• Meta-Analysis •

Diagnostic value of urinary albumin creatinine ratio in predicting vision-threatening diabetic retinopathy in patients with diabetes: a systematic review and Meta-analysis

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Received: 2025-07-28 Accepted: 2025-12-18

Abstract

● **AIM:** To evaluate the predictive value of urinary albumin creatinine ratio (UACR), albumin excretion rate (AER), and estimated glomerular filtration rate (eGFR) for vision-threatening diabetic retinopathy (VTDR) in individuals with diabetes.

● **METHODS:** A comprehensive literature search across PubMed, Embase, Web of Science, Scopus, and the Cochrane Library from their inception to February 2024 were performed. The diagnostic accuracy of microalbuminuria (MA; including UACR and AER) and eGFR in predicting VTDR using sensitivity, specificity, positive likelihood ratio and negative likelihood ratio, diagnostic odds ratio (DOR), and the area under the summary receiver operating characteristic (ROC) curve were assessed. Analyses incorporated both bivariate generalized linear mixed models and random-effects models to ensure a robust and unbiased interpretation of the data.

● **RESULTS:** The review included 14 studies with a total of 87 223 patients. The pooled sensitivity and specificity of MA and eGFR for predicting VTDR were 0.77 [95% confidence interval (CI), 0.57–0.89] and 0.51 (95%CI, 0.31–0.72), respectively. The DOR was 3.47 (95%CI, 1.94–6.18), with the area under the summary ROC curve at 0.70 (95%CI, 0.66–0.74). Notably, UACR as a predictor showed a sensitivity of 0.88 (95%CI, 0.43–0.99) and specificity of 0.55 (95%CI, 0.22–0.84), with an area under the curve of 0.78 (95%CI, 0.74–0.82). Despite significant heterogeneity among the studies (P<0.01), no publication bias was detected.

● **CONCLUSION:** UACR is a highly sensitive but moderately specific indicator for early detection and management strategies in this high-risk population.

● **KEYWORDS:** vision-threatening diabetic retinopathy; albumin excretion rate; urinary albumin creatinine ratio; estimated glomerular filtration rate

DOI:10.18240/ijo.2026.09.16

Citation: Gao Y, Zhuang JY, Ren YY, Zhang HZ, Hu YM, Li CH, Hu M, Zhou H, Luo XX. Diagnostic value of urinary albumin creatinine ratio in predicting vision-threatening diabetic retinopathy in patients with diabetes: a systematic review and Meta-analysis. *Int J Ophthalmol* 2026;19(9):1800-1808

INTRODUCTION

According to the International Diabetes Federation, 537 million adults (20–79 years old) worldwide are currently living with diabetes mellitus, and this number is expected to rise to 783 million by 2045[1]. Vision-threatening diabetic retinopathy (VTDR), which includes proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME), is one of the major microvascular complications of diabetes and the leading cause of visual impairment and blindness among adults in their most productive years[2-3]. The critical importance of early detection and precise diagnosis of VTDR cannot be overstated, as these steps are essential for preventing serious vision loss in diabetic patients[4].

While fundus fluorescein angiography remains the diagnostic gold standard for VTDR, its use is impractical in many parts of the world, particularly in low-income regions where access to advanced medical equipment and specialized care is severely limited[5]. In this context, clinical biomarkers such as microalbuminuria (MA) and estimated glomerular filtration rate (eGFR) serve a dual role: they predict the risk of VTDR while assessing renal function[6]. Among these, the urinary albumin creatinine ratio (UACR) and albumin excretion rate (AER) are crucial for detecting MA[7]. Evidence from various studies supports the relationship between these biomarkers and the severity of diabetic retinopathy. For instance, the work by Saini *et al*[8] underscores that worsening diabetic retinopathy is associated with increasing levels of albuminuria. Further, a comprehensive study involving over a thousand type 2 diabetes mellitus patients in Korea established that the urinary albumin creatinine ratio (UACR) is an independent predictor of diabetic retinopathy[9]. A prospective cohort study included 25 825 participants with diabetes from the UK Biobank suggests monitoring eGFR in the high-risk patients may offer significant benefits for the early identification of VTDR[10].

The significance of utilizing MA and eGFR as predictors in routine screenings is particularly profound in resource-constrained settings[11-12]. These biomarkers are not only cost-effective and simple to assess but also carry the potential to significantly reduce healthcare costs and protect patients' visual function by enabling early diagnosis and intervention. This systematic review and Meta-analysis are dedicated to rigorously evaluating the predictive accuracy of MA (including UACR and AER) and eGFR for VTDR in individuals with diabetes mellitus. By establishing reliable predictive markers, this research aims to contribute significantly to improving the clinical management of diabetes, enhancing the quality of life for millions affected worldwide, and potentially transforming the landscape of diabetic care in settings most in need.

MATERIALS AND METHODS

Data Sources and Searches The protocol for this systematic review was duly registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42023489393. To collate potentially relevant studies, a comprehensive search was performed across PubMed, Embase, Web of Science, Scopus, and the Cochrane Library, covering publications from their inception through February 2024. This search strategy employed a meticulous combination of Medical Subject Headings (MeSH) and related synonyms, specifically targeting AER, UACR, eGFR, and VTDR. For a detailed exposition of the PubMed search methodology, refer to Table 1. In the revision process, the search strategy was updated by supplementing the original Search Formula #8 with the terms "urinary albumin-creatinine

Table 1 Characteristics of the 14 studies included in the systematic review and Meta-analysis

Study	Country	Design	Sample size	Males (%)	Type of diabetes mellitus	Renal function biomarkers	VTDR evaluation	ARFB VTDR/N-VTDR	NARFB VTDR/N-VTDR
Kalter-leibovici, 1991[15]	Israel	Cross-sectional study	231	45	Type 1	AER>21.5 mg/24h	Direct and indirect ophthalmoscopy after dilation of pupils	20/68	8/127
Johansen, 1994[16]	Denmark	Cross-sectional study	138	52	Type 1	AER>20 μg/min	Ophthalmoscopy and fundus photography after dilation of pupils	17/26	6/55
Parving, 1996[24]	Denmark	Longitudinal study	127	75	Type 2	AER>300 mg/24h	Fundus photography after dilation of pupils	13/39	4/49
Gilbert, 1998[25]	Australia	Longitudinal study	80	72.5	NA	AER>20 μg/min	Direct and indirect ophthalmoscopy	8/5	5/62
Banerjee, 2004[17]	India	Cross-sectional study	100	55	Type 2	AER>30 mg/24h	Fluorescein angiography	19/73	0/8
Manaviat, 2004[18]	Iran	Cross-sectional study	590	41.4	Type 2	UACR>30 mg/g	Fundoscopy or fluorescein angiography	21/202	7/323
Tamadon, 2015[19]	Iran	Cross-sectional study	253	NA	Type 2	AER>30 mg/24h	Fluorescein angiography or OCT	3/7	80/163
Kaewput, 2019[20]	Thailand	Cross-sectional study	13192	30.4	Type 2	eGFR<90 mL/min·1.73 m^2	Fundus photography	451/1071	68/242
Yu, 2020[27]	USA	Longitudinal study	69982	NA	NA	eGFR<90 mL/min·1.73 m^2	Fundus photography	9233/40165	2254/11127
Cho, 2020[26]	Republic of Korea	Longitudinal study	1527	47.4	Type 2	eGFR<90 mL/min·1.73 m^2	Fundus photography or OCT	100/866	34/303
Aman, 2020[21]	Indonesia	Cross-sectional study	120	36.7	Type 2	Albuminuria>30 μg/mg	Funduscopic examinations	54/44	5/17
Saini, 2021[8]	India	Cross-sectional study	57	NA	NA	UACR>30 mg/24h	Direct and indirect ophthalmoscopy, fundus photography and OCT	3/49	0/5
Barreto, 2022[22]	Brazil	Cross-sectional study	576	59	Type 2	UACR>30 mg/g	Direct and indirect ophthalmoscopy or OCT	30/26	45/178
Dash, 2022[23]	India	Cross-sectional study	250	56	NA	UACR>30 μg/mg	Direct and indirect ophthalmoscopy, fluorescein angiography or OCT	15/84	0/151

ARFB: Abnormal renal function biomarker; AER: Albumin excretion rate; UACR: Urinary albumin creatinine ratio; eGFR: Estimated glomerular filtration rate; VTDR: Vision-threatening diabetic retinopathy; N-VTDR: No vision-threatening diabetic retinopathy; NARFB: Normal renal function biomarker; NA: Not mentioned; OCT: Optical coherence tomography.

ratio" and "albumin to creatinine ratio", and supplementing Search Formula #13 with "microalbuminuria" and "albuminuria". The literature search was conducted exclusively in English, ensuring a focused and systematic approach to identifying studies pertinent to the review's objectives, which may have introduced language bias.

Study Selection These articles underwent a systematic assessment process, initially based on their titles and abstracts, followed by a thorough review of the full texts. The criteria for inclusion were meticulously defined to ensure the relevance and specificity of the selected studies. Specifically, the criteria included: 1) studies involving patients diagnosed with diabetes; 2) the identification of VTDR, determined through fundus photography, fundus fluorescein angiography (FFA), or optical coherence tomography (OCT), with VTDR defined as either PDR or clinically significant DME; 3) reports on the presence of MA and eGFR along with the classification of patients into different VTDR groups. During the citation screening phase, two independent reviewers (Gao Y and Zhuang JY) meticulously evaluated the search results to ascertain the eligibility of articles for inclusion. Any discrepancies encountered between the reviewers were resolved by reaching a consensus through discussion, with the senior author (Zhou H) providing the final decision when necessary. This collaborative and structured approach ensured a comprehensive and unbiased selection of studies for inclusion in the review.

Data Extraction and Quality Assessment Data extraction was meticulously carried out by the same investigators (Gao Y and Zhuang JY), who utilized standardized forms to ensure uniformity and precision in gathering data. The information extracted included author names, publication year, study design, percentage of male participants, type of diabetes, markers of renal function, criteria for diagnosing VTDR, as well as true positive, false positive, true negative, and false negative values. For longitudinal studies, data were extracted at baseline to provide a consistent point of comparison across studies.

Two researchers (Gao Y and Zhuang JY) independently conducted quality assessment of the included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) checklist, covering four domains: Patient Selection, Index Test, Reference Standard, and Flow and Timing[13]. During the assessment, the risk of bias and applicability of each domain were evaluated simultaneously. In cases of discrepancies in opinions between the two researchers, a third researcher (Luo XX) was consulted, and a consensus was reached through joint discussion to finalize the quality assessment results. The QUADAS-2 checklist facilitates a thorough and critical appraisal of potential sources of bias and variability among the included studies, ensuring a rigorous evaluation of their diagnostic accuracy in relation to MA and eGFR and VTDR.

Statistical Analysis For each study included in this systematic review and meta-analysis, sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were computed following the construction of a 2×2 contingency table. Pooled estimates along with their 95% confidence intervals (CIs) were derived using a random-effects model to account for the anticipated variability among studies. To evaluate the diagnostic accuracy comprehensively, a summary receiver operating characteristic (sROC) curve analysis was conducted, assessing the trade-off between sensitivity and specificity across studies. Heterogeneity among the included studies was quantified using the I^2 test. To further investigate the sources of heterogeneity, Meta-regression analyses were performed considering factors such as study design (cross-sectional *vs* longitudinal), type of diabetes (type 2 *vs* others), and sample size (greater than 200 *vs* less than 200). Additionally, a Fagan nomogram was plotted to integrate the pre-test probability with the post-test probabilities, enhancing the clinical applicability of the diagnostic test results by providing positive and negative predictive values. The Deeks' funnel plot asymmetry test was employed to assess the potential for publication bias among the studies[14]. All statistical tests were two-sided, adopting a significance threshold of $P<0.05$. The statistical analyses were conducted using Stata statistical software version 18.0 for Windows (Stata Corp, College Station, TX, USA) and Review Manager (RevMan) version 5.3.

RESULTS

Literature Search Results and Study Characteristics A comprehensive literature search across multiple databases yielded an initial tally of 3268 articles. Following a meticulous screening and evaluation process, 14 unique studies were ultimately selected for inclusion in this analysis (Figure 1). The final sample included 10 cross-sectional studies[8,15-27] and 4 longitudinal studies[24-27], comprising a diverse international cohort of 87 223 participants from various countries, including Israel, Denmark, Australia, India, Iran, Thailand, the United States, the Republic of Korea, Indonesia, and Brazil (Table 1). The gender distribution within these studies varied, with male participation ranging from 30.4% to 75%. Regarding biomarkers, 11 studies employed MA as an indicator of renal dysfunction[8,15-19,21-25], while the remaining three utilized eGFR[20,26-27]. Notably, six studies defined significant AER thresholds for MA at greater than 20 μg/min, 21.5 mg/24h, 30 mg/24h, and 300 mg/24h to delineate the presence of MA[15-17,19,24-25]. Conversely, four studies identified MA with a UACR greater than 30 mg/g[8,18,22-23]. The methods used to diagnose VTDR varied among the included studies:

ophthalmoscopy after mydriasis was employed in two studies[15,25], fundus photography after pupil dilation in four studies[20-21,24,27], FFA after mydriasis in one study[17], and a combination of detection tools in seven studies[8,16,18-19,22-23,26]. The quality of the included studies was appraised using the QUADAS-2 tool, which revealed that the majority exhibited risks of bias, particularly concerning patient selection, index testing, and applicability (Figure 2). This evaluation highlights the need for careful consideration of potential biases and limitations when interpreting the results of this systematic review and Meta-analysis.

MA and eGFR Predicting VTDR Forest plots (Figures 3A and 3B) illustrate the pooled sensitivity and specificity of MA and eGFR in predicting VTDR. The combined data from fourteen cross-sectional and longitudinal studies yielded a pooled sensitivity of 0.77 (95%CI, 0.57–0.89) and a specificity of 0.51 (95%CI, 0.31–0.72). The DOR, as shown in Figure 3C, suggests that MA and eGFR increase the odds of positively predicting VTDR by 3.47 times in individuals with VTDR compared to those without.

The summary area under the curve (AUC) for MA and eGFR in forecasting VTDR in diabetic patients was 0.70 (95%CI, 0.66–0.74), as depicted in Figure 4A. Data integration from all included studies indicated that the summary PLR and NLR for predicting VTDR using MA and eGFR were 1.58 (95%CI, 1.16–2.15) and 0.46 (95%CI, 0.29–0.71), respectively. The Fagan nomogram indicates that a positive MA and eGFR result increases the probability of VTDR from 8% to 12%, while a negative result reduces it from 8% to 4%.

Meta-regression analysis showed no significant differences in the predictive sensitivity or specificity of MA and eGFR between cross-sectional and longitudinal studies (P=0.68 and P=0.95, respectively), or between type 2 diabetes and other diabetes types (P=0.41 and P=0.89, respectively). However, larger studies (sample sizes greater than 200) demonstrated lower sensitivity (P=0.05) compared to smaller studies, though their specificity remained unchanged (P=0.44). Analysis of publication bias *via* Deeks' funnel plot test indicated its presence.

Additional forest plots based on 11 studies evaluating MA as a biomarker showed a pooled sensitivity of 0.80 (95%CI, 0.51–0.94) and a specificity of 0.61 (95%CI, 0.37–0.81). The DOR was 6.19 (95%CI, 3.51–10.91). The summary ROC curves demonstrated strong predictive capabilities for VTDR with an AUC of 0.76 (95%CI, 0.72–0.79), with a pooled PLR of 2.04 (95%CI, 1.42–2.95) and a pooled NLR of 0.33 (95%CI, 0.16–0.68). Examination of the funnel plot and subsequent analysis using the Deeks test showed no significant publication bias (P=0.19), suggesting an absence of sample size-related effects on reported diagnostic accuracy.

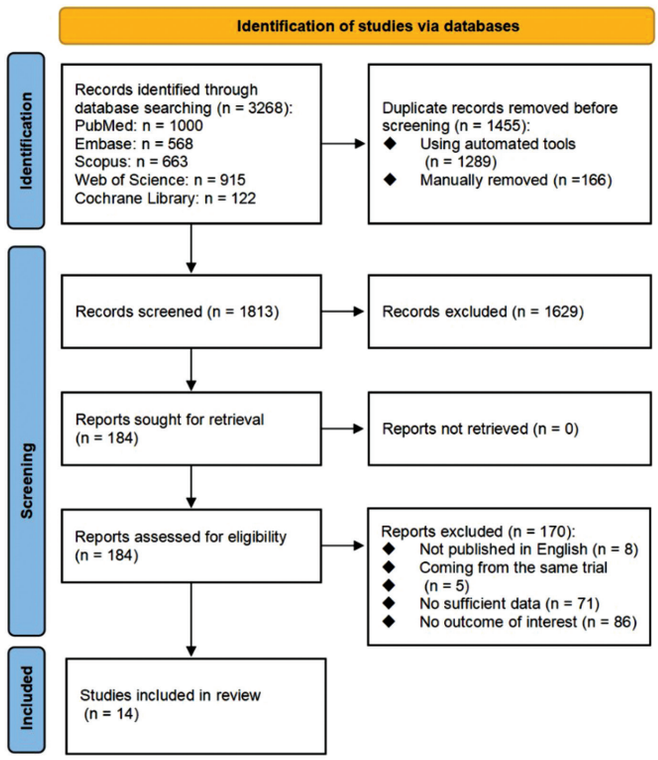

Figure 1 PRISMA flow diagram illustrating the systematic literature search and selection process.

Figure 2 Comprehensive risk of bias assessment for included studies using QUADAS-2 checklist.

UACR Predicting VTDR Forest plots displaying the pooled sensitivity and specificity for the UACR in predicting VTDR are shown in Figure 5A and 5B. The sensitivity of UACR varied considerably across studies, ranging from 0.40 to 1.00, which resulted in a pooled sensitivity of 0.88 (95%CI,

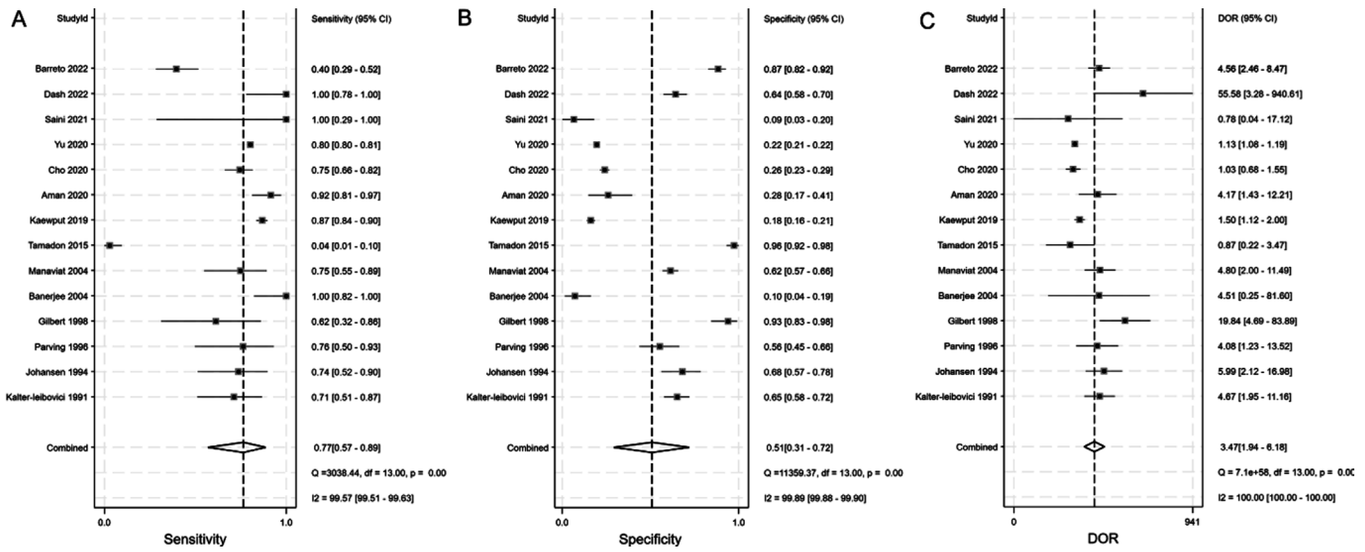

Figure 3 Forest plots of microalbuminuria and estimated glomerular filtration rate predicting vision-threatening diabetic retinopathy A: Forest plots of pooled sensitivity of microalbuminuria and estimated glomerular filtration rate predicting vision-threatening diabetic retinopathy; B: Forest plots of pooled specificity of microalbuminuria and estimated glomerular filtration rate predicting vision-threatening diabetic retinopathy; C: Forest plots of diagnostic odds ratio (DOR) of microalbuminuria and estimated glomerular filtration rate predicting vision-threatening diabetic retinopathy.

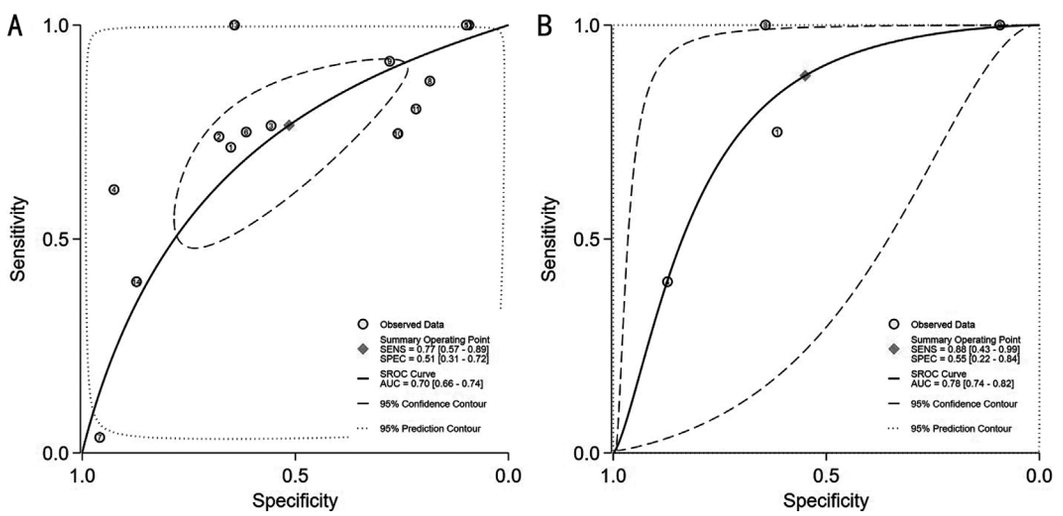

Figure 4 The summary receiver operating characteristic curve predicting vision-threatening diabetic retinopathy A: The summary ROC curves of microalbuminuria and estimated glomerular filtration rate predicting vision-threatening diabetic retinopathy; B: The summary ROC curves of urinary albumin creatinine ratio predicting vision-threatening diabetic retinopathy. ROC: Receiver operating characteristic; AUC: Area under the curve.

0.43–0.99). Specificity also varied widely, from as low as 0.09 to as high as 0.87, culminating in a pooled specificity of 0.55 (95%CI, 0.22–0.84). The pooled DOR is presented in Figure 5C as 9.08 (95%CI, 2.85–28.95), and the AUC was 0.78 (95%CI, 0.74–0.82) as depicted in Figure 4B. Data integration from all included studies yielded summary PLR and NLR values for predicting VTDR using UACR of 1.96 (95%CI, 1.09–3.50) and 0.22 (95%CI, 0.05–0.92), respectively. According to the Fagan nomogram, a positive UACR result increases the probability of VTDR from 8% to 15%, while a negative result reduces it from 8% to 2%. The Deeks test for publication bias yielded a non-significant result (P=0.92), indicating no significant publication bias.

DISCUSSION

This systematic review and meta-analysis synthesized data from 14 studies to assess the predictive value of MA, including UACR and AER, and eGFR for VTDR, with a focus on understanding their role as early biomarkers in a clinical setting. The analysis highlighted that MA and eGFR collectively demonstrate a pooled sensitivity of 0.77 and a specificity of 0.51, accompanied by a PLR of 1.58 and a NLR of 0.46. Notably, the DOR of 3.47 and an AUC of 0.70 underscore their moderate discriminative ability in predicting VTDR. Furthermore, the UACR greater than 30 mg/g emerged as a robust predictor, demonstrating a high pooled sensitivity of 0.88 and a specificity of 0.55, with an AUC of 0.78 indicating

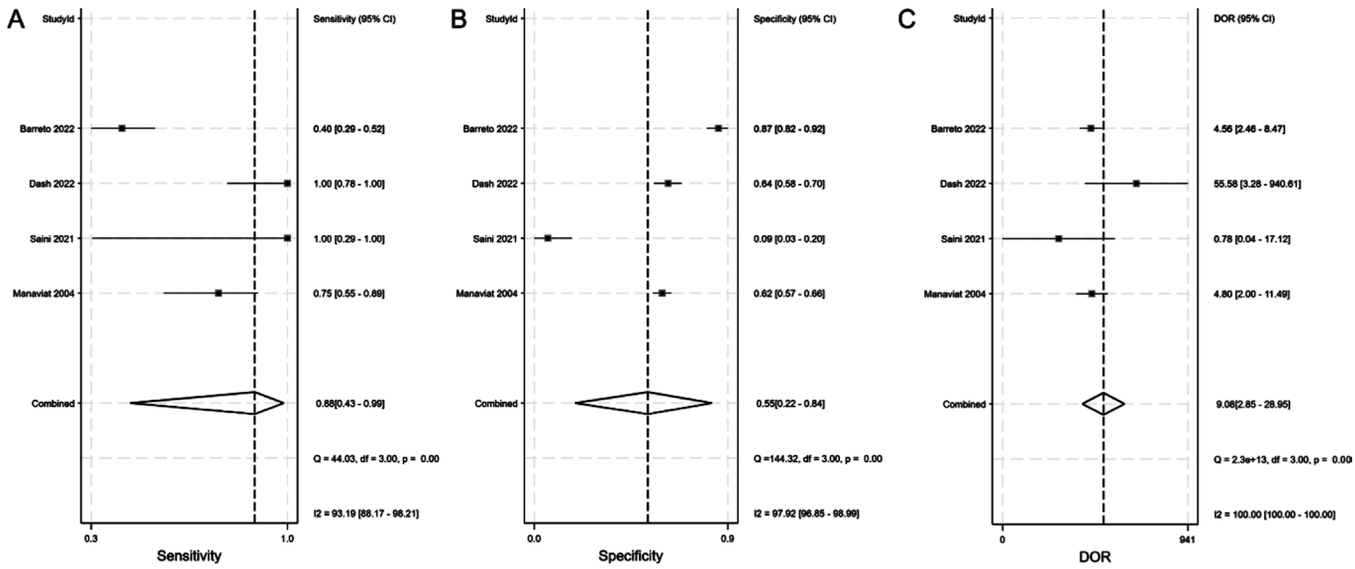

Figure 5 Forest plots of urinary albumin creatinine ratio predicting vision-threatening diabetic retinopathy A: Forest plots of pooled sensitivity of urinary albumin creatinine ratio predicting vision-threatening diabetic retinopathy; B: Forest plots of pooled specificity of urinary albumin creatinine ratio predicting vision-threatening diabetic retinopathy; C: Forest plots of diagnostic odds ratio (DOR) of urinary albumin creatinine ratio predicting vision-threatening diabetic retinopathy.

good discriminative potential. This suggests that UACR, in particular, may serve as a critical marker for early detection of VTDR, offering a significant opportunity for primary prevention and timely intervention. The results for eGFR are not reliable and should be regarded as preliminary evidence.

VTDR remains a leading cause of blindness among diabetic patients, underscoring the necessity of early and accurate predictors like MA and eGFR in clinical practice. While previous studies have focused on the correlation between the severity of diabetic retinopathy and renal pathology, the role of these biomarkers in early detection and management has often been overlooked[28-29]. The findings from Benitez-Aguirre *et al*[30] support this perspective, showing that adolescents with type 1 diabetes possessing a UACR in the upper tertile of the normal range are at increased risk for diabetic retinopathy progression, independent of glycemic control. Fang *et al*[31] confirmed the positive correlation of VTDR with MA and eGFR from the perspective of genetics through a two-sample Mendelian randomization study. Our study showed that MA and eGFR are useful indication for predicting VTDR. The strength of this Meta-analysis lies in its comprehensive evaluation of the predictive value of VTDR through both cross-sectional and longitudinal studies, encompassing over 80 000 cases of diabetes that enhances the generalizability of the findings.

The 14 studies identified for our meta-analysis varied in certain characteristics. For instance, studies included patients with AER greater 21.5 mg/24h[15] and 30 mg/24h[17,19] and 300 mg/24h[24]. In addition, there was significant diversity in the methods used to assess VTDR, and only four studies applied gold standard for VTDR diagnose[17-19,23]. We also found significant heterogeneity, which may be explained by the following limitations. First, baseline risk factors were not standardized between studies. Most of the included studies were conducted in Southeast Asian countries, and to a lesser extent in European countries. Second, variability in the UACR assay results from differences between fully automated analyzers and enzyme-linked immunosorbent assay (ELISA) methods. Additionally, factors such as the duration of diabetes, hyperglycemia, and hypertension among participants may all impact the diagnosis of VTDR. Furthermore, the presence of six studies with sample sizes smaller than 200 helps explain the observed publication bias in Meta-analyses predicting VTDR using MA and eGFR[8,16-17,21,24-25]. Meanwhile, subgroup analyses indicated that larger studies demonstrated lower sensitivity, suggesting that sample size is a potential source of heterogeneity and may influence the estimated predictive accuracy of these biomarkers.

In the 14 studies included in this study, there is no Chinese population data (Table 1 shows that the research sources cover 10 countries, including Israel and Denmark, and China is not included), which may lead to limited applicability of the results to Chinese diabetes patients. As the country with the largest number of diabetes patients (prevalence rate in 2023 is about 11.9%), its population genetic background (such as *ACE* gene polymorphism), diet structure (high carbohydrate intake) and European and American populations are different, which may affect the association strength between UACR and VTDR[32-33]. In the future, large-scale studies based on the Chinese population are needed to verify the value of UACR in VTDR screening in China.

Our Meta-analysis revealed significant heterogeneity among the included studies (I^2=95.87%–97.89%). While Meta-regression indicated that study design and diabetes type were not significant sources of this heterogeneity, we identified key clinical and methodological variations as the underlying causes. For instance, clinicians using UACR to assess VTDR risk may need to adjust threshold interpretation based on whether local laboratories adopt automated *vs* manual assay methods, as variability in quantification could alter the clinical significance of a given UACR value. Specifically, studies applied different thresholds for defining microalbuminuria (*e.g.*, UACR>30 mg/g; AER ranging from >20 μg/min to >300 mg/24h), leading to inconsistent classification of "abnormal" renal function. Additionally, UACR/AER quantification methods varied (from fully automated analyzers to ELISA), and importantly, the diagnostic criteria for VTDR differed substantially across studies (ranging from ophthalmoscopy to combined FFA/OCT). Given the superior sensitivity of FFA and OCT in detecting DME and early neovascularization in PDR, studies relying solely on ophthalmoscopy may have underdiagnosed VTDR[34]. Accordingly, clinicians should select UACR thresholds referenced to local assay methods and VTDR diagnostic tools, and exercise caution when extrapolating our pooled results to settings with different technical specifications to avoid misinterpreting risk stratification for patients. Accordingly, clinicians should select UACR thresholds referenced to local assay methods and VTDR diagnostic tools, and exercise caution when extrapolating our pooled results to settings with different technical specifications to avoid misinterpreting risk stratification for patients.

This heterogeneity substantially impacts the clinical applicability of our pooled estimates. The summary sensitivity and specificity should be interpreted as average values derived from diverse clinical settings and diagnostic criteria. The generalizability of our findings is optimal when local clinical conditions—including chosen renal biomarker thresholds and available retinal diagnostic methods—align with the protocols used in the included studies. To enhance the validity and clinical utility of future research, we recommend adopting standardized UACR thresholds (*e.g.*, >30 mg/g) and implementing more precise VTDR diagnostic approaches, such as combined fundus photography and OCT, to improve the reliability of predictive accuracy estimates. The predictive performance of renal biomarkers (AUC 0.70–0.78) in our analysis positions them as a practical alternative to more complex VTDR prediction models. While artificial intelligence (AI)-based retinal imaging algorithms can achieve higher AUC values (>0.90), they require specialized equipment not universally available[35]. Similarly, clinical risk scores incorporating diabetes duration and hemoglobin A1c (HbA1c) typically show comparable discriminative ability (AUC 0.77–0.79) but lack the direct reflection of microvascular pathology that renal biomarkers provide[36]. UACR thus represents an accessible and biologically relevant predictor, particularly valuable in resource-limited settings[37]. The strong association between renal biomarkers and VTDR finds support in their shared microvascular pathophysiology. Both complications involve endothelial dysfunction, oxidative stress, and advanced glycation end product accumulation, leading to vascular permeability and basement membrane thickening. Microalbuminuria, as detected by UACR, serves as a marker of this systemic microangiopathy, providing a biological rationale for its predictive value in VTDR development[38].

Despite its methodological robustness, this review does face limitations. First, the predominance of cross-sectional studies (10 of 14 included studies) limits the ability to establish temporal relationships and draw causal inferences between renal biomarkers and VTDR development. Second, the assessment of eGFR was based on only three studies with relatively small sample sizes, which may affect the reliability of its pooled diagnostic estimates. Third, we were unable to adjust for important clinical confounders such as diabetes duration, glycemic control (HbA1c), and hypertension status, which are known to influence both renal function and retinopathy progression. Finally, the varied diagnostic thresholds and patient populations across studies introduce the potential for spectrum bias, which may affect the generalizability of our findings. Future large-scale longitudinal studies with standardized protocols and adjusted analyses are needed to validate these associations.

In summary, our findings confirm a significant association between abnormal renal function markers—MA, eGFR, and particularly UACR—and the development of VTDR in individuals with diabetes mellitus. Although the overall test performance indicates room for improvement, the UACR assay, which avoids the cumbersome 24-hour urine collection, has simplicity and non-invasiveness of these measurements make them invaluable tools for clinicians. This review strongly advocates for the integration of UACR monitoring into routine diabetes care, which could facilitate timely ophthalmological referrals and interventions, thus effectively managing VTDR and potentially preventing significant vision loss in diabetic populations.

In conclusion, MA and eGFR are valuable tools for diagnosing or screening VTDR. Additionally, the UACR may serve as a highly specific indicator for this condition.

ACKNOWLEDGEMENTS

The authors extend their gratitude to all the participants involved in the survey and to Dr. Qianling Shi for her expert guidance in the statistical analysis of this study.

Authors' Contributions: Zhou H and Luo XX were involved in conceptualization; Gao Y and Zhuang JY were involved in methodology and formal analysis; Gao Y and Zhuang JY participated in data curation and writing-original draft preparation; Ren YY, Zhang HZ, Hu YM, Li CH, and Hu M supervised the study; Zhang HZ and Luo XX participated in writing, reviewing and editing.

AI-Generated Content Disclosure: No artificial intelligence (AI) tools were used in the preparation, analysis, or interpretation of this study.

Foundations: Supported by the Natural Science Foundation of Gansu Province (No.24JRRA566); National Natural Science Foundation of China (No.81960888); Gansu Provincial Key R&D Program (No.20YF3FA019); Excellent Doctoral Program of Gansu Natural Science Foundation (No.23JRRA1223).

Conflicts of Interest: Gao Y, None; **Zhuang JY,** None; **Ren YY,** None; **Zhang HZ,** None; **Hu YM,** None; **Li CH,** None; **Hu M,** None; **Zhou H,** None; **Luo XX,** None.

REFERENCES

1 Sun H, Saeedi P, Karuranga S, *et al*. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* 2022;183:109119.

2 Hou X, Wang L, Zhu D, *et al*. Prevalence of diabetic retinopathy and vision-threatening diabetic retinopathy in adults with diabetes in China. *Nat Commun* 2023;14:4296.

3 Yau JW, Rogers SL, Kawasaki R, *et al*. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;35(3):556-564.

4 Vujosevic S, Aldington SJ, Silva P, *et al*. Screening for diabetic retinopathy: new perspectives and challenges. *Lancet Diabetes Endocrinol* 2020;8(4):337-347.

5 Marques AP, Ramke J, Cairns J, *et al*. The economics of vision impairment and its leading causes: a systematic review. *EClinicalMedicine* 2022;46:101354.

6 Kjaergaard AD, Teumer A, Witte DR, *et al*. Obesity and kidney function: a two-sample Mendelian randomization study. *Clin Chem* 2022;68(3):461-472.

7 Xu R, Sun S, Huo Y, *et al*. Effects of ACEIs versus ARBs on proteinuria or albuminuria in primary hypertension: a meta-analysis of randomized trials. *Medicine (Baltimore)* 2015;94(39):e1560.

8 Saini DC, Kochar A, Poonia R. Clinical correlation of diabetic retinopathy with nephropathy and neuropathy. *Indian J Ophthalmol* 2021;69(11):3364-3368.

9 Lee MK, Han KD, Lee JH, *et al*. Normal-to-mildly increased albuminuria predicts the risk for diabetic retinopathy in patients with type 2 diabetes. *Sci Rep* 2017;7:11757.

10 He D, Gao B, Wang J, *et al*. The difference between cystatin C- and creatinine-based estimated glomerular filtration rate and risk of diabetic microvascular complications among adults with diabetes: a population-based cohort study. *Diabetes Care* 2024;47(5):873-880.

11 Ulasi II, Awobusuyi O, Nayak S, *et al*. Chronic kidney disease burden in low-resource settings: regional perspectives. *Semin Nephrol* 2022;42(5):151336.

12 Korsa A, Tesfaye W, Sud K, *et al*. Risk factor-based screening for early detection of chronic kidney disease in primary care settings: a systematic review. *Kidney Med* 2025;7(4):100979.

13 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.

14 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.

15 Kalter-Leibovici O, Van Dyk DJ, Leibovici L, *et al*. Risk factors for development of diabetic nephropathy and retinopathy in Jewish IDDM patients. *Diabetes* 1991;40(2):204-210.

16 Johansen J, Sjølie AK, Elbøl P, *et al*. The relation between retinopathy and albumin excretion rate in insulin-dependent diabetes mellitus: From the Funen County Epidemiology of Type 1 Diabetes Complications Survey. *Acta Ophthalmol (Copenh)* 1994;72(3):347-351.

17 Banerjee S, Ghosh US, Basu AK, *et al*. Diabetic microvasculopathy: the renal-retinal link. *J Indian Med Assoc* 2004;102(8):410-413,416.

18 Manaviat MR, Afkhami M, Shoja MR. Retinopathy and microalbuminuria in type II diabetic patients. *BMC Ophthalmol* 2004;4(1):9.

19 Tamadon MR, Ghorbani R, Rezaei S, *et al*. Assessing of the relationship between renal function tests and retinopathy stage in patients with type II diabetes. *J Renal Inj Prev* 2015;4(1):11-14.

20 Kaewput W, Thongprayoon C, Rangsin R, *et al*. Associations of renal function with diabetic retinopathy and visual impairment in type 2 diabetes: a multicenter nationwide cross-sectional study. *World J Nephrol* 2019;8(2):33-43.

21 Aman M, Rasyid H, Sartika SD, *et al*. Albumin excretion rate among patients with diabetic retinopathy. *Caspian J Intern Med* 2020;11(2):177-182.

22 Barreto J, Chaves F, Fernandes VHR, *et al*. Proteinuria in early referral to spectral domain optical coherence tomography for macular edema detection in type 2 diabetes individuals: results from the Brazilian diabetes study. *Curr Med Res Opin* 2022;38(12):2141-2148.

23 Dash S, Chougule A, Mohanty S. Correlation of albuminuria and diabetic retinopathy in type-II diabetes mellitus patients. *Cureus* 2022;14(2):e21927.

24 Parving HH, Nielsen FS, Bang LE, *et al*. Macro-microangiopathy and endothelial dysfunction in NIDDM patients with and without diabetic nephropathy. *Diabetologia* 1996;39(12):1590-1597.

25 Gilbert RE, Tsalamandris C, Allen TJ, *et al*. Early nephropathy predicts vision-threatening retinal disease in patients with type I diabetes mellitus. *J Am Soc Nephrol* 1998;9(1):85-89.

26 Cho A, Park HC, Lee YK, *et al*. Progression of diabetic retinopathy and declining renal function in patients with type 2 diabetes. *J Diabetes Res* 2020;2020:8784139.

27 Yu Y, Ying GS, Maguire MG, *et al*. Association of diagnosis code-based and laboratory results-based kidney function with development of vision threatening diabetic retinopathy. *Ophthalmic Epidemiol* 2020;27(6):498-503.

28 Betzler BK, Chee EYL, He F, *et al*. Deep learning algorithms to detect diabetic kidney disease from retinal photographs in multiethnic populations with diabetes. *J Am Med Inform Assoc* 2023;30(12):1904-1914.

29 Tofte N, Lindhardt M, Adamova K, *et al*. Early detection of diabetic kidney disease by urinary proteomics and subsequent intervention with spironolactone to delay progression (PRIORITY): a prospective observational study and embedded randomised placebo-controlled trial. *Lancet Diabetes Endocrinol* 2020;8(4):301-312.

30 Benitez-Aguirre PZ, Marcovecchio ML, Chiesa ST, *et al*. Urinary albumin/creatinine ratio tertiles predict risk of diabetic retinopathy progression: a natural history study from the Adolescent Cardio-Renal Intervention Trial (AdDIT) observational cohort. *Diabetologia* 2022;65(5):872-878.

31 Fang J, Luo C, Zhang D, *et al*. Correlation between diabetic retinopathy and diabetic nephropathy: a two-sample Mendelian randomization study. *Front Endocrinol (Lausanne)* 2023;14:1265711.

32 Ke J, Li K, Cao B. A nomogram for predicting vision-threatening diabetic retinopathy among mild diabetic retinopathy patients: a case-control and prospective study of type 2 diabetes. *Diabetes Metab Syndr Obes* 2023;16:275-283.

33 Yaegashi A, Sunohara S, Kimura T, *et al*. Association between dietary carbohydrate intake and risk of type 2 diabetes: a systematic review and meta-analysis of cohort studies. *Diabetol Int* 2023;14(4):327-338.

34 Zeng QZ, Li SY, Yao YO, *et al*. Comparison of 24×20 mm^2 swept-source OCTA and fluorescein angiography for the evaluation of lesions in diabetic retinopathy. *Int J Ophthalmol* 2022;15(11):1798-1805.

35 Yao J, Lim J, Lim GYS, *et al*. Novel artificial intelligence algorithms for diabetic retinopathy and diabetic macular edema. *Eye Vis (Lond)* 2024;11(1):23.

36 Royce N, Cronjé HT, Kengne AP, *et al*. HbA1c comparable to fasting glucose in the external validation of the African Diabetes Risk Score and other established risk prediction models in Black South Africans. *BMC Endocr Disord* 2024;24(1):213.

37 Dai H, Liu L, Xu W. Association of albumin-to-creatinine ratio with diabetic retinopathy among US adults (NHANES 2009-2016). *Endocrinol Diabetes Metab* 2025;8(1):e70029.

38 Zhang H, Yang S, Wang H, *et al*. Assessing the diagnostic utility of urinary albumin-to-creatinine ratio as a potential biomarker for diabetic peripheral neuropathy in type 2 diabetes mellitus patients. *Sci Rep* 2024;14(1):27198.