

Diagnostic value of neutrophil gelatinase-associated lipocalin in diabetic nephropathy: a meta-analysis

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ABSTRACT

Purpose: This meta-analysis aimed to determine the diagnostic performance of neutrophil gelatinase-associated lipocalin (NGAL) in diabetic nephropathy (DN).

Methods: We searched the PubMed, Embase, Wanfang, and China National Knowledge Infrastructure databases for articles published up to 24 April 2019. The meta-analyses were conducted by Stata 11.0, and diagnostic accuracy, sensitivity, specificity, negative and positive likelihood ratios (NLR and PLR), diagnostic odds ratio (DOR), and receiver operating characteristic (ROC) curve data were pooled. Moreover, heterogeneity and small trials bias were evaluated.

Results: Six cross-sectional studies were included in the meta-analysis. For the studies of microalbuminuria versus normoalbuminuria, the estimates (95% confidence interval) were as follows: sensitivity, 0.75 (0.51–0.89); specificity, 0.78 (0.70–0.84); PLR, 3.37 (2.49–4.56); NLR, 0.33 (0.16–0.69); DOR, 10.31 (4.05–26.25); and area under the ROC curve (AUC), 0.81 (0.77–0.84). For the studies of microalbuminuria + macroalbuminuria versus normoalbuminuria, the results were as follows: sensitivity, 0.83 (0.66–0.93); specificity, 0.88 (0.67–0.97); PLR, 7.20 (1.97–26.31); NLR, 0.19 (0.08–0.46); DOR, 37.83 (4.84–295.65); AUC, 0.92 (0.90–0.94). Deeks' funnel plot suggested that small trials bias was insignificant in this study.

Conclusions: Our findings suggest that NGAL is a potential diagnostic marker for patients with DN and that its diagnostic value for microalbuminuria + macroalbuminuria is superior to that for microalbuminuria.

HIGHLIGHTS

- The first meta-analysis to investigate NGAL diagnostic role in DN.
- NGAL is valuable for the early diagnosis of DN.
- The diagnostic value of NGAL in microalbuminuria + macroalbuminuria was much higher.

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Introduction

Diabetic nephropathy (DN), clinically characterized by proteinuria and decreased kidney function, blood pressure, and glucose, is a severe complication of diabetes [1,2]. As the leading cause of end-stage kidney disease worldwide, DN increases the morbidity and mortality rates of patients with type I or II diabetes [3,4]. Evidence suggests that complex interactions between hemodynamic, hyperglycemia-induced metabolic, and inflammatory factors comprise the molecular pathophysiology of DN [5]. Current treatments for DN are limited to blocking of the renin–angiotensin–aldosterone system [6]; moreover, despite the identification of an

increasing number of biomarkers that can accurately reflect the degree of histopathologic changes in DN patients [7], their sensitivity and specificity are unsatisfactory. Therefore, potential reliable biomarkers for the prediction of DN are still needed.

Neutrophil gelatinase-associated lipocalin (NGAL; lipocalin-2), a 25-kDa molecule that belongs to the superfamily of lipocalin proteins, was initially identified in neutrophils [8,9]. Moreover, NGAL is a large glycosylated protein synthesized in renal tubular epithelial cells that is related to antibacterial properties or cellular apoptosis [10]. Usually, NGAL is expressed in small amounts in several human tissues, including the

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stomach, lungs, and kidneys [11]. Emerging evidence show that NGAL is observably up-regulated in the blood and urine when acute tubular damage of various causes occurs [12]; hence, it has been used as an early diagnostic marker of acute or chronic kidney injury [13,14]. Currently, although clinical studies have highlighted the role of NGAL for detecting DN [15–20], the results remain inconsistent. Thus, our study aimed to determine the diagnostic value of NGAL in DN using a meta-analysis of published data.

Materials and methods

Search strategy

The systematic literature search was performed of PubMed, Embase, Cochrane Library, China Biomedical Literature Database (CBM), and Wanfang and China National Knowledge Infrastructure (CNKI) database using the key search terms (combination of subject and free words): ‘Diabetic nephropathy,’ ‘DN,’ ‘diabetes,’ ‘neutrophil gelatinase-associated lipocalin,’ ‘NGAL,’ ‘lipocalin-2,’ ‘Lcn-2,’ and ‘siderocalin.’ Furthermore, the retrieval strategy was adjusted for different databases based on the combination of different search terms and free words (‘or’ and ‘and’) (Supplementary Table 1). The search period was up to 24 April 2019, and there was no language limitation in the literature search. Additionally, to identify more studies that could be included in the meta-analysis, we manually retrieved the papers and screened their reference lists.

Study selection

The study inclusion criteria were as follows: (1) adults (≥ 18 years old) with diabetes; (2) patients with diabetes mellitus with or without nephropathy based on the indexes of ‘microalbuminuria’ and ‘macroalbuminuria’; (3) availability of indexes including true positive (TP), false positive (FP), false negative (FN), and true negative (TN); (5) inclusion of diagnostic thresholds for NGAL; and (6) no restriction in study types. Exclusion criteria: (1) reviews, letters, or conference extracts; (2) repeated publications; and (3) failure to report effective data.

Data extraction and assessment

According to the inclusion and exclusion criteria, the following data from each identified study were independently extracted by two independent researchers: first author; publication year; study location; subject sex and age; sample size; study type; NGAL detection method; and indexes of TP, FP, FN, and TN. Any

disagreements between the two reviewers were resolved based on a group discussion with the third researcher.

The quality of each study was analyzed using the Quality Assessment of Diagnostic Accuracy Studies tool [21].

Statistical analysis

The diagnostic meta-analyses were performed using Stata 11.0 software (Stata Corporation, College Station, TX), with pooled effect sizes including sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) with their 95% confidence intervals (CIs). Interstudy heterogeneity was assessed using the Cochran Q test and I^2 statistics test [22]. If the heterogeneity was statistically significant ($p < .05$ or $I^2 > 50\%$), the data were pooled using the random effects model; otherwise, the fixed-effect method was used. Furthermore, the publication bias was investigated using Deeks’ funnel plot method, and values of $p < .05$ were considered statistically significant.

Results

Characteristics of included studies

A total of 1968 articles were identified in the initial search of PubMed ($n = 380$), Embase ($n = 1048$), Cochrane library ($n = 90$), CBM ($n = 113$), Wanfang ($n = 177$), and CNKI ($n = 160$). After the removal of 192 duplicate studies and 370 irrelevant publications, 1406 articles remained (Figure 1). After the abstract review, 27 articles were excluded. The remaining nine articles were subjected to full-text review; of them, six publications [15–20] were finally included in the meta-analysis. The consistent results of the literature screening were: Kappa = 0.881, SE = 0.023, and $p < .001$.

The basic characteristics of the six eligible studies are summarized in Table 1. All studies were of cross-sectional design, published in 2016–2018, and conducted in China, India, Saudi Arabia, and Egypt. In all studies, NGAL level was detected by enzyme-linked immunosorbent assay, and an albumin–creatinine ratio (ACR) ≥ 30 mg/g was considered an early marker of DN. Among these publications, four [15,16,19,20] included type 2 diabetes mellitus (T2DM) with microalbuminuria and T2DM with macroalbuminuria, while the other two studies [17,18] only included T2DM with microalbuminuria. In addition to the urine NGAL level tested in Vijay’s study [18], the serum NGAL levels were measured in the other studies. Moreover, the interstudy

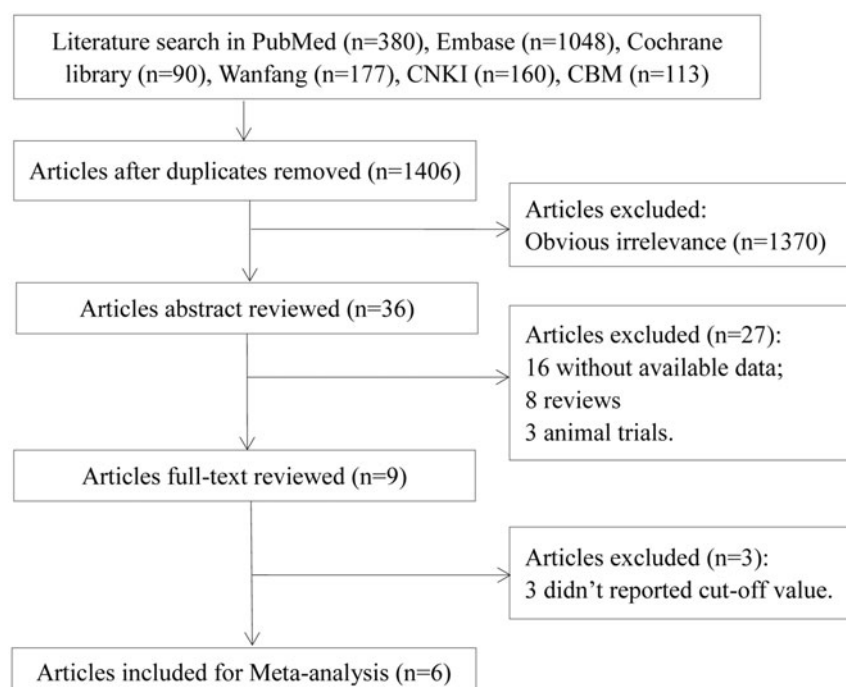


Figure 1. Flowchart of the study selection process.

Table 1. Characteristics of the studies included in the meta-analysis.

Study	Area	Type of study	Age, years	N, M/F	Type of NGAL	Determination of NGAL	Definition of early albuminuria
Kaul et al. [15]	India	Cross-sectional	51–60	144, 89/55	Serum	ELISA	ACR \geq 30 mg/g
Mahfouz et al. [16]	Saudi Arabia	Cross-sectional	55.7 \pm 6.2, 53.4 \pm 6.9, 55.9 \pm 5.3 ^a	150, 59/91	Serum	ELISA	ACR \geq 30 mg/g
Motawi [17]	Egypt	Cross-sectional	48.76 \pm 7.75, 50.52 \pm 9.21 ^b	50, 40/10	Serum	ELISA	ACR \geq 30 mg/g
Vijay et al. [18]	India	Cross-sectional	49.2 \pm 11.37, 54.25 \pm 13.06 ^b	136, 68/58	Urine	ELISA	ACR \geq 30 mg/g
Wen et al. [19]	China	Cross-sectional	55.39 \pm 8.28, 56.97 \pm 12.05, 57.63 \pm 10.55 ^a	84, 45/39	Serum	ELISA	ACR \geq 30 mg/g
Zhu et al. [20]	China	Cross-sectional	54	220, 125/95	Serum	ELISA	ACR \geq 30 mg/g

N: number of participants; M: male; F: female; NGAL: neutrophil gelatinase-associated lipocalin; ELISA: enzyme-linked immunosorbent assay; ACR: albumin/creatinine ratio.

^aAge of T2DM with normoalbuminuria, T2DM with microalbuminuria, T2DM with macroalbuminuria.

^bAge of T2DM with normoalbuminuria, T2DM with microalbuminuria.

differences in sex and age were not significant. Taken together, the consistency results of the data extraction were: Kappa = 0.549, SE = 0.096, and $p < .001$.

According to the quality assessment result (Table 2), the included studies had a high risk of bias in terms of patient selection and index test, but a low risk of bias in reference standard and flow and timing. Taken together, the overall quality of these included studies was moderate.

Meta-analysis

Microalbuminuria versus normoalbuminuria

The pooled diagnostic accuracy analysis revealed that four studies [17–20] reported the diagnostic value of NGAL in T2DM with microalbuminuria. As shown in

Figure 2(A), the pooled sensitivity and specificity were 0.75 (95% CI, 0.51–0.89) and 0.78 (95% CI, 0.70–0.84), respectively. Moreover, the sensitivity heterogeneity was high ($I^2=88.03\%$, $p < .001$); however, the heterogeneity of specificity ($I^2=1.18\%$, $p=.39$) was not significant. Meanwhile, the pooled PLR was 3.37 (95% CI, 2.49–4.56) with low heterogeneity ($I^2=0.0\%$, $p=.61$), and the pooled NLR was 0.33 (95% CI, 0.16–0.69) with significant heterogeneity ($I^2=83.21\%$, $p < .001$) (Figure 3(A)). As shown in Figure 4(A), the pooled DOR was 10.31 (95% CI, 4.05–26.25), with high significantly heterogeneity ($I^2=96.43\%$, $p < .001$). Additionally, the pooled summarized receiver operating characteristic (SROC) curve was calculated by sensitivity against (1 – specificity), and the AUC was 0.81 (95% CI, 0.77–0.84), indicating a high diagnostic accuracy of NGAL for T2DM with microalbuminuria (Figure 5(A)).

Table 2. Outcomes of the studies included in the meta-analysis.

Study	Area	Normoalbuminuria, <i>n</i> (M/F)	Microalbuminuria, <i>n</i> (M/F)	Macroalbuminuria, <i>n</i> (M/F)	Case	Control	TP	FN	FP	TN	Cut-off, ng/mL
Kaul et al. [15]	India	36, 22/14	59, 34/25	49, 33/16	108 ^b	36	103	5	0	36	78.73
Mahfouz et al. [16]	Saudi Arabia	50, 17/33	50, 23/27	50, 19/31	100 ^b	50	87	13	13	37	91.5
Motawi [17]	Egypt	25, 23/2	25, 17/8	–	25 ^a	25	24	1	5	20	77.72
Vijay et al. [18]	India	63, 35/28	63, 33/30	–	63 ^a	63	52	11	18	45	146.28
Wen et al. [19]	China	21, 12/9	29, 14/15	34, 19/15	29 ^a	21	15	14	3	18	98
					63 ^b	21	43	20	3	18	98
Zhu et al. [20]	China	83, 48/35	77, 42/35	60, 35/25	77 ^a	83	43	34	16	67	180
					137 ^b	83	93	44	16	67	180

M: male; F: female; TP: true positive; FN: false negative; FP: false positive; TN: true negative.

^aMicroalbuminuria vs. normoalbuminuria.

^bMicroalbuminuria + macroalbuminuria vs. normoalbuminuria.

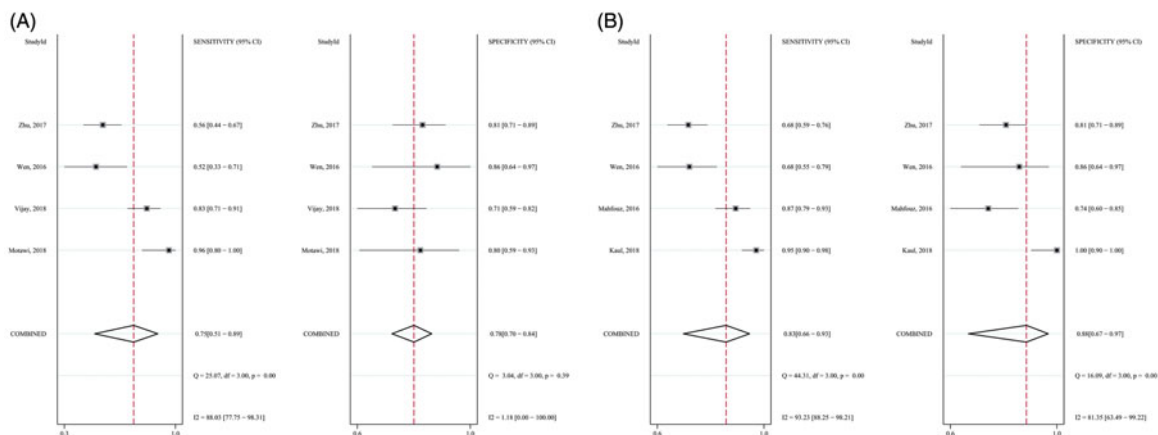


Figure 2. Diagnostic sensitivity and specificity of neutrophil gelatinase-associated lipocalin in the diagnosis of diabetic nephropathy with microalbuminuria vs. normoalbuminuria (A) or 'microalbuminuria + macroalbuminuria' vs. normoalbuminuria (B).

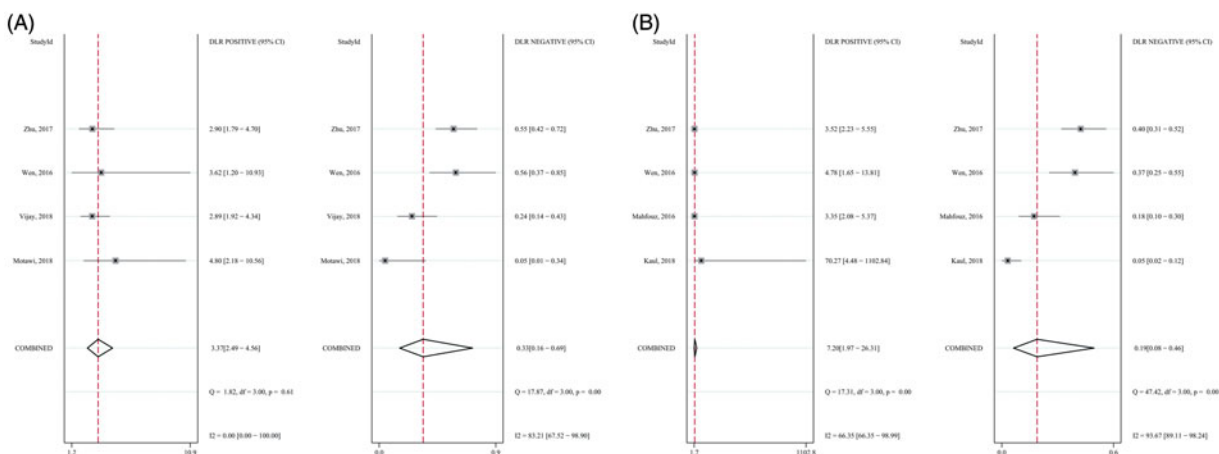


Figure 3. The positive or negative likelihood ratio of the quantitative analysis of neutrophil gelatinase-associated lipocalin (NGAL) in the diagnosis of diabetic nephropathy with microalbuminuria vs. normoalbuminuria (A) or 'microalbuminuria + macroalbuminuria' vs. normoalbuminuria (B).

Microalbuminuria + macroalbuminuria versus normoalbuminuria

A total of four studies [15,16,19,20] reported the diagnostic value of NGAL in T2DM with microalbuminuria + macroalbuminuria. Forest plots demonstrated that the pooled sensitivity and specificity were 0.83 (95% CI,

0.66–0.93) and 0.88 (95% CI, 0.08–0.46), respectively; moreover, the heterogeneity was high (I^2 for sensitivity, 93.23%, $p < .001$; I^2 for specificity, 81.35%, $p < .001$) (Figure 2(B)). As illustrated in Figure 3(B), the overall pooled PLR was 7.20 (95% CI, 1.97–26.31), and NLR was 0.19 (95% CI, 0.08–0.46), of which the heterogeneity

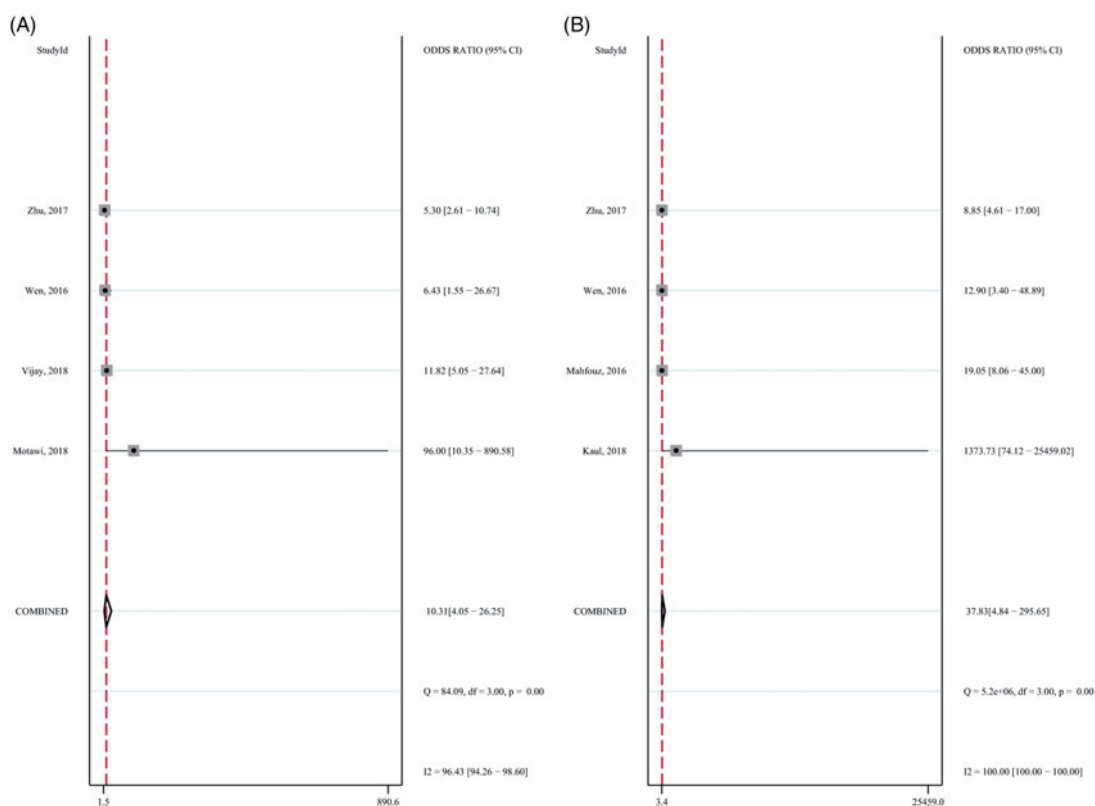


Figure 4. Diagnostic odds ratio (DOR) for quantitative analysis of neutrophil gelatinase-associated lipocalin (NGAL) in the diagnosis of diabetic nephropathy with microalbuminuria vs. normoalbuminuria (A) or 'microalbuminuria + macroalbuminuria' vs. normoalbuminuria (B).

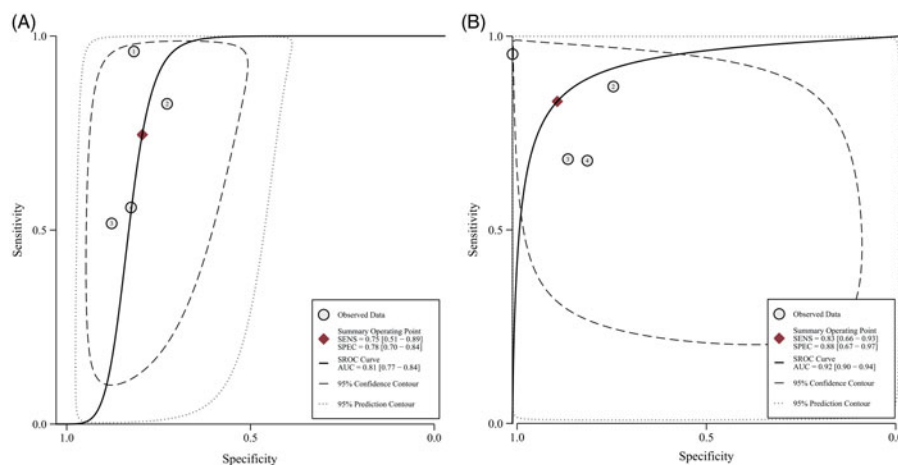


Figure 5. The summarized receiver operating characteristics (SROC) curve for quantitative analysis of neutrophil gelatinase-associated lipocalin (NGAL) in the diagnosis of diabetic nephropathy with microalbuminuria vs. normoalbuminuria (A) or 'microalbuminuria + macroalbuminuria' vs. normoalbuminuria (B).

were both significant ($I^2 > 50\%$, $p < .05$). Moreover, the pooled DOR was calculated as 37.83 (95% CI, 4.84–295.65) with high significant heterogeneity ($I^2 = 100.0\%$, $p < .001$) (Figure 4(B)). The SROC curve revealed that NGAL had high diagnostic value for T2DM with microalbuminuria + macroalbuminuria (AUC, 0.92; 95% CI, 0.90–0.94) (Figure 5(B)).

Small trials bias estimate

Deeks' funnel plots revealed no small trials bias of NGAL in the diagnosis of DN in the eligible studies (microalbuminuria versus normoalbuminuria, $p = .39$; Figure 6(A); microalbuminuria + macroalbuminuria versus normoalbuminuria, $p = .68$; Figure 6(B)).

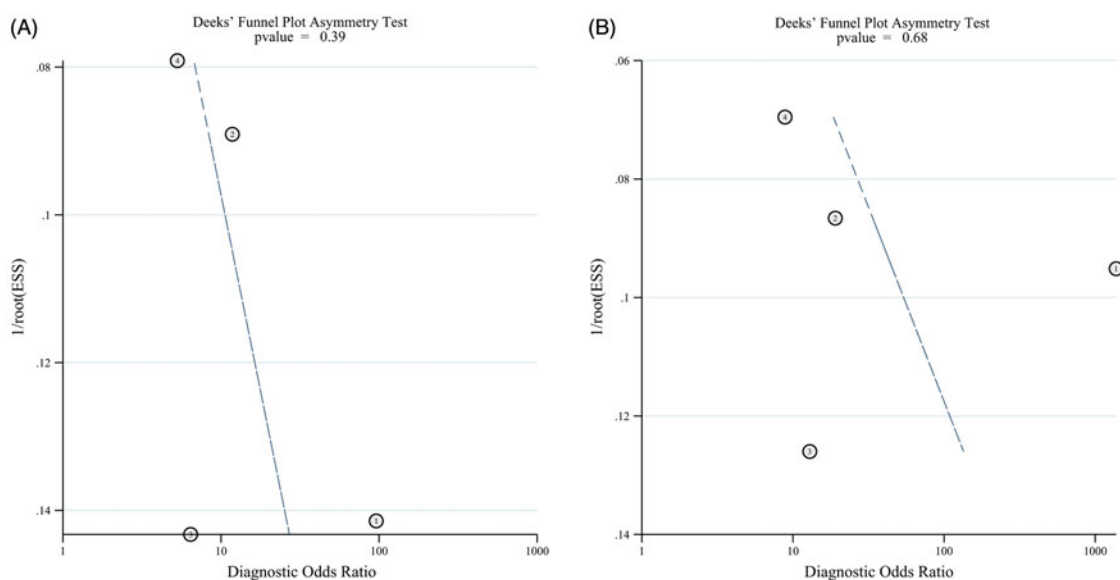


Figure 6. Deeks' funnel plot for detecting small trials bias of the included studies. Neutrophil gelatinase-associated lipocalin (NGAL) in the diagnosis of diabetic nephropathy with microalbuminuria vs. normoalbuminuria (A) or 'microalbuminuria + macroalbuminuria' vs. normoalbuminuria (B).

Discussion

As a reliable marker for the detection and monitoring of chronic kidney disease or acute kidney injury, NGAL is abnormally expressed in plasma and urine when acute tubular damage occurs [14,23]. It is well known that NGAL can primarily bind siderophores to activate cytoplasmic iron-dependent pathways and protect the same cells from oxidative stress [24]. Han et al. [25] reported that NGAL protects against endotoxin-induced renal tubular cell damage by suppressing apoptosis. More importantly, accumulative evidence has revealed the diagnostic feature of NGAL in DN [15–20]; however, the studies were inconsistent because of single-center design or small sample size. Therefore, here we performed a systematic meta-analysis to investigate the diagnostic value of NGAL in DN patients. Our results suggested that NGAL could be valuable for the diagnosis of DN, and its diagnostic value in patients with 'microalbuminuria + macroalbuminuria' was superior to those with microalbuminuria only.

To date, a number of meta-analyses have revealed the diagnostic value of NGAL in acute kidney injury [26,27], breast cancer [28], and colorectal cancer [29]. However, a systematic evaluation related to the role of NGAL in the early prediction of DN is lacking. In the current meta-analysis, six publications relevant to NGAL as a predictor of DN were included. To our knowledge, ACR is a sensitive clinical index of early renal injury in diabetes [30]. Moreover, based on ACR, patients with DN are usually stratified into different groups, such as normoalbuminuria with an ACR level < 30 mg/g

creatinine, microalbuminuria with an ACR of 30–299 mg/g creatinine, and macroalbuminuria with an ACR > 300 mg/g creatinine. Among the studies included in the present meta-analysis, four included T2DM with microalbuminuria and macroalbuminuria, while the other two included only T2DM with microalbuminuria.

In the meta-analysis of the studies examining microalbuminuria versus normoalbuminuria, the pooled sensitivity and specificity of NGAL were 0.75 (95% CI, 0.51–0.89) and 0.78 (95% CI, 0.70–0.84), respectively. However, the overall pooled sensitivity and specificity of studies evaluating microalbuminuria + macroalbuminuria versus normoalbuminuria were 0.83 (95% CI, 0.66–0.93) and 0.88 (95% CI, 0.08–0.46), respectively, suggesting that NGAL had better sensitivity and specificity in cases of microalbuminuria + macroalbuminuria than in those of microalbuminuria only. The likelihood ratio is regarded useful for assessing degree of sensitivity and specificity as well as diagnostic test value [31]. In this study, the pooled PLR and NLR of NGAL in studies of microalbuminuria versus normoalbuminuria were 3.37 (95% CI, 2.49–4.56) and 0.33 (95% CI, 0.16–0.69), respectively, indicating satisfactory value of likelihood ratios. Meanwhile, the likelihood ratios in studies of microalbuminuria + macroalbuminuria versus normoalbuminuria seemed to be better with a pooled PLR of 7.20 (95% CI, 1.97–26.31) and NLR of 0.19 (95% CI, 0.08–0.46). DOR, which combines sensitivity, specificity, PLR, and NLR data of a diagnostic test, is used to assess diagnostic efficiency [32]. The pooled DOR in this meta-analysis was 10.31 (95% CI, 4.05–26.25, microalbuminuria versus normoalbuminuria), and 37.83 (95% CI,

4.84–295.65, microalbuminuria + macroalbuminuria versus normoalbuminuria), indicating a relatively high overall accuracy. Likewise, the AUC of SROC for NGAL was 0.81 (95% CI, 0.77–0.84, microalbuminuria versus normoalbuminuria) and 0.92 (95% CI, 0.90–0.94, microalbuminuria + macroalbuminuria versus normoalbuminuria). Taken together, the advantages of the study were that: (1) it was the first meta-analysis to reveal that NGAL had a relatively higher accuracy for DN diagnosis in studies of microalbuminuria + macroalbuminuria than that in studies of microalbuminuria, and we speculated the reason might be that NGAL levels changed significantly in macroalbuminuria populations and (2) there was no significant publication bias of the included studies, which suggests that our results are reliable.

Heterogeneity is considered the most important element of a meta-analysis [33]. In the present study, significant heterogeneity was detected among the overall pooled analyses. The reasons for this, which could be considered the limitations of our meta-analysis, were as follows: (1) this meta-analysis was not registered online; (2) the included studies and sample sizes were small; (3) the diagnostic thresholds of the various studies were inconsistent; and (4) the heterogeneity of the included studies was relatively large, but the sources of heterogeneity could not be quantitatively assessed due to the limited number of articles included.

In summary, this is the first meta-analysis to comprehensively investigate the value of NGAL in the early diagnosis of DN. Our results provided evidence that NGAL is a potential diagnostic marker for patients with DN and that its diagnostic value for microalbuminuria + macroalbuminuria is superior to that for microalbuminuria.

Disclosure statement

No potential conflict of interest was reported by the authors.

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