

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

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Abstract. The objective of the present study was to assess the diagnostic value of urine, serum and plasma neutrophil gelatinase-associated lipocalin (NGAL) for the early diagnosis of acute kidney injury (AKI) among patients with suspected sepsis. Therefore, a meta-analysis was carried out to evaluate diagnostic accuracy data from the literature regarding the diagnosis of AKI in patients with sepsis. Electronic databases were systematically searched for relevant studies and quality assessment was conducted using the Quality Assessment for Diagnostic Accuracy Studies 2 tool. A summary receiver operating characteristic curve analysis was performed, and several parameters including sensitivity, specificity, diagnosis odds ratio (DOR) and area under the curve (AUC) were calculated to evaluate the diagnostic performance of urine, serum and plasma NGAL. Meta-regression, sensitivity and subgroup analysis were also conducted to identify the source of heterogeneity in the eligible studies. In total, 28 studies were included. The pooled sensitivities for urine, serum and plasma NGAL were 0.87, 0.83 and 0.80, respectively. Pooled specificity was 0.84, 0.79 and 0.74. The DORs were 35, 18 and 11, respectively. The AUC for urine, serum and plasma NGAL were 0.92, 0.87 and 0.84, respectively. Urine NGAL presented superior performance for the diagnosis of AKI with the highest AUC and other diagnostic accuracy values, compared with serum and plasma NGAL. Further studies are needed to clarify the controversial issue between the usefulness of serum and plasma NGAL.

Introduction

Acute kidney injury (AKI; also referred to as acute kidney failure or acute renal failure) is defined as a sudden loss of renal function. AKI has a high incidence in critically-ill patients, particularly those in intensive care units (1). Delayed diagnosis of AKI may result in deterioration of renal function, long hospital stays or even death. In addition, sepsis has been consistently found to be an important contributing factor of AKI (2,3). Mortality associated with septic AKI is significantly higher than that of non-septic AKI, and >50% of AKI cases are considered septic (4,5). Sepsis-induced AKI has been independently associated with an increased risk of longer hospital stays and mortality (6). Thus, due to the high morbidity and mortality of septic AKI, early prediction and diagnosis of this condition is essential.

Neutrophil gelatinase-associated lipocalin (NGAL) has been identified as a biomarker for AKI, as its concentration is significantly increased in urine, plasma and serum following ischemic kidney injury (7). NGAL is a 24-kDa secreted glycoprotein, which was originally purified from a culture of murine kidney cells infected with simian virus 40 (7,8). Zhang *et al* (6) demonstrated that NGAL was an independent predictor of AKI that is not influenced by age, sex, ethnicity, severity of injury and factors unrelated to renal function. Serum, urine and plasma are the main fluid types used in the diagnosis of AKI via the detection of NGAL (7). Previous studies have evaluated the diagnostic value of NGAL and its potential value in predicting outcomes of treatment, such as renal replacement therapy (6,9) Although NGAL appears to hold promise in the prediction of AKI among patients with suspected sepsis, the diagnostic accuracy of NGAL according to sample source (serum, urine or plasma) is still unclear. In the present study, the diagnostic performance of NGAL for AKI was evaluated using a meta-analysis. The secondary objective of this study was to identify an optimal source of NGAL for the diagnosis of sepsis-induced AKI.

Materials and methods

Literature search. The present study was based on previously published articles and, as such, did not require ethics

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approval or patient consent. Eligible studies were identified using an electronic database search and by cross-checking the references of relevant papers up to June 2020. The PubMed, ScienceDirect, Web of Science, Embase, OVID, Cochrane Library and China National Knowledge Infrastructure databases were systematically searched using search terms, including 'neutrophil gelatinase-associated lipocalin', 'sepsis', 'severe sepsis and septic shock', 'acute kidney injury', 'serum NGAL', 'plasma NGAL' and 'urine NGAL', as well as their abbreviations and synonyms and all possible combinations. Moreover, references from the retrieved articles were also reviewed to identify additional relevant studies.

Study selection. Two investigators (JC and YL) independently extracted data from the eligible papers complying with the inclusion and exclusion criteria. Disagreements were subsequently reviewed and resolved through discussion. Studies were included in the analysis if they met the following inclusion criteria without time limitation: i) Use of serum, urine or plasma NGAL for prediction of AKI in patients with suspected sepsis; ii) stratification of septic patients into an AKI group and a non-AKI group; iii) definition of sepsis according to the standards of The American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) (10), Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/American Thoracic Society/Surgical Infection Society (SCCM/ESICM/ACCP/ATS/SIS) (11), or the Survival Sepsis Campaign 2012 consensus criteria (12); iv) definition of AKI according to the Risk, Injury, Failure, Loss, End-Stage Kidney Disease (RIFLE) (13), Acute Kidney Injury Network (AKIN) (14) or Kidney Disease Improving Global Outcomes (KDIGO) criteria (15); v) full-text articles written in English or Chinese; and vi) presence of detailed clinical data that can be used to calculate sensitivity and specificity, including and the number of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) cases.

Exclusion criteria were defined as follows: i) Studies not including patients with sepsis; ii) studies not reporting data for the diagnostic accuracy of NGAL; and iii) studies providing insufficient data regarding the TP, FP, TN and FN numbers within the original published study. Only original articles were considered. Other publications, including letters, reviews, case reports or editorial articles were excluded. The two investigators reached a consensus on each item through discussion.

Data extraction and quality assessment. For each eligible study, the first author's name, year of publication, admission setting (intensive care unit or emergency room), country, study design, number of participants and the reference standards used to define sepsis and AKI were recorded. Diagnostic accuracy data for serum, urine and plasma NGAL, the area under the curve (AUC), optimal cut-off values, sensitivity, specificity and the number of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) responses were recorded or calculated. The same two investigators (JC and YL) also evaluated the quality of the included studies in the data extraction process. The Quality Assessment for Diagnostic Accuracy studies-2 (QUADAS-2) tool by RevMan version 5.3 was used to assess the quality of eligible studies (16). The risk of bias for each item was graded as 'low', 'unclear' and 'high'. Two investigators

appraised the study quality independently and discrepancies were resolved by discussion. Each study was ranked as having a high, low or unclear risk of bias according to four different areas: i) Patient selection; ii) index test; iii) reference standard; and iv) flow of patients through the study and timing of the index tests and reference standard (flow and timing).

Statistical analysis. TPs, TNs, FPs and FNs recorded in the included studies are the primary data used to assess the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratios (DOR) and AUC using Stata (version 15.1). The diagnostic performance of serum, urine and plasma NGAL was determined by calculating pooled sensitivity, specificity, PLR, NLR and DOR, with 95% CIs. Likelihood ratios (positive and negative likelihood ratio) are a ratios of the probabilities that a test result is correct to the probability that the test is incorrect [positive likelihood ratios=sensitivity/(1-specificity); negative likelihood ratios=specificity/(1-sensitivity)]. The larger the ratio of PLR, the greater probability of a true positive when the result is positive. The smaller the ratio of NLR, the greater probability of a true negative when the result is negative. The DOR [(TP x TN)/(FP x FN)] was used to reflect the relationship between diagnostic test and disease. Higher numbers would indicate improved performance in diagnosing patients with/without sepsis-AKI. Summary receiver operating characteristic (SROC) curves were generated to estimate the effect of sensitivity and specificity and were constructed based on TP and FP rates. TP and FP rates can be calculate through the following two formulas: TP rates=TP/(TP + FP) x100; FP rates=FP/(FP + TN) x100. The area under the curve (AUC) of the SROC was calculated to assess the performance of serum, urine and plasma NGAL individually.

The heterogeneity between studies was assessed using the χ^2 test and the inconsistency index (I^2). An $I^2 > 50\%$ with $P < 0.05$ from the χ^2 test is indicative of significant heterogeneity (17). In this case, a random effect model was chosen to pool the data of sensitivity, specificity and AUC. Otherwise, a fixed effect model was used.

The threshold effect is considered as a possible cause of heterogeneity in diagnostic accuracy analysis (18). Spearman correlation was used to analyse the logit of sensitivity and the logit of (1-specificity) and to verify the existence of threshold effect. A strong positive correlation (correlation > 0.6) between sensitivity and (1-specificity), with $P < 0.05$ was considered to indicate a statistically significant threshold effect (18).

Sensitivity analyses and subgroup analyses were also conducted to determine if a certain variance could affect the heterogeneity and overall diagnostic effect. Sensitivity analysis was performed by omitting one study at a time to examine stability of the pooled results. Meta-regression and subgroup analyses were performed to identify factors that could influence heterogeneity and the overall diagnostic effect.

Publication bias was analyzed by using the Deeks' funnel plot and an asymmetry test (19). $P < 0.05$ is considered to indicate the existence of publication bias.

Statistical analysis was performed using Stata version 15.1 (StataCorp LP). Quality assessment of the included studies was conducted using RevMan version 5.3 (The Nordic Cochrane Centre; The Cochrane Collaboration).

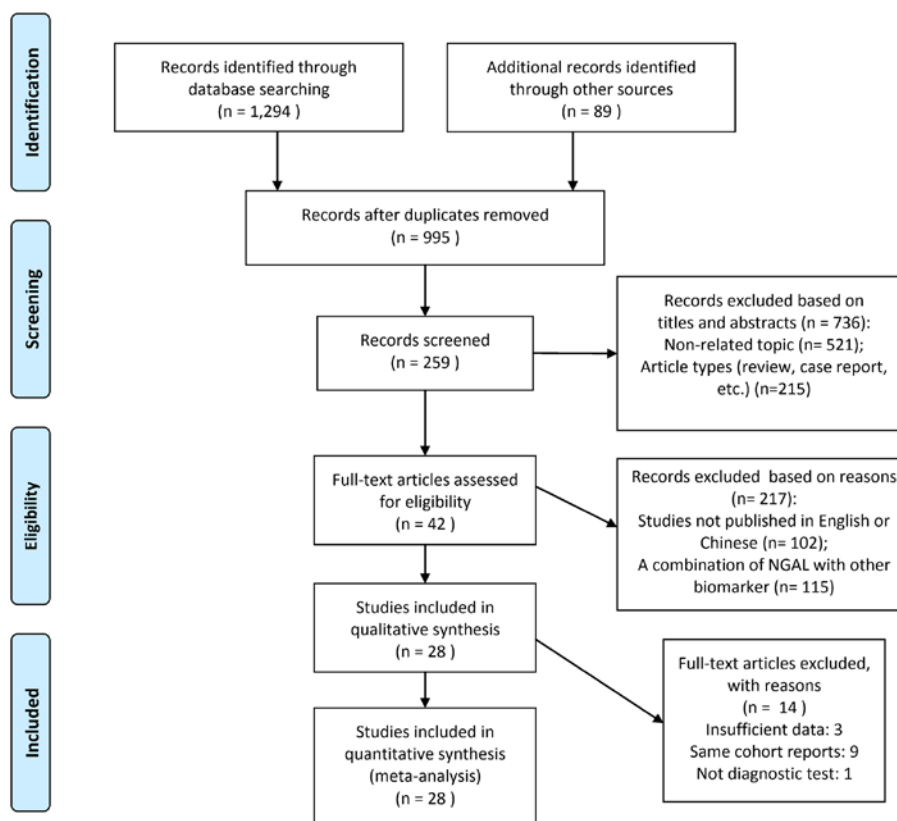


Figure 1. Flowchart of the literature search design and study selection. NGAL, neutrophil gelatinase-associated lipocalin.

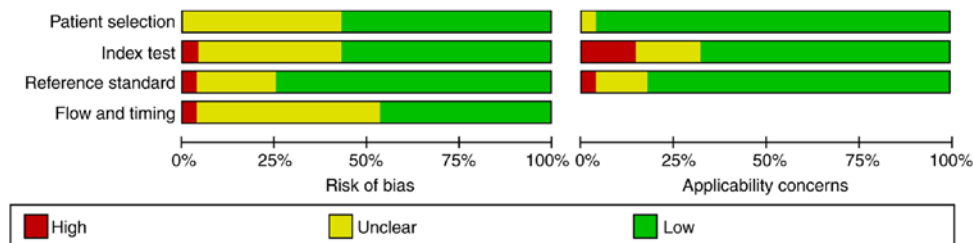


Figure 2. Risk of bias and applicability concerns graph of the 28 included studies.

Results

Study evaluation. Overall, 1,383 potential citations were identified for inclusion into the study through multiple database searches and cross-checking of reference lists. After removing duplicates, 338 studies were excluded. Of these, 259 articles were included based on titles and abstracts. A further 217 studies were excluded since they did not meet the eligibility of the present study and 42 studies remained as potential candidates for our meta-analysis. After reviewing the full text according to the inclusion and exclusion criteria, 28 studies were ultimately considered eligible and used for subsequent analysis (5,13,20-45). The study selection process is illustrated in Fig. 1.

Study characteristics. The included studies were conducted on different continents (Europe, Asia, North and South America) over a period spanning 10 years (2010-2020). Of the 28 studies, 9 described the diagnostic performance of serum

NGAL (5,20,21,24,28,31,34,37,41), 10 of plasma NGAL (13, 23,25,27,32,35,38,39,43,44) and 14 of urine NGAL (22,24, 26,29-31,33,34,36,37,40,42,44,45). Collectively, these studies included a total of 2,561 participants. Prospective studies took up ~43% of the included studies. The samples of NGAL were taken in two admission settings (ICU or ER) and samples from ICU took up 24 studies of the included studies. The remaining studies were of ER. Detailed information regarding study design, sample sizes and reference standards from the included studies are included in Table I.

Quality assessment. The quality and potential bias of the studies were assessed using the QUADAS-2 tool. The 'risk of bias' tool evaluates four items, patient selection, index test, reference standard and flow and timing. High risk was mostly observed in the 'index test' category because many studies did not provide the interpretation method of the NGAL test results and did not provide a threshold. Detailed information of the included studies and the results of distribution are presented in Fig. 2.

Table I. Characteristics of included studies for NGAL to predict sepsis-induced AKI.

First author/s, year	Country	Design	Setting	AKI definition	Sepsis definition	Source	Number of patients, AKI/total number of patients	Sampling time (h)	NGAL assay type	(Refs.)
Aydođdu <i>et al.</i> , 2013	Turkey	PC	ICU	RIFLE	SCCM, ESICM, ACCP, ATS	Urine	63/129	NR	ELISA	(40)
Camou <i>et al.</i> , 2013	France	PC	ICU	RIFLE, AKIN	SCCM, ESICM, ACCP, ATS, SIS	Plasma	43/50	Admission	ELISA	(39)
De Geus <i>et al.</i> , 2013	The Netherlands	PC	ICU	AKIN	ACCP, SCCM	Plasma	50/75	Admission	ELISA	(38)
El-Farghail <i>et al.</i> , 2012	Egypt	NR	NICU	AKIN	NR	Serum	35/60	Admission	ELISA	(41)
Fan <i>et al.</i> , 2014	China	PC	ICU	RIFLE	SCCM, ESICM, ACCP, ATS, SIS	Urine	58/126	Peak	RIA	(36)
Hjortrup <i>et al.</i> , 2015	Denmark	PC	ICU	KDIGO	ACCP, SCCM	Plasma	31/124	Admission	NR	(32)
Huang <i>et al.</i> , 2016	China	PC	ICU	KDIGO	NR	Plasma	30/76	NR	ELISA	(27)
Khawaja <i>et al.</i> , 2019	Pakistan	NR	ICU	RIFLE	NR	Plasma	32/46	12	NR	(13)
Li and Xu, 2010	China	PC	ICU	AKIN	ACCP, SCCM	Urine	17/74	24	ELISA	(45)
Liu <i>et al.</i> , 2019	China	NR	ICU	KDIGO	SSC	Serum	42/89	Admission	ELISA	(21)
Mårtensson <i>et al.</i> , 2010	Sweden	NR	ICU	RIFLE, AKIN	ACCP, SCCM	Plasma, Urine	18/45	12	RIA	(44)
Md Ralib <i>et al.</i> , 2017	Malaysia	NR	ICU	NR	ACCP, SCCM	Plasma	67/129	24	NR	(25)
Meng <i>et al.</i> , 2015	China	NR	ICU	AKIN	SSC	Serum, Urine	34/66	Peak	ELISA	(31)
Nga <i>et al.</i> , 2015	Brazil	PC	ER	AKIN	SSC	Urine	34/168	24	ELISA	(30)
Niu <i>et al.</i> , 2015	China	PC	ER	AKIN	SCCM, ESICM, ACCP, ATS, SIS	Urine	26/60	12	ELISA	(29)
Patel <i>et al.</i> , 2016	India	PC	NR	RIFLE, AKIN	SSC	Urine	88/155	12	NR	(26)
Rocha <i>et al.</i> , 2018	Brazil	NR	ICU	KDIGO	SSC	Urine	47/75	48	ELISA	(22)
Shang <i>et al.</i> , 2017	China	NR	ICU	RIFLE	NR	Serum, Urine	35/50	Admission	ELISA	(24)
Shapiro <i>et al.</i> , 2010	USA	PC	ER	RIFLE	ACCP, SCCM	Plasma	24/66	Admission	ELISA	(43)
Wang HX <i>et al.</i> , 2014	China	NR	ICU	KDIGO	ACCP, SCCM	Plasma	38/90	48	ELISA	(35)
Wang and Zhang, 2014	China	NR	ICU	KDIGO	ACCP, SCCM	Serum, Urine	28/51	48	ELISA	(34)
Wu <i>et al.</i> , 2019	China	NR	ICU	KDIGO	ESICM, SCCM	Serum	29/60	Admission	NR	(5)
Xing <i>et al.</i> , 2013	China	NR	ICU	AKIN	SCCM, ESICM, ACCP, ATS, SIS	Serum	35/73	NR	ELISA	(37)
Yan <i>et al.</i> , 2011	China	PC	ICU	AKIN	ACCP, SCCM	Urine	27/112	2	ELISA	(42)
Yang <i>et al.</i> , 2019	China	NR	ICU	NR	NR	Serum	71/156	NR	ELISA	(20)

Table I. Continued.

First author/s, year	Country	Design	Setting	AKI definition	Sepsis definition	Source	Number of patients, AKI/total number of patients	Sampling time (h)	NGAL assay type	(Refs.)
Zhang <i>et al.</i> , 2016	China	NR	ICU	NR	SSC	Serum	30/58	NR	ELISA	(28)
Zheng <i>et al.</i> , 2017	China	NR	ICU	NR	ACCP, SCCM	Plasma	52/150	Admission	ELISA	(23)
Zhou <i>et al.</i> , 2014	China	NR	ICU	AKIN	SCCM, ESICM, ACCP, ATS, SIS	Urine	46/148	8	ELISA	(33)

ACCP, American College of Chest Physicians; SCCM, Society of Critical Care Medicine; ESICM, European Society of Intensive Care Medicine; ATS, American Thoracic Society; SIS, Surgical Infection Society; SSC, Survival Sepsis Campaign 2012; RIFLE, Risk, Injury, Failure; Loss, End-Stage Kidney Disease; AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease Improving Global Outcomes; NGAL, neutrophil gelatinase-associated lipocalin; ER, emergency room; AKI, acute kidney injury; NR, not reported; PC, prospective cohort; RIA, radioimmunoassay, Sampling time, 8, 12, 24 or 48 h after admission into the ICU or ER; Admission, sampling on admission; Peak, sampling on peak value.

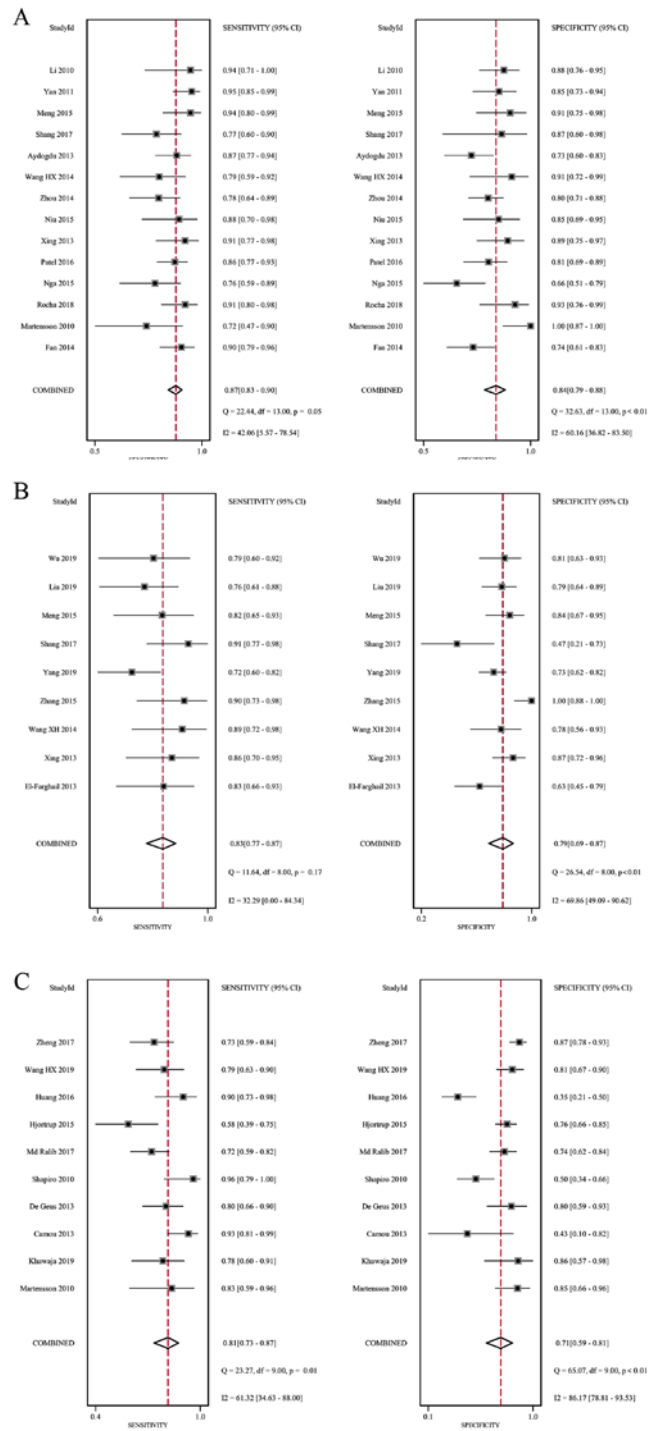


Figure 3. Forest plots of sensitivity and specificity for NGAL for the diagnosis of sepsis-AKI. Forest plots of (A) urine NGAL, (B) serum NGAL and (C) plasma NGAL. The red dotted line represents the point estimate of the averaged studies. NGAL, neutrophil gelatinase-associated lipocalin; df, degrees of freedom; CI, confidence interval; Q, heterogeneity chi-squared.

Diagnostic accuracy of urine NGAL. The discriminatory accuracy of a diagnostic test is commonly assessed by measuring how well it correctly identifies true-positive and true-negative result in terms of sensitivity and specificity (46). The pooled sensitivity of the 14 studies that reported the use of urine NGAL was 0.87 (95% CI, 0.83-0.90) and the pooled specificity was 0.84 (95% CI, 0.79-0.88; Fig. 3A). The pooled positive likelihood ratio (PLR) was 5.5 (95% CI, 4.0-7.5)

Table II. Diagnostic value of NGAL to predict AKI in septic patients.

First author/s, year	Source	AUC	95% CI	Cut-off value	Sensitivity,	Specificity,	DOR ^b	TP, n	FP, n	FN, n	TN, n	(Refs.)
Aydođdu <i>et al.</i> , 2013	Urine	0.44	NR	29.5 ng/ml	0.88	0.73	18.33	55	18	8	48	(40)
Camou <i>et al.</i> , 2013	Plasma	0.90	NR	150 ng/ml	0.93	0.44	10.00	40	4	3	3	(39)
De Geus <i>et al.</i> , 2011	Plasma	0.80	0.69-0.88	979 ng/ml	0.80	0.80	16.00	40	5	10	20	(50)
El-Farghail <i>et al.</i> , 2012	Serum	0.95	NR	117.5 ng/ml	0.82	0.89	8.18	29	13	6	22	(41)
Fan <i>et al.</i> , 2014	Urine	0.86	0.81-0.93	402 ng/ml	0.89	0.74	24.07	52	18	6	50	(36)
Hjortrup <i>et al.</i> , 2015	Plasma	0.66	0.54-0.77	558 ng/ml	0.58	0.76	4.47	18	22	13	71	(32)
Huang <i>et al.</i> , 2016	Plasma	0.73	0.61-0.85	150 ng/ml	0.90	0.35	4.80	27	30	3	16	(27)
Khawaja <i>et al.</i> , 2019	Plasma	0.82	0.68-0.96	150 ng/ml	0.71	0.91	33.22	23	1	9	13	(13)
Li and Xu, 2010	Urine	0.94	0.68-0.97	50 ng/ml	0.94	0.88	114.29	16	7	1	50	(45)
Liu <i>et al.</i> , 2019	Serum	0.78	0.76-0.82	16.32 ng/ml	0.75	0.79	11.84	32	10	10	37	(21)
Mårtensson <i>et al.</i> , 2010	Plasma	0.85	0.39-0.94	120 ng/ml	0.83	0.86	28.75	15	4	3	23	(44)
	Urine	0.86	0.68-1.00	68 ng/ml	0.71	1.00	135.00	13	0	5	27	
Md Ralib <i>et al.</i> , 2017	Plasma	0.72	0.66-0.83	454 ng/ml	0.72	0.74	7.26	48	16	19	46	(25)
Meng <i>et al.</i> , 2015	Serum	0.89	0.82-0.97	93.5 ng/ml	0.83	0.84	25.20	28	5	6	27	(31)
	Urine	0.99	0.89-1.00	117.5 ng/ml	0.94	0.91	154.67	32	3	2	29	
Nga <i>et al.</i> , 2015	Urine	0.83	0.64-0.81	3.36 ng/ml	0.77	0.66	6.30	26	16	8	31	(30)
Niu <i>et al.</i> , 2015	Urine	0.91	NR	NR ^a	0.88	0.87	44.47	23	5	3	29	(29)
Patel <i>et al.</i> , 2016	Urine	0.81	0.73-0.89	34.32 ng/ml	0.86	0.81	26.31	76	13	12	54	(26)
Rocha <i>et al.</i> , 2018	Urine	0.61	0.48-0.73	13.3 ng/ml	0.92	0.93	139.75	43	2	4	26	(22)
Shang <i>et al.</i> , 2017	Serum	0.69	0.50-0.88	2.37 ng/ml	0.91	0.47	9.33	32	8	3	7	(24)
	Urine	0.83	0.70-0.97	4.85 ng/ml	0.78	0.87	21.94	27	2	8	13	
Shapiro <i>et al.</i> , 2010	Plasma	0.82	0.76-0.88	NR	0.96	0.51	23.00	23	21	1	21	(43)
Wang HX <i>et al.</i> , 2014	Plasma	0.86	0.83-0.90	119.30 ng/ml	0.79	0.80	15.75	30	10	8	42	(35)
Wang and Zhang, 2014	Serum	0.83	0.79-0.87	162.2 ng/ml	0.88	0.80	30.00	25	5	3	18	(34)
	Urine	0.81	0.71-0.91	150 ng/ml	0.79	0.90	38.50	22	2	6	21	
Wu <i>et al.</i> , 2019	Serum	0.84	0.74-0.94	NR	0.79	0.81	15.97	23	6	6	25	(5)
Xing <i>et al.</i> , 2013	Serum	0.86	0.77-0.94	70 ng/ml	0.85	0.87	39.60	30	5	5	33	(37)
	Urine	0.93	0.88-0.93	101.5 ng/ml	0.93	0.89	90.67	32	4	3	34	

Table II. Continued.

Author, year	Source	AUC	95% CI	Cut-off value	Sensitivity	Specificity	DOR ^b	TP, n	FP, n	FN, n	TN, n	(Refs.)
Zheng <i>et al.</i> , 2017	Plasma	0.82	0.75-0.90	171 ng/ml	0.79	0.75	11.49	41	24	11	74	(23)
Zhou <i>et al.</i> , 2014	Urine	0.80	0.71-0.93	85 ng/ml	0.78	0.80	14.76	36	20	10	82	(33)
Yan <i>et al.</i> , 2011	Urine	0.93	0.88-0.98	65 ng/ml	0.95	0.86	105.75	54	8	3	47	(42)
Yang <i>et al.</i> , 2019	Serum	0.78	0.71-0.86	69.7 ng/ml	0.72	0.73	6.87	51	23	20	62	(20)
Zhang <i>et al.</i> , 2015	Serum	0.88	NR	NR	0.90	0.99	447.86	27	0	3	28	(28)

^aThe cut-off value of NGAL_u was 52 $\mu\text{g/g}\cdot\text{Cr}$. The unit $\mu\text{g/g}\cdot\text{Cr}$ cannot be convert to ng/ml, thus no specific data was presented in table. ^bDOR=(sensitivity x specificity)/(1-sensitivity) x (1-specificity). AKI, acute kidney injury; AUC, area under the curve; DOR, diagnostic odds ratio FP, false positive; FN, false negative; TP, true positive; TN, true negative; NGAL, neutrophil gelatinase-associated lipocalin; NR, not reported.

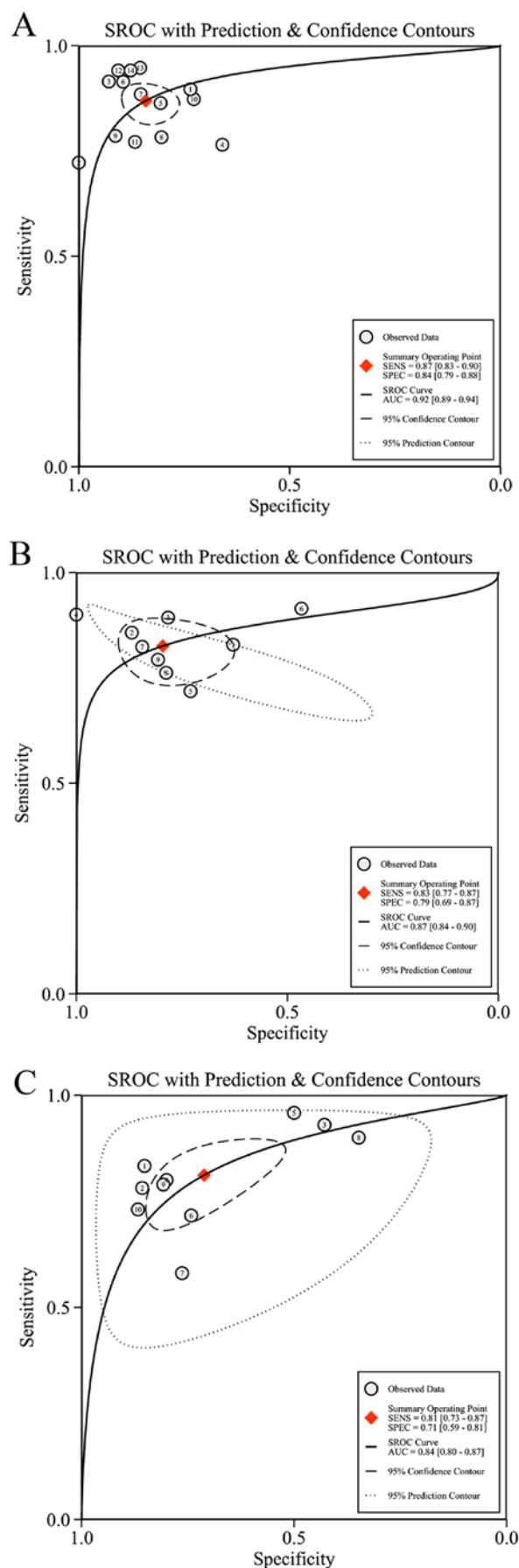


Figure 4. SROC for each type of NGAL assay. SROC curves of (A) urine NGAL, (B) serum NGAL and (C) plasma NGAL. SROC, summary receiver operating characteristic curve; NGAL, neutrophil gelatinase-associated lipocalin; AUC, area under the curve; SENS, sensitivity; SPEC, specificity.

Table III. Result of meta-regression, subgroup analysis.

Source	Number of studies	Sensitivity (95% CI)	P-value	Specificity (95% CI)	P-value
Plasma NGAL					
Prospective	3	0.89 (0.82-0.95)	<0.01	0.71 (0.52-0.91)	0.36
Non-prospective	7	0.76 (0.70-0.82)		0.74 (0.62-0.85)	
Urine NGAL					
Prospective	7	0.86 (0.82-0.90)	<0.01	0.74 (0.69-0.78)	<0.01
Non-prospective	2	0.87 (0.80-0.95)		0.82 (0.76-0.89)	

Table IV. Result of sensitivity analysis.

A, Serum NGAL						
Included studies	Sensitivity	I ² (%)	P-value	Specificity	I ² (%)	P-value
All	0.83 (0.77-0.87)	32.29	0.17	0.79 (0.69-0.87)	69.86	0.00
Without Zhang <i>et al</i> (23)	0.82 (0.76-0.86)	22.40	0.25	0.75 (0.68-0.82)	53.70	0.03
B, Urine NGAL						
Included studies	Sensitivity	I ² (%)	P-value	Specificity	I ² (%)	P-value
All	0.87 (0.83-0.90)	42.06	0.05	0.84 (0.79-0.80)	60.16	0.00
Without Mårtensson <i>et al</i> (44)	0.88 (0.84-0.91)	38.37	0.08	0.82 (0.78-0.86)	52.28	0.01
C, Plasma NGAL						
Included studies	Sensitivity	I ² (%)	P-value	Specificity	I ² (%)	P-value
All	0.81 (0.73-0.87)	61.32	0.01	0.71 (0.59-0.81)	86.17	0.00
Without Hjortrup <i>et al</i> (32)	0.83 (0.75-0.88)	48.24	0.05	0.71 (0.57-0.82)	87.21	0.00

and the pooled negative likelihood ratio (NLR) was 0.16 (95% CI, 0.12-0.20; Table II). Using a random effect model, the DOR was 35 (95% CI, 21-58). There was no threshold effect, as indicated by Spearman correlation analysis ($\rho=0.50$; $P=0.25$; data not shown). An SROC analysis was conducted to evaluate the diagnostic accuracy of urine NGAL (Fig. 4A). An AUC of 0.92 was obtained from the SROC curve, suggesting that urine NGAL achieved high diagnostic accuracy in diagnosing sepsis-AKI, due to the observation that $AUC > 0.9$.

Estimation of the inconsistency index for sensitivity and specificity ($I^2=42.06\%$ and 60.16% , respectively; $P=0.07$ and 0.01 , respectively; Fig. 3A) indicated that there was heterogeneity in the pooled specificity of urine NGAL between the included studies. Therefore, a subgroup analysis and meta-regression were conducted based on the study design (prospective and non-prospective; Table III). The study design significantly affected the results of sensitivity and specificity. Indeed, the use of a prospective design resulted in a significantly lower sensitivity ($P \leq 0.01$) and specificity ($P \leq 0.01$), compared with a non-prospective design.

Diagnosis accuracy of serum NGAL. A total of nine studies reported the use of serum NGAL. The pooled sensitivity for these studies in the diagnosis of sepsis-related AKI was 0.83 (95% CI, 0.77-0.87), whereas the pooled specificity was 0.79 (95% CI, 0.69-0.87; Fig. 3B). The pooled PLR was 4.00 (95% CI, 2.6-6.2), while the pooled NLR was 0.22 (95% CI, 0.16-0.30). The DOR was 18 (95% CI, 9-36) with higher values indicating better discriminatory performance. An SROC analysis was carried out to evaluate the diagnostic accuracy of serum NGAL, demonstrating an AUC of 0.87 (95% CI, 0.84-0.90; Fig. 4B). There was no notable threshold effect in the nine studies included in this meta-analysis ($\rho=0.34$; $P=0.12$; data not shown).

An I^2 of 32.29% for sensitivity ($P=0.17$) and 69.86% for specificity ($P < 0.001$; Fig. 3B) indicated that there was a significant heterogeneity in the pooled specificity in the included studies. A sensitivity analysis was conducted to eliminate factors that influence of heterogeneity. In the interpretation of the heterogeneity of the diagnostic accuracy of serum NGAL, sensitivity analysis suggested that the study by Zhang *et al* (28) had an impact on heterogeneity. Omitting the

study by Zhang *et al* (28) decreased the I^2 both in sensitivity (from 31.29 to 22.4%; $P=0.25$) and specificity (from 69.86 to 53.70%; $P=0.03$; Table IV). The value of I^2 in the pooled specificity reduced by 16% but the heterogeneity did not disappear.

Diagnostic accuracy of plasma NGAL. In total, 10 studies reported the use of plasma NGAL for AKI diagnosis. These studies had a pooled sensitivity of 0.81 (95% CI, 0.73-0.87) and a pooled specificity of 0.71 (95% CI, 0.59-0.81; Fig. 3C). The pooled PLR was 2.8 (95% CI, 2.0-3.9) and the pooled NLR was 0.26 (95% CI, 0.20-0.36). The DOR was 11 (95% CI, 7-16), which was the worst performer among the three NGALs tested using a random effect model. In addition, the AUC obtained from SROC analysis was 0.84 (95% CI, 0.80-0.87; Fig. 4C). There was no notable threshold effect in the meta-analysis ($q=-0.93$; $P=0.87$; data not shown). The estimation of sensitivity and specificity ($I^2=61.32$ and 86.17%, respectively; $P=0.01$ and <0.001 , respectively; Fig. 3C) indicated that there was heterogeneity between the studies. Thus, a subgroup analysis was performed based on study design (prospective and non-prospective). Meta-regression and subgroup analysis revealed that study design had a significant effect on the diagnostic accuracy of plasma NGAL. The use of a prospective design resulted in a significantly higher sensitivity ($P\leq 0.01$) but no effect on specificity ($P=0.36$), compared with those from a non-prospective design (Table III).

Evaluation of publication bias. Publication bias was analysed using a Deeks' funnel plot and an asymmetry test. No publication bias was detected among the studies in the urine ($P=0.16$), serum ($P=0.052$) and plasma NGAL ($P=0.16$) groups.

Discussion

The morbidity and mortality of patients with sepsis in intensive care units remain high (2). In addition, AKI is among the most severe complications of sepsis (4). NGAL is the most extensively researched biomarker for the diagnosis of AKI in blood and urine specimens. Zhang *et al* (6) previously examined the diagnostic values of plasma and urine NGAL using meta-analysis. However, the number of studies included in their analysis was limited, and the reported high diagnostic value for urine NGAL was later questioned by Törnblom *et al* (47). Moreover, in the Zhang *et al* (6) study, the role of serum NGAL in diagnosing AKI was not examined. Thus, the optimal source of NGAL for the diagnosis of sepsis-induced AKI remains unknown.

The aim of the present meta-analysis was to assess the diagnostic accuracy of serum, plasma and urine NGAL among patients with suspected sepsis. In the present study, urine NGAL presented improved performance compared with serum and plasma, with a relatively high sensitivity, specificity and DOR, as well as the highest AUC. The present findings further support the notion that urine NGAL can predict sepsis-related AKI, which is consistent with the prospective cohort studies carried out by da Rocha *et al* and Patel *et al* (22,26). Urine NGAL is an independent predictor of AKI, as it is not affected by the presence of sepsis (48). By contrast, NGAL levels in the bloodstream of patients with sepsis may increase due to

injury to the kidney, thereby influencing the diagnosis of AKI through plasma and serum specimens (49). Additionally, urine testing represents a convenient, fast and non-invasive collection technique. Thus, the majority of patients would be eligible for diagnosis of AKI through the urine, especially paediatric patients. Notably, compared with serum creatinine as a diagnostic reference, the time to diagnose AKI with urine NGAL is 2 h shorter (45).

In the present study, serum NGAL also demonstrated a relatively high AUC. Although only a limited number of studies included in the present meta-analysis reported the use of serum NGAL, a recent prospective cohort study has demonstrated that the combined performance of serum and urine NGAL can increase the early diagnostic accuracy of sepsis-induced AKI (50). Furthermore, previous studies by Meng *et al* and Xing *et al* (31,37) demonstrated that the predictive performance of serum and urine NGAL for sepsis-related AKI increased significantly in combination compared with that in either alone. Notably, AKI diagnosis through serum NGAL would be available to patients suffering from oliguria or other conditions that cause inconvenience for urine sampling.

The use plasma NGAL for the prediction of AKI in septic patients remains controversial. There is no consensus on the predictive ability of plasma NGAL according to previous studies (40,44). Mårtensson *et al* (44) reported a poor predictive ability for plasma NGAL and suggested that NGAL levels in the plasma may be affected by other non-renal factors such as inflammation. Aydođdu *et al* (40) demonstrated that concurrent sepsis could increase the levels of plasma NGAL in the absence of AKI and thus, the diagnostic accuracy of plasma NGAL may have been corrupted. By contrast, previous studies by Huang *et al* and Shapiro *et al* (27,43) suggested that plasma NGAL could predict sepsis-related AKI. The different locations in which these studies were conducted may have led to the discrepancies in study outcomes, as suggested by Md Ralib *et al* (25). In the present meta-analysis, plasma NGAL was less useful than other NGAL sources in diagnosing sepsis-related AKI. Indeed, compared with urine and serum specimens, plasma NGAL presented the poorest sensitivity, specificity and AUC.

Nevertheless, the present study has certain limitations that should be taken into consideration when interpreting its findings. High heterogeneity performed in the meta-analysis for plasma NGAL was a substantial problem. Although sensitivity analysis omitted studies that affected heterogeneity, the results only changed slightly. Subgroup analyses were performed to identify factors that influenced heterogeneity, yet the causes of heterogeneity could not be determined. Moreover, as aforementioned, there is still a controversial in the use of plasma NGAL. Further prospective studies focusing on plasma NGAL should also be considered in the future.

In conclusion, the present findings suggested that urine NGAL was a robust diagnostic biomarker of AKI, with the highest sensitivity, specificity and AUC. However, each specimen type had its own advantages and weaknesses. For instance, the use of serum and plasma NGAL in combination may enhance the strengths and reduce the deficiencies of each, resulting in a more accurate diagnosis. Further studies are encouraged to provide more robust evidence.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

HZ analysed the research data and was the major contributor in the preparation and writing of the manuscript. JC collected the original data and quality assessment and conducted the data processing of the meta-analysis. YL collected the original data and quality assessment. JS is responsible for interpretation of data for the work, visualization and tables and figures production. JL made substantial contributions to the conception and design of the study and drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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