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Diabetic Retinopathy and Chronic Kidney Disease: Associations and Comorbidities in a Large Diabetic Population – The Tongren Health Care Study

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Type 2 diabetes · Diabetic retinopathy · Chronic kidney disease · Diabetic microvascular complication · Albuminuria · Estimated glomerular filtration rate · Albumin-to-creatinine ratio

Abstract
Introduction: The aim of the study was to investigate associations between diabetic retinopathy (DR) and chronic kidney disease (CKD) in patients with type 2 diabetes (TD2). ***Methods:*** The participants of the cross-sectional, community-based Tongren Health Care Study underwent a detailed medical and ophthalmological examination. We defined TD2 by a fasting plasma glucose concentration of ≥7.0 mmol/L or a medical history. CKD was classified as either reduced estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 mm^2 or presence of albuminuria. DR was assessed using color fundus photographs. ***Results:*** Out of 62,217 participants of the Tongren Health Care Study, 5,103 (8.2%) patients had TD2. The prevalence of DR was 12.8% (95% CI, 11.8%, 13.7%), CKD was 13.3% (95% CI, 12.4%, 14.3%), and the subtypes of CKD including reduced eGFR and albuminuria was 4.6% (95% CI, 4.2%, 5.1%) and 10.1% (95% CI, 9.3%, 10.9%), respectively. DR was detectable in 21.0% of the patients with CKD, while CKD was present in 20.9% of the DR patients. Higher DR prevalence was associated with higher prevalence of albuminuria and reduced eGFR (both $p < 0.05$). Factors independently associated with the presence of CKD instead of DR were older age ($p < 0.001$, OR = 1.05), a higher body mass index ($p < 0.001$, OR = 1.14), a higher serum concentration of triglycerides ($p < 0.001$, OR = 1.26), and a lower blood glucose

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($p < 0.001$, OR = 0.93). Having hypertension was additionally associated with the presence of reduced eGFR as compared with DR ($p = 0.005$, OR = 4.47). ***Conclusions:*** TD2 patients of older age and with higher body mass index, hypertension, and dyslipidemia had a higher probability of being affected by CKD rather than DR, while those with a higher blood glucose level were more prone to DR than CKD.

Introduction

The prevalence of diabetes has markedly increased in recent decades, with the number of individuals with diabetes being forecasted to be 783 million in the year 2045 [1]. Diabetic retinopathy (DR) and chronic kidney disease (CKD) belong to the most common microvascular complications of diabetes, both occurring in approximately 30% of diabetic patients [2–4]. It has been assumed that the eye and kidney share similar diabetes-related microvascular changes [5–7]. Nephropathy was found to be a risk factor for developing retinopathy and vice versa in diabetes [8]. Recent studies have suggested that these two diabetic microvascular complications may differ in their associations with other risk parameters, in particular in patients with type 2 diabetes (TD2) [9]. Unlike that in type 1 diabetes, in which DR can be found in more than 90% of the patients with CKD, CKD and DR often occur independently of each other in patients with TD2 [10–13]. In addition, the temporal relationship between albuminuria and a reduced estimated glomerular filtration rate (eGFR) is variable in patients with TD2, with an eGFR reduction often occurring without albuminuria and being only loosely associated with the occurrence of DR [6, 11–16]. These observations may suggest disparities in the pathogenesis of DR and CKD in TD2 patients, supporting the notion that there might be structural and functional differences between the renal and retinal vasculature [5].

Consistent with these observations, previous studies have noted that individuals with TD2, even with comparable glycemic control, exhibited variations in diabetic organ damage. It was found that systemic factors, including obesity, arterial hypertension, and dyslipidemia, may be key factors associated with normo-albuminuric CKD, independently of hyperglycemia [6, 11–18].

These studies, however, either included study populations recruited in a hospital-based manner, or they examined epidemiologically recruited populations containing only a relatively small number of diabetic patients. A comprehensive analysis of the risk factors for DR and CKD, and a quantitative comparison of their roles in potentially different etiologies have not been carried out yet.

Identifying the demographic and clinical features of DR and CKD as defined by a reduced eGFR or albuminuria may assist in the clinical evaluation and prediction of diabetic microvascular complications and may be helpful to further elucidate the underlying pathogenetic mechanisms. We therefore examined in the current community-based study on TD2 patients the prevalence of DR and CKD and their concurrence and assessed differences between subgroups of diabetic patients being affected only by DR or only by CKD.

Methods

The cross-sectional, community-based Tongren Health Care Study included individuals who attended regular health care check-up examinations in the Beijing Tongren Hospital between January 2014 and December 2019. The study protocol was approved by the Medical Ethics Committee of Beijing Tongren Hospital and was in adherence with the Declaration of Helsinki. The individuals underwent a detailed medical examination including taking the medical history, basic physical examinations, and biochemical analysis of blood and urine samples. In addition, the individuals were ophthalmologically examined, and fundus photographs (non-mydriatic 45° fundus camera, Topcon camera TRG-NW7SF (Topcon Co., Tokyo, Japan), or Cannon camera CR6-45NM (Canon Co., Tokyo, Japan) were taken. The design of the study has been described in detail previously [19]. Arterial hypertension was defined as a systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg, or a history of physician-based diagnosis of hypertension history or use of antihypertensive medication. Diabetes mellitus was defined by a history of previously diagnosed diabetes, taking a serum glucose-lowering therapy, or a fasting blood glucose concentration of ≥7.0 mmol/L. Patients with type 1 diabetes and gestational diabetes were excluded from the study. Cardiovascular disease was defined based on the history of physician-based diagnosis.

Kidney Function Assessment and the Definition of CKD

The serum creatinine concentration was measured using a standardized enzymatic method. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [20]. A reduced eGFR was defined as an eGFR of <60 mL/min/1.73 m^2. The urine protein concentration was measured by the dipstick test (reagent strip) using morning fresh urine samples and reporting the results as negative, trace, 1+, 2+, 3+, or higher. Those gradings were aligned to albuminuria stage: A1 (albumin-to-creatinine ratio (ACR) <3 mg/mmol) represents the "negative" and "trace" results, A2 (ACR: 3–30 mg/mmol) corresponding to "1+", and A3 (ACR >30 mg/mmol) corresponding to ≥ "2+". Albuminuria was defined as a value of ≥1+ (A2) [21]. According to the guidelines of the "Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group", CKD was defined based either on the presence of a reduced eGFR or on the presence of albuminuria [21]. To analyze the potential

variations in renal dysfunction associated with DR, our assessment focused on two specific groups: (1) individuals with reduced eGFR, and (2) individuals with albuminuria.

Assessment of DR

DR was defined by the presence of one or more retinal microaneurysms or retinal dot hemorrhages and was categorized into four levels: mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative DR (PDR) [22]. When DR was present in both eyes, the data of the eye with the more advanced DR grade were chosen for statistical analysis. All fundus images were examined by two experienced ophthalmologists (LQG, JX). The inter-observer variability in assessing the presence of DR in randomly selected 100 photographs showed an excellent Cohen's kappa coefficient of 0.85.

Statistical Analyses

The statistical software SPSS 27.0 (SPSS for Windows, version 27.0, IBM-SPSS, Chicago, IL, USA) was used for data analysis. Continuous variables were presented as mean ± standard deviation and median (interquartile range), and categorical variables as the number of cases/percentages. We stratified diabetic participants into four groups: group 1: with DR alone, group 2: with CKD alone, group 3: with both DR and CKD, and group 4: without DR and without CKD. Differences among the four groups were analyzed using the χ^2 test for categorical variables, and the continuous variables were compared by a one-way analysis of variances when the assumption of the homogeneity of variances was achieved; otherwise, Wilcoxon-Mann-Whitney test was applied. Post host tests adjusted by the Bonferroni method were performed when a significant difference was detected among the four groups. Binary logistic regression analysis was performed to investigate the associations between the prevalence of DR and the prevalence of CKD, adjusting for parameters which showed a significant association ($p < 0.05$) with the outcome parameter in the univariate analyses. Furthermore, we performed separate analyses with two subtypes of CKD, including: (1) a subgroup of participants with an eGFR of <60 mL/min/1.73 mm^2, and (2) a subgroup of participants with albuminuria. We calculated the odds ratios (ORs) and their 95% confidence intervals (CIs). For multivariable regression analyses, a variance inflation factor higher than 5 was considered to indicate collinearity. A two-tailed p value of <0.05 was considered to be statistically significant.

Results

Among 62,217 individuals (52.7% men) with a mean age of 42.5 ± 14.4 years (range: 18–101 years), 5,346 had diabetes. After excluding 243 (0.39%) individuals with type 1 diabetes or gestational diabetes, TD2 was present in 5,103 participants (52.7% men), with a prevalence of 8.2% (95% CI: 8.0%, 8.4%). A flowchart depicting the participant recruitment process, including the inclusion/exclusion criteria, can be found in Supplemental Figure 1 (for all online suppl. material, see https://doi.org/10.1159/000535059).

Patients with TD2 were older than those without diabetes (57.3 ± 13.2 years vs. 41.2 ± 13.8 years; $p < 0.001$). Men as compared with women had a higher prevalence of TD2 (men: 10.2%; 95% CI, 9.9%, 10.5%; women: 6.0%; 95% CI, 5.7%, 6.2%; $p < 0.001$). Among the 5,103 patients with TD2, 3,858 (75.6%) were diagnosed by medical history, while the remaining 1,245 (24.5%) were detected based solely on a fasting blood glucose concentration of ≥7.0 mmol/L. The mean reported known diabetic duration was 5.6 ± 7.2 years (range: 0–53 years).

The prevalence of DR, detected in 598 participants, was 12.8% (95% CI, 11.9%, 13.8%), excluding 435 participants (8.5% of the TD2 patients) with ungradable fundus photographs. The prevalence rates of mild NPDR, moderate NPDR, severe NPDR, and PDR were 7.5% (95% CI, 6.9%, 8.2%), 3.0% (95% CI, 2.6%, 3.4%), 0.9% (95% CI, 0.8%, 1.1%), and 1.3% (95% CI, 1.1%, 1.6%). DR was more frequently detected in men (13.9%, 95% CI, 12.7%,15.1%) than in women (10.7%, 95% CI, 9.3%, 12.1%) ($p = 0.03$, age-adjusted OR = 1.24). The prevalence of DR decreased significantly with age in men ($p < 0.001$), in women ($p = 0.016$), and in the whole population ($p < 0.001$) (linear-by-linear association) (Table 1) (Fig. 1).

CKD, an eGFR of <60 mL/min/1.73 mm^2, and albuminuria were detected in 664, 240, and 503 participants, respectively, with respective prevalences of 13.5% (95% CI, 12.5%, 14.4%), 4.7% (95% CI, 4.3%, 5.2%), and 10.2% (95% CI, 9.4%, 11.0%) (Table 1). A higher prevalence of CKD was related to older age (OR = 1.03; $p < 0.001$) and male sex (OR = 1.25; $p = 0.016$). The prevalence of reduced eGFR increased with older age (OR = 1.15; $p < 0.001$) and with female sex (OR = 1.35; $p = 0.04$). In contrast, the prevalence of albuminuria was higher in men than in women (OR = 1.61; $p < 0.001$) but showed no significant association with age ($p = 0.47$) (Table 1) (Fig. 1).

Association between DR and CKD

Within the group of patients with TD2, the concurrence rates of DR with CKD, albuminuria, and reduced eGFR were 2.7% (95% CI, 2.3%, 3.0%), 2.4% (95% CI, 2.1%, 2.7%), and 0.49% (95% CI, 0.40%, 0.60%) (Fig. 2). Within the group of patients with CKD, albuminuria, and reduced eGFR, 21.0%, 24.4%, and 13.1% also presented with DR. Conversely, in DR patients, the proportion with CKD, albuminuria, and reduced eGFR was 20.9%,18.8%, 3.9%.

The presence of DR and its severity were positively associated with the prevalence of albuminuria, without or with adjustment for age and sex (all $p < 0.05$), while their association with reduced eGFR was only significant after age and sex adjustment ($p = 0.014$) (Table 2, Fig. 3). Similarly, severe albuminuria was associated with a

Table 1. Prevalence of diabetic retinopathy (DR), chronic kidney disease (CKD) and the two subtypes of CKD, including reduced estimated glomerular filtration rate (eGFR) and albuminuria, stratified by sex and age groups

	Age group, years	DR		CKD		Reduced eGFR		Albuminuria	
		cases	% (95% CI)	cases	% (95% CI)	cases	% (95% CI)	cases	% (95% CI)
All	22–39	73/511	14.3 (11.5, 17.4)	73/492	14.8 (11.9, 18.0)	3/511	0.6 (0.3, 1.0)	72/493	14.6 (11.7, 17.8)
	40–49	127/820	15.4 (13.1, 18.0)	102/816	12.5 (10.4, 14.8)	4/831	0.5 (0.3, 0.8)	99/819	12.1 (10.0, 14.3)
	50–59	216/1,483	14.6 (12.9, 16.4)	122/1,524	8.0 (6.8, 9.3)	14/1,551	0.9 (0.6, 1.2)	113/1,525	7.4 (6.3, 8.6)
	60–69	140/1,199	11.7 (10.0, 13.5)	143/1,282	11.2 (9.6, 12.8)	42/1,305	3.2 (2.5, 4.0)	110/1,285	8.6 (7.2, 10.0)
	70–97	42/655	6.4 (4.9, 8.2)	224/821	27.3 (24.3, 30.4)	177/867	20.4 (17.8, 23.2)	109/822	13.3 (11.1, 15.6)
	Total	598/4,668	12.8 (11.9, 13.8)	664/4,935	13.5 (12.5, 14.4)	240/5065	4.7 (4.3, 5.2)	503/4,944	10.2 (9.4, 11.0)
Men	22–39	63/414	15.2 (12.0, 18.8)	64/402	15.9 (12.6, 19.6)	3/412	0.7 (0.3, 1.3)	63/403	15.6 (12.3, 19.3)
	40–49	103/628	16.4 (13.7, 19.4)	79/625	12.6 (10.2, 15.3)	3/635	0.5 (0.2, 0.8)	77/628	12.3 (9.9, 14.8)
	50–59	154/1,015	15.2 (13.1, 17.4)	97/1,056	9.2 (7.6, 10.9)	13/1,072	1.2 (0.8, 1.7)	89/1,057	8.4 (7.0, 10.0)
	60–69	87/703	12.4 (10.1, 14.8)	94/752	12.5 (10.3, 14.9)	24/764	3.1 (2.3, 4.2)	76/753	10.1 (8.2, 12.2)
	70–97	22/324	6.8 (4.6, 9.4)	109/414	26.3 (22.2, 30.7)	74/441	16.8 (13.5, 20.4)	71/414	17.1 (13.7, 20.9)
	Total	429/3,084	13.9 (12.7, 15.1)	443/3,249	13.6 (12.5, 14.8)	117/3,324	3.5 (3.0, 4.0)	376/3,255	11.6 (10.5, 12.6)
Women	22–39	10/97	10.3 (5.4, 16.6)	9/90	10.0 (5.0, 16.5)	0/99	0 (0, 0)	9/90	10.0 (5.0, 16.5)
	40–49	24/192	12.5 (8.4, 17.3)	23/191	12.0 (8.0, 16.8)	1/196	0.5 (0.1, 1.2)	22/191	11.5 (7.6, 16.2)
	50–59	62/468	13.3 (10.4, 16.4)	25/468	5.3 (3.8, 7.2)	1/479	0.2 (0.1, 0.4)	24/468	5.1 (3.6, 6.9)
	60–69	53/496	10.7 (8.3, 13.4)	49/530	9.2 (7.1, 11.6)	18/541	3.3 (2.3, 4.6)	34/532	6.4 (4.7, 8.3)
	70–97	20/331	6.0 (4.0, 8.5)	115/407	28.3 (24.0, 32.7)	103/426	24.2 (20.2, 28.4)	38/408	9.3 (6.9, 12.1)
	Total	169/1,584	10.7 (9.3, 12.1)	221/1,686	13.1 (11.6, 14.7)	123/1,741	7.1 (6.0, 8.2)	127/1,689	7.5 (6.4, 8.7)

Data are presented as frequency and percentage (95% CI). CI, confidence interval.

higher proportion of both mild-moderate NPDR and severe NPDR-PDR (both $p < 0.05$). Concerning the eGFR, a reduced eGFR was associated with an increased risk of severe NPDR-PDR ($p < 0.05$) but not with mild-moderate NPDR ($p > 0.05$) (online suppl. Table 1).

The characteristics of patients stratified by the presence/absence of DR and CKD (as well as either reduced eGFR or albuminuria) were presented in Table 3, online supplementary Tables 2 and 3. In the multivariable model, by comparing group only with DR and only with CKD, diabetic patients tended to have reduced eGFR and/or albuminuria instead of DR in those with older age ($p < 0.001$, OR = 1.05), a higher BMI ($p < 0.001$, OR = 1.14), and a higher serum triglyceride concentration ($p < 0.001$, OR = 1.26). Instead, diabetic patients tended to have DR instead of reduced eGFR and/or albuminuria if they had a higher blood glucose concentration ($p = 0.001$, OR = 1.08) (Fig. 4).

For every 10-year increase in age, the probability of diabetic patients developing a reduced eGFR increased 12-fold compared to developing DR (OR = 1.18; $p < 0.01$)

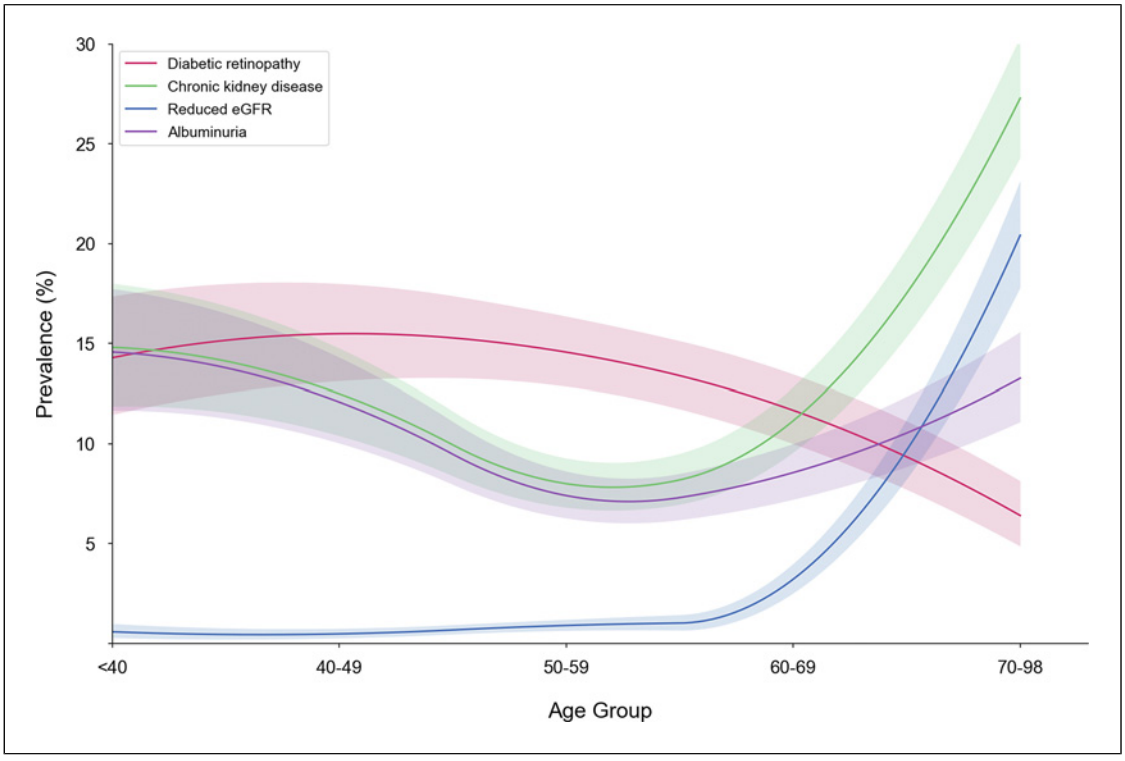

Fig. 1. Prevalence of DR and CKD, and two specific subtypes of CKD, including reduced estimated glomerular filtration rate (eGFR) and albuminuria, in relationship to age in patients with diabetes. Solid lines: percentages; shadows: and standard error.

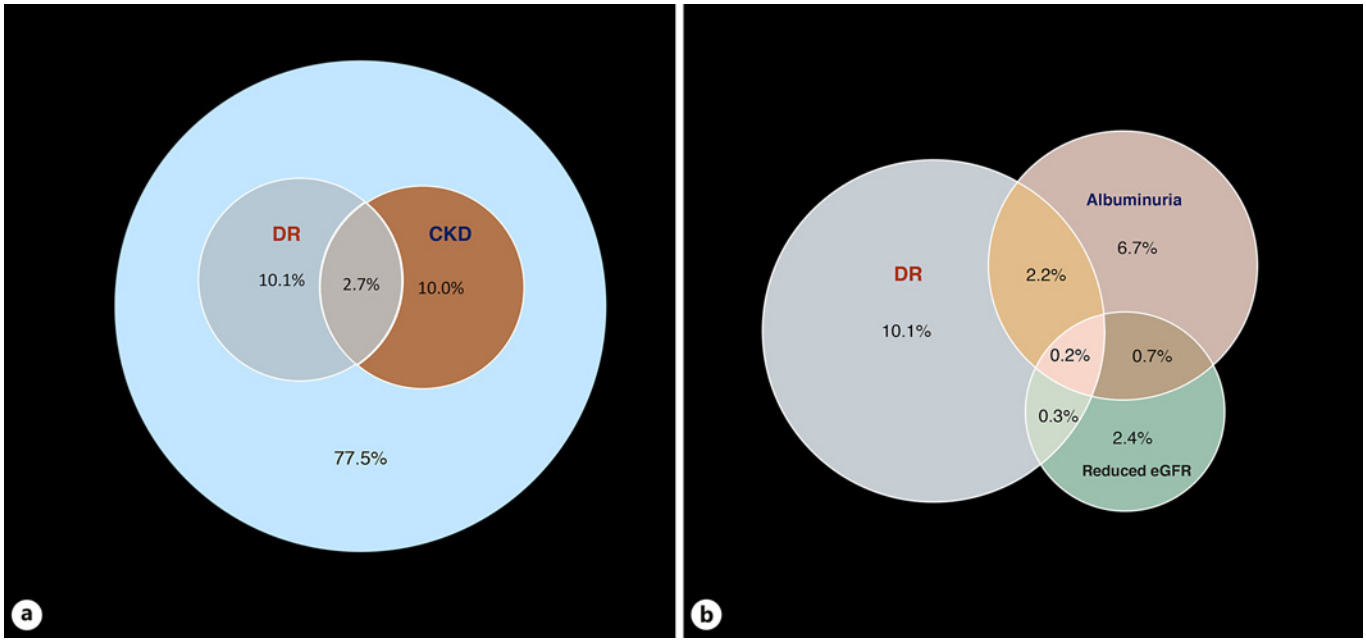

Fig. 2. Venn diagram of the prevalence of diabetic retinopathy (DR) and chronic kidney disease (CKD) and its two subtypes, reduced eGFR and albuminuria. **a** The overlap between DR and CKD in type 2 diabetes population. **b** The overlap between DR, reduced eGFR and albuminuria.

Table 2. Associations of the diabetic retinopathy (DR) and its severity with chronic kidney disease (CKD), reduced estimated glomerular filtration rate (eGFR), and albuminuria

	Non-DR versus DR						≤Mild NPDR versus ≥moderate NPDR					
	prevalence, %		crude comparison		age, sex-adjusted comparison		prevalence, %		crude comparison		age, sex-adjusted comparison	
	non-DR	DR	*p* value	OR (95% CI)	*p* value	OR (95% CI)	≤mild NPDR	≥moderate NPDR	*p* value	OR (95% CI)	*p* value	OR (95% CI)
CKD	11.4	20.9	<0.001	2.04 (1.63, 2.55)	<0.001	2.19 (1.75, 2.7)	11.7	31.0	<0.001	3.41 (2.54, 4.58)	<0.001	3.52 (2.62, 4.73)
Reduced eGFR	3.8	3.9	0.93	1.02 (0.65, 1.60)	0.014	1.87 (1.143.08)	3.6	8.3	<0.001	2.45 (1.51, 3.97)	<0.001	3.25 (1.92, 5.49)
Albuminuria	8.5	18.8	<0.001	2.5 (1.97, 3.17)	<0.001	2.44 (1.92, 3.10)	8.9	26.3	<0.001	3.66 (2.68, 4.99)	<0.001	3.66 (2.68, 4.99)

OR, odds ratio; CI, confidence interval. The prevalence (%) represents the proportion of patients with CKD, isolated reduced eGFR, and isolated albuminuria, within groups either with or without DR, or with varied levels of DR.

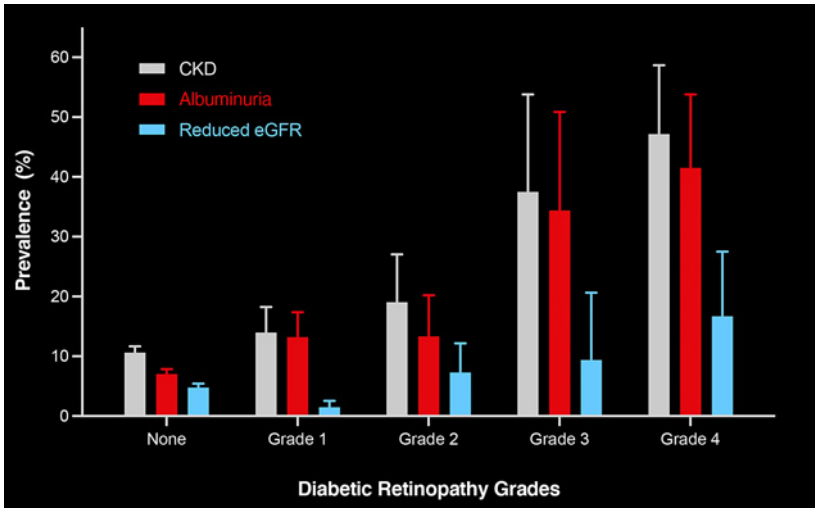

Fig. 3. Prevalence of CKD/albuminuria/reduced estimated glomerular filtration rate (eGFR) in diabetes patients with different stages of retinopathy. Bars: standard error.

(Fig. 4, 5a, b). With every 1 mmol/L increase in blood glucose concentration, the probability of developing DR increased by 1.07-fold compared to developing albuminuria and by 1.14-fold compared to developing a reduced eGFR. For every 1 unit increase in BMI (kg/m^2) or in serum triglyceride level (mmol/L), there was a 1.1-fold increase in the probability of having albuminuria rather than DR. The combination of diabetes and arterial hypertension resulted in a 4.7-fold increase in the probability of having a reduced eGFR compared to having DR (Fig. 4).

Although not included in the multivariable model due to a confounding relationship with age, diabetes duration was significantly shorter in patients with albuminuria (p = 0.002; OR: 0.96; 95% CI: 0.93, 0.98) than in patients with only DR (multivariable adjustment). Patients with both DR and CKD had a higher systolic and diastolic blood pressure (all $p < 0.005$, adjusted by the Bonferroni test) as compared with the other three groups (all $p < 0.005$, adjusted by the Bonferroni test) (Table 3).

Discussion

In our community-based study enrolling 62,217 individuals with 5103 (8.2%) patients affected by TD2, the prevalence of DR, CKD, reduced eGFR, and albuminuria was 12.8%, 13.5%, 4.7%, and 10.2%, respectively, with a

Table 3. Demographic and clinical characteristics of participants, categorized by the presence or absence of diabetic retinopathy (DR) and chronic kidney disease (CKD)

	Group 1	Group 2	Group 3	Group 4	*p* value
	DR+/CKD- (*n* = 455)	DR−/CKD+ (*n* = 452)	DR+/CKD+ (*n* = 120)	DR−/CKD- (*n* = 3,496)	
Age, years	53.7±11.0 54 (46, 61)	60.5±16.4[a] 61 (47, 74)	54.5±12.8[b] 56 (45.3, 62)	56.0±12.1[ab] 57 (48, 64)	<0.001[1]
Sex Male, *n*/% Female, *n*/%	 324/71.2 131/28.8	 296/65.5 156/34.5	 90/75.0[b] 30/25.0[b]	 2,288/65.4[ac] 1,208/34.6[ac]	0.017[2]
Hypertension, *n*/%	317/70.3	384/85.3[a]	106/88.3[a]	2,226/63.9[abc]	<0.001[2]
Systolic blood pressure, mm Hg	140.4±20.5 139.5 (125, 153.3)	145.0±20.4[a] 144 (130, 158)	152.3±19[ab] 151 (140,164)	136.4±18.5[abc] 135 (122, 148)	<0.001[1]
Diastolic blood pressure, mm Hg	83.8±11.8 83 (76, 90)	84.3±13.6 83 (75, 93)	88.7±15.1[ab] 88.5 (80, 97)	82.0±11.1[abc] 81 (74, 90)	<0.001[1]
Cardiovascular disease, *n*/%	28/6.3	64/14.5[a]	12/10.1	219/6.3[b]	<0.001[2]
Body weight, kg	73.2±12.8 73 (63.9, 81)	75.5±15 74 (66, 83.5)	78.1±16.1[a] 77.1 (68.1, 84.7)	72.6±13.6[bc] 71.6 (63.1, 80.8)	<0.001[1]
Body height, cm	167.3±8.3 168 (161, 173)	166.4±9.5 167 (159, 174)	168.7±9.0[b] 170 (164, 175)	166.8±8.6 167 (160, 173)	0.032[1]
Body mass index, kg/m^2	26.0±3.3 25.9 (23.9, 28.0)	27.1±3.9[a] 26.8 (24.4, 29.4)	27.3±4.3 26.7 (24.5, 29.4)	26.0±3.6[bc] 25.7 (23.6, 28.0)	<0.001[1]
Triglycerides, mmol/L	2.01±1.90 1.54 (0.99, 2.32)	2.62±2.69[a] 1.86 (1.29, 2.73)	2.95±3.58[a] 1.86 (1.17, 3.18)	2.0±1.82[bc] 1.53 (1.04, 2.32)	<0.001[1]
Total cholesterol, mmol/L	4.94±1.02 4.85 (4.26, 5.56)	5.03±1.21 4.96 (4.23, 5.7)	5.06±1.29 5.04 (4.18, 5.74)	4.98±1.11 4.93 (4.25, 5.62)	0.796[1]
Low-density lipoprotein, mmol/L	3.0±0.85 3.01 (2.4, 3.56)	2.96±0.98 2.94 (2.25, 3.57)	2.88±0.95 2.86 (2.17, 3.66)	3.01±0.90 2.98 (2.38, 3.59)	0.406[1]
High-density lipoprotein, mmol/L	1.24±0.33 1.19 (0.98, 1.41)	1.18±0.33[a] 1.12 (0.95, 1.33)	1.15±0.30 1.08 (0.95, 1.31)	1.25±0.34[bc] 1.19 (1.01, 1.43)	<0.001[3]
Diabetes duration, years	7.4±7.3 6 (0, 12)	5.7±8.0[a] 1 (0, 10)	9.0±10.0[b] 5 (0, 17)	4.7±6.3[ac] 2 (0, 8)	<0.001[1]
Blood glucose, mmol/L	9.9±3.9 8.6 (7.2, 11.9)	8.8±2.9[a] 7.8 (6.9, 10.2)	10.9±4.0[b] 9.8 (7.6, 14.6)	7.9±2.5[abc] 7.3 (6.3, 8.5)	<0.001[1]
HbA1c, %	8.1±1.8 7.6 (6.6, 9.1)	7.5±1.5[a] 7.1 (6.4, 8.4)	8.5±1.8[b] 8.4 (7.2, 9.6)	7.0±1.4[abc] 6.6 (6.0, 7.5)	<0.001[1]
HbA1c, mmoL/moL	64.7±19.9 59.6 (48.6, 76.0)	58.9±16.9[a] 54.1(46.5, 68.3)	69.9±19.6[b] 67.8 (55.2, 81.4)	53.0±15.6[abc] 48.6 (42.1, 58.5)	<0.001[1]

Data are presented as mean ± standard deviation and median (interquartile range) for continuous variables, and the number of cases and their percentage (%) for categorical variables in each group. CKD here was defined as the presence of reduced eGFR or albuminuria. The comparison was conducted among patients with complete data on DR, serum creatinine and urine protein assessment (n = 4,523). Two-tailed values of $p < 0.05$ were considered statistically significant. [a]Compared with group 1, $p < 0.05$. [b]Compared with group 2, $p < 0.05$. [c]Compared with group 3, $p < 0.05$, adjusted by Bonferroni test. [1]Compared by independent-sample Kruskal-Wallis test. [2]Compared by the χ^2 test. [3]Compared by one-way analysis of variance.

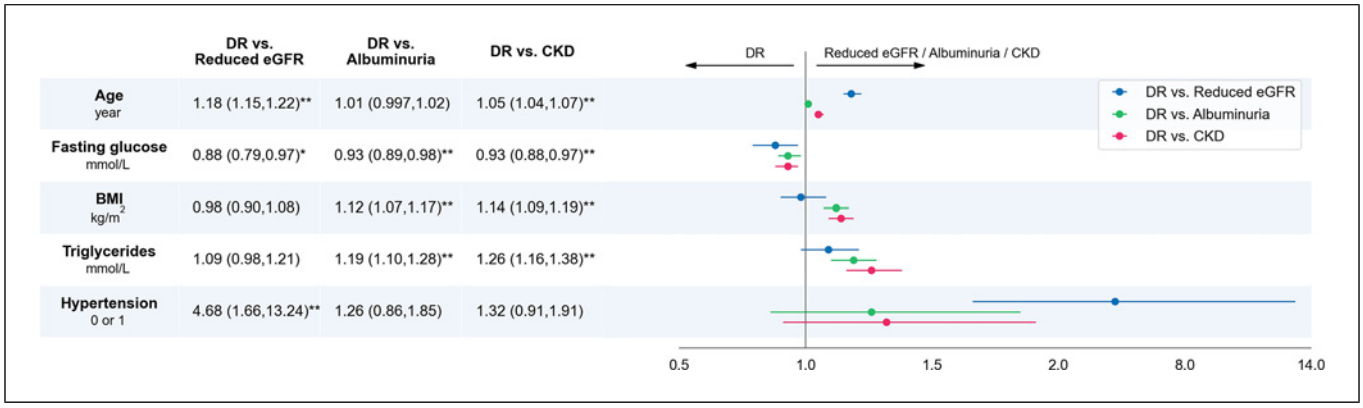

Fig. 4. Forest plot showing the odds ratio for risk of having DR or having reduced eGFR/albuminuria/CKD in diabetes patients. The coordinate of the X-axis was modified to reduce the length. For the comparison between DR and CKD, variables included in the multivariable model were age, sex, hypertension, cardiovascular disease, body mass index, triglycerides, high-density lipoprotein, and blood glucose, with a variance inflation factor of ≤1.72. For the comparison between DR and albuminuria, variables included in the multivariable model were age, sex, hypertension, body mass index, triglycerides, total cholesterol, high-density lipoprotein, and blood glucose, with a variance inflation factor of ≤1.66. For the comparison between DR and reduced eGFR, the variables were age, sex, hypertension, cardiovascular disease, body mass index, low-density lipoprotein, and blood glucose, with a variance inflation factor of ≤2.83. DR, diabetic retinopathy; CKD, chronic kidney disease; BMI, body mass index. ** two sides p value <0.01; * two-sides p value <0.05.

concordance of DR and CKD observed in 2.7% among all diabetes patients. DR was present in 21.0% of patients with CKD, while CKD was detected in 20.9% of the patients with DR. Individuals with moderate or advanced DR as compared to patients without DR or with mild DR had a significantly increased, 3.3-fold–3.7-fold higher probability of having a reduced eGFR, having albuminuria, or having CKD. Diabetic patients were more prone to have CKD than DR if they were older, had a higher BMI, and had a higher serum triglyceride concentration, while they were more prone to have DR than CKD, if the serum glucose concentration was higher and the diabetes duration was longer. Diabetes combined with arterial hypertension as compared with diabetes without hypertension had 4.7-fold increased probability of a having reduced eGFR instead of having DR.

The observations made in our study population with respect to the prevalence of TD2s (8.2%) agree with the results of previous investigations from China [23]. In contrast, the prevalence of DR and CKD and their concordance were lower in our study population than in previously examined populations with TD2 [6, 7, 12, 13]. In the hospital-based Renal Insufficiency and Cardiovascular Events (RIACE) study enrolling 15,773 Caucasian patients with TD2, the prevalence of DR and CKD were 22.17% and 37.47%, respectively, with a concordance of DR and CKD found in 1,814 (11.5%) individuals [12]. In the population-based Singapore Prospective Study Program, the prevalence of a reduced eGFR and albuminuria in the diabetic group (n = 301) was 17.8% and 38.5%, respectively, with 41% of patients with reduced eGFR having no albuminuria. The prevalence of DR was 33% within the whole diabetic group, and it was 44% (24/54) in those patients with a reduced eGFR and 47% (46/116) in the individuals with albuminuria [6]. Possible reasons for the discrepancy between our study and previous reports may be differences in the glycemic control, diabetes duration, coexisting diseases, ethnicity, and characteristics of the study population. Our relatively large study population was recruited on a community basis as compared to hospital-based recruitment in most of the previous studies. In addition, the medical infrastructure in our study region was better developed during the period when our study was performed as compared to previous investigations conducted earlier in other study regions. Correspondingly, a recent meta-analysis revealed that the pooled prevalence of CKD in TD2 patients in China (mean: 21.8%) varied among regions, with the lowest value found in the Beijing area (15.6%) [24]. That value was comparable to the figure of 13.3% detected in our study population.

We found a stronger association between DR and the presence of albuminuria, as compared to the presence of a reduced eGFR. Around 10% of the patients with albuminuria had additional DR, while 4.7% of the patients had a reduced eGFR. The finding corresponded to results of previous studies [6, 7]. In the population-based

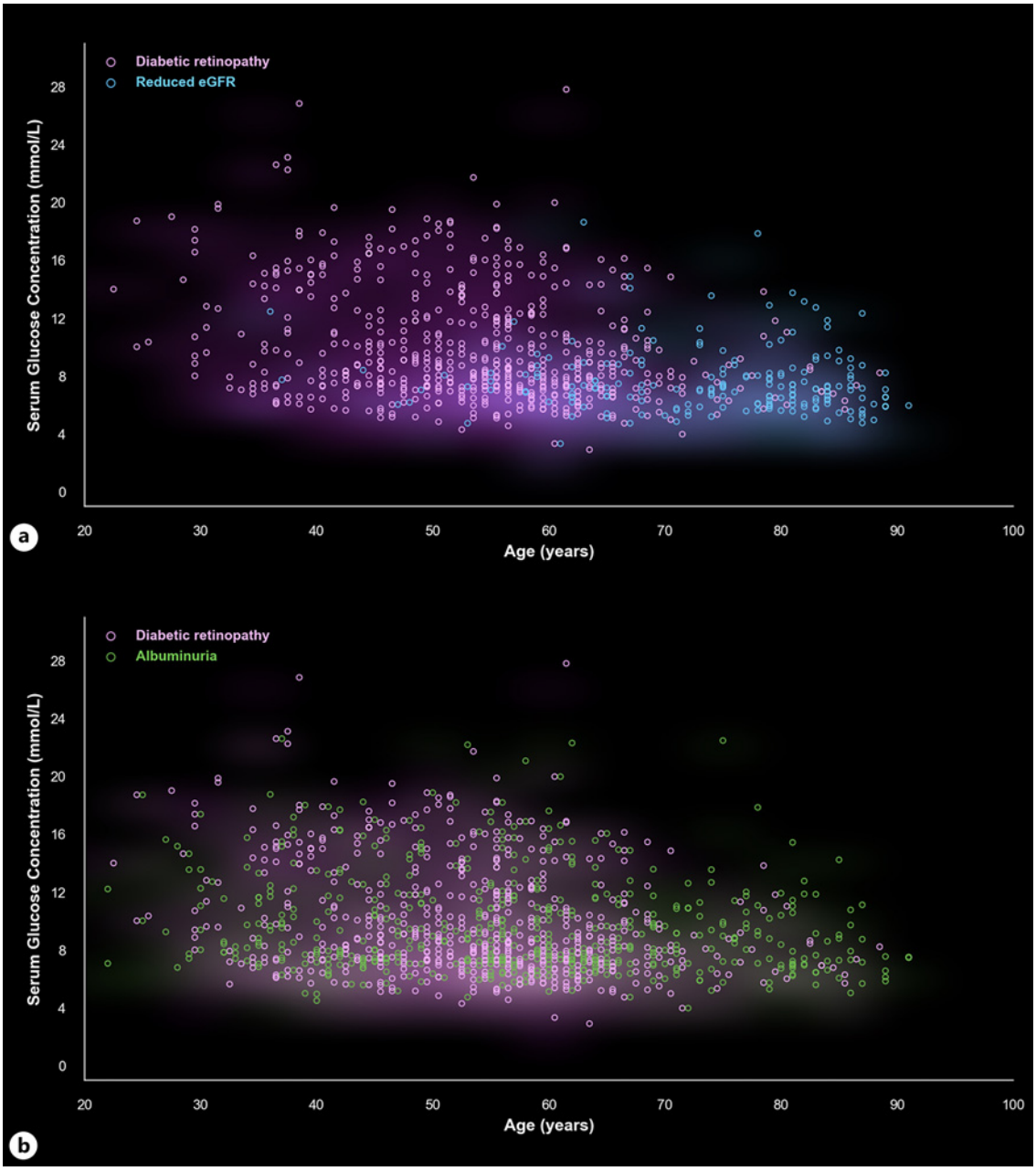

Fig. 5. Distribution of age and the serum glucose level of patients with DR and varied manifestation of CKD in the type 2 diabetes population. **a** Scatter plot showing the relationship between age and the serum glucose level in patients with DR (pink) and patients with reduced eGFR (blue). **b** Scatter plot showing the relationship between age and the serum glucose level of patients with DR (pink) and patients with albuminuria (green). DR, diabetic retinopathy; CKD, chronic kidney disease.

Singapore Prospective Study Program, Sabanayagam and colleagues reported that the prevalence of CKD was associated with the DR prevalence only in the presence of albuminuria [6]. In the Beijing Communities Diabetes Study, enrolling 2,007 diabetic patients from 15 community health centers in urban Beijing, the prevalence of DR (24.7%) was significantly associated with a higher prevalence of microalbuminuria but not with the creatine level [7]. Chen reported that patients with albuminuria had a higher risk for development and progression of DR

as compared with patients with a low eGFR [14]. In the Korea National Health and Nutrition Examination Surveys (2008–2010), the prevalence of proteinuria was significantly associated with the prevalence of DR and vision-threatening DR, but the association was not valid for a reduced eGFR [25].

Diabetes is associated with long-term damage to the macrovascular and microvascular systems throughout the body, and the latter induces the complications in the kidney, eyes, and nerves [26]. It has been discussed that vascular remodeling and impaired vessel dilation in diabetes may contribute to the concordance of DR and albuminuria. As for the weaker association between reduced eGFR and DR, it may be explained by the glomerular filtration rate increase in the early stage in diabetic kidney damage. Findings from clinical trials suggested that the early stage of nephrological microvascular damage was accompanied by massive glucose filtration and glomerular hyperfiltration as one of the upstream mechanisms, leading to tubular hyper-reabsorption of glucose and sodium, while eventually developing into glomerulosclerosis and tubule atrophy [2, 27].

In the current study, there was a 1.1-fold increase in the probability of albuminuria instead of DR for every unit increase in BMI (kg/m^2) or serum triglyceride level (mmol/L). Although comparisons of their roles in developing either CKD or DR have not been reported before, the importance of dyslipidemia and the BMI in pathogenesis in diabetes and its macro- and microvascular complications have been discussed widely. Consistent with our findings, a data-driven cluster analysis of 8,980 newly diagnosed diabetes patients showed that patients with severe insulin deficiency were more prone to retinopathy, while those with insulin resistance were more prone to kidney disease. A subsequent comparison revealed that patients with insulin resistance had a higher BMI than those with insulin deficiency [28]. In the hospital-based RAICE Study and the Japan Diabetes Complications Study, the patients with CKD only tended to have a higher BMI than those patients with DR only [12, 29]. Similarly, in a global case-control study performed in 13 countries, a higher level of plasma triglyceride was related to a higher risk for having kidney disease with an odds ratio of 1.23. The association between retinopathy and the serum triglycerides concentration was significant in a matched analysis but did not prevail after additional adjustments [18]. It is of interest to explore the differed roles and their mechanisms of the presence of dyslipidemia and a higher BMI in DR and renal impairment in future studies.

A potential confounding factor in our study may have been that TD2 is often associated with a multitude of systemic risk factors including obesity, dyslipidemia, hypertension, and smoking, which can directly lead to non-diabetic kidney disease, in addition to diabetes-associated secondary kidney damage. It may thus contribute to a heterogeneous pathogenesis of CKD in patients with TD2 [2]. Correspondingly, the classical histopathological pattern of diabetic kidney disease is frequently observed only in type 1 diabetes, while biopsy samples from patients with TD2 and CKD suggested a non-diabetic etiology of the kidney changes. Studies examining renal biopsies reported that one third to two thirds of patients with TD2 and kidney damage had non-diabetic kidney disease [2]. Interestingly, this heterogeneity in the etiology of kidney damage in patients with TD2 also existed in patients with albuminuria, which hitherto was considered a sign of classical diabetic glomerulonephritis. Based on the examination of renal biopsies, Fioretto and colleagues identified three histological categories of renal injury in TD2 patients with microalbuminuria, with DR present in all patients with typical diabetic glomerular sclerosis, while only half of the patients with normal, near-normal, or atypical renal histological lesions showed DR [30]. An additional reason for the phenotypical heterogeneity of CKD may have been the concurrent medication in patients with TD2, including the intake of renin-angiotensin-system (RAS) inhibitors which can influence the progression of CKD. RAS inhibitors have widely been used in patients with TD2 for the management of hypertension during the past decades [2]. It may also be a reason for the relative low concordance of DR with CKD in our study population and for the differences in the associations of DR, albuminuria, and reduced eGFR with other systemic parameters in our study population.

Limitations of our study should be discussed. First, the albuminuria was semi-quantitatively assessed using a dipstick test without adjustment for the urine creatinine concentration, which tends to be less robust than the ACR. Second, the measurements of the urine protein concentration and serum creatinine concentration were not repeated, so a misclassification might have occurred in some study participants. This limitation might have led to a misclassification of some CKD cases. However, it is worth noting that employing a single reading is a common practice in epidemiological studies. Third, we did not incorporate HbA1c concentration into the multivariable analysis model as this measurement was only available for one-third of the study participants. Instead, we used fasting blood glucose concentration. Forth, one-

field fundus photograph taken without pupillary dilation was used for the assessment of DR instead of multi-field retinal photographs. While this technique has become the most commonly used method for DR screening in epidemiologic studies, it may result in underestimation of DR [7]. Fifth, we could not exclude the confounding effects of medication such as RAS inhibitors, as relevant information was not available. Given all these limitations and the cross-sectional design of our study, it is imperative to validate our findings through prospective studies.

In conclusion, in our TD2 population, around a fifth of CKD patients had a concurrent DR, and a fifth of DR patients had concurrent CKD. Diabetic patients of older age, with a higher BMI, higher serum triglyceride concentration, and a combination with arterial hypertension had a higher chance of being affected by CKD, while diabetic patients with poorer glycemic control and longer diabetes duration had a higher chance of being affected by DR. The finding may be helpful for screening for and treatment of the microvascular complications in TD2 patients.

Statement of Ethics

The study protocol was approved by the Medical Ethics Committee of Beijing Tongren Hospital (approval number TRECKY2020-066) and was in adherence with the Declaration of Helsinki. The study has been granted an exemption from requiring written informed consent by the Ethics Committee of Beijing Tongren Hospital.

Conflict of Interest Statement

Jost B. Jonas: Patent holder with Biocompatibles UK Ltd. (Franham, Surrey, UK) (title: Treatment of eye diseases using encapsulated cells encoding and secreting neuroprotective factor and/or anti-angiogenic factor; patent number: 20120263794), and European patent EP 3 271 392, JP 2021-119187, and US 2021 0340237 A1: Agents for use in the therapeutic or prophylactic treatment of myopia or hyperopia and European patent application 23196899.1 EGFR antagonists for the treatment of diseases involving unwanted migration, proliferation, and metaplasia of retinal pigment epithelium (RPE) cells. All other authors have no conflicts of interest to declare.

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Author Contributions

Ya Xing Wang, Dong Ning Chen, and Chun Zhang were responsible for initiating the project, forming the study team, and managing the overall research enterprise; Can Can Xue and Jing Cui were responsible for examining the study participants and clinically examining the database; Li Qin Gao and Jie Xu were responsible for quality control and retinal image reading; Jost B. Jonas and Ya Xing Wang were responsible for the research direction; Can Can Xue and Li Qin Gao were responsible for writing the first draft of the manuscript; Ya Xing Wang and Jost B. Jonas were responsible for drafting the work or revising critically for important intellectual content. Ya Xing Wang is the guarantor of this work. All authors have full access to all the data in the study, take responsibility for the integrity and the accuracy of the data, provided important feedback on the methods and results, and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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