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ORIGINAL ARTICLE

Is chronic kidney disease associated with diabetic retinopathy in Asian adults?

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Abstract

Background: Diabetic nephropathy (DN) is commonly associated with diabetic retinopathy (DR). Few studies have demonstrated that chronic kidney disease (CKD) is associated with DR. However, it is not clear if CKD in the absence of albuminuria is associated with DR.

Methods: We included 301 participants with diabetes (Chinese, Malay and Indian ethnicity aged ≥24 years who participated in the Singapore Prospective Study Program (2003–2007). Retinal photographs taken from both eyes were graded for DR using the modified Airlie House Classification. We examined the association of CKD defined by low estimated glomerular filtration rate (eGFR) (<60 mL/min per 1.73 m^2, $n = 54$), and albuminuria (urinary albumin-to-creatinine ratio ≥30, $n = 116$) with any-DR ($n = 99$) in logistic regression models. We replicated this analysis in another independent population-based sample of Malay adults ($n = 265$) with similar methodology in Singapore.

Results: 41% of those with low-eGFR had normoalbuminuria. In separate models, while albuminuria was significantly associated with any-DR, low-eGFR was not significantly associated with any-DR. In a model combining both markers, compared to the referent group (normal-eGFR+normoalbuminuria), the odds ratio (OR) (95% confidence interval [CI]) of any-DR were: 2.33 (1.27–4.27) for normal-eGFR+albuminuria, 1.38 (0.49–3.91) for low-eGFR + normoalbuminuria, and 2.64 (1.05–6.63) for low-eGFR+albuminuria. Similar findings for any-DR were observed in the replication cohort of Malay persons (3.56 [1.49–8.54] for normal-eGFR+albuminuria, 1.69 (0.52–5.55) for low-eGFR+normoalbuminuria, 4.34 [1.68–11.24] for low-eGFR+albuminuria.

Conclusion: We demonstrated that CKD is associated with DR only in the presence of albuminuria suggesting that CKD is more likely related to diabetes in the presence of albuminuria.

Keywords: albuminuria, diabetic retinopathy, estimated glomerular filtration rate.

Significant findings of this study: Lower eGFR is not significantly associated with DR in the absence of albuminuria, while it is strongly associated with DR in the presence of albuminuria.
What this study adds: Nonalbuminuric CKD is not associated with DR in Asian adults with diabetes.

ASIA TRACK

Introduction

The prevalence of diabetes is increasing worldwide[1] associated with a rise in diabetes-related microvascular complications including diabetic retinopathy (DR) and diabetic nephropathy (DN). The Kidney Disease Outcome Quality Initiative (KDOQI) suggests that in persons with diabetes, in the absence of kidney biopsy, chronic kidney disease (CKD) defined by lower estimated glomerular filtration rate (eGFR) is attributed to diabetes if there is albuminuria and retinopathy.[2] Several studies have reported concordance between albuminuria and DR,[3–7] with microvascular disease being the mechanism central to both DN and DR.[8] However, not all subjects with diabetes and kidney disease have albuminuria. Prevalence studies have shown that from a third[9] up to a half of subjects[10] with diabetes and lower eGFR do not have albuminuria (nonalbuminuric CKD). It has been postulated that nonalbuminuric CKD in diabetes may be mediated by mechanisms distinct from DN including vascular disease, aging kidney or nephropathy pathways independent of diabetes.[2,11] Although the association between albuminuria, a marker for DN and DR is well established, it is not clear if lower eGFR in the absence of albuminuria (nonalbuminuric CKD) is associated with DR. Few studies that examined the association between lower eGFR and DR have shown mixed results.[12–14] While Chen et al.[12] found that lower eGFR is associated with severe DR only in the presence of albuminuria in diabetic patients, Penno et al. reported an association between lower eGFR and severe DR both in the presence and absence of albuminuria[14] and Grunwald et al. reported an association between lower eGFR and DR independent of albuminuria in a cohort of CKD patients.[13] These studies, however, considered only severe DR and were conducted in clinic populations. The independent association of lower eGFR with DR in general populations is still not clear. In this context, we examined the association between lower eGFR and DR in the presence and absence of albuminuria in a population-based sample of Asian adults in Singapore. We hypothesize that lower eGFR is associated with DR in the absence of albuminuria and the association would be stronger in the presence of albuminuria. To test the robustness of our findings, we replicated the analysis in another independent population-based cohort in Singapore.

Methods

Study population

The Singapore Prospective Study Program (SP2, 2003–2007) is a population-based cross-sectional study of Chinese, Malay and Indians aged ≥24 years in Singapore. Details of recruitment and study methods have been published elsewhere.[15] For the current analysis we included only those with diabetes ($n = 393$) defined as a fasting plasma glucose ≥7 mmol/L (126 mg/dL) or self-reported physician diagnosed diabetes or use of glucose-lowering medication or glycated hemoglobin (HbA1C) ≥6.5%.[16] Of the 393 participants, we further excluded those with missing data on urinary albumin-to-creatinine ratio (ACR) ($n = 16$), serum creatinine ($n = 2$), and other key variables ($n = 74$), leaving 301 participants available for the current analysis.

Assessment of outcome – diabetic retinopathy

Digital retinal photographs were taken after pupil dilation following the Early Treatment for Diabetic Retinopathy Study (ETDRS) protocol.[15] Images were graded for retinopathy by trained graders blinded to the participant characteristics at the Centre for Vision Australia, University of Sydney.[17,18] Participants were considered to have retinopathy if any of the following lesions were present in any eye: microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading, and new vessels. For each eye, retinopathy severity score was assigned according to ETDRS adaptation of the modified Airlie House Classification System.[19] Based on the severity score of the worse eye, any-DR was defined as a severity score of level 15 and above.[20] Moderate DR, defined as an ETDRS severity score of level above 43, was assessed as a secondary outcome.

Assessment of chronic kidney disease and albuminuria

Chronic kidney disease was defined as a low eGFR of <60 mL/min per 1.73 m^2 as recommended by the KDOQI guidelines.[2] GFR was estimated from plasma creatinine using the recently developed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[20] Plasma creatinine was measured by enzymatic method (ADVIA 2400, Bayer Diagnostics, Tarrytown, NY, USA) calibrated to the National Institute of Standards and Technology (NIST) Liquid Chromatography Isotope Dilution Mass Spectrometry (LC-IDMS).[21] Random urinary spot albumin and creatinine were measured using commercial assays (Immulite, DPC, UK and Roche Diagnostics GmbH [Mannheim, Germany] for urinary albumin and creatinine, respectively). Albumin was measured in milligrams per litre and creatinine in millimoles per litre. The lower detection limits for urinary albumin and creatinine were 0.5 mg/L and 0.027 mmol/L, respectively. Presence of albuminuria was

defined as a urinary albumin-to-creatinine ratio (ACR) ≥30 mg/g.[2]

Measurement of other risk factors

Information on sociodemographic and lifestyle factors was collected from an interviewer-administered questionnaire. Anthropometric measurements, blood pressure (BP) and detailed ocular examination were performed as part of the clinical examination. Laboratory examination included measurement of fasting plasma glucose, lipids, HbA1C, and serum creatinine. All serum biochemistry tests were carried out at the National University Hospital Reference Laboratory.

Replication cohort

We validated our findings, using an independent cohort of Malay adults ($n = 265$ with diabetes) who participated in the Singapore Malay Eye Study (SiMES), a population-based cross-sectional study of 3280 Malay adults aged 40 and above in Singapore. Details of the study participants and methods have been described elsewhere.[22] Participants from SiMES were examined in the same study clinic as participants in the current cohort. Clinic examinations, grading protocol and the outcome assessment were identical in the two studies except that blood samples were collected in the fasting state in SP2 and in the non-fasting state in SiMES. Diabetes in SiMES was defined as a casual plasma glucose ≥11.1 mmol/L (200 mg/dL) or self-reported physician diagnosed diabetes or use of glucose-lowering medication or glycated hemoglobin (HbA1C) ≥6.5%. The prevalence of diabetes was 23% in this cohort. Of the 3280 participants, urine was collected in all participants with known diabetes and 1 in 5 without known diabetes. Thus, 944 had urine for ACR assessed. After excluding those without diabetes and those with missing data on serum creatinine and retinopathy, 265 diabetic participants were included for the current analysis.

Written, informed consent was obtained from all participants. Tenets of the Declaration of Helsinki were followed and ethical approval was obtained from the Institutional Review Board of the Singapore Eye Research Institute for both SP2 and SiMES studies.

Statistical analyses

All statistical analyses were performed using SAS version 9.1. For the current analysis, we categorized eGFR into normal (≥60) and low (<60) and albuminuria into absent/normal (ACR<30) and present (ACR ≥30). We also defined a composite variable with four categories combining the eGFR and albuminuria categories: (i) normal-eGFR+normoalbuminuria (referent), (ii) normal-eGFR+albuminuria, (iii) low-eGFR+normoalbuminuria, (iv) low-eGFR and albuminuria. DR was used as a dependent variable. We examined the association of the separate and combined categories of eGFR and albuminuria with any-DR separately in two models: (i) age, sex-adjusted (ii) multivariable models additionally adjusted for ethnicity, education, smoking, alcohol consumption, hypertension, body mass index (BMI), total cholesterol-to HDL cholesterol ratio, history of CVD and duration of diabetes. We then repeated the analyses using moderate DR as the outcome. Statistical interaction between eGFR categories and albuminuria was examined in the corresponding logistic regression models by including cross-product interaction terms. In a separate analysis, to examine if severity of albuminuria is associated with severity of DR, we examined mean ACR levels across categories of DR (mild, moderate and severe). To examine if albuminuric CKD is associated with severe DR compared to non-albuminuric CKD, we then examined the association of low-eGFR and albuminuria with moderate retinopathy using normal-eGFR+albuminuria as the reference category.

In a supplementary analysis, we tested an alternative scenario of whether low-eGFR is associated with albuminuria in the absence of DR. For this analysis, we used albuminuria as a dependent variable and examined the association between low-eGFR and albuminuria in the presence and absence of DR.

Results

Baseline characteristics of the SP2 participants are summarized in Table 1. Compared to those without DR, those with DR had higher levels of HbA1c and longer duration of diabetes. 17.8% ($n = 54$) of the individuals had low-eGFR, of which 41% had normoalbuminuria (nonalbuminuric CKD) (data not shown).

Association of eGFR and albuminuria with DR

Table 2 shows the separate associations of eGFR, albuminuria with both any and moderate retinopathy in the SP2 population. The prevalence of any and moderate DR were 32.9% and 22.9%, respectively, in the study population (data not shown). The prevalence of both any and moderate DR were higher among those with low-eGFR and albuminuria. However, while low-eGFR was not associated with either any or moderate DR in any of the two models, albuminuria showed a significant association with these two outcomes in both age, sex-adjusted and the multivariable model.

Table 1 Characteristics of the Singapore Prospective Study Program (SP2) study population with diabetes

Characteristics	Retinopathy absent (n = 202)	Retinopathy present (n = 99)	P-value
Age (years), mean, SD	58.0 (10.2)	60.5 (10.4)	0.05
Gender, female, %	42.6	45.5	0.6
Race, %			
Chinese	36.1	32.3	0.9
Malay	20.8	23.2	
Indian	35.1	35.4	
Education, secondary and above, %	57.4	48.5	0.1
Current smoking, %	9.4	16.2	0.2
Alcohol consumption, %	27.2	17.2	0.06
Hypertension, %	70.3	74.7	0.4
Cardiovascular disease, %	14.4	13.1	0.8
Body mass index (kg/m^2), mean, SD	26.5 (4.8)	25.9 (4.9)	0.3
HbA1c, %	7.7 (1.7)	8.4 (1.8)	0.001
Fasting blood glucose, mmol/L, mean, SD	7.3 (2.6)	8.1 (4.1)	0.08
Duration of diabetes, y, mean, SD	7.3 (9.0)	10.9 (10.1)	0.003
Total to HDL cholesterol ratio, mean, SD	3.9 (1.0)	4.2 (1.0)	0.08

P-value represents the difference in characteristics by retinopathy status based on χ^2 test or analysis of variance as appropriate for the variable.
HDL, high-density lipoprotein; SD, standard deviation.

Table 2 Association between chronic kidney disease (CKD), albuminuria and diabetic retinopathy (DR) in the SP2 population

	n (cases)	Prevalence of any retinopathy	Age, sex adjusted OR (95% CI)	Multivariable OR (95% CI)*
Any-DR				
eGFR				
Low	54 (24)	44.4%	1.60 (0.85, 3.01)	1.37 (0.68, 2.75)
Normal	247 (75)	30.4%	1.00 (Reference)	1.00 (Reference)
Albuminuria				
No	185 (45)	24.3%	1.00 (Reference)	1.00 (Reference)
Yes	116 (54)	46.6%	2.58 (1.55, 4.29)	2.28 (1.32, 3.95)
Moderate DR				
eGFR				
Low	54 (20)	37.0%	2.01 (1.03, 3.93)	1.32 (0.62, 2.85)
Normal	247 (49)	19.8%	1.00 (Reference)	1.00 (Reference)
Albuminuria				
No	185 (23)	12.4%	1.00 (Reference)	1.00 (Reference)
Yes	116 (46)	39.7%	4.35 (2.42, 7.82)	3.96 (2.07–7.57)

*Model adjusted for age (years), gender (male, female), ethnicity (Chinese, Malay, Indian, others), body mass index (kg/m^2), education (primary and below, secondary and above), smoking (never, current, ex-smoker), alcohol consumption (no, yes), hypertension (no, yes), total cholesterol to high-density lipoprotein cholesterol ratio, history of cardiovascular disease (no, yes) and duration of diabetes (years).
CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; SD, standard deviation; SP2, Singapore Prospective Study Program.

Association of combined categories of eGFR and albuminuria with DR in the study cohort

Table 3 shows the combined categories of eGFR and albuminuria with any and moderate DR in the SP2 population. The prevalence of any DR was highest among those with low-eGFR+albuminuria. Compared to those with normal-eGFR+normoalbuminuria (referent), the association with any DR was stronger among those with low-eGFR+albuminuria with an odds ratio (OR) of 3.38 in the age, sex adjusted model. In models adjusted for potential confounders, the association still remained significant and stronger with an OR of 2.64. Although isolated albuminuria in the absence of low-eGFR was significantly associated with any-DR in both age, sex adjusted (OR = 2.53) and the multivariable models (OR = 2.33), isolated low-eGFR in the absence of albuminuria was not significantly associated with DR

Table 3 Association between combined categories of eGFR, albuminuria and DR in SP2 population

Categories of CKD and albuminuria	*n* (cases)	Prevalence of DR, %	Age, sex adjusted OR (95% CI)	Multivariable OR (95% CI)*
Any-DR				
Normal-eGFR+normoalbuminuria	163 (38)	23.3	1.00 (Reference)	1.00 (Reference)
Normal- eGFR+albuminuria	84 (37)	44.0	2.53 (1.43, 4.48)	2.33 (1.27, 4.27)
Low-eGFR+ normoalbuminuria	22 (7)	31.8	1.42 (0.53, 3.81)	1.38 (0.49, 3.91)
Low-eGFR+albuminuria	32 (17)	53.1	3.38 (1.48, 7.72)	2.64 (1.05, 6.63)
Moderate DR				
Normal-eGFR+normoalbuminuria	163 (19)	11.7	1.00 (Reference)	1.00 (Reference)
Normal-eGFR+albuminuria	84 (30)	35.7	4.09 (2.11, 7.93)	4.14 (2.01–8.53)
Low-eGFR+ normoalbuminuria	22 (4)	18.2	1.56 (0.47, 5.19)	1.26 (0.35–4.52)
Low-eGFR+albuminuria	32 (16)	50.0	6.84 (2.81, 16.65)	4.01(1.46–10.99)

*Model adjusted for age (years), gender (male, female), ethnicity (Chinese, Malay, Indian, others), body mass index (kg/m^2), education (primary and below, secondary and above), smoking (never, current, ex-smoker), alcohol consumption (no, yes), hypertension (no, yes), total cholesterol to high-density lipoprotein cholesterol ratio, history of cardiovascular disease (no, yes) and duration of diabetes (years). P-interaction between low-eGFR and albuminuria = 0.7.

CI, confidence interval; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; OR, odds ratio; SD, standard deviation; SP2, Singapore Prospective Study Program.

Table 4 Association between combined categories of eGFR, albuminuria and DR in SiMES population

Categories of eGFR and ACR	*n* (cases)	Prevalence of DR, %	Age, sex adjusted OR (95% CI)	Multivariable OR (95% CI)*
Any DR				
Normal-eGFR+normoalbuminuria	97 (11)	11.3	1.00 (Reference)	1.00 (Reference)
Normal- eGFR+albuminuria	63 (20)	31.8	3.69 (1.62–8.42)	3.56 (1.49–8.54)
Low-eGFR+ normoalbuminuria	40 (6)	15.0	1.62 (0.52–5.00)	1.69 (0.52–5.55)
Low-eGFR+albuminuria	65 (22)	33.9	4.56 (1.90–10.94)	4.34 (1.68–11.24)
Moderate DR				
Normal-eGFR+normoalbuminuria	97 (3)	1.1	1.00 (Reference)	1.00 (Reference)
Normal-eGFR+albuminuria	63 (5)	7.9	3.02 (0.52–17.49)	1.96 (0.41–9.29)
Low-eGFR+ normoalbuminuria	40 (3)	7.5	2.69 (0.61–11.88)	2.44 (0.39–15.27)
Low-eGFR+albuminuria	65 (12)	18.5	7.86 (1.91–32.27)	4.52 (1.01–20.20)

*Model adjusted for age (years), gender (male, female), body mass index (kg/m^2), education (primary and below, secondary and above), smoking (never, current, ex-smoker), alcohol consumption (no, yes), hypertension (no, yes), total cholesterol to high-density lipoprotein cholesterol ratio, history of cardiovascular disease (no, yes) and duration of diabetes (years). P-interaction between low-eGFR and albuminuria = 0.8.

ACR, albumin-to-creatinine ratio; CI, confidence interval; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; OR, odds ratio; SD, standard deviation; SiMES, Singapore Malay Eye Study.

in either model (OR = 1.42 and 1.38). There was no significant interaction between low-eGFR and albuminuria on DR (P-interaction = 0.7). Similar to any DR, the association of moderate DR was significant and stronger among those with normal eGFR + albuminuria and among those with both low-eGFR+albuminuria.

Association of combined categories of eGFR and albuminuria with DR in the replication cohort

Table 4 shows the association between the combined categories of eGFR and albuminuria with any and moderate DR in the replication cohort (SiMES). The associations were similar to those observed in the SP2 cohort. The prevalence of any-DR was higher among those with normal-eGFR+ albuminuria (44%) and among those with low-eGFR+albuminuria (53.1%). Compared to those with normal eGFR+normoalbuminuria, those with low-eGFR+albuminuria were 4.34 times more likely to have any-DR in the multivariable model. While isolated low-eGFR in the absence of albuminuria was not associated with any-DR, isolated albuminuria with normal eGFR showed a significant association with any-DR (P-interaction = 0.8). Similar to any-DR, compared to those with normal eGFR+normoalbuminuria, both normal-eGFR+albuminuria and low-eGFR+ albuminuria had a significant positive association with moderate DR in both age, sex-adjusted and the multivari-

able models. In contrast, the association of low-eGFR+ normoalbuminuria with moderate DR was not significant in either model.

Albuminuria, albuminuric CKD and severity of DR

Mean ACR levels increased with increasing severity of DR, however it was not statistically significant ($P = 0.2$). In analysis using normal-eGFR and albuminuria as the reference category, those with low-eGFR and albuminuria had higher prevalence of moderate DR (50% vs 35.7%); however, the association was not significant in logistic models adjusted for age, and sex OR (95% confidence interval [CI]) = 2.13 (0.81–5.60) (data not shown).

Supplementary analyses

In a separate analysis, using albuminuria as a dependent variable, we examined the association of low-eGFR and any-DR with albuminuria. We found that low-eGFR was not associated with albuminuria in the absence of any-DR (OR [95%CI] = 1.99 [0.82–4.85]), whereas low-eGFR showed a strong association with albuminuria in the presence of any-DR (OR [95%CI] = 3.93 [1.32–11.65]) (data not shown). Similar findings were also observed in the replication cohort with OR (95% CI) of albuminuria being 1.84 (0.92–3.68) for CKD and no-DR and 5.70 (2.06–15.82) for CKD and any-DR (data not shown).

Discussion

In a multi-ethnic sample of Asian adults, we found that isolated low-eGFR in the absence of albuminuria (non-albuminuric CKD) was not significantly associated with any-DR, while low-eGFR in the presence of albuminuria (albuminuric CKD) was significantly associated with any-DR. The findings were similar when moderate retinopathy was used as an outcome. In addition, these findings for both any and moderate DR were mirrored in the replication cohort with similar methodology as the initial study. The consistency of our findings with any and moderate DR and in both studies demonstrates the robustness of our findings.

We found that albuminuria, a marker for DN, is significantly associated with DR even in the absence of low-eGFR. This is not surprising given the well-established relationship between DN and DR.[4,5,23,24] Microvascular damage from chronic hyperglycemia, oxidative stress and concomitant hypertension leads to vascular remodeling and impaired vessel dilation contributing to the concordance of DR and albuminuria in diabetic subjects.[8,23] In addition, factors associated with renal damage including poor BP control,[25] elevated levels of fibrinogen,[26,27] lipids and lipoproteins[28] also accelerate retinopathy. Besides being a marker for renal damage, albuminuria has also been shown to be associated with other micro and macrovascular complications in diabetic subjects[29] suggesting its role as an indicator of generalised vascular damage.

In the current study, 41% of the individuals with low-eGFR had normal levels of albuminuria. This is consistent with earlier reports that showed that up to 50% of the subjects with diabetes and CKD had normoalbuminuria.[10,14] We found that isolated low-eGFR in the absence of albuminuria is not significantly associated with DR. Isolated low-eGFR in the absence of albuminuria was also not associated with advanced DR in a clinical study involving veterans with diabetes in Taiwan.[12] Penno et al.[14] in Italy showed an association between lower eGFR and advanced DR both in the presence and absence of albuminuria although the association was stronger in the albuminuric CKD than in the nonalbuminuric CKD phenotypes.[14] This is also consistent with earlier studies reporting the nonalbuminuric CKD phenotypes posing a decreased risk for CKD progression and death,[30] cardiovascular disease,[30–32] other microvascular complications including retinopathy[33] and peripheral neuropathy[34] compared to the albuminuric CKD phenotypes. As albuminuria is an indicator of diabetic nephropathy, the nonalbuminuric low-eGFR picture suggests that low-eGFR in these subjects may be due to non-diabetic causes[11] and may represent a less severe phenotype[30] that explains the weaker non-significant association of isolated low-eGFR with DR in the current study.

In the current study, 59% of those with CKD had albuminuria. We found that low-eGFR in the presence of albuminuria (albuminuric CKD) is significantly associated with DR. These findings support the recent KDOQI guidelines, which recommend including information on albuminuria at all stages of CKD to improve classification and prognostication.[35] This is also consistent with the findings of two previous studies[12,14] that evaluated the association between eGFR, albuminuria, and severe DR in large cohorts of diabetic patients. Chen et al. in Taiwan found that isolated albuminuria was a better predictor of severe DR compared to isolated low-eGFR in diabetic patients.[12] In the Renal Insufficiency and Cardiovascular Events (RIACE) Italian multicentre study,[14] Penno et al. showed that in patients with type 2 diabetes, the albuminuric, low-eGFR phenotypes were stronger correlates of severe DR than the non-albuminuric one.[14] Our study results are consistent with these two studies and further extend the findings to population-based subjects with stable DR. Few other

studies have also shown that low-eGFR is associated with DR in diabetic subjects.[13,36,37] Yet, these studies did not take into account the effect of albuminuria in the association between low-eGFR and DR. The association of albuminuric CKD with DR could be explained by systemic microvascular damage resulting from diabetes. Chronic hyperglycemia induced oxidative stress plays an important role in the initiation of microvascular complications through many metabolic and structural alterations, including the production of advanced glycation end products (AGE), abnormal activation of protein kinase C [PKC]), elevated production of reactive oxygen species,[38] and abnormal activation of the renin-angiotensin system (RAS).[39] The presence of albuminuria in diabetes patients is a risk marker not only for kidney and cardiovascular disorders, but also for severe ocular morbidity.[40,41]

In the current study, while we found an association between low-eGFR and DR only in the presence of albuminuria, in the analysis testing an alternative scenario, we found an association between low-eGFR and albuminuria only in the presence of DR. Similar findings were also observed in the replication cohort. These findings are consistent with the KDOQI guidelines, which suggest that in diabetic subjects, CKD is attributed to diabetes in the presence of albuminuria or DR.[2]

The strengths of our study are that firstly, this study is a population-based multi-ethnic sample with stable chronic kidney disease over cohort-based diabetic patients, and that an objective assessment of DR was used via digital retinal photography with comprehensive information on confounders. The cross-sectional nature of our study limits making causal inferences. In addition, assessment of albuminuria based on a single spot urinary ACR measurement could have also resulted in non-differential misclassification of the albuminuria status and either overestimated or underestimated the prevalence of albuminuria.

In summary, we found that low-eGFR is not significantly associated with DR in the absence of albuminuria, while it is strongly associated with DR in the presence of albuminuria. If confirmed by future prospective studies, our findings may have important clinical implications for DR screening in diabetic subjects with both low-eGFR and albuminuria, such as providing an increased frequency of DR screening for these diabetic patients compared to those with isolated low-eGFR.

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Disclosure

The authors declare no conflict of interest.

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