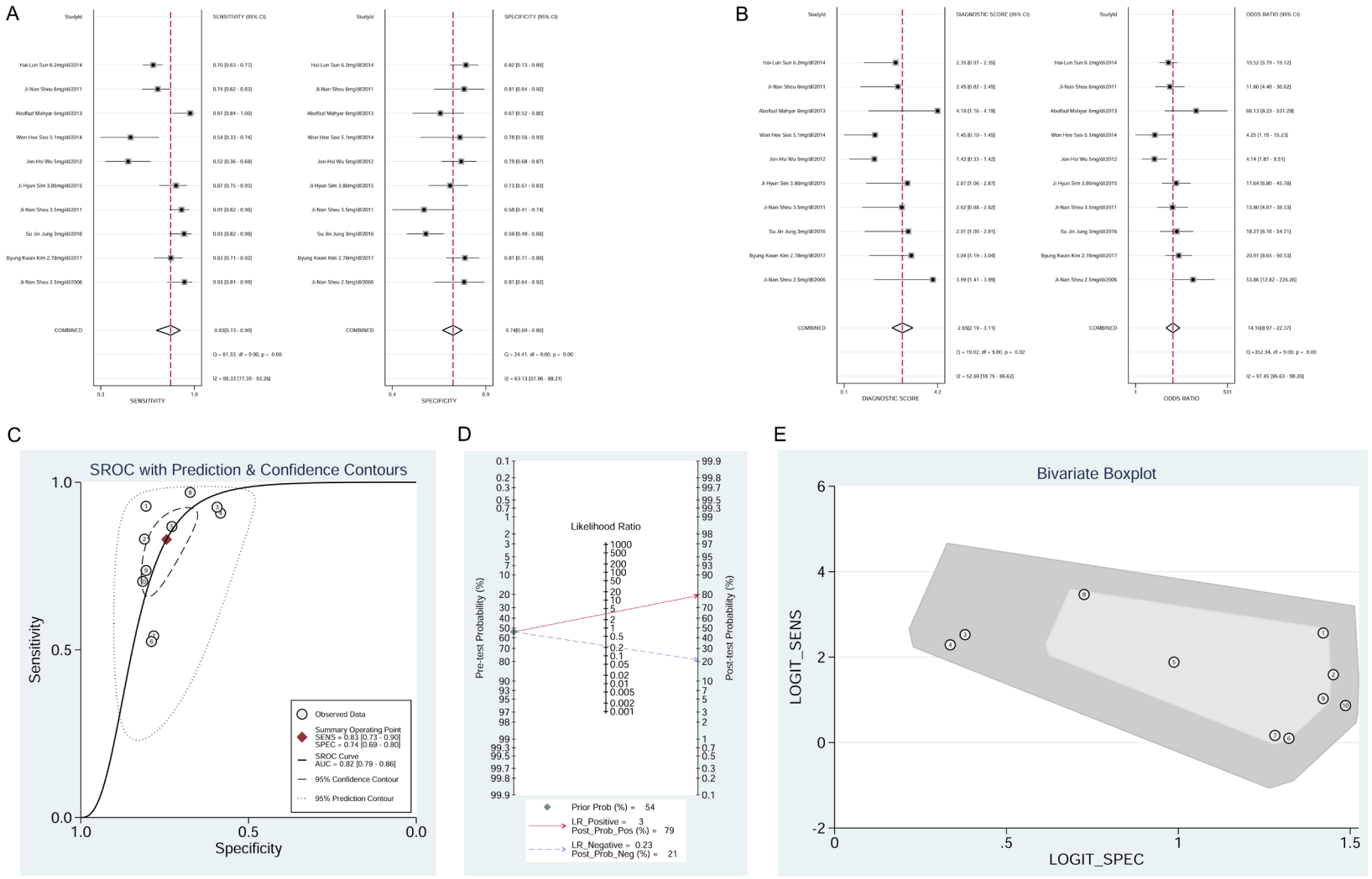

Figure 4. A. Forest plots of pooled sensitivity and specificity of CRP level used for diagnosis of APN from UTI in children with fever. The pooled sensitivity and specificity for ten studies with cut-off value between 2.5 and 7. B. Forest plots of pooled diagnostic score and DOR of CRP level used for diagnosis of APN from UTI in children with fever. The pooled diagnostic score and DOR for ten studies with cut-off value between 2.5 and 7. C. AUROC of CRP level for diagnosis of APN from UTI in children with fever. Every asterisk stands for a study and ten studies with cut-off value between 2.5 and 7 were shown here. SENS, sensitivity; SPEC, specificity; SROC, summary receiver operating curve; AUC, area under the curve. D. Fagan's nomogram analysis of pre-test probability and post-test probability for ten studies with cut-off value between 2.5 and 7. LR, likelihood ratio; Post_Pro_Pos, post probability positive; Post_Pro_Neg, post probability negative. E. Bivariate Boxplot used to estimate outliers for ten studies with cut-off value between 2.5 and 7.

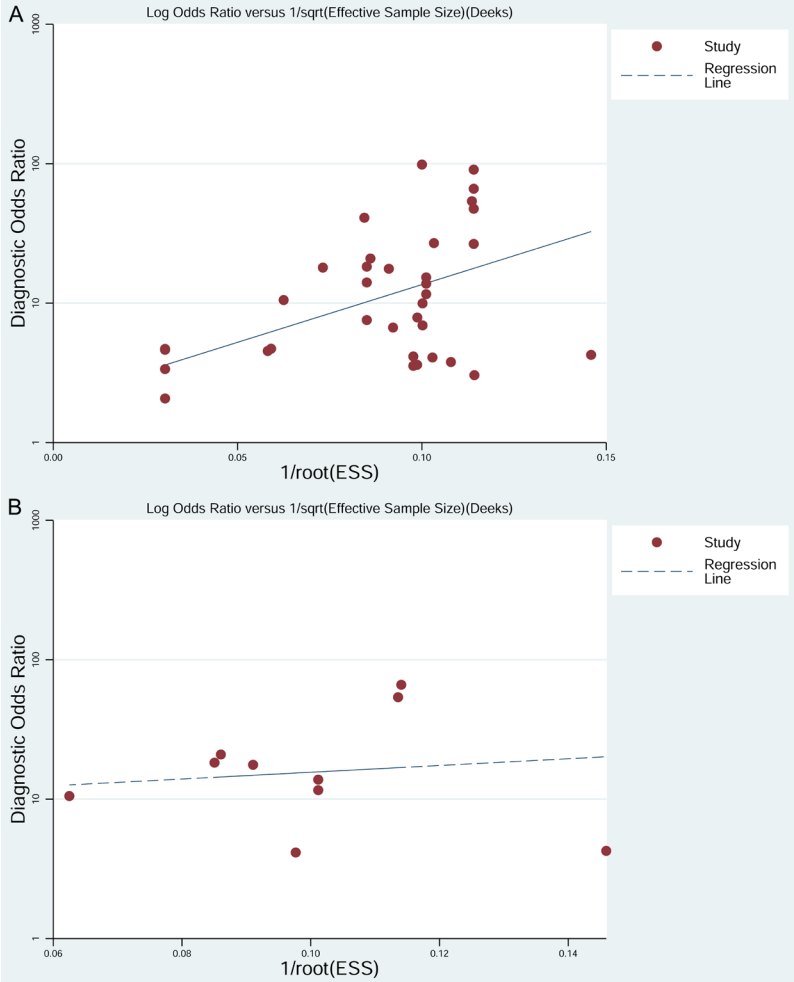

Figure 5. A. Publication bias from Deeks' test is shown by funnel plots for all included studies. ESS, effective sample size. B. Publication bias from Deeks' test is shown by funnel plots for ten studies with cut-off value between 2.5 and 7. ESS, effective sample size.

of log odds ratios on inverse root of effective sample sizes as a test for funnel plot asymmetry in diagnostic meta-analysis. A non-zero slope coefficient was suggestive of significant small study bias (*P* value < 0.10). In our study we found that the combination of 35 cut-off values had a large publication bias (*P* = 0.000) (**Figure 5A**). But there was no publication bias in the merged result of cut-off values between 2.5 and 7 (*P* = 0.44) (**Figure 5B**).

Discussion

A total of 3861 cases from 21 studies were included in this meta-analysis, and the pooled results suggested that sensitivity and specificity of the CRP level used for diagnosis of APN from UTI in children with fever were 0.826 and 0.669, corresponding AUROC and DOR were 0.81 and 9.605, respectively. This indicated a moderate value of CRP level used to diagnose APN from UTI [20]. Furthermore, compared to the 53% of pre-test probability, post-test probability of PLR increased by 21% and post-test probability of NLR decreased by 30%.

This meta-analysis is not the first one diagnostic meta-analysis about evaluating the diagnostic value of CRP used to diagnose APN from UTI. In 2015, the first one study had been published and a related conclusion had been reached [42]. In the early one, a low CRP value (< 20 mg/L) appeared to contribute to the exclusion of pyelonephritis (the likelihood of reduced pyelonephritis < 20%), and the pooled sensitivity and specificity were 0.94 (95% CI: 0.85 to 0.97) and 0.39 (95% CI: 0.23 to 0.58), respectively. But the inexplainable heterogeneity in that study got in the way of our recommendations. In our meta-analysis, nevertheless, the results showed a moderate accuracy of CRP used for diagnosing APN from UTI though there also was heterogeneity. Although the pooled sensitivity (0.826, 95% CI: 0.744 to 0.886) was slightly lower compared to this in the early study, the pooled specificity was much higher (0.669, 95% CI: 0.582 to 0.747), especially in the subgroup analysis, the pooled specificity was increased to 0.74 (95% CI: 0.69 to 0.80) when the CRP level was between 2.5 mg/L and 7 mg/L.

In this study, there was no threshold effect (Spearman correlation coefficient -0.804, P > 0.05), but there was a large heterogeneity (I^2 >

50%, $P < 0.05$). Those studies selected in this meta-analysis had consistent characteristics such as the first episode of febrile UTI and Tc-99m dimercaptosuccinic acid renal scan as the gold standard for the diagnosis of APN. But ages of included children, and the time between detection of APN and UTI were both might be heterogeneous sources, which could not be analyzed because of no original data. Similarly, though the detection of CRP level was also one of the causes of heterogeneity, subgroup analysis could not be performed from detection methods of CRP level without detailed information.

Similarly, there was a large publication bias between the included studies ($P < 0.10$). The reasons may be as follows: the publication of language bias, in the relevant meta-analysis published in 2015, into the 26-letter-based language, and this meta from the English published literature; Secondly, the meta analysis selected the publication with published searchable data, but for those in abstract form, conference papers, academic papers and other forms of the article were excluded.

There are some limitations in this system evaluation: 1. There may be a certain degree of selective bias, as only English literatures were included; 2. Different measurement instruments used in these studies were included in this meta-analysis, so the measurement results may be affected by the improvement of the instrument and the systematic error; 3. The variable quality of included original studies may affect the reliability of the conclusions; 4. Meta regression analysis through QUADAS score wasn't performed due to the limited number of included literatures. In addition, we can not explore whether the design, including blindness, random design and forward-looking design, will affect the accuracy of the diagnosis.

In summary, to a certain extent, CRP helps the diagnosis of APN from the UTI. But more diagnostic research with rigorous, large sample size are needed to carry out by more researchers to provide a more scientific and objective reference for clinical application. Meanwhile, a unified detection method and strict quality control measures are needed in these studies to ensure the quality of research, resulting in a high degree of credibility and strong guiding significance of the results. It will provide a more secure, economical, convenient and accurate mean for APN screening and prevention of kidney damage and scarring, which could cause hypertension and chronic renal failure.

Disclosure of conflict of interest

None.

Address correspondence to: Jing Zhao, Department of Obstetrics and Gynecology, Qilu Hospital of Shandong University, 107 Wenhua Xi Road, Jinan 250012, Shandong, China. Tel: +86-18560082051; Fax: +86-531-82169570; E-mail: wenhua0206@126.com

References

[1] Wilson ML and Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. Clin Infect Dis 2004; 38: 1150-1158.
[2] Caione P, Ciofetta G, Collura G, Morano S and Capozza N. Renal damage in vesico-ureteric reflux. BJU Int 2004; 93: 591-595.
[3] Montini G, Tullus K and Hewitt I. Febrile urinary tract infections in children. N Engl J Med 2011; 365: 239-250.
[4] Hari P, Mantan M and Bagga A. Management of urinary tract infections. Indian J Pediatr 2003; 70: 235-239.
[5] Slekovec C, Leroy J, Vernaz-Hegi N, Faller JP, Sekri D, Hoen B, Talon D and Bertrand X. Impact of a region wide antimicrobial stewardship guideline on urinary tract infection prescription patterns. Int J Clin Pharm 2012; 34: 325-329.
[6] Routh JC, Grant FD, Kokorowski PJ, Nelson CP, Fahey FH, Treves ST and Lee RS. Economic and radiation costs of initial imaging approaches after a child's first febrile urinary tract infection. Clin Pediatr (Phila) 2012; 51: 23-30.
[7] Black S, Kushner I and Samols D. C-reactive Protein. J Biol Chem 2004; 279: 48487-48490.
[8] de Carvalho JF, Hanaoka B, Szyper-Kravitz M and Shoenfeld Y. C-Reactive protein and its implications in systemic lupus erythematosus. Acta Reumatol Port 2007; 32: 317-322.
[9] Pepys MB and Baltz ML. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid a protein. Adv Immunol 1983; 34: 141-212.
[10] Eisenhardt SU, Thiele JR, Bannasch H, Stark GB and Peter K. C-reactive protein: how conformational changes influence inflammatory properties. Cell Cycle 2009; 8: 3885-3892.
[11] Gershov D, Kim S, Brot N and Elkon KB. C-Reactive protein binds to apoptotic cells, protects

the cells from assembly of the terminal complement components, and sustains an antiinflammatory innate immune response: implications for systemic autoimmunity. J Exp Med 2000; 192: 1353-1364.
[12] Clyne B and Olshaker JS. The C-reactive protein. J Emerg Med 1999; 17: 1019-1025.
[13] Vigushin DM, Pepys MB and Hawkins PN. Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. J Clin Invest 1993; 91: 1351-1357.
[14] Reny JL, Vuagnat A, Ract C, Benoit MO, Safar M and Fagon JY. Diagnosis and follow-up of infections in intensive care patients: value of C-reactive protein compared with other clinical and biological variables. Crit Care Med 2002; 30: 529-535.
[15] Deville WL, Buntinx F, Bouter LM, Montori VM, de Vet HC, van der Windt DA and Bezemer PD. Conducting systematic reviews of diagnostic studies: didactic guidelines. BMC Med Res Methodol 2002; 2: 9.
[16] Baratloo A, Safari S, Elfil M and Negida A. Evidence based emergency medicine part 3: positive and negative likelihood ratios of diagnostic tests. Emerg (Tehran) 2015; 3: 170-171.
[17] Safari S, Baratloo A, Elfil M and Negida A. Evidence based emergency medicine; part 4: pretest and post-test probabilities and fagan's nomogram. Emerg (Tehran) 2016; 4: 48-51.
[18] Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM and Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 2005; 58: 982-990.
[19] Deeks JJ, Macaskill P and Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005; 58: 882-893.
[20] Swets JA. Measuring the accuracy of diagnostic systems. Science 1988; 240: 1285-1293.
[21] Mahyar A, Ayazi P, Ahmadi R, Daneshi-Kohan MM, Hashemi HJ, Dalirani R, Moshiri SA, Habibi M, Sahmani M and Sahmani AA. Are serum procalcitonin and interleukin-1 beta suitable markers for diagnosis of acute pyelonephritis in children? Prague Med Rep 2014; 115: 16-23.
[22] Biggi A, Dardanelli L, Pomero G, Cussino P, Noello C, Sernia O, Spada A and Camuzzini G. Acute renal cortical scintigraphy in children with a first urinary tract infection. Pediatr Nephrol 2001; 16: 733-738.
[23] Fretzayas A, Moustaki M, Gourgiotis D, Bossios A, Koukoutsakis P and Stavrinadis C. Polymorphonuclear elastase as a diagnostic marker of acute pyelonephritis in children. Pediatrics 2000; 105: E28.
[24] Banuelos-Andrio L, Espino-Hernandez M, Ruperez-Lucas M, Villar-Del Campo MC, Romero-Carrasco CI and Rodriguez-Caravaca G. Usefulness of analytical parameters in the management of paediatric patients with suspicion of acute pyelonephritis. Is procalcitonin reliable? Rev Esp Med Nucl Imagen Mol 2017; 36: 2-6.
[25] Kim BK, Yim HE and Yoo KH. Plasma neutrophil gelatinase-associated lipocalin: a marker of acute pyelonephritis in children. Pediatr Nephrol 2017; 32: 477-484.
[26] Garin EH, Olavarria F, Araya C, Broussain M, Barrera C and Young L. Diagnostic significance of clinical and laboratory findings to localize site of urinary infection. Pediatr Nephrol 2007; 22: 1002-1006.
[27] Sun HL, Wu KH, Chen SM, Chao YH, Ku MS, Hung TW, Liao PF, Lue KH and Sheu JN. Role of procalcitonin in predicting dilating vesicoureteral reflux in young children hospitalized with a first febrile urinary tract infection. Pediatr Infect Dis J 2013; 32: e348-354.
[28] Lee IR, Shin JI, Park SJ, Oh JY and Kim JH. Mean platelet volume in young children with urinary tract infection. Sci Rep 2015; 5: 18072.
[29] Wu JH, Chiou YH, Chang JT, Wang HP, Chen YY and Hsieh KS. Urinary tract infection in infants: a single-center clinical analysis in southern Taiwan. Pediatr Neonatol 2012; 53: 283-288.
[30] Sim JH, Yim HE, Choi BM, Lee JH and Yoo KH. Plasma neutrophil gelatinase-associated lipocalin predicts acute pyelonephritis in children with urinary tract infections. Pediatr Res 2015; 78: 48-55.
[31] Sheu JN, Chen MC, Lue KH, Cheng SL, Lee IC, Chen SM and Tsay GJ. Serum and urine levels of interleukin-6 and interleukin-8 in children with acute pyelonephritis. Cytokine 2006; 36: 276-282.
[32] Sheu JN, Chang HM, Chen SM, Hung TW and Lue KH. The role of procalcitonin for acute pyelonephritis and subsequent renal scarring in infants and young children. J Urol 2011; 186: 2002-2008.
[33] Lee JW, Kim SH, Park SJ, Lee KH, Park JH, Kronbichler A, Eisenhut M, Kim JH, Lee JW and Shin JI. The value of delta neutrophil index in young infants with febrile urinary tract infection. Sci Rep 2017; 7: 41265.
[34] Ansari Gilani K, Modaresi Esfeh J, Gholamrezanezhad A, Gholami A, Mamishi S, Eftekhari M, Beiki D, Fard-Esfahani A, Fallahi B and Anvari A. Predictors of abnormal renal cortical scintigraphy in children with first urinary tract infection: the importance of time factor. Int Urol Nephrol 2010; 42: 1041-1047.
[35] Pecile P, Miorin E, Romanello C, Falleti E, Valent F, Giacomuzzi F and Tenore A. Procalcito-

nin: a marker of severity of acute pyelonephritis among children. Pediatrics 2004; 114: e249-254.
[36] Ayazi P, Mahyar A, Daneshi MM, Jahani Hashemi H, Pirouzi M and Esmailzadehha N. Diagnostic accuracy of the quantitative C-reactive protein, erythrocyte sedimentation rate and white blood cell count in urinary tract infections among infants and children. Malays J Med Sci 2013; 20: 40-46.
[37] Leroy S, Fernandez-Lopez A, Nikfar R, Romanello C, Bouissou F, Gervaix A, Gurgoze MK, Bressan S, Smolkin V, Tuerlinckx D, Stefanidis CJ, Vaos G, Leblond P, Gungor F, Gendrel D and Chalumeau M. Association of procalcitonin with acute pyelonephritis and renal scars in pediatric UTI. Pediatrics 2013; 131: 870-879.
[38] Han SY, Lee IR, Park SJ, Kim JH and Shin JI. Usefulness of neutrophil-lymphocyte ratio in young children with febrile urinary tract infection. Korean J Pediatr 2016; 59: 139-144.
[39] Jung SJ and Lee JH. Prediction of cortical defect using C-reactive protein and urine sodium to potassium ratio in infants with febrile urinary tract infection. Yonsei Med J 2016; 57: 103-110.
[40] Seo WH, Nam SW, Lee EH, Je BK, Yim HE and Choi BM. A rapid plasma neutrophil gelatinase-associated lipocalin assay for diagnosis of acute pyelonephritis in infants with acute febrile urinary tract infections: a preliminary study. Eur J Pediatr 2014; 173: 229-232.
[41] Chiou YY, Chen MJ, Chiu NT, Lin CY and Tseng CC. Bacterial virulence factors are associated with occurrence of acute pyelonephritis but not renal scarring. J Urol 2010; 184: 2098-2102.
[42] Shaikh N, Borrell JL, Evron J and Leeflang MM. Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children. Cochrane Database Syst Rev 2015; 1: CD009185.