Value of Urinary Neutrophil Gelatinase-Associated Lipocalin in Diagnosing Urinary Tract Infections in Children: A Systematic Review and Meta-Analysis

Weiping Ye[1], Zhenyu Nie[2], Beiyan Bao[2], Yu Zhao[2], Chaojie Feng[2]*

[1]Department of Pediatrics, Zhejiang Hospital, Hangzhou, China
[2]Department of Nephrology, Ningbo Urology and Nephrology Hospital, Ningbo, China

Keywords. Neutrophil gelatinase-associated lipocalin; Urinary tract infection; Acute pyelonephritis; Meta-analysis

This study presents a comprehensive review of the literature regarding the use of urinary neutrophil gelatinase-associated lipocalin (uNGAL) as a diagnostic tool for urinary tract infection (UTI) in children. Meta-analysis was conducted to evaluate the effectiveness of uNGAL in diagnosing UTI and differentiating acute pyelonephritis (APN) from other sites infection in pediatric patients. We searched PubMed, Web of Science, the Cochrane Library and EMBASE for reports published up to January 2023. We only included published literature that addressed the diagnosis of UTI and APN with the use of uNGAL in children aged 0-18 years. Two authors independently reviewed the included studies and extracted the corresponding data according to the inclusion and exclusion criteria. The sensitivity, specificity and area under the curve for each study were pooled by using a bivariate mixed-effects model. A total of 13 studies met the inclusion criteria for this review: 8 reported on uNGAL diagnosis of UTI, 2 on uNGAL diagnosis of APN, and 3 on both UTI and APN. Among all included studies, uNGAL had good sensitivity (0.88, 95% CI 0.79-0.94) and good specificity (0.86, 95% CI 0.78-0.92) for the diagnosis of UTI. The sensitivity and specificity of uNGAL for the diagnosis of APN were 0.79 (95% CI 0.72-0.85) and 0.78 (95% CI 0.50-0.93), respectively. uNGAL has good sensitivity and specificity in the diagnosis of UTI in children and is a promising marker. However, the use of uNGAL still does not provide significant advantages in the diagnosis of APN in children. Consequently, there is a need to optimize and further explore the assay for improved diagnostic accuracy.

IJKD 2024;18:255-69
www.ijkd.org
DOI: 10.52547/ijkd.7850

Brief review

INTRODUCTION

Urinary tract infection (UTI) is one of the most common forms of bacterial infections in infants and children, especially in infants under three months of age, with a prevalence of 7%.[1] Approximately 2% of boys and 8% of girls under the age of 6 years have a history of UTI.[2] If left untreated, the infection can progress to a chronic state and potentially result in the development of chronic kidney disease (CKD).[3] Therefore, early diagnosis and treatment of UTI is of particular importance.

Screening of children with UTI can be done by routine urine analysis (UA) and urine culture testing. Since urine culture usually takes at least

two days to obtain results, the diagnosis of UTI is usually made first by UA in clinical practice, followed by further urine culture to clarify the diagnosis. However, there are challenges in clinical practice that can interfere with urine culture results, including UR false negatives, sample contamination, and the use of antibiotics before sampling. In addition, parental refusal to catheterize or suprapubic aspirate (SPA) makes it difficult to obtain urine samples from infants and children, and urine cultures cannot differentiate between upper and lower UTI. Therefore, there is an urgent clinical need for an efficient biomarker to aid in diagnosis.

Neutrophil gelatinase-associated liposomal (NGAL) is a 25 kilodalton (kDa) human protein belonging to the lipocalin superfamily.[4] Research has demonstrated that NGAL functions as an inflammatory modulator of the innate immune system and possesses the ability to inhibit bacterial growth.[5] In addition to its clinical value in the diagnosis of acute kidney injury,[6] urinary neutrophil gelatinase-associated liposomal (uNGAL) also performs very well in the diagnosis of UTIs. Valdimarsson *et al.* reported that the sensitivity and specificity of uNGAL in the diagnosis of UTI were 92.6% and 95.3%, respectively.[7] It has also been reported that uNGAL can be used to diagnose acute pyelonephritis (APN).[8] Therefore, we conducted a meta-analysis of relevant evidence to assess the accuracy of uNGAL in the diagnosis of UTI. Additionally, we investigated the potential of uNGAL in differentiating acute pyelonephritis (APN) from other sites infection, other than acute pyelonephritis, in pediatric patients.

MATERIALS AND METHODS

Search strategy

The study was designed, conducted, analyzed, and reported in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement.[9] We systematically searched PubMed, EMBASE, Cochrane Library and Web of Science databases for studies the use of uNGAL in the diagnosis of UTI. We searched for relevant diagnostic studies published up to January 2023 that used the following terms: (NGAL OR Neutrophil gelatinase-associated lipocalin OR urine Neutrophil gelatinase-associated lipocalin OR urine NGAL OR Lcn2 OR Lipocalin 2) AND (scar kidney OR scar renal OR DMSA OR dimercaptosuccinic acid OR Urinary tract infections OR UTI OR pyelonephritis OR cystitis) AND (infants OR children OR pediatric patients). The papers included in this study were limited to humans, and there were no restrictions on language.

Study selection

The included studies were screened independently and in parallel by two investigators The study selection process involved multiple steps. Initially, the filtering of relevant studies was performed based on the evaluation of titles and abstracts. Subsequently, the full texts of potentially eligible articles were examined to further screen them according to the predefined inclusion criteria. For articles that lacked complete information, we made efforts to gather additional details by reaching out to the corresponding authors via email. This allowed us to obtain as much complete information as possible. The final decision regarding the inclusion of these articles was made on the basis of the fulfillment of the inclusion criteria, once sufficient information was obtained. Throughout the review (study selection, data extraction and quality assessment), in case of disagreement between two researchers, a third researcher was consulted for assessment. Inclusion criteria were: (i) children younger than 18 years of age in the study; (ii) use of uNGAL for screening of UTI and APN; and (iii) standardized testing to determine the presence of UTI and/or APN in both the experimental and control groups in the study; (iiii) presenting sufficient information such as true and false positives and negatives to construct a 2 × 2 association table. Urine bacterial culture and colony count was the primary basis for the diagnosis of UTI. Urine culture was considered positive when it showed the growth of individual bacteria with the following colony counts: (1) any culture from suprapubic bladder puncture, (2) catheter-collected urine culture > 50,000 colony-forming unit/ml (CFU/ml), or (3) clean midstream urine culture > 100,000 CFU/ml.[10] The dimercaptosuccinic acid (DMSA) scan within 2 weeks of the diagnosis of UTI was the criterion for the diagnosis of APN.[11] Exclusion criteria were: (i) Screening patients with other inflammatory markers (C-reactive protein, white blood cell count, erythrocyte sedimentation rate, etc.); (ii) inclusion of participants with neurogenic bladder or with

severe genitourinary abnormalities. (iii) studies that did not meet the observational criteria.

Data extraction

For each included study data were extracted independently by two investigators (1) basic information of the studies: year, authors, study country and study type; (2) basic information of the subjects: mean age, sex, sample size, subgroup status, method of uNGAL detection, source of urine (mid-stage urine, catheterization or suprapubic cystocentesis); (3) basic information of the diagnostic results: the number of true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN), the intercept value and area under the receiver operating characteristic (ROC) curve for uNGAL.

Quality assessment

We applied Quality Assessment of Diagnostic Accuracy Studies II[12] (QUADAS II) independently by two investigators to assess the risk of bias for all studies that met the inclusion criteria. We performed sensitivity analyses to evaluate the

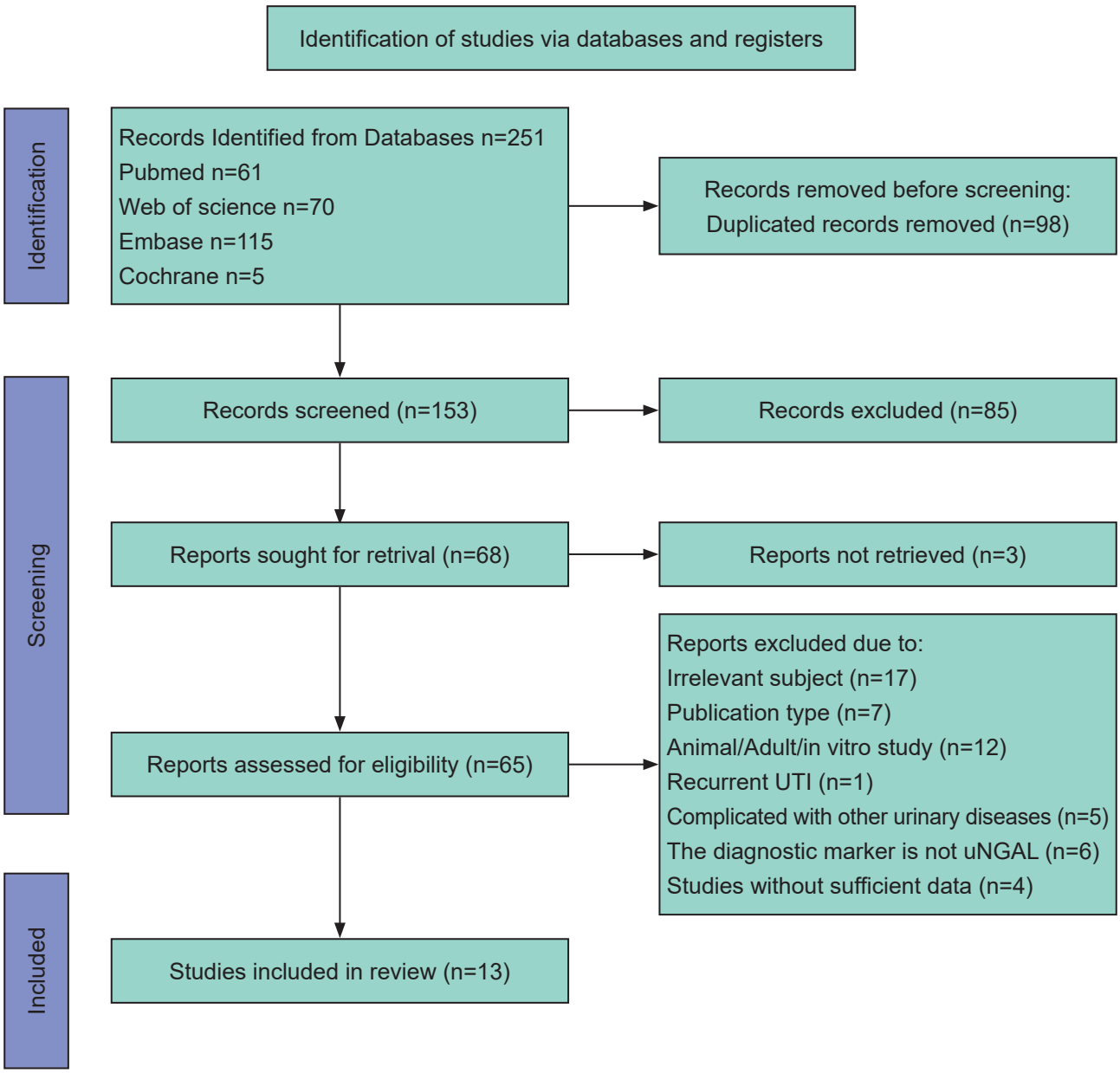


Figure 1. Study selection

Table 1. Study characteristics

Study	Study type	Setting	N	Age(mean)	Group		uNGAL assay	Cutoff (ng/mL)	Urine collection method	diagnose disease
					Case (N)	Control (N)				
Jagadesan et al. 2019[19]	PCS	Suspected UTI	100	22.09M (3M-5Y)	Ungrouped		Turbidometric immunoassay	27.0	SPA or clean middle urine	UTI
Nani Jung et al.2018[20]	RCS	Suspected UTI	422	56.4days (0-3M)	UTI (102)	Non-UTI (320)	CMIA	46.2	Bags	UTI
Safdar et al. 2015[21]	PCS	Suspected UTI	73	26.3M (0-14Y)	Ungrouped		NR	35.83	UC or clean middle urine	UTI
Lubell et al. 2017[22]	PCS	Suspected UTI	260	213days (0-2Y)	Ungrouped		ELISA	39.1	UC	UTI
Yilmaz et al. 2009[23]	CCS	UTI and non-UTI	89	5.59 ± 3.84Y (2M-12Y)	UTI (60)	Healthy (29)	ELISA	20.0	UC or bags or clean middle urine	UTI
Krzemien et al. 2017[24]	PCS	Suspected UTI	60	5.8 ± 3.4M (1-12M)	UTI (42)	Healthy (18)	ELISA	42.2	UC or clean middle urine	UTI
Valdimarsson et al. 2017[7]	CCS	UTI and non-UTI	185	0-1Y	UTI (108)	Non-UTI (56)	ELISA	38	SPA	UTI
Shaikh et al. 2021[25]	PCS	Suspected UTI	144	12.5M	Febrile UTI (75)	Febrile without UTI (69)	ELISA	71.1	UC or clean middle urine	UTI
Yim et al. 2014[26]	CCS	UTI and non-UTI	129	23.04M	UTI (73)	Healthy (56)	ELISA	23.95	UC or bags or clean middle urine	UTI
		APN and Lower UTIs	73	21.3M	APN (46)	Lower UTIs (27)		73		APN
Moon et al. 2021[8]	RCS	Suspected UTI	321	39.02M (1-14Y)	UTI (157)	Non-UTI (164)	CMIA	36.5	UC or clean middle urine	UTI
		Suspected APN	157	16.8M (1-14Y)	APN (70)	Lower UTIs (87)		53.1		APN
Nickavar et al. 2016[28]	CCS	APN and non-UTI	63	40.9M (1-14Y)	UTI/APN (37)	Non-UTI (26)	ELISA	0.2	UC or bags or clean middle urine	UTI/APN
Ghasemi et al. 2016[27]	PCS	Suspected APN	89	2-168M	APN (43)	Lower UTIs (46)	ELISA	5	UC or clean middle urine	APN
Arambašić et al. 2015[29]	CCS	APN and non-APN	134	33M	APN (80)	Non-APNa (54)	CMIA	38.5	bags or clean middle urine	APN

UTI = Urinary tract infection; APN = Acute pyelonephritis; ELISA = Enzyme-linked immunosorbent assay; NGAL = Neutrophil gelatinase-associated lipocalin; CMIA = Chemiluminiscent microparticle immunoassay
RCS = Retrospective cross-sectional study; PCS = Prospective cross-sectional study; CCS = Case-Control study
NR = not reported; TP = true positive; FP = false positive; TN = true negative; FN = false negative
SPA = Suprapubic aspirate; UC = Urinary catheterization; bags = bags for urine collection
a = Non-APN includes cystitis and other infections

influence of literature quality on the study results by excluding studies with a high risk of bias.

Statistical analysis

QUADAS II charting was performed in RevMan V.5.3 software (Cochrane Collaboration, Oxford, UK). Based on a bivariate mixed-effects regression model developed by Van Houwelingen HC *et al.* for analysing treatment effects,[13,14] which was later adapted for use in combining data from diagnostic tests.[15,16] With the above model fitting, we could obtain the logit-transformed sensitivity, specificity, standard error and 95% CI to construct summary receiver operating characteristic (SROC) curve of uNGAL. Meta-analyses were performed in the MIDAS module in STATA version 12.0 (Stata Corp, College Station, TX).[17] We assessed heterogeneity by calculating I^2. If heterogeneity existed among studies, the potential sources of heterogeneity were investigated by meta-regression. We constructed an effective sample size funnel plot and associated asymmetric regression test (Deeks' test) to detect publication bias.[18]

RESULTS

We searched the PubMed, EMBASE, Cochrane Library and Web of Science databases to retrieve papers related to uNGAL diagnose UTIs in children (n = 251), and after reviewing the titles, abstracts and full texts, 13 literatures were finally included, the relevant filtering steps are shown in Figure 1. Tables 1 and 2 shows the relevant parameters of the included studies, involving a total of 2299 children aged 0-14 years. Among the 13 included studies in the analysis, 8 studies focused on using uNGAL solely for the diagnosis of UTI. Additionally, 2 studies examined the use of uNGAL exclusively for the diagnosis of APN. Furthermore, 3 studies investigated the utility of uNGAL for both the diagnosis of UTI and APN. In terms of the study design, out of the 13 included studies, there were 6 prospective studies, 2 retrospective studies, and 5 case-control studies. The majority of the studies were conducted as single-center studies. Among them, 8 studies utilized enzyme-linked immunosorbent assay (ELISA) as the experimental method, 3 studies employed chemiluminescent microparticle immunoassay (CMIA), one study utilized immunoturbidimetry, and one study did not specify the experimental method used. The cut-off value of uNGAL also varied widely among studies in the diagnosis of UTI, ranging from 0.2ng/ml to 73ng/ml.

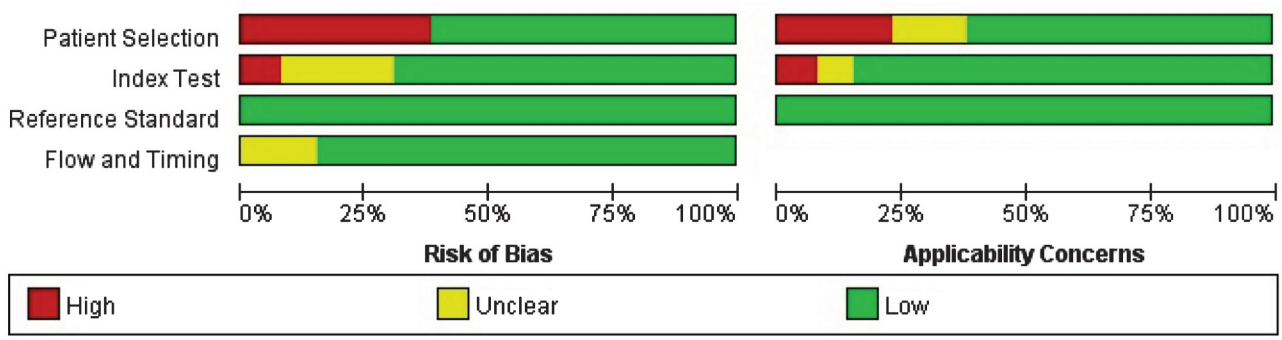
We applied the QUADAS II checklist to assess the methodological quality of diagnostic studies. The checklist used for assessing bias consisted of four indicators. Studies with more than two indicators, indicating a high risk of bias, were excluded from the analysis. In terms of the methodological quality, it was generally deemed to be fair. A total of six studies were found to have a low risk of bias across all assessment indicators. Five of the studies were case-control studies and were considered to have case inclusion bias, all had reference standards

Table 2. Sensitivity and specificity of included studies

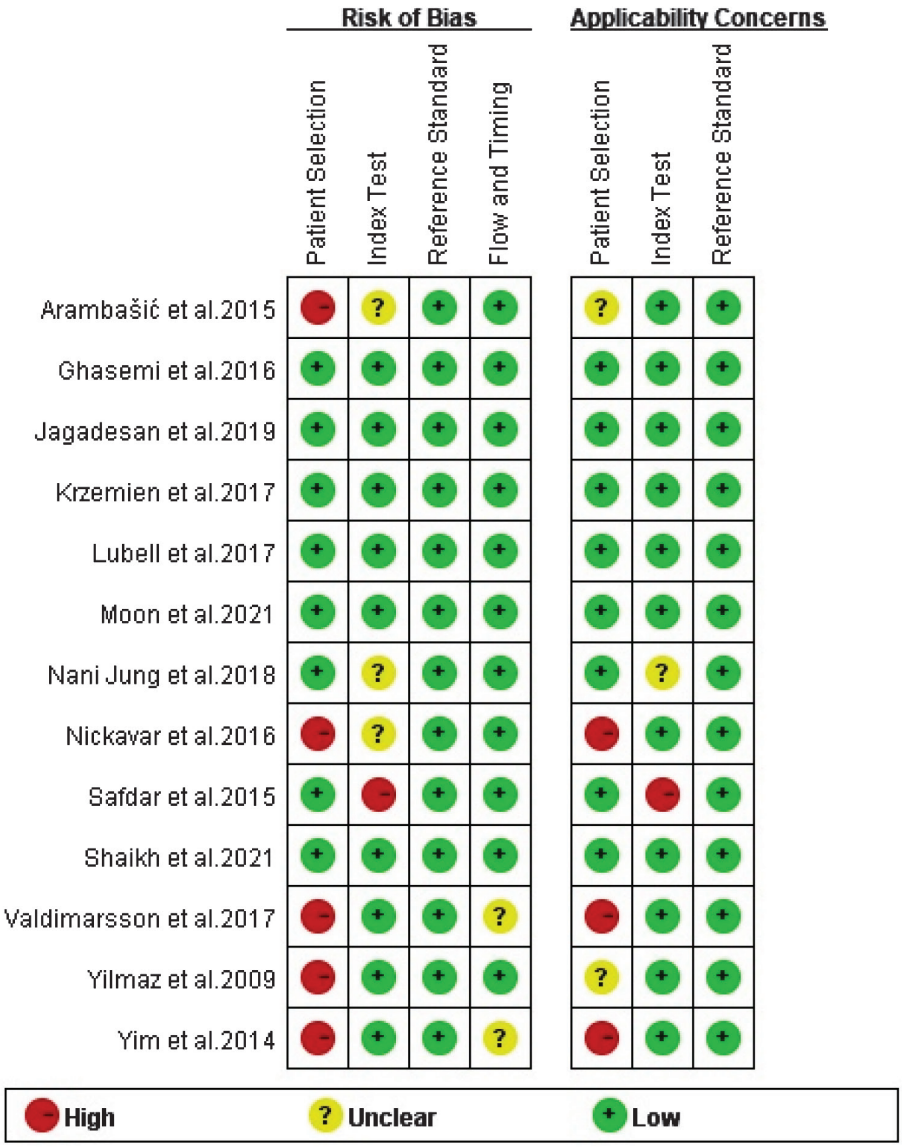
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jagadesan et al. 2019[19]	27	21	7	45	0.794 (0.62-0.91)	0.682 (0.56-0.79)
Nani Jung et al.2018[20]	92	24	10	296	0.902 (0.83-0.95)	0.925 (0.89-0.95)
Safdar et al. 2015[21]	25	10	17	21	0.594 (0.43-0.74)	0.683 (0.49-0.83)
Lubell et al. 2017[22]	34	10	1	215	0.971 (0.85-1.00)	0.956 (0.92-0.98)
Yilmaz et al. 2009[23]	58	7	2	22	0.97 (0.88-1.00)	0.76 (0.56-0.90)
Krzemien et al. 2017[24]	31	5	11	13	0.738 (0.58-0.86)	0.722 (0.47-0.90)
Valdimarsson et al. 2017[7]	100	1	8	12	0.926 (0.86-0.97)	0.953 (0.64-1.00)
Shaikh et al. 2021[25]	75	2	0	67	1.00 (0.95-1.00)	0.97 (0.90-1.00)
Yim et al. 2014[26]	60	9	13	47	0.824 (0.71-0.90)	0.836 (0.72-0.92)
	35	7	11	20	0.76 (0.61-0.87)	0.737 (0.54-0.89)
Moon et al. 2021[8]	128	34	29	130	0.815 (0.75-0.87)	0.793 (0.72-0.85)
	57	58	13	29	0.817 (0.70-0.90)	0.333 (0.24-0.44)
Nickavar et al. 2016[28]	28	6	9	20	0.76 (0.59-0.88)	0.77 (0.56-0.91)
Ghasemi et al. 2016[27]	29	1	14	45	0.674 (0.51-0.81)	0.978 (0.88-1.00)
Arambašić et al. 2015[29]	70	12	10	42	0.875 (0.78-0.94)	0.786 (0.64-0.88)

that adequately differentiated the disease status of the included participants, one study had a clinical assessment that preceded the uNGAL test and was considered to have bias. The above results are shown in Supplement Figures 1 and 2.

We did not find publication bias of uNGAL in



Supplement Figure 1. Risk of bias assessment



Supplement Figure 2. Risk of bias assessment

the diagnosis of UTI and APN by Deeks' regression test. (P = .68; P = .53; respectively) (Supplement Figures 3 and 4)

uNGAL for UTI

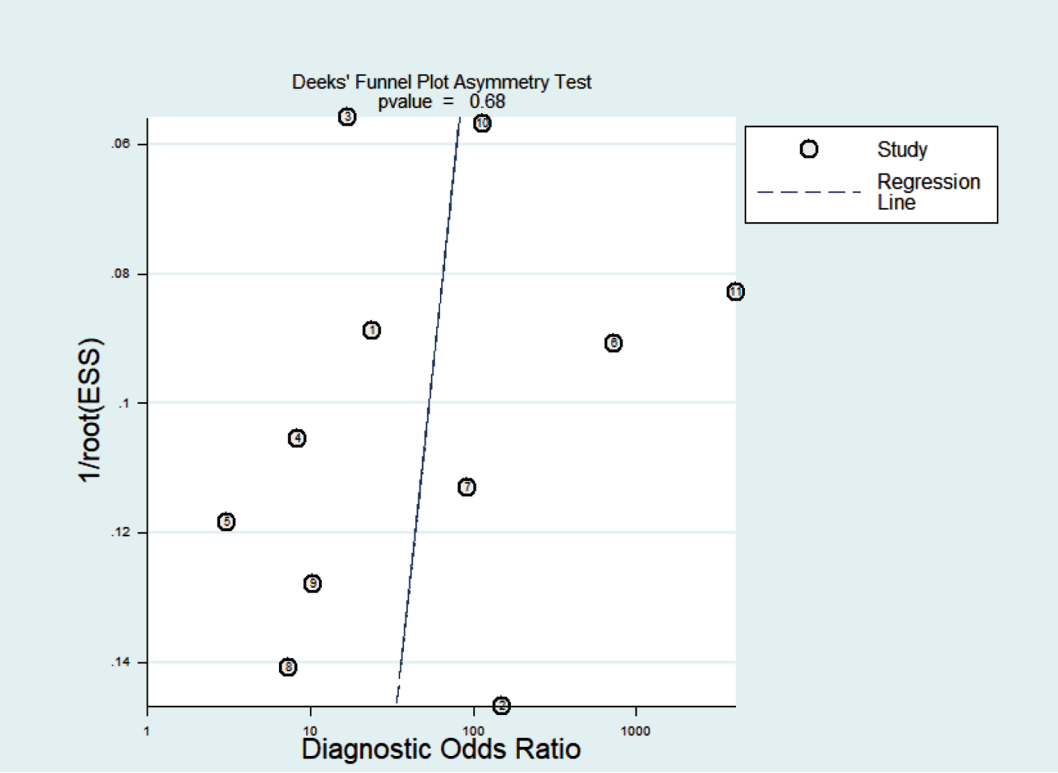
A total of 11 studies were included in the analysis, four of them had used urine collection bags to collect urine specimens. For uNGAL in the diagnosis of UTI, the sensitivity was 0.88 (95% CI 0.79–0.94) and the specificity was 0.86 (95% CI 0.78–0.92) for the 11 studies pooled (Figure 2). The area under the SROC curve was 0.93 (95% CI 0.91–0.95). (Figure 3). No heterogeneity exists among the studies (overall I^2 = 0, 95% CI 0–100). A sensitivity analysis was conducted to evaluate the impact of literature quality on the results. The analysis excluded studies deemed to have one or more high risk of bias, and subsequently, the meta-analysis was performed again with the use of only high-quality literature (n = 5). The sensitivity was 0.92 (95% CI 0.72–0.98) and the specificity was 0.88 (95% CI 0.71–0.95) for the 5 studies pooled (Supplement Figure 5). The area under the SROC curve was 0.95 (95% CI 0.93–0.97). (Supplement Figure 6). No heterogeneity exists among the five studies (overall I^2 = 0, 95% CI 0–100). This result is similar to the results of the full literature meta-analysis, indicating the robustness of the meta-analysis results.

uNGAL for APN

A total of five studies were included in this

STATISTICAL TESTS FOR SMALL STUDY EFFECTS/PUBLICATION BIAS

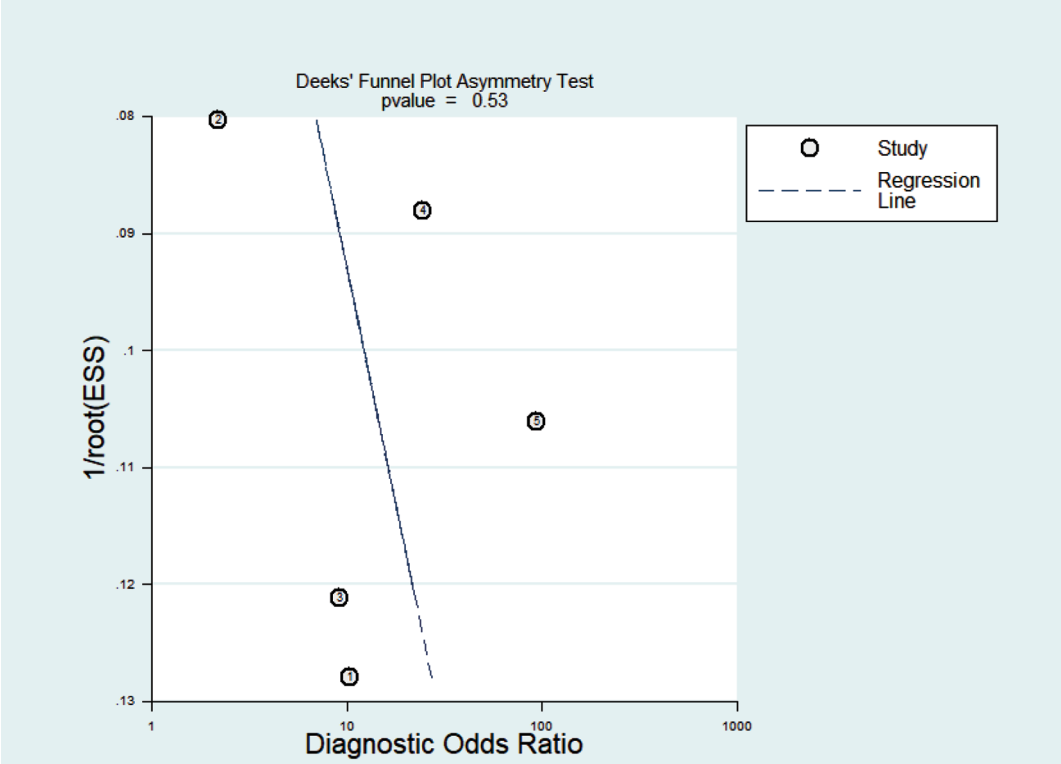
yb	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Bias	-9.828088	22.93498	-0.43	0.678	-61.71062	42.05445
Intercept	4.958292	2.017823	2.46	0.036	.3936589	9.522926



Supplement Figure 3. Publication bias among uNGAL for diagnosis of UTI

STATISTICAL TESTS FOR SMALL STUDY EFFECTS/PUBLICATION BIAS

yb	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
Bias	28.51355	40.07385	0.71	0.528	-99.01933	156.0464
Intercept	-.3492496	3.998807	-0.09	0.936	-13.07524	12.37674



Supplement Figure 4. Publication bias among uNGAL for diagnosis of APN

analysis; three of them had used urine collection bags to collect urine specimens. For uNGAL in the diagnosis of APN, the sensitivity was 0.79 (95% CI 0.72–0.85) and the specificity was 0.78 (95% CI 0.50–0.93) for the 5 studies pooled (Figure 4). The area under the SROC curve was 0.82 (95% CI 0.79–0.85). (Figure 5). Substantial heterogeneity exists among the studies (overall $I^2 = 0.95$, 95% CI 90–99). Meta-regression was not performed to analyze sources of heterogeneity due to insufficient number of included papers. Sensitivity analyses was not complete due to insufficient numbers of articles after the exclusion.

DISCUSSION

We conducted a meta-analysis by pooling available articles on the use of uNGAL in the diagnosis of UTI in children, to present the results of systematic reviews. The objective was to determine the accuracy of uNGAL in diagnosing UTI in children, and specifically, its ability to differentiate acute pyelonephritis (APN) from other sites infection. The results of the meta-analysis showed that uNGAL has a high sensitivity and specificity in diagnosing UTI in children, but is still not able to differentiate APN from other sites of infection, other than pyelonephritis, in children, which means that uNGAL could not definitively diagnose APN.

NGAL also known as human neutrophil lipocalin, has been found to have a high clinical value in the diagnosis of acute kidney injury (AKI)[30] and

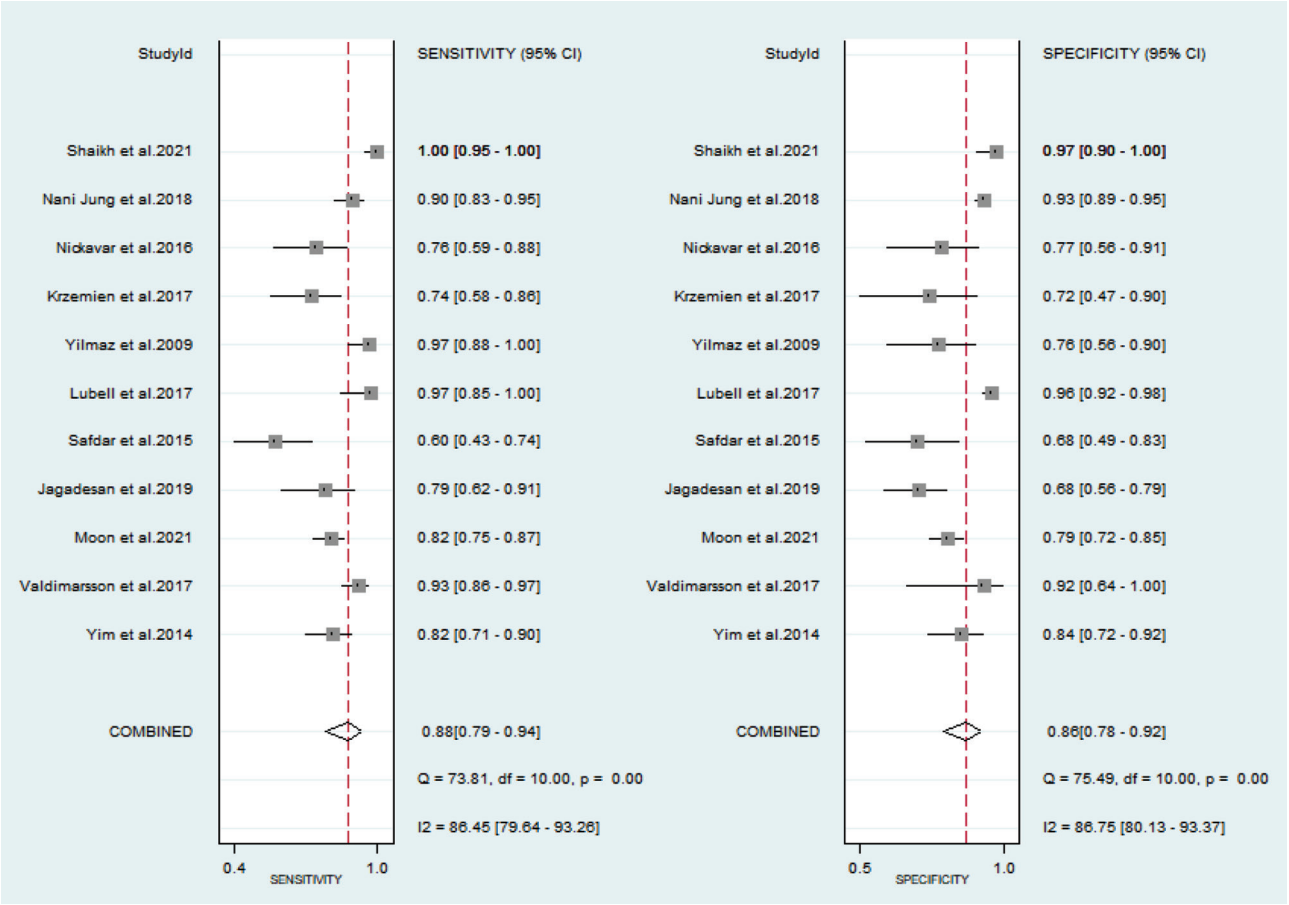


Figure 2. Sensitivity and specificity of uNGAL for diagnosis of UTI

its clinical implication for the diagnosis of UTIs have been extensively studied. NGAL is found in various human tissues including renal tubular endothelial cells and neutrophil granules[31] and plays a key role in the innate immune response to various bacterial infections.[32,33] In the immune response, the release of NGAL increases due to activated neutrophils, which inhibit bacterial growth by blocking the uptake of iron by bacteria.[34] It has been shown that low levels of uNGAL are a risk factor for the recurrence of febrile urinary tract infections.[35] Meanwhile Flo TH *et al.* found that when mice were given intraperitoneal injections of E. coli, wild-type mice survived, while most mice, who lacked NGAL, died within 2 days.[32]

Although urine cultures are definitive evidence in determining UTI, they remain limited in clinical use due to numerous inconveniences. The impact of sample contamination and the use of antibiotics on uNGAL is still uncertain and requires further investigation supported by a substantial body of evidence-based medical research. The literature included in this study has a variety of different urine collection methods such as collection bags, intermediate urine, catheterization and SPA. Lubell *et al.* found that the sensitivity and specificity of uNGAL in both bagged and catheterized urine samples were inconsistent,[36] so different urine collection methods may have different diagnostic thresholds, but further research is needed as there is a paucity of relevant literature.

This study sought to provide additional clarification regarding the potential use of uNGAL as a diagnostic tool for identifying APN based on the diagnosis of UTI. Previous studies by Majd *et al.* showed that the sensitivity and specificity of dimercaptosuccinic acid (DMSA) in diagnosing APN was 91% and 99%, respectively,[37] whereas the results of the five studies pooled in our review show that uNGAL is not sufficient to replace DMSA as a criterion for diagnosing APN. Upon further investigation, it was discovered that

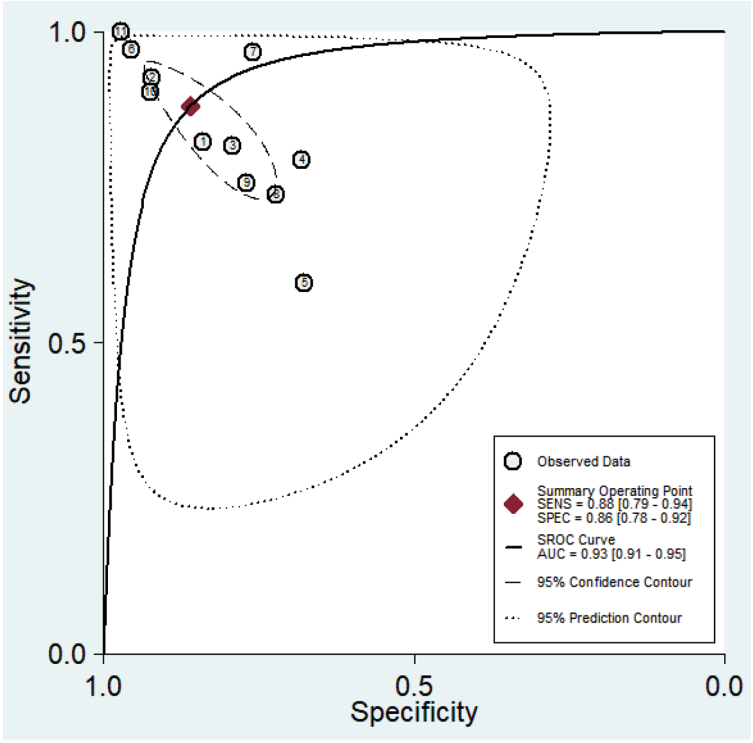
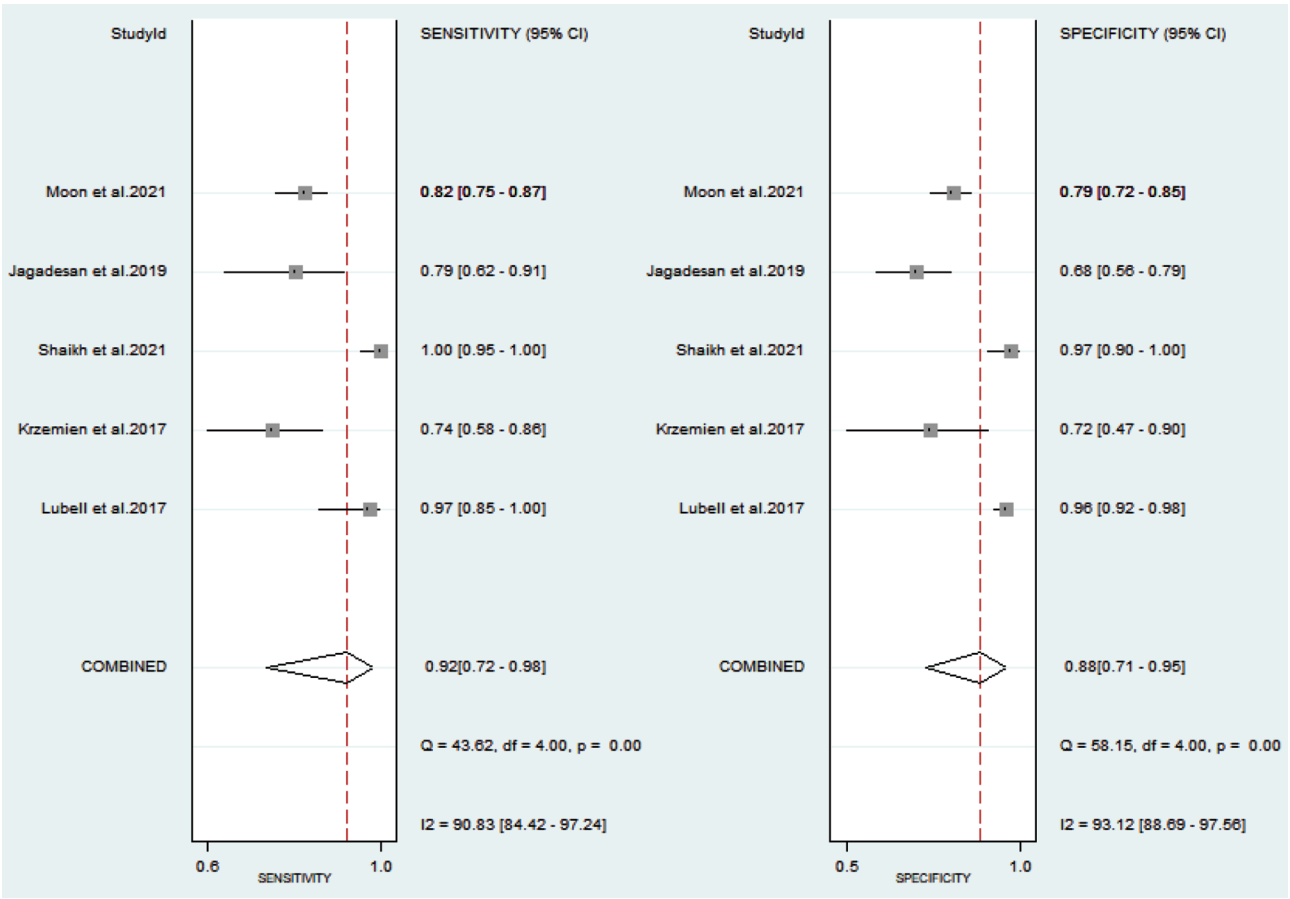
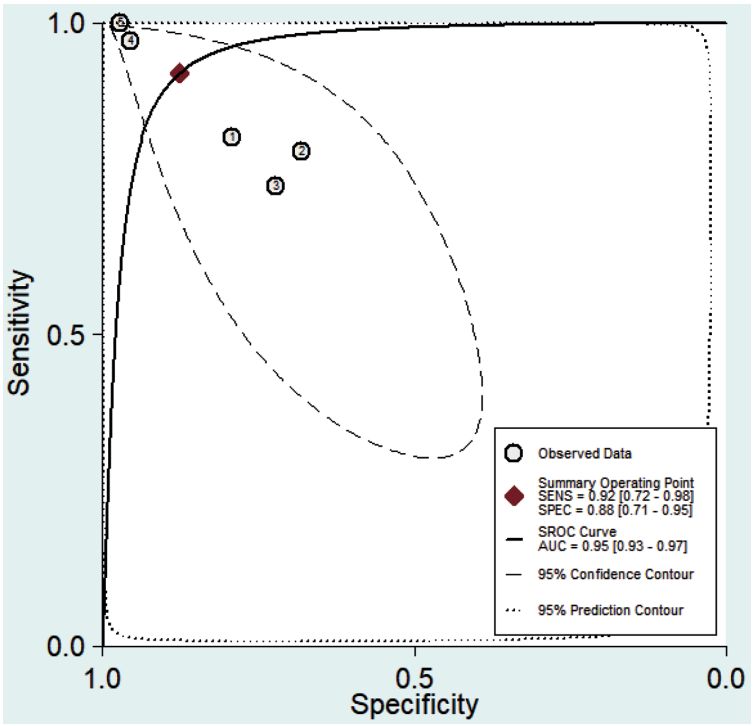


Figure 3. Summary receiver operating characteristic curve of uNGAL for diagnosis of UTI. CI: Confidence interval



Supplement Figure 5. Sensitivity and specificity of uNGAL for diagnosis of UTI (High quality literature)



Supplement Figure 6. Summary receiver operating characteristic curve of uNGAL for diagnosis of UTI. CI: Confidence interval (High quality literature)

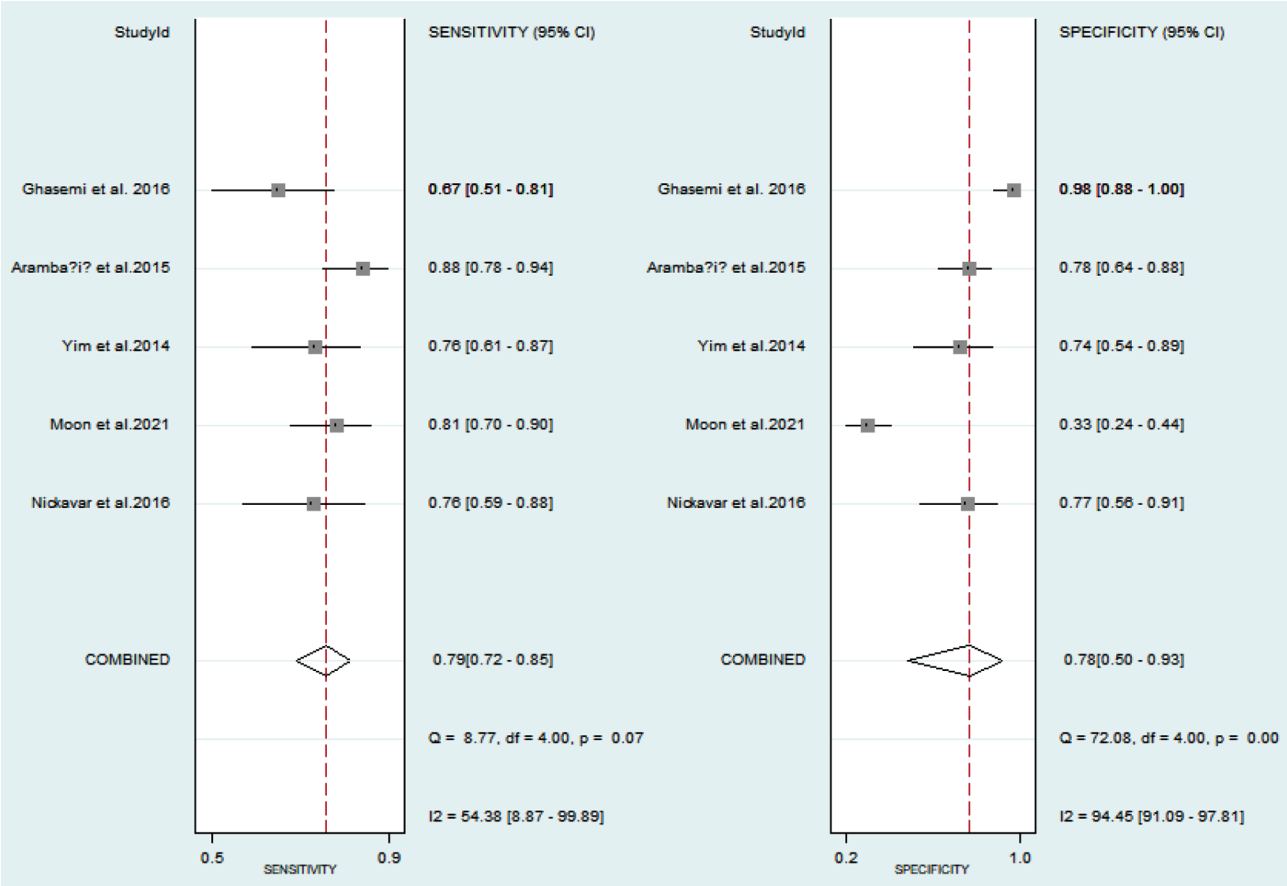


Figure 4. Sensitivity and specificity of uNGAL for diagnosis of APN

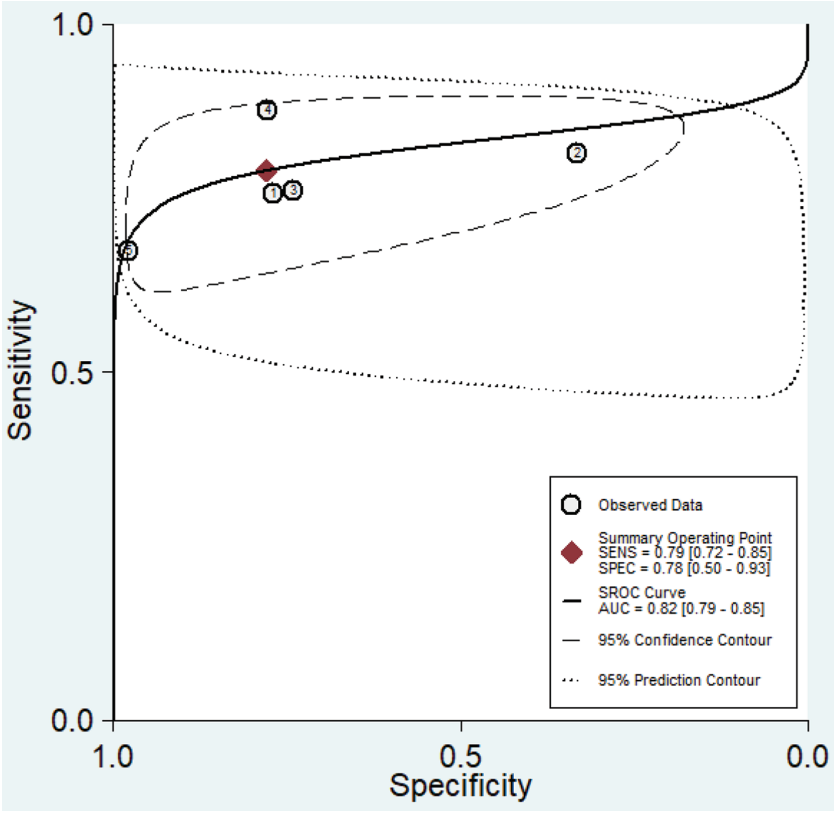


Figure 5. Summary receiver operating characteristic curve of uNGAL for diagnosis of APN. CI: Confidence interval

one potential factor that may impact the accuracy of uNGAL as a diagnostic marker for APN is the inability to differentiate between the monomeric and dimeric forms of the protein. Earlier research has demonstrated that the production of NGAL by the renal epithelium is primarily in its monomeric form, whereas activated neutrophils in the urine predominantly secrete NGAL as a dimer.[38] Western blot analysis showed that NGAL molecules are present in blood and urine in three different molecular forms: 25kDa monomer, 45kDa disulfide-linked homodimer and 135kDa heterodimer covalently coupled with matrix metalloproteinase (MMP)-9.[39,40] The urinary dimer MMP-NGAL/cr was found to be used as a diagnostic biomarker in the diagnosis of UTI in children in the study conducted by Hatipoglu *et al.*[41] However, data from related studies are scarce. Therefore, any method for the quantification of NGAL in urine must consider the possibility of this diversity. By developing new assays that can selectively identify NGAL originating from the tubular endothelium, it would greatly enhance the specificity and sensitivity of uNGAL assessment for diagnosing APN. Overall, uNGAL can be used as an adjunct to the diagnosis of APN and is a promising marker for the future.

This study included a control group of healthy and febrile children in the literature. However, it is unclear whether fever affects changes in NGAL expression, which may affect the results of this study. It was mentioned above that neutrophils can also produce NGAL, so what are the altered uNGAL levels due to other fever caused by infections? It has been noted that uNGAL levels in healthy children were 4377.5 pg/mL and 8006.9 pg/mL in febrile children, both much lower than the 419990.8 pg/mL in children with UTI, but it is not clear whether the difference is statistically significant.[25] As uNGAL is also a good predictor of AKI, if a febrile patient presents with an elevated uNGAL, it is important to be cautious of the possibility of sepsis complicating AKI in addition to UTI.[42]

In addition to urine NGAL, serum NGAL is also a hot topic of current research. In studies of short-term outcome prediction in heart failure, Wettersten *et al.* clarified that serum NGAL was superior to uNGAL.[43] However, in studies focusing

on UTI, there is a lack of direct evidence supporting this claim. Furthermore, our investigation revealed that out of the six studies included in the meta-analysis on serum NGAL for the diagnosis of UTI, only two exhibited sensitivities and specificities above 80%.[44] This falls short of the pooled sensitivity and specificity of uNGAL for UTI diagnosis in our study, indirectly suggesting that uNGAL is a more representative biomarker than serum NGAL for diagnosing UTI.

Based on our results and discussion, we propose the following recommendations regarding the use of uNGAL for diagnosing UTIs in children. In an outpatient clinic setting, where obtaining a urine culture may be challenging, we suggest using uNGAL and urine analysis as rapid screening tests to diagnose and initiate treatment for patients with suspected UTI. However, it is important to note that in children presenting with fever and renal percussive pain (costo-vertebral angle tenderness), it is necessary to conduct a DMSA scan as the first step, as the diagnosis cannot be solely based on uNGAL results. In an inpatient setting, where urine culture tests are routinely performed, uNGAL testing can serve as a complementary method to indirectly confirm the diagnosis of UTI; this is particularly valuable in children who are unable to provide a suitable urine sample for culture. Overall, while uNGAL can aid in the diagnosis of UTIs, it should be used in conjunction with other clinical and diagnostic measures.

There are still some limitations to this study. Firstly, despite an adequate search, there is still literature that was not fully included. Secondly, due to the limited number of articles, it was not possible to complete a heterogeneity analysis study of the meta results, which may affect the accuracy of the meta results.

CONCLUSION

In conclusion, the meta-analysis showed that uNGAL has a good sensitivity and specificity in diagnosing UTI in children and is a promising marker. However, there is currently no clear advantage in using uNGAL for the diagnosis of APN in children. This underscores the need for more precise tests that can accurately identify NGAL originating from tubular epithelial cells and, consequently, enable an accurate localization of the infection.

CONTRIBUTORS

Study conception or design: W.Y., C.F., and B.B; Data analyzing and draft manuscript preparation: W.Y., Z.N., B.B., and Y. Z.; Critical revision of the paper: W.Y., Z.N., and C.F.; Supervision of the research: W.Y., Z.N., and C.F.; Final approval of the version to be published: W.Y., Z.N., B.B., Y. Z., and C.F.;

All authors read and approved the final version of the manuscript.

FUNDING

The current study was founded by the Science and Technology Projects in Yinzhou District (2022AS035).

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Chaudhari PP, Monuteaux MC, Bachur RG. Urine Concentration and Pyuria for Identifying UTI in Infants. Pediatrics. 2016,138(5).
2. Becknell B, Schober M, Korbel L, Spencer JD. The diagnosis, evaluation and treatment of acute and recurrent pediatric urinary tract infections. Expert Rev Anti Infect Ther. 2015,13(1):81-90.
3. Das R, Ahmed T, Saha H, et al. Clinical risk factors, bacterial aetiology, and outcome of urinary tract infection in children hospitalized with diarrhoea in Bangladesh. 2017,145(5):1018-1024.
4. Kjeldsen L, Bainton DF, Sengeløv H, Borregaard N. Identification of neutrophil gelatinase-associated lipocalin as a novel matrix protein of specific granules in human neutrophils. Blood. 1994,83(3):799-807.
5. Paragas N, Kulkarni R, Werth M, et al. α-Intercalated cells defend the urinary system from bacterial infection. J Clin Invest. 2014,124(7):2963-2976.
6. Shemin D, Dworkin LD. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for early acute kidney injury. Crit Care Clin. 2011,27(2):379-389.
7. Valdimarsson S, Jodal U, Barregård L, Hansson S. Urine neutrophil gelatinase-associated lipocalin and other biomarkers in infants with urinary tract infection and in febrile controls. Pediatr Nephrol. 2017,32(11):2079-2087.
8. Moon JH, Yoo KH, Yim HE. Urinary neutrophil gelatinase-associated lipocalin: a marker of urinary tract infection among febrile children. Clin Exp Pediatr. 2021,64(7):347-354.
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Bmj. 2009,339:b2700.
10. Yang SS, Tsai JD, Kanematsu A, Han CH. Asian

guidelines for urinary tract infection in children. J Infect Chemother. 2021,27(11):1543-1554.

11. Stokland E, Hellström M, Jacobsson B, et al. Early 99mTc dimercaptosuccinic acid (DMSA) scintigraphy in symptomatic first-time urinary tract infection. Acta Paediatr. 1996,85(4):430-436.
12. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011,155(8):529-536.
13. Van Houwelingen HC, Zwinderman KH, Stijnen T. A bivariate approach to meta-analysis. Stat Med. 1993,12(24):2273-2284.
14. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med. 2002,21(4):589-624.
15. Riley RD, Abrams KR, Sutton AJ, Lambert PC, Thompson JR. Bivariate random-effects meta-analysis and the estimation of between-study correlation. BMC Med Res Methodol. 2007,7:3.
16. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol. 2005,58(10):982-990.
17. B D. MIDAS: Stata module for meta-analytical integration of diagnostic test accuracy studies. Statistical Software Components. 2019, 14(Feb).
18. Deeks JJ, Macaskill P, 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(9):882-893.
19. Jagadesan I, Agarwal I, Chaturvedi S, et al. Urinary Neutrophil Gelatinase Associated Lipocalin - A Sensitive Marker for Urinary Tract Infection in Children. Indian J Nephrol. 2019,29(5):340-344.
20. Jung N, Byun HJ, Park JH, et al. Diagnostic accuracy of urinary biomarkers in infants younger than 3 months with urinary tract infection. Korean J Pediatr. 2018,61(1):24-29.
21. Osama Y Safdar; Mohammed A Shalaby; Wael M Toffaha; Alanoud A Turki; Waleed M Toffaha AHGSMNAMAAKB. Neutrophil Gelatinase-Associated Lipocalin as an Early Marker for the Diagnosis of Urinary Tract Infections in Saudi Children. Journal of Nephrology & Therapeutics. 2015,2015(06).
22. Lubell TR, Barasch JM, Xu K, et al. Urinary Neutrophil Gelatinase-Associated Lipocalin for the Diagnosis of Urinary Tract Infections. Pediatrics. 2017,140(6).
23. Yilmaz A, Sevketoglu E, Gedikbasi A, et al. Early prediction of urinary tract infection with urinary neutrophil gelatinase associated lipocalin. Pediatr Nephrol. 2009,24(12):2387-2392.
24. Krzemień G, Pańczyk-Tomaszewska M, Adamczuk D, et al. Neutrophil Gelatinase-Associated Lipocalin: A Biomarker for Early Diagnosis of Urinary Tract Infections in Infants. Adv Exp Med Biol. 2018,1047:71-80.
25. Shaikh N, Liu H, Kurs-Lasky M, Forster CS. Biomarkers for febrile urinary tract infection in children. Pediatr Nephrol. 2022,37(1):171-177.
26. Yim HE, Yim H, Bae ES, Woo SU, Yoo KH. Predictive value of urinary and serum biomarkers in young children with febrile urinary tract infections. Pediatr Nephrol. 2014,29(11):2181-2189.
27. Ghasemi K, Esteghamati M, Borzoo S, Parvaneh E, Borzoo S. Predictive Accuracy of Urinary neutrophil gelatinase associated lipocalin (NGAL) for renal parenchymal involvement in Children with Acute Pyelonephritis. Electron Physician. 2016,8(2):1911-1917.
28. Nickavar A, Safaeian B, Valavi E. Validity of Neutrophil Gelatinase Associated Lipocaline as a Biomarker for Diagnosis of Children with Acute Pyelonephritis. 2016,13(5):2860-2863.
29. Arambašić J, Mandić S, Debeljak Ž, et al. Differentiation of acute pyelonephritis from other febrile states in children using urinary neutrophil gelatinase-associated lipocalin (uNGAL). Clin Chem Lab Med. 2016,54(1):55-61.
30. Zou Z, Chen B, Tang F, Li X, Xiao D. Predictive value of neutrophil gelatinase-associated lipocalin in children with acute kidney injury: A systematic review and meta-analysis. Front Pediatr. 2023,11:1147033.
31. Lee HE, Kim DK, Kang HK, Park K. The diagnosis of febrile urinary tract infection in children may be facilitated by urinary biomarkers. Pediatr Nephrol. 2015,30(1):123-130.
32. Flo TH, Smith KD, Sato S, et al. Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. Nature. 2004,432(7019):917-921.
33. Borregaard N, Cowland JB. Neutrophil gelatinase-associated lipocalin, a siderophore-binding eukaryotic protein. Biometals. 2006,19(2):211-215.
34. Goetz DH, Holmes MA, Borregaard N, et al. The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. Mol Cell. 2002,10(5):1033-1043.
35. Yamanouchi S, Kimata T, Akagawa Y, et al. Reduced urinary excretion of neutrophil gelatinase-associated lipocalin as a risk factor for recurrence of febrile urinary tract infection in children. 2021,36(6):1473-1479.
36. Lubell TR, Barasch JM, King B, et al. Urinary tract infections in children: Testing a novel, noninvasive, point-of-care diagnostic marker. Acad Emerg Med. 2022,29(3):326-333.
37. Majd M, Rushton HG. Renal cortical scintigraphy in the diagnosis of acute pyelonephritis. Semin Nucl Med. 1992,22(2):98-111.
38. Cai L, Rubin J, Han W, Venge P, Xu S. The origin of multiple molecular forms in urine of HNL/NGAL. Clin J Am Soc Nephrol. 2010,5(12):2229-2235.
39. Kjeldsen L, Johnsen AH, Sengeløv H, Borregaard N. Isolation and primary structure of NGAL, a novel protein associated with human neutrophil gelatinase. J Biol Chem. 1993,268(14):10425-10432.
40. Xu SY, Carlson M, Engström A, et al. Purification and characterization of a human neutrophil lipocalin (HNL) from the secondary granules of human neutrophils. Scand J Clin Lab Invest. 1994,54(5):365-376.
41. Hatipoglu S, Sevketoglu E, Gedikbasi A, et al. Urinary MMP-9/NGAL complex in children with acute cystitis. Pediatr Nephrol. 2011,26(8):1263-1268.
42. Zhou H, Cui J, Lu Y, Sun J, Liu J. Meta-analysis of the

diagnostic value of serum, plasma and urine neutrophil gelatinase-associated lipocalin for the detection of acute kidney injury in patients with sepsis. Exp Ther Med. 2021,21(4):386.

43. Wettersten N, Horiuchi Y, van Veldhuisen DJ, et al. Short-term prognostic implications of serum and urine neutrophil gelatinase-associated lipocalin in acute heart failure: findings from the AKINESIS study. Eur J Heart Fail. 2020,22(2):251-263.
44. Shaikh K, Rajakumar V, Osio VA, Shaikh N. Neutrophil gelatinase-associated lipocalin for urinary tract infection and pyelonephritis: a systematic review. 2021,36(6):1481-1487.

*Correspondence to:
Chaojie Feng
Department of Nephrology, Ningbo Urology and Nephrology Hospital, Ningbo, China.
E-mail addresses: 820865530@qq.com

Received July 2023
Accepted November 203