Original Article

Neutrophil gelatinase-associated lipocalin as a predictive biomarker of acute kidney injury in COVID-19 infection: A systematic review and meta-analysis

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Abstract

Background: Coronavirus 2019 (COVID-19) is an infectious disease caused by a novel coronavirus, SARS-CoV-2. Acute kidney injury (AKI) affects approximately 20–40% of patients with COVID-19 admitted to the intensive care unit (ICU), and it is a complication that has been linked to increased morbidity and mortality. Neutrophil gelatinase-associated lipocalin (NGAL) is a biomarker of acute kidney injury. **Methods:** Articles were searched from databases such as PubMed, Google Scholar, and Cochrane Library till June 2023. Pooled sensitivity, specificity, area under the curve (AUC), diagnostic odds ratio (DOR), and summery receiver operating curve (SROC) were calculated with 95% confidence interval. I^2 statistics and Chi-square test were used to look for the heterogeneity in between studies. Meta-regression was conducted to look for the source of heterogeneity and GRADE analysis was performed to look for the certainty of evidence. **Results:** Altogether, eight studies were selected (4 serum/5 urine), out of which one study had both serum and urine NGAL data. The total sample size was 1,067 (349 serum/718 urine). For serum and urine NGAL, the pooled sensitivity was 0.79 (95% CI: 0.72–0.84) and 0.75 (95% CI: 0.68–0.80), pooled specificity was 0.87 (95% CI: 0.81–0.91) and 0.85 (95% CI: 0.77–0.91), DOR was 24 (95% CI: 14–43), and 17 (95% CI: 9–32) and AUC was 0.90 (95% CI: 0.87–0.92) and 0.80 (95% CI: 0.76–0.83), respectively. **Conclusion:** Both serum and urine NGAL have favourable pooled sensitivity, specificity, DOR and AUC for the diagnosis of AKI in COVID-19 infection, however, with low certainty of evidence.

Keywords: AKI, COVID-19 infection, meta-analysis, NGAL, systematic review

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Introduction

COVID-19 also known as SARS-CoV-2 is an infectious disease caused by a novel corona virus.[1] Usually, it presents as features

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of acute cold with initial symptoms of cough, fever, headache, blocked nose, myalgia, sore throat, etc., Some patients may develop diarrhoea and vomiting. Increased morbidity and mortality are due to the involvement of the respiratory tract as acute respiratory distress syndrome (ARDS) needing intensive care unit (ICU) admission.[2,3] About 20-40% ICU admission cases may have renal involvement in the form of acute kidney injury (AKI) due to multifactorial causes such as secondary inflammatory response causing cytokine storm and is responsible for tubular damage, appearance of microthrombi and also by direct viral invasion of the kidney leading to increased morbidity and mortality further.[4-7] Direct viral invasion is facilitated by an angiotensin converting enzyme-2 (ACE-2)-dependent pathway causing infection of the renal tubular epithelium and podocytes.[8-12] This finally leads to the loss of kidney function sharply, which can be regularly monitored by measuring an increased level of serum creatinine. However, we can detect serum creatinine level only after certain time has advanced after AKI. Hence, we cannot detect substantial kidney damage in early phase. Additionally, exact changes in the level of serum creatinine cannot be detected following incomplete or focal kidney damage due to compensatory increase in uninjured nephrons leading to maintenance of rising serum creatinine level toward normal. Not only that, serum creatinine level can be affected by different patient's characteristics such as age, gender, muscular build along with anabolic and catabolic activity, amount of fluid in the body, type of diet consumption etc.[13] Neutrophil gelatinase-associated lipocalin (NGAL), discharged by the epithelial cells of damaged kidney, attaining its peak level in the blood about 6 h after acute renal injury, is an additional biomarker of AKI.

In a meta-analysis by Zhou *et al.* (2021),[14] researchers assessed the diagnostic accuracy of NGAL in diagnosing acute kidney injury (AKI) among suspected sepsis patients. They analysed data from 28 studies to evaluate urine, serum, and plasma NGAL. Following analysis, urine NGAL demonstrated a sensitivity of 0.87 and specificity of 0.84 with a diagnostic odds ratio (DOR) of 35 and area under the curve (AUC) of 0.92. Serum NGAL and plasma NGAL demonstrated a sensitivity of 0.83 and 0.81, specificity of 0.79 and 0.71, DOR of 18 and 11, and an AUC of 0.87 and 0.84 respectively. This study achieved that urine NGAL is a robust biomarker for AKI diagnosis, offering high sensitivity and specificity. Although serum and plasma NGAL also showed diagnostic potential, urine NGAL outperformed them both. Combining serum and urine NGAL could enhance diagnostic accuracy further. So, in this meta-analysis, we have looked for the diagnostic test accuracy of serum and urine NGAL to diagnose AKI in COVID-19 infection.

Methods

The protocol for this meta-analysis was registered in PROSPERO 2023 with the registration number CRD42023400330 and it was carried out as per the guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA).[15]

PICO Criteria: Patients (P) were COVID-19 infected subjects with complication of acute kidney injury (AKI) as mentioned in the incorporated studies for this meta-analysis. AKI was defined as per the KDIGO criteria.[16] Index test (I) is measuring value of urinary or serum NGAL with their cut-off value as given in the selected studies. Comparison (C): Serum creatinine reference standard for AKI diagnosis was used to compare and segregate AKI and non -AKI patients. Outcome (O) is the diagnostic accuracy of serum and urine NGAL to detect AKI in COVID-19 infection.

Study selection

Inclusion Criteria: Age group of participants more than 18 years, clinically diagnosed COVID-19 cases with AKI, published in a peer-reviewed journal, investigated the diagnostic accuracy of urinary or serum NGAL in predicting AKI in COVID-19 patients, reported sensitivity, specificity, or other measures of diagnostic accuracy and provided data on the reference standard for AKI diagnosis (e.g. serum creatinine).

Exclusion Criteria: Editorial case reports, preprints, letter to editor, abstract, literature in other language, conference proceedings.

Information sources: The articles admissible for this meta-analysis including their references, published till June 2023 were sought from different databases such as PubMed, Google scholar and Cochrane library.

Search strategy

A comprehensive search of electronic databases was conducted using a combination of medical subject headings (MeSH) terms and keywords related to urinary and serum NGAL, acute kidney injury (AKI), and COVID-19 infection. The search strategy was tailored to each database and included terms such as "NGAL," "neutrophil gelatinase-associated lipocalin," "acute kidney injury," "COVID-19," "diagnosis," "accuracy," "sensitivity," and "specificity." The studies were finalised and followed by retrieval of necessary data by two individual authors. Any disparity in opinion were sort out by mutual consent and argument.

Data Extraction: The data retrieved from the admissible studies were as follows: name of the first author, year of publication, country, ethnicity, type of data (prospective or retrospective), mean age, gender, NGAL measurement methods, serum, and urine NGAL mean, diagnostic cut-off level of NGAL, reference standard for AKI diagnosis, sensitivity, specificity, and true-positive, false-negative, true-negative and false-positive data. In case of lack of any information, the term "NA" (not available) was used in the table.

Quality Assessment: Under four key disciplines, that is, patient selection, index test, reference standard and flow and timing, which were further graded as low, high and unclear, the quality of selected articles were assessed using the QUADAS-2 tool (Bristol, England, University of Bristol).[17] Out of these four domains, the first three were used for applicability concern.

Statistical analysis

Pooled sensitivity, specificity, area under the curve (AUC) and diagnostic odds ratio (DOR) with 95% confidence interval (CI) were worked out for the diagnostic accuracy of serum and urine NGAL separately to diagnose AKI in COVID-19 infection using the random effect model if the heterogeneity was more than 50%. To determine the discriminatory accuracy of serum and urine NGAL to diagnose AKI in COVID-19 infection, AUC was calculated from the summary receiver operating curve (SROC) individually for serum and urine NGAL. I^2 statistics and Chi-square test were used to assess the heterogeneity in between incorporated studies in this meta-analysis. A P value < 0.05 was treated as significant. Positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were computed to find the clinical usefulness of NGAL by Fagon plot.

Meta-regression was executed to search for the possible source of heterogeneity. A P value < 0.05 for a given variable following meta-regression would be considered significant to execute sub-group analysis. Deek's funnel plot was used to look for publication bias in the incorporated studies. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis was used to know the certainty of evidence of serum and urine NGAL to be used as a biomarker for the early diagnosis of AKI in COVID-19 infection. For all these statistical analyses, STATA version 13 (College Station, TX: StataCorp LLC) was used and for risk of bias assessment, Review Manager version 5.4 (Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration) was used.

Ethical considerations

The study did not involve any primary data collection and did not collect any personal information from participants. Therefore, ethical approval was not required.

Results

A total of 5010 records were identified by PubMed, Google Scholar, and Cochrane Library. Out of these, the majority were eliminated by looking the title and abstract. Following that, only 27 articles continued to exist for full-text review. In total, 21 articles were finally eliminated due to varied grounds as specified in the PRISMA 2020 flow diagram [Figure 1]. Two studies[18,19] were identified from websites and found to be eligible for our meta-analysis. So, eight studies remained for final analysis, out of which 1 letter to the editor byKomaru *et al.*[20] having desired data was also included due to the absence of sufficient number of studies in the literature. Among these studies, four studies[18,19,21,22] corresponded to serum NGAL, whereas five studies[18,20,23-25] corresponded to urine NGAL. One study by Bhardwaj *et al.*[18] had both serum and urine NGAL data [Figure 1].

Characteristics of studies

The total sample size for serum NGAL studies was 349 and varied from 52 to 105, whereas for urine NGAL, it was 718 and varied from 17 to 371. All were prospective studies except one study by Komaru *et al.*,[20] which was a retrospective study. The mean age of subjects belonging to serum NGAL studies varied

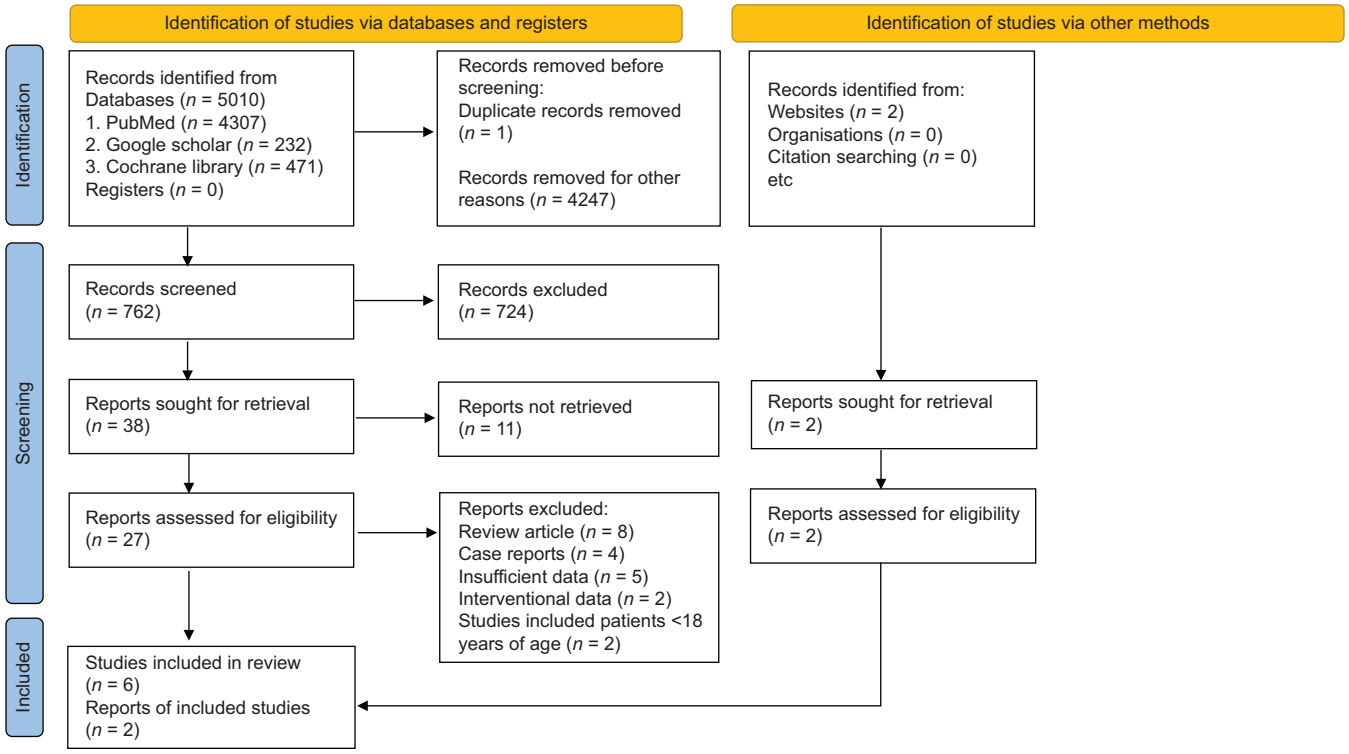

Figure 1: PRISMA flow diagram representing the selection and inclusion of different studies. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

from 53.88 to 61.4 years, whereas the male percentage was 54.27 to 74%. The age of subjects belonging to urine NGAL studies varied from 53 to 69 years (both values mentioned as median in the literature) and male percentage was from 47.7 to 82.4%. Table 1 shows the characteristics of these studies.

Methodological quality

Serum NGAL

We did not find any definite particular describing the method for patient selection in these studies. Moreover, these studies were biased about the index test as it is not mentioned that whether the index test results were interpreted without knowledge of the results of the reference standard test or not and, due to lack of a pre-specified threshold for the index test. About 75% tests were biased about the reference standard due to the absence of information about whether the reference standard results interpreted without knowledge of the results of index tests or not. The full description of the evaluation by RevMan 5.4 is given in Figure 2 and Supplementary Figure 1.

Urine NGAL

Only one study by Xu *et al.*[23] out of five had reported about the method for patient selection. All studies were biased about the index test as (1) it was not clear that whether the index test results were interpreted without knowledge of the results the reference standard test or not and (2) due to lack of a pre-specified threshold for the index test. About 40% tests were biased about the reference standard due to the absence of information about whether the reference standard test results were interpreted without knowledge of the results of index test or not. The full description of the evaluation by RevMan 5.4 is given in Figure 2 and Supplementary Figure 1.

Diagnostic performance of Serum NGAL and Urine NGAL for diagnosis of AKI in Covid 19 Infection

For the diagnosis of AKI in COVID-19 infection, sensitivities and specificities of serum and urine NGAL separately are shown in Table 1. We obtained inspiring results both for serum and urine NGAL regarding their diagnostic accuracy to identify AKI with pooled sensitivity of 0.79 (95% CI: 0.72–0.84) and 0.75 (95% CI: 0.68–0.80), specificity of 0.87 (95% CI: 0.81–0.91) and 0.85 (95% CI: 0.77–0.91) [Figure 3] and DOR 24 (95% CI: 14–43) and 17 (95% CI: 9–32), respectively, for serum NGAL and urine NGAL. Similarly, we obtained promising results both for serum and urine NGAL regarding their efficiency to differentiate between AKI and non-AKI patients in COVID-19 infection with the SROC curve value of 0.90 (95% CI: 0.87–0.92) and 0.80 (95% CI: 0.76–0.83), respectively, for serum NGAL and urine NGAL [Figure 4]. Regarding serum NGAL, heterogeneity for the pooled sensitivity was 33.62 (CI = 0.00–100.00) and for pooled specificity, it was 0.00 (CI = 0.00–100.00). However, in both the cases, confidence interval (CI) was large; hence the precision became less. If we assume the pre-test probability of 20% for identifying AKI with the help of serum NGAL depending upon our clinical exposure, then it will enhance the post-test probability

Table 1: Characteristics of studies

First author	Year	Data	Country	Race	AKI	Non-AKI	Mean age (years)	Sex (%) Males	Reference standard	Cut off (ng/mL)	NGAL assay method	SN (%)	SP (%)	TP	FN	TN	FP
Sara Bülow Anderberg[21]	2021	P	Sweden	C	67	36	60.5+14.1	74	Serum Creatinine	191 (S)	ELISA technique	78.6	88.7	53	14	32	4
Anubhuti Bhardwaj[18]	2021	P	India	A	60	45	58.71	54.27	Serum Creatinine	91 (S)	ELISA kit-ELABSCIENCE® using the sandwich ELISA principle	85	86.7	51	9	39	6
Naomi Pode Shakked[22]	2022	P	United States	C	22	30	53.88	59.6	Serum Creatinine	120 (S)	Particle-enhanced turbidimetric immunoassay	64	93	14	8	28	2
Sanaa F. Wasfy[19]	2022	P	Egypt	C	25	64	61.40	57.29	Serum Creatinine	242.5 (S)	ELISA immuno-enzymatic assay	76	82.8	19	6	53	11
Komaru Y[20]	2020	R	Japan	A	10	7	69 med	82.4	Serum creatinine	73 (U)	Chemiluminescent immunoassay	70	86	7	3	6	1
Katherine Xu[23]	2021	P	US	C	155	216	NA	NA	Serum Creatinine	150 (U)	ELISA using NGAL: BioPorto, (KIT036) NGAL gRAD dipsticks (BioPorto)	75	80	116	39	173	43
Li He [24]	2021	P	China	A	20	154	63.59+13.79	47.7	Serum Creatinine	150 (U)	Bedside dry fluorescence immunoanalyzer (model tz-320; Relia, Jiangsu, China)	80	92.9	16	4	143	11
Anubhuti Bhardwaj[18]	2021	P	India	A	60	45	58.71	54.27	Serum Creatinine	80.6 (U)	NGAL was tested by the ELISA kit-ELABSCIENCE® using the sandwich ELISA principle	75	85	45	15	38	7
Gustavo Casas-Aparicio[25]	2022	P	Mexico	C	25	26	53 med	58.8	Serum Creatinine	45 (U)	Using the NGAL kit and the Abbott™ ARCHITECT™ analyzer.	64.7	77.4	16	9	20	6

P- Prospective, R- Retrospective, A- Asian, C- Caucasian, AKI- Acute kidney injury, med- median, NA- Not available, ng/mL- nanogram per milli-litre, S- Serum, U- Urine, NGAL- Neutrophil Gelatinase-Associated Lipocalin, ELISA- - Enzyme linked immunosorbent assay, SN- Sensitivity, SP- Specificity, TP- True positive, FN- False negative, TN- True negative, FP- False positive

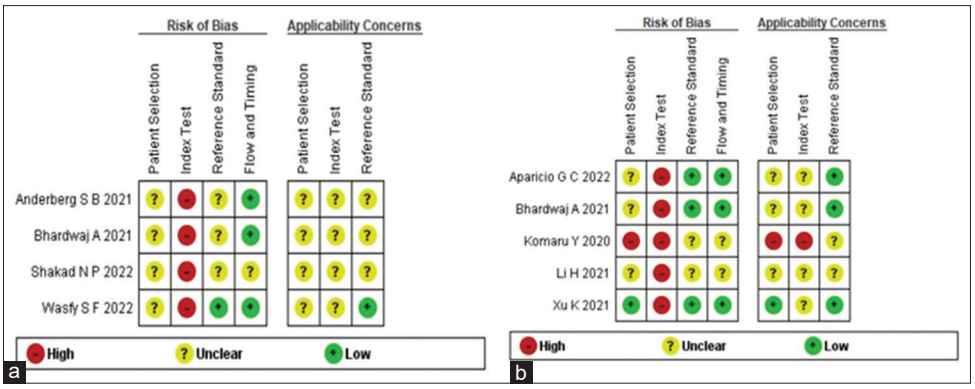

Figure 2: Risk of bias and applicability concerns summary, review author's judgment about each domain for each included study for serum (a) and urine (b)

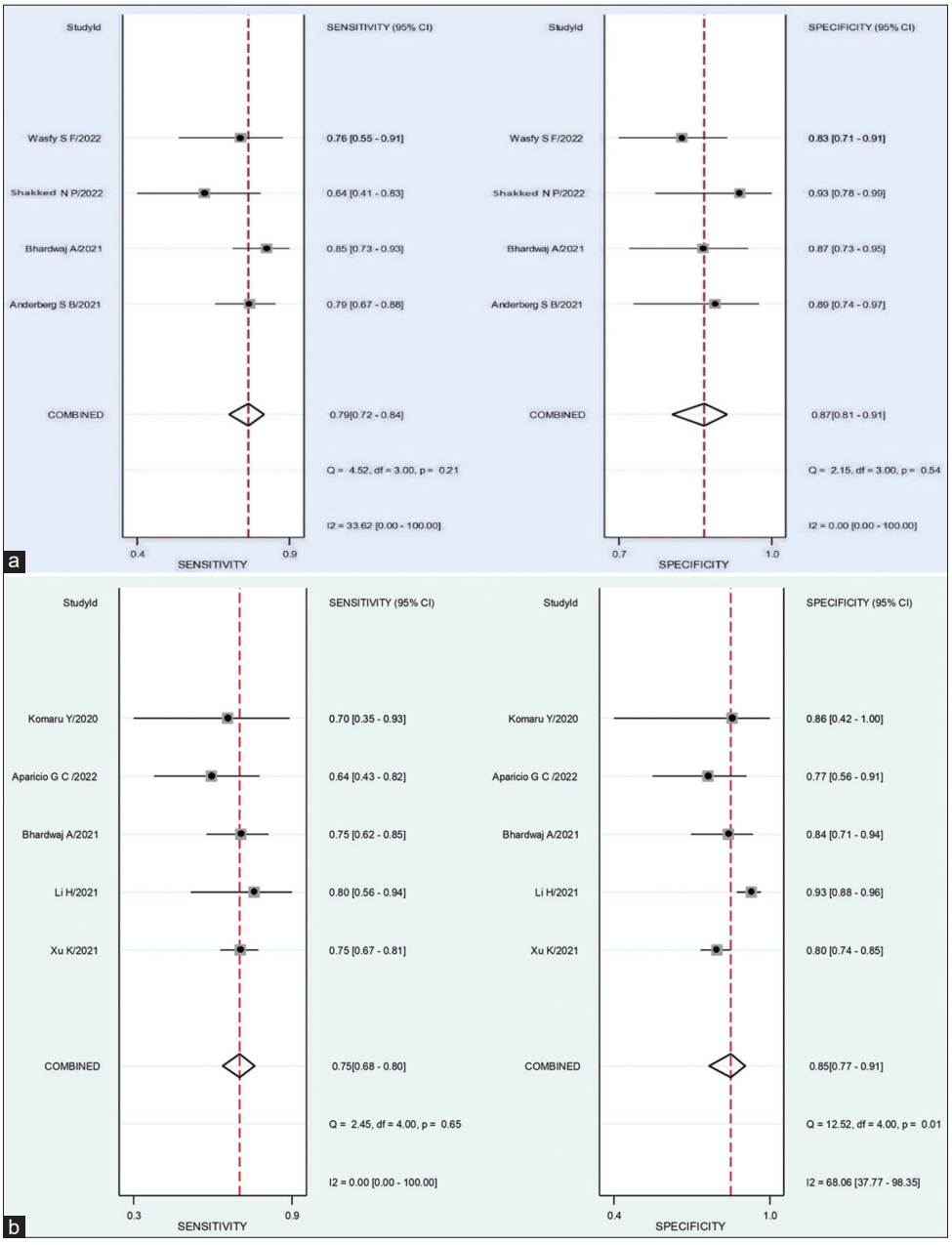

Figure 3: Forest plot of pooled sensitivity and specificity of serum (a) and urine (b) NGAL for the diagnosis of AKI in COVID-19 infection. NGAL, neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury; COVID-19, coronavirus disease 2019

up to 60% with positive likelihood ratio (PLR) of 6 (95% CI: 4.1–8.8) and negative likelihood ratio (NLR) of 0.24 (95% CI: 0.18–0.33) and a post-test probability of 6% as observed in the Fagan plot [Supplementary Figure 2]. Regarding urine NGAL, heterogeneity for the pooled sensitivity was 0.00 (CI = 0.00–100.00), for the pooled specificity it was 68.06 (CI = 37.77–98.35).

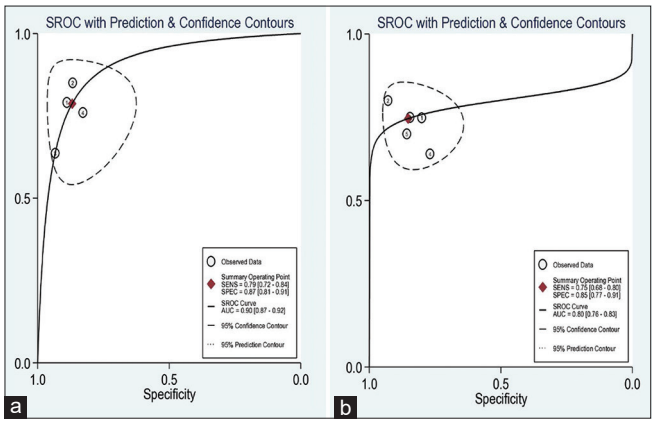

Figure 4: Summary ROC curve with confidence and prediction contours showing discriminatory power of serum (a) and urine (b) NGAL in the diagnosis of AKI in COVID-19 infection. X-axis, specificity of serum (a) and urine (b) NGAL for its discriminating accuracy to diagnose AKI in COVID-19 infection. Y-axis, the sensitivity of serum (a) and urine (b) NGAL for its discriminating accuracy to diagnose AKI in COVID-19 infection. ROC, receiver operating characteristic; NGAL, neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury; COVID-19, coronavirus disease 2019

In the case of heterogeneity for sensitivity, CI was large; hence, precision became less and heterogeneity is more than 50% in the case of specificity. Hence, it was significant. Again, if we assume the pre-test probability of 20% to identify AKI with the help of urine NGAL depending upon our clinical exposure, the post-test probability will be enhanced up to 56% with a PLR of 5 (95% CI: 3.2–8) and NLR of 0.30 (95% CI: 0.23–0.39) with a post-test probability of 7% as observed in the Fagan plot [Supplementary Figure 2].

Publication bias

We did not find any notable publication bias both in the case of serum NGAL studies ($P = 0.41$) [Supplementary Figure 3] and urine NGAL studies ($P = 0.74$) [Supplementary Figure 3] after the evaluation of risk of publication bias by Deek's funnel plot as in both the cases P value was > 0.05 hence, not significant.

Meta-regression

To look for the source of heterogeneity, meta-regression was executed. For serum NGAL, variables for meta-regression were sample size (<100/>100), cut-off for serum NGAL (<130/>130 ng/mL), race (Asian/Caucasian), diagnostic method (ELISA/non-ELISA) and sex (male/female). Although variables for urine NGAL were the type of study or data (prospective/retrospective), sample size (<100/>100), cut-off for urine NGAL (<100/>100 ng/mL), race (Asian/Caucasian) and diagnostic method (ELISA/non-ELISA). All

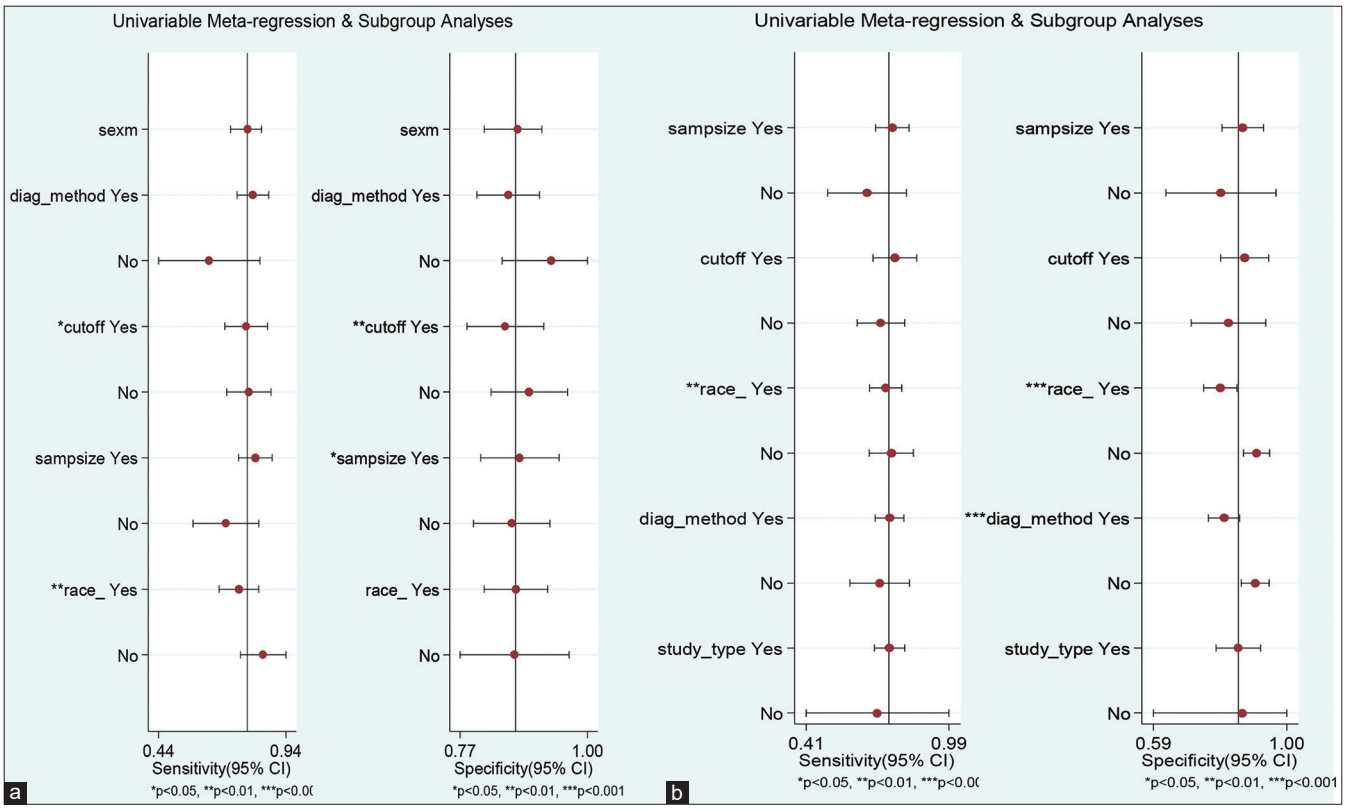

Figure 5: Meta-regression analysis to find the possible sources of heterogeneity for serum (a) and urine (b) NGAL. NGAL, neutrophil gelatinase-associated lipocalin

variables for serum and urine NGAL were categorical variables. The result for serum NGAL [Figure 5] showed that serum NGAL cut-off, sample size and race could be the possible source of heterogeneity, whereas the result for urine NGAL [Figure 5] showed that race and diagnostic method used to measure urine NGAL could be the possible source of heterogeneity. However, to analyse further for this source of heterogeneity, a sub-group analysis could not be performed due to lack of sufficient numbers of studies to form a sub-group.

GRADE analysis

GRADE analysis was conducted to look for the certainty of evidence to diagnose AKI in COVID-19 infection by the estimation of serum NGAL and urine NGAL separately. For serum NGAL, the certainty of evidence to diagnose AKI in COVID-19 infection was graded as low both for sensitivity and specificity [Supplementary Table 1], whereas for urine, NGAL was graded as low for sensitivity and very low for specificity [Supplementary Table 2].

Discussion

COVID-19 presents a significant challenge globally with a spectrum of clinical presentations starting from mild respiratory symptoms to severe acute respiratory failure with or without multiorgan involvement. It can be complicated by acute kidney injury (AKI), which is observed to be a frequent cause of increased morbidity and mortality in COVID-19 infection. So, understanding the pathophysiological mechanisms underlying COVID-19 infection-associated AKI is crucial for the early diagnosis and effective management. In this meta-analysis, having eight studies with a sample size of 1,067 patients, we evaluated the diagnostic utility of NGAL as a biomarker for AKI in COVID-19 infection. NGAL, released from injured epithelial cells, has come out as an assuring biomarker for the early detection of AKI in various clinical settings [Zhou *et al.*, 2021].[14]

Our findings demonstrates that serum NGAL exhibit slightly higher diagnostic power than urine NGAL in diagnosing AKI in COVID-19 infection with a higher pooled sensitivity and specificity (79% and 87%, respectively) than urine NGAL (75% and 85%, respectively), higher AUC (0.90) than urine NGAL (0.80) and a higher DOR (24) than urine NGAL (17). Thereby, it implies that serum NGAL is slightly more sensitive and specific than urine NGAL in detecting AKI in COVID-19 infection. Higher AUC (1.125 times) than urine NGAL implies slightly better diagnostic accuracy than urine NGAL in detecting AKI in COVID-19 infection and a higher DOR (1.41 times) for serum NGAL than urine NGAL implies 1.41 times higher discriminatory accuracy for serum NGAL. Positive predictive value for serum NGAL was also higher (60%) than urine NGAL (56%) as per the Fagan nomogram [Supplementary Figure 2]. It means that the probability of AKI in COVID-19 infection was slightly higher (1.07 times) for patients who tested positive for serum NGAL than urine NGAL. Serum NGAL results lowered the probability of AKI in COVID-19-infected patients to as low as 6% when negative as compared to 7% of a negative urine NGAL result. PLR was also slightly higher for serum NGAL (6) than urine NGAL (5). It means that patients with confirmed AKI in COVID-19 infection had a slightly higher (1.2 times) chance of a high serum NGAL than urine NGAL, whereas NLR was lower for serum NGAL (0.24) than urine NGAL (0.30), meaning that the probability of patients with AKI in COVID-19 infection having negative serum NGAL result was about 80% lesser than for urine NGAL. These results slightly underscore the capability of serum NGAL as a valuable tool for the early identification of AKI in COVID-19 patients over urine NGAL.

To search for the source of heterogeneity, meta-regression was executed that showed that the racial variation could be the possible source of heterogeneity in both the cases of serum and urine NGAL. Although the sample size along with different cut-off values of serum NGAL to diagnose AKI in COVID-19 infection and different methods used to detect urine NGAL respectively could be the additional source of heterogeneity in serum NGAL and urine NGAL groups. However, due to the absence of sufficient number of studies to form a subgroup, a sub-group analysis could not be executed. However, both in the serum NGAL and urine NGAL groups, heterogeneity could be due to the presence of bias related to patient selection method, Index test, reference standard used as mentioned, in methodological quality sub-section of results and due to variations in patient population.

To judge for the certainty of evidence of serum NGAL and urine NGAL to diagnose AKI in COVID-19 infection, GRADE analysis was performed, which showed that serum NGAL has low certainty of evidence due to very serious risk of bias and serious inconsistency both for sensitivity and specificity [Supplementary Table 1]. Although urine NGAL has low certainty of evidence for sensitivity due to very serious risk of bias and serious inconsistency, whereas very low certainty of evidence for specificity owing to very serious risk of bias and inconsistency [Supplementary Table 2].

A meta-analysis conducted by Zhou *et al.*[14] in 2021 incorporating 28 studies for the diagnostic value of serum, plasma, and urine NGAL to identify AKI in patients with sepsis showed a superior diagnostic accuracy of urine NGAL to detect sepsis-related AKI as compared to serum and plasma NGAL. It exhibited higher sensitivity, specificity, DOR, and AUC. Independence of urine NGAL from the presence of sepsis enhanced its predictive value for AKI, unlike plasma and serum NGAL affected by kidney injury in septic patients. It is in contrary to our findings, where serum NGAL slightly outweighs over urine NGAL in detecting AKI in COVID-19 infection. Considering the fact that the incorporated studies and sample size in our meta-analysis was less, further good-quality and increased number of studies with more sample size, related to AKI in COVID-19 infection are required to address the issue of whether serum or urine NGAL is a better marker for AKI in COVID-19 infection.

Our meta-analysis is the first to analyse the diagnostic accuracy of serum as well as urine NGAL to detect AKI in COVID-19 infection. We have reported this meta-analysis as per the PRISMA guidelines and even the quality assessment of incorporated studies was conducted by the latest method to assess the diagnostic studies (QUADAS-2). Meta-regression was performed to look for the source of heterogeneity. To search for the publication bias, Deek's funnel plot was used, which did not found any publication bias. This strengthens the robustness of our findings and enhances their generalizability. The GRADE approach was used to find the certainty of evidence for serum and urine NGAL to be used as a biomarker of AKI in COVID-19 infection.

Despite the promising diagnostic accuracy of NGAL to detect AKI in COVID-19 infection, it is essential to acknowledge certain limitations. The number of studies and hence, the total sample size was less in our meta-analysis due to the absence of desired studies in the literature. Methodological quality assessment revealed biases in patient selection, index test interpretation and reference standard implementation over included studies, highlighting the need for standardized protocols in future research. A sub-group analysis could not be performed due to the absence of sufficient number of studies for the desired variables after meta-regression, which could had been helpful to identify the additional cause of heterogeneity. Additionally, there could be language bias as we have included articles in English language only.

Conclusion

In conclusion, our meta-analysis provides compelling evidence supporting the usefulness of NGAL as a diagnostic biomarker for AKI in COVID-19 infection. Serum and urine NGAL demonstrate favourable sensitivity, specificity, and diagnostic odds ratio, suggesting their potential for early detection and risk stratification in COVID-19 infection patients, however, with low certainty of evidence.

Ethics approval and consent to participate

Not applicable (PROSPERO registration done).

Consent for publication

All authors have read and approved the manuscript.

Availability of data and materials

All the data sheets are available with the authors and can be shared on request.

Authors' contributions

Study concept and design: MKP
Data search and retrieval: MKP, PD and NM
Analysis and interpretation of data: AK
Tables and figures: PK, PD, NM, MKP, and AK
Drafting of manuscript: MKP, PD and NM
Supervision: MKS, RTG, BM and PKC
Writing-original draft: MKP, PD and NM
Writing-review and editing: SK, DK, MLP, BM, RTG, MKS, RS, US, PKC, PK, AK, NM, PD and MKP.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: GRADE analysis for serum NGAL

Question: Should [Serum NGAL] be used to diagnose [AKI in Covid-19 infection] in [health problem]?

Sensitivity							0.79 (95% CI: 0.72 to 0.84)				
Specificity							0.87 (95% CI: 0.81 to 0.91)				
Prevalences			10%			15%			20%		
Outcome	**No of studies (No of patients)**	**Study design**	**Factors that may decrease certainty of evidence**					**Effect per 1,000 patients tested**			**Test accuracy CoE**
			Risk of bias	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication bias**	**Pre-test probability of 10%**	**Pre-test probability of 15%**	**Pre-test probability of 20%**	
True positives (patients with [AKI in Covid-19 Infection)	4 studies 349 patients	cross-sectional (cohort type accuracy study)	very serious	not serious	serious	not serious	all plausible residual confounding would reduce the demonstrated effect	79 (72-84)	119 (108-126)	158 (144-168)	⨁⨁◯◯ Low
False negatives (patients incorrectly classified as not having [AKI in Covid-19 Infection])								21 (16-28)	31 (24-42)	42 (32-56)	
True negatives (patients without [AKI in Covid-19 Infection])	4 studies 349 patients	cross-sectional (cohort type accuracy study)	very serious	not serious	serious	not serious	all plausible residual confounding would reduce the demonstrated effect	783 (729-819)	739 (689-774)	696 (648-728)	⨁⨁◯◯ Low
False positives (patients incorrectly classified as having [AKI in Covid-19 Infection])								117 (81-171)	111 (76-161)	104 (72-152)	

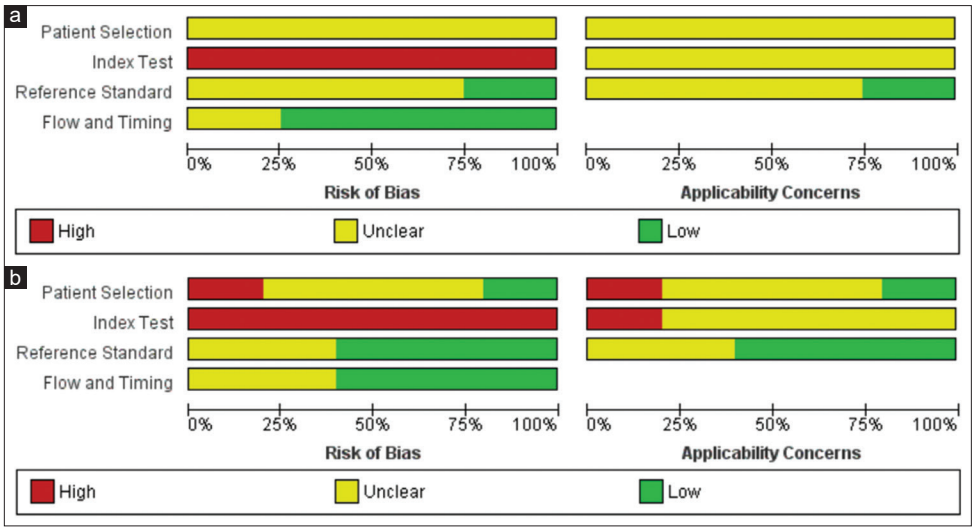
GRADE- grading of recommendations, assessment, development and evaluation; NGAL- Neutrophil gelatinase-associated lipocalin, CI- confidence interval, AKI- acute kidney injury, Covid-19- coronavirus disease 2019, No- number, CoE- certainty of evidence

Supplementary Table 2: GRADE analysis for urine NGAL

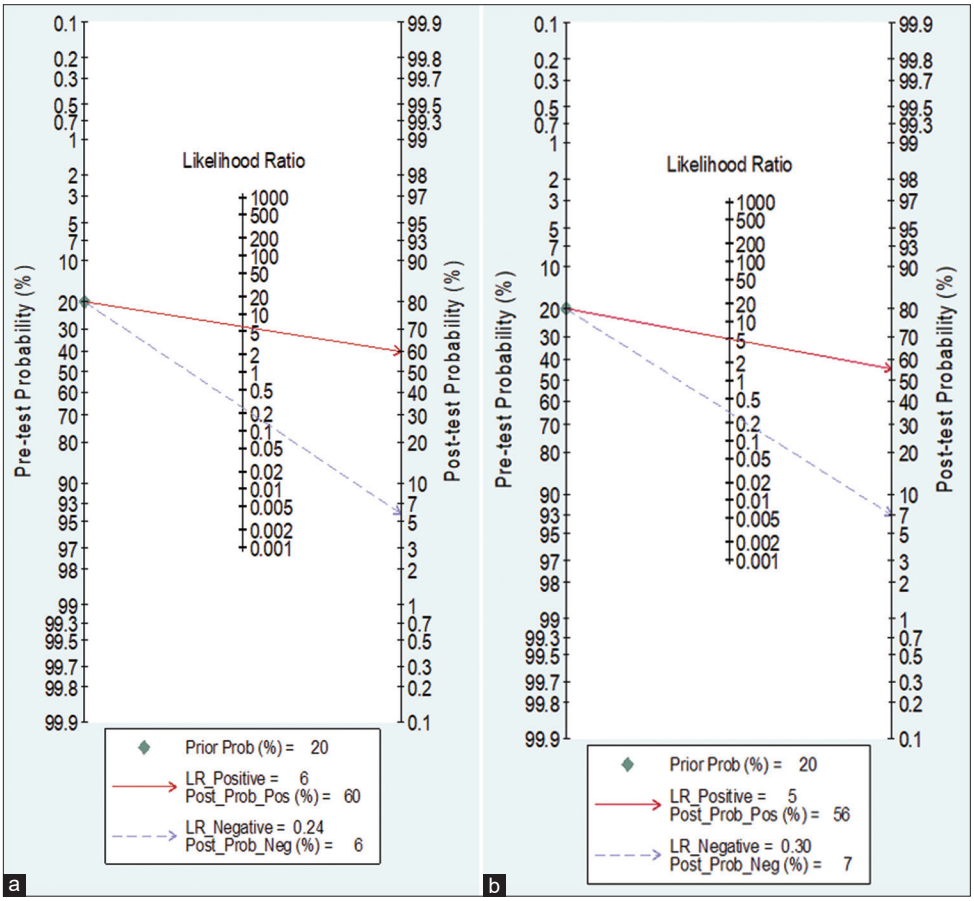
Question: Should [Urine NGAL] be used to diagnose [AKI in Covid-19 Infection] in [health problem]?

Sensitivity							0.75 (95% CI: 0.68-0.80)			
Specificity							0.85 (95% CI: 0.77-0.91)			
Prevalences			10%			15%			20%	
Outcome	**No of studies (No of patients)**	**Study design**	**Factors that may decrease certainty of evidence**					**Effect per 1,000 patients tested**			**Test accuracy CoE**
			Risk of bias	**Indirectness**	**Inconsistency**	**Imprecision**	**Publication bias**	**Pre-test probability of 10%**	**Pre-test probability of 15%**	**Pre-test probability of 20%**	
True positives (patients with [AKI in Covid-19 Infection])	5 studies 718 patients	cohort & case-control type studies	very serious	not serious	serious	not serious	all plausible residual confounding would reduce the demonstrated effect	75 (68-80)	112 (102-120)	150 (136-160)	⊕⊕◯◯ Low
False negatives (patients incorrectly classified as not having [AKI in Covid-19 Infection])								25 (20-32)	38 (30-48)	50 (40-64)	
True negatives (patients without [AKI in Covid-19 Infection])	5 studies 718 patients	cohort & case-control type studies	very serious	not serious	very serious	not serious	all plausible residual confounding would reduce the demonstrated effect	765 (693-819)	722 (655-774)	680 (616-728)	⊕◯◯◯ Very low
False positives (patients incorrectly classified as having [AKI in Covid-19 Infection])								135 (81-207)	128 (76-195)	120 (72-184)	

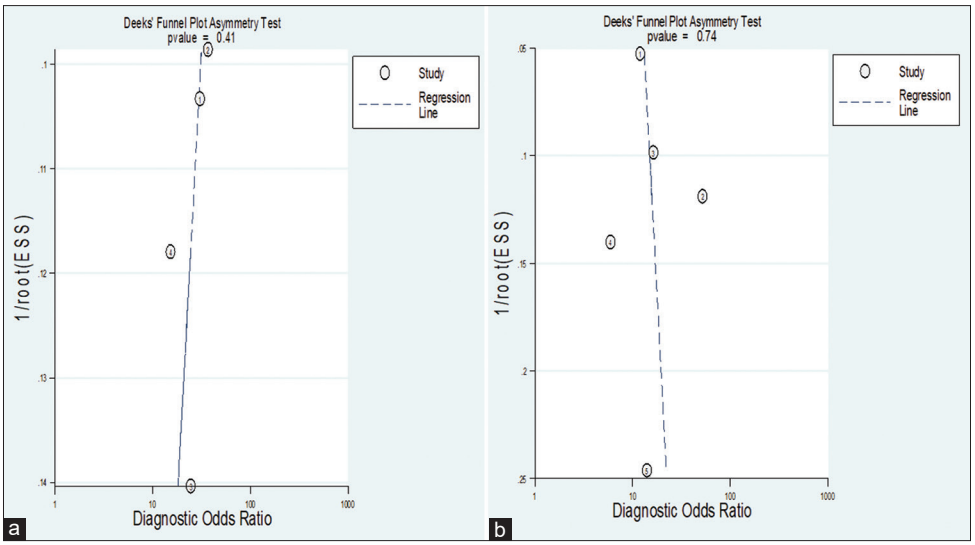
GRADE- grading of recommendations, assessment, development and evaluation; NGAL- Neutrophil gelatinase-associated lipocalin, CI- confidence interval, AKI- acute kidney injury, Covid-19- coronavirus disease 2019, No- number, CoE- certainty of evidence



Supplementary Figure 1: Risk of bias and applicability concerns graph: review author's judgments about each domain presented as percentages across included studies for serum (a) and urine (b)



Supplementary Figure 2: Fagan plot showing pre-test and post-test probability of serum (a) and urine (b) NGAL for the diagnosis of AKI in COVID-19 infection. NGAL, Neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury; COVID-19, Coronavirus disease 2019



Supplementary Figure 3: Fagan plot showing pre-test and post-test probability of serum (a) and urine (b) NGAL for the diagnosis of AKI in COVID-19 infection. NGAL, Neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury; COVID-19, Coronavirus disease 2019