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Review

Meta-Analysis of Diagnostic Accuracy of Retinopathy for the Detection of Diabetic Kidney Disease in Adults With Type 2 Diabetes

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Key Messages

- This meta-analysis, which included the largest sample size studied of people with diabetes, found that retinopathy may lack adequate evidence either to verify diabetic kidney disease or to exclude nondiabetic renal diseases in people with type 2 diabetes.
- The severity of diabetic retinopathy may not parallel the presence of diabetic kidney disease.

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ABSTRACT

Objectives: The study aimed to explore whether diabetic retinopathy (DR) could distinguish diabetic kidney disease (DKD) from nondiabetic renal diseases (NDRDs) in patients with type 2 diabetes mellitus and renal disease.
Methods: We searched PubMed, Embase, Cochrane, MEDLINE and China National Knowledge Internet for articles that enrolled patients with DKD and NDRD. The results were summarized as sensitivity, specificity and the area under the curve of summary receiver operating characteristic curve with their 95% confidence intervals (CIs).
Results: A total of 51 studies that included 4,990 participants were collected for evaluation. The overall pooled sensitivity, specificity and area under the curve with their 95% CIs were 0.67 (95% CI 0.61, 0.73), 0.77 (95% CI 0.72, 0.81) and 0.78 (95% CI 0.75 to 0.82), respectively. If the test for DR is negative, the probability of DKD would decrease to 10%, but if the test for DR is positive, the probability would increase only to 42%. In addition, although the mean specificity of proliferative DR for detection of DKD was 0.98 (95% CI 0.92 to 1.00), the mean sensitivity was 0.25 (95% CI 0.16, 0.35).
Conclusions: DR may lack adequate evidence either to verify DKD or to exclude NDRD, and the severity of DR may not parallel the presence of DKD.

Mots Clés :
néphropathie diabétique
rétinopathie diabétique
néphropathie non diabétique
diabète de type 2

RÉSUMÉ

Objectifs : L'étude visait à déterminer si la rétinopathie diabétique (RD) pouvait distinguer la néphropathie diabétique (ND) des néphropathies non diabétiques (NND) chez les patients atteints de diabète sucré de type 2 et de maladie rénale.
Méthodes : Nous avons effectué des recherches dans PubMed, Embase, Cochrane, MEDLINE et China National Knowledge Internet pour trouver des articles sur les patients atteints de ND et de NND. Les résultats ont été résumés selon la sensibilité, la spécificité et l'aire sous la courbe de la fonction d'efficacité du récepteur avec leurs intervalles de confiance (IC) à 95 %.
Résultats : Un total de 51 études comprenant 4,990 participants ont été recueillies aux fins d'évaluation. L'ensemble des données regroupées concernant la sensibilité, la spécificité et l'aire sous la courbe avec

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leurs IC à 95 % étaient respectivement de 0.67 (IC à 95 %: 0.61, 0.73), 0.77 (IC à 95 %: 0.72, 0.81) et 0.78 (IC à 95 %: 0.75 à 0.82). Si le test de détection de la RD est négatif, la probabilité de ND diminuerait à 10 %, mais si le test de RD est positif, la probabilité augmenterait seulement à 42 %. De plus, bien que la spécificité moyenne de la DR proliférative pour la détection de la ND était de 0.98 (IC à 95 %: 0.92 à 1.00), la sensibilité moyenne était de 0.25 (IC à 95 %: 0.16 à 0.35).
Conclusions : La RD peut manquer de preuves adéquates pour valider la ND ou pour exclure la NND, et la gravité de la RD peut ne pas correspondre à la présence de ND.

Introduction

Diabetes mellitus is a group of metabolic disorders, and the number of people with diabetes is growing fast; it was estimated that there are 451 million people (18 to 99 years of age) worldwide with diabetes in 2017, and the number is expected to increase to 693 million by 2045 (1). Diabetic kidney disease (DKD) is 1 of the major complications of diabetes and is the leading cause of end-stage renal disease (ESRD) in the developed world. It is estimated that about 40% of patients with diabetes will develop DKD, which is commonly confirmed on clinical grounds, such as albuminuria, hypertension and impaired glomerular filtration rates (2).

However, another renal disease, known as nondiabetic renal disease (NDRD), has been reported, especially in patients with type 2 diabetes. It can occur either alone or superimposed on DKD (3–6). Considering their quite different treatments, it is necessary to distinguish DKD from NDRD early so as to provide effective treatments (7). Kidney biopsy still remains a gold standard for renal disease, but it can cause several complications, such as gross hematuria, perinephric hematoma and so on because of its invasive nature (8). Therefore, in order to avoid those complications, it is essential to find another way to diagnose DKD.

Several studies have reported that the presence of diabetic retinopathy (DR) may be helpful in distinguishing DKD from NDRD (6,9,10). However, the diagnostic accuracy of DR has not been uniform in individual studies. One meta-analysis from 2012 explored the accuracy of DR for the diagnosis of DKD (11), but it did not evaluate the clinical application of DR and did not further explore potential sources of heterogeneity. Also, there were very limited studies that summarized diagnostic test performance of proliferative DR (PDR) for detection of DKD. Finally, there have been many new studies of this subject since the publication of the meta-analysis, and our understanding of DR is still developing.

Therefore, in order to deal with these issues, we conducted another meta-analysis to explore the diagnostic accuracy of DR for the detection of DKD in people with type 2 diabetes.

Methods

Search strategy

We searched PubMed, Embase, Cochrane, MEDLINE and China National Knowledge Internet for articles without time restrictions up to August 15, 2018. The keywords and medical subject headings included *diabetic kidney disease* or *diabetic nephropathy*, *biopsy* or *pathology* and *nondiabetic renal disease* or *nondiabetic nephropathy*. We also manually scanned the reference lists of eligible articles and related reviews to identify other potentially relevant studies.

Study criteria

The included criteria for studies were: 1) patients were diagnosed as having type 2 diabetes, not only according to the 1998 World Health Organization criteria for diabetes mellitus but also as defined by an exclusion diagnosis, which occurs when patients do not have type 1 diabetes, secondary diabetes or monogenic forms of diabetes, although they have been diagnosed as having type 2 diabetes and renal disease as defined by kidney biopsy; and 2) based on renal pathology, patients were divided into 2 groups: 1) the group with DKD (case) and 2) the group with NDRD (control). Biopsy characteristics of mixed and NDRD were categorized as NDRD. Studies were expected to provide the number of patients with DR in each group. The exclusion criteria were: 1) duplication; 2) studies that included type 1 diabetes or did not show the type of diabetes; 3) renal disease was not defined by biopsy and 4) studies, such as systemic reviews, meta-analyses, case reports, animal experimental studies, etc.

Data extraction and quality assessment

Two reviewers (DR, WK) independently extracted and cross-checked data from identified articles that satisfied the criteria. We also gave priority to the PubMed database so as to distinguish duplications easily. The details of the selection process are shown in Figure 1. All disagreements existing in the process were settled by consensus or discussion with a third reviewer (GX). The following information was collected: study design, first author, publication time, country, race, sample size, percentage of men, causes of renal biopsy, the number of true-positive, false-positive, true-negative and false-negative and the methods of evaluating DR.

The methodologic quality of the studies included in our meta-analysis was assessed by the Quality Assessment of Diagnostic Accuracy Studies-2 score system (12), which consists of 2 parts: the risk of bias (4 sections: patient selection, index test, reference standard and flow and timing) and the applicability concerns (the first 3 sections). Each item is assessed as low, high or unclear.

Statistical analysis

Data were abstracted and analyzed using Stata (v. 12.0) software (College Station, Texas, United States). The bivariate mixed-effects regression model was employed to calculate the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) with their 95% confidence intervals (CIs). The summary receiver operating characteristic curve and the area under the curve (AUC) was used to summarize the results and evaluate the overall diagnostic accuracy of DR for the detection of DKD in people with type 2 diabetes (13,14). The score of the AUC, respectively, represented excellent ($\geq$0.97), very good (0.93 to $\sim$0.96) and good (0.75 to $\sim$0.92) diagnostic accuracy, but an AUC $<$0.75 could still be reasonable (15).

PLR above 5 and NLR below 0.2 have been noted to provide strong diagnostic evidence (16). The clinical utility of the diagnostic test is evaluated using the likelihood ratios to calculate post-test probability based on the Bayes theorem, as follows:

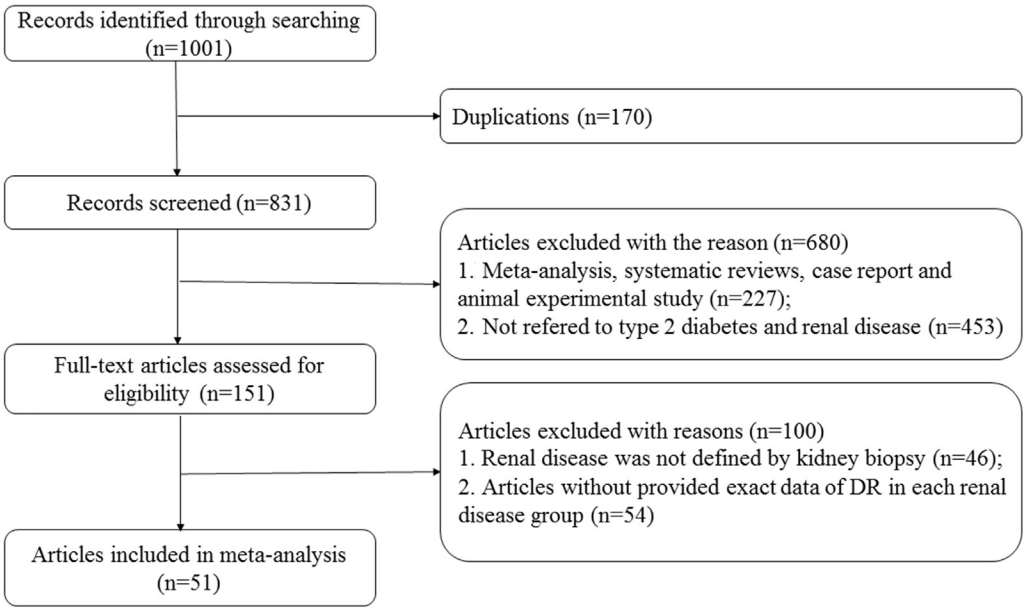

Figure 1. Flow diagram of article selection. *DR*, diabetic retinopathy.

Pretest probability = prevalence of target condition. Post-test probability = likelihood ratio (LR) × pretest probability / ([1 − pretest probability] × [1 − LR]) (17).

The potential source of heterogeneity was investigated by subgroup analysis and meta-regression. We inspected the publication bias of the included studies using the Deeks funnel plot; $p<0.05$ was considered statistically significant to evaluate all statistical tests.

Results

Study characteristics

The process of identifying qualified studies is shown in Figure 1. We identified 51 studies (3–6,9,10,18–62) that ultimately met our criteria. They included a total of 4,990 patients, including 16 prospective studies (4,6,9,10,51–62) and 35 retrospective studies (3,5,18–50). The characteristics of the selected studies are summarized in Table 1. The publication years ranged from 1988 to 2018. Patients were divided into 2 races according to ethnic characteristics: Mongolian (24 studies) (5,6,10,18,19,21,25–27,32,34–39,41–44,47,54,57,60) and Caucasian (27 studies) (3,4,9,20,22–24,28–31,33,40,45,46,48–53,55,56,58,59,61,62). Indications for renal biopsy in patients with type 2 diabetes were extremely variable across studies. In 10 studies, renal biopsy was performed based on differing degrees of proteinuria (4,26,39,44,54,58–62); others (41 studies) were based on clinical suspicion of NDRD, including absence of diabetic retinopathy, abrupt increase in serum creatinine or proteinuria, rapid worsening of renal function and unexplained microscopic hematuria (3,5,6,9,10,18–25,27–38,40–43,45–53,55–57). Of the studies, 30 (3,4,6,9,10,19–22,26,31,34,36–39,41,43,44,47,48,51,52,56–62) reported differing methods used to evaluate DR, such as ophthalmoscopy with or without mydriasis, fluorescein angiography and ophthalmoscopy/fundoscopy and fluorescein angiography, and 21 studies (5,18,23–25,27–30,32,33,35,40,42,45,46,49,50,53–55) did not provide relevant details. The quality of included studies in our meta-analysis was assessed by Quality Assessment of Diagnostic Accuracy Studies-2 (Supplementary Table 1), and the majority of the studies were ranked as having moderately high quality.

Pooled diagnostic accuracy of DR in detecting DKD

The pooled diagnostic accuracy of DR in detecting DKD was conducted by Stata 12 software. After pooling 51 studies (4,900 patients), DR demonstrated a sensitivity of 0.67 (95% CI 0.61 to 0.73) and a specificity of 0.77 (95% CI 0.72 to 0.81). The pooled AUC of the summary receiver operating characteristic curve was 0.78 (95% CI 0.75 to 0.82), which represents moderately good accuracy (Figures 2 and 3, and Supplementary Figure 1).

Potential sources of heterogeneity and subgroup analysis of DR in detecting DKD in patients with type 2 diabetes

Analysis indicated significant heterogeneity in sensitivity (I^2=86.20; $p<0.01$) and specificity (I^2=87.05; $p<0.01$) in the included studies. Therefore, we performed metaregression analyses to explore the potential sources of heterogeneity by using Stata 12.0 software. The p values of the potential variables in a joint model, such as study design, race, year of publication and indications for renal biopsy, were 0.56, 0.07, 0.26 and 0.47, respectively, which were >0.05, indicating that none of them contributed to interstudy heterogeneity. The subgroup meta-analyses were also conducted, and the detailed results are presented in Supplementary Table 2.

According to the study design, all data sets were divided into subgroups of prospective studies (16 studies) and retrospective studies (35 studies). The pooled sensitivity, specificity and AUC of prospective studies were 0.64, 0.72 and 0.75, respectively, while in the retrospective studies subgroup, they were 0.64, 0.77 and 0.79, respectively.

We also divided the data into 2 subgroups according to race, as follows: Mongolian (24 studies) and Caucasian (27 studies). The pooled sensitivity, specificity and AUC of the Mongolian studies were 0.69, 0.81 and 0.81, respectively, whereas in the Caucasian studies, they were 0.56, 0.70 and 0.71, respectively.

Furthermore, all data sets were divided into subgroups: the years before 2010 (24 studies) and after 2010 (including studies published in 2010) (27 studies), according to the publication year. The pooled sensitivity, specificity and AUC of the years before the 2010 subgroup were 0.61, 0.72 and 0.73, respectively, whereas in

Table 1
Summary of characteristics of the included studies

Studies	Country	Race	Patients included (n)	Men (%)	Indications for renal biopsy	Retinopathy DKD/NDRD (n)	No retinopathy DKD/NDRD (n)	DR evaluation
Retrospective studies								
Kritmetapak et al, 2018 (18)	Thailand	Mongolian	101	57	Suspected NDRD	44/22	8/27	NR
Fan J-Z et al, 2018 (19)	China	Mongolian	88	64.77	Suspected NDRD	12/8	6/62	Direct ophthalmoscopy
Kanodia et al, 2017 (20)	India	Caucasian	152	73	Suspected NDRD	10/4	72/66	Funduscopy
Lee et al, 2017 (21)	Korea	Mongolian	220	57	Suspected NDRD	84/24	30/82	Ophthalmoscopy
Mami et al, 2017 (22)	Tunisia	Caucasian	75	62	Suspected NDRD	9/15	9/42	Ophthalmoscopy and fluorescein Angiography
Erdogmus et al, 2017 (23)	Turkey	Caucasian	48	46	Suspected NDRD	15/3	5/25	NR
Tan J et al, 2017 (24)	New Zealand	Caucasian	245	NR	Suspected NDRD	71/83	17/74	NR
Li L et al, 2016 (25)	China	Mongolian	328	61	Suspected NDRD	100/32	88/108	NR
Dong Z-Y et al, 2016 (26)	China	Mongolian	248	70	Proteinuria (>0.15 g/day)	79/12	17/140	Ophthalmoscopy after mydriasis
Liu S et al, 2016 (27)	China	Mongolian	273	63	Suspected NDRD	18/19	50/186	NR
Bermejo et al, 2016 (28)	Spain	Caucasian	110	79.09	Suspected NDRD	14/10	24/62	NR
Pallayova et al, 2015 (29)	UK	Caucasian	51	65	Suspected NDRD	16/12	0/23	NR
Wagrowska-D et al, 2015 (30)	Poland	Caucasian	76	66	Suspected NDRD	19/22	8/27	NR
Yenigun et al, 2015 (31)	Turkey	Caucasian	71	41	Suspected NDRD	16/6	18/31	Funduscopy
Liu M-Y et al, 2014 (32)	China	Mongolian	200	69	Suspected NDRD	73/16	20/91	NR
Horvatic et al, 2014 (33)	Croatia	Caucasian	80	70	Suspected NDRD	24/7	13/36	NR
Byun et al, 2013 (34)	Korea	Mongolian	110	62	Suspected NDRD	31/13	10/56	Funduscopy and fluorescein angiography
Jin Kim et al, 2013 (35)	Korea	Mongolian	65	NR	Suspected NDRD	5/18	4/38	NR
Chong et al, 2012 (5)	Malaysia	Mongolian	89	58	Suspected NDRD	50/17	5/17	NR
Oh et al, 2012 (36)	Korea	Mongolian	126	68.25	Suspected NDRD	50/17	5/17	Ophthalmoscopy after mydriasis
Bi et al, 2011 (37)	China	Mongolian	220	70	Suspected NDRD	92/10	28/90	Ophthalmoscopy
Chang et al, 2011 (38)	Korea	Mongolian	119	54	Suspected NDRD	34/17	9/59	Direct ophthalmoscopy and fluorescein angiography
Mou et al, 2010 (39)	China	Mongolian	69	52	Proteinuria (>1 g/day)	25/4	8/32	Ophthalmoscopy
Ghani et al, 2009 (40)	Kuwait	Caucasian	31	55	Suspected NDRD	11/3	6/11	NR
Lin Y-L et al, 2009 (41)	China	Mongolian	50	64	Suspected NDRD	12/12	12/14	Ophthalmoscopy after mydriasis and fluorescein angiography
Chawarnkul et al, 2009 (42)	Thailand	Mongolian	54	NR	Suspected NDRD	25/2	19/8	NR
Akimito et al, 2008 (43)	Japan	Mongolian	50	58	Suspected NDRD	21/7	13/9	Direct ophthalmoscopy after mydriasis
Huang F et al, 2007 (44)	China	Mongolian	52	62	proteinuria (>0.5 g/day)	14/3	18/17	Ophthalmoscopy
Pham et al, 2007 (45)	USA	Caucasian	233	53	Suspected NDRD	21/20	43/149	NR
Soni et al, 2006 (46)	India	Caucasian	160	74	Suspected NDRD	34/65	10/51	NR
Tone et al, 2005 (47)	China	Mongolian	81	60	Suspected NDRD	20/4	3/54	Direct ophthalmoscopy and fluorescein angiography
Nzerue et al, 2000 (48)	USA	Caucasian	31	47	Suspected NDRD	9/6	4/12	Fluorescence angiography
Olsen et al, 1996 (49)	Demark	Caucasian	33	NR	Suspected NDRD	19/1	10/3	NR
Richards et al, 1992 (50)	UK	Caucasian	46	NR	Suspected NDRD	14/7	10/15	NR
Amoah et al, 1988 (3)	USA	Caucasian	60	NR	Suspected NDRD	21/3	21/15	Ophthalmoscopy after mydriasis
Prospective studies								
Prakash et al, 2015 (51)	India	Caucasian	31	NR	Suspected NDRD	6/4	6/15	Ophthalmoscopy
Soleymanian et al, 2015 (52)	Iran	Caucasian	46	41	Suspected NDRD	10/8	6/22	Funduscopy and/or fluorescein angiography
Harada et al, 2013 (6)	Japan	Mongolian	55	67	Suspected NDRD	18/3	12/22	Funduscopy
Wilfred et al, 2013 (53)	India	Caucasian	93	69.89	Suspected NDRD	18/22	11/42	NR
Zhou J-H et al, 2008 (54)	China	Mongolian	110	70	Proteinuria (UPE ≥0.5 g/d)	46/5	14/45	NR
Moger et al, 2005 (55)	India	Caucasian	26	80.77	Suspected NDRD	9/11	0/6	NR
Serra et al, 2002 (56)	Spain	Caucasian	35	63	Suspected NDRD	9/3	17/6	Fluorescein angiography
Wong et al, 2002 (10)	China	Mongolian	68	56	Suspected NDRD	17/8	7/36	Ophthalmoscopy
Suzuki et al, 2001 (57)	Japan	Mongolian	98	68	Suspected NDRD	46/8	24/20	Ophthalmoscopy after mydriasis

(*continued on next page*)

Table 1 (*continued*)

Studies	Country	Race	Patients included (n)	Men (%)	Indications for renal biopsy	Retinopathy DKD/NDRD (n)	No retinopathy DKD/NDRD (n)	DR evaluation
Christensen et al, 2001 (58)	Denmark	Caucasian	49	82	Macroalbuminuria (UAE ≥0.3 g/day)	17/11	17/4	Fundus photography after mydriasis
Christensen et al, 2000 (59)	Denmark	Caucasian	34	94	Macroalbuminuria (UAE ≥0.3 g/day)	17/0	9/8	Direct ophthalmoscopy
Mak et al, 1997 (60)	China	Mongolian	51	71	Proteinuria (>1 g/day)	20/10	14/7	Ophthalmoscopy after mydriasis
Brocco et al, 1997 (4)	Italy	Caucasian	53	66	Microalbuminuria (AER 20–200 μg/min)	14/15	0/24	Ophthalmoscopy after mydriasis
Fioretto et al, 1996 (61)	Italy	Caucasian	34	76.5	Microalbuminuria (AER 20–200 μg/min)	10/13	0/11	Ophthalmoscopy after mydriasis
John et al, 1994 (9)	India	Caucasian	74	NR	Suspected NDRD.	6/7	8/53	Ophthalmoscopy
Parving et al, 1992 (62)	Denmark	Caucasian	35	94.3	Macroalbuminuria (UAE ≥0.3 g/day)	16/0	11/8	Ophthalmoscopy and fundus photography after mydriasis

AER, albumin excretion ratio; *DKD,* diabetic kidney disease; *DR,* diabetic retinopathy; *NDRD,* nondiabetic renal disease; *NR,* not reported; *UAE,* urinary albumin excretion.

the years after the 2010 subgroup, they were 0.66, 0.78 and 0.81, respectively.

Finally, we performed subgroup analyses based on indications for renal biopsy: differing degrees of proteinuria (10 studies) and clinical suspicion of NDRD (41 studies). The pooled sensitivity, specificity and AUC of the former were 0.70, 0.80 and 0.82, respectively, while in the latter group, they were 0.63, 0.75 and 0.77.

In the above subgroup analysis, all values of I^2 were >50%, indicating there was still significant heterogeneity.

Evaluating clinical application

Of all the studies, the PLR for DR in diagnosis of DKD was 2.86 (95% CI 2.37 to 3.45) and the NLR was 0.43 (95% CI 0.36 to 0.51), indicating that DR is not good for detecting DKD (16). Then we performed the Fagan nomogram, and we found that if a pretest probability is 20%, the post-test probability of a positive result is 42%. At the same time, an NLR of 0.43 reduces the post-test probability to 10% for a negative test result (Figure 4).

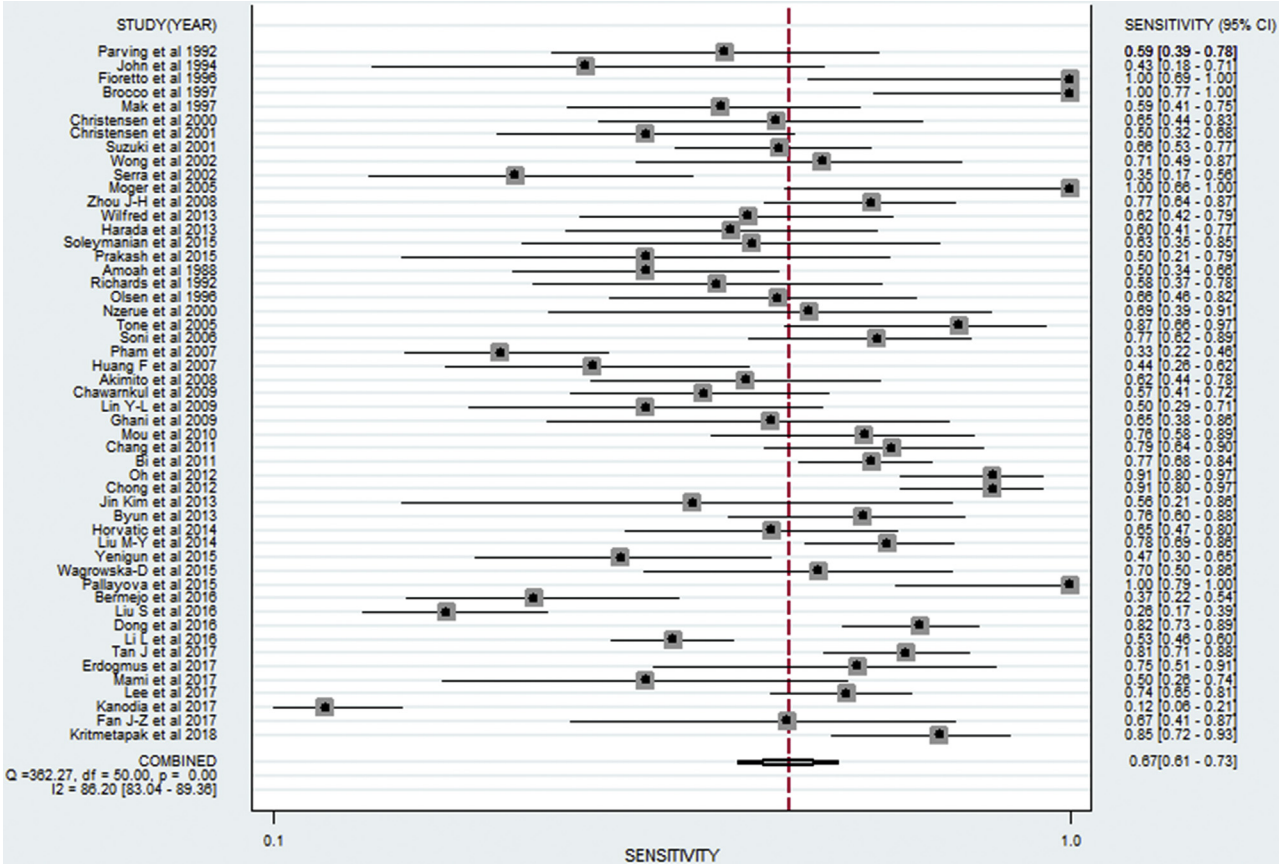

Figure 2. Sensitivity of diabetic retinopathy for the diagnosis of diabetic kidney disease, which shows that the overall pooled sensitivity is 0.67 (95% CI 0.61, 0.73).

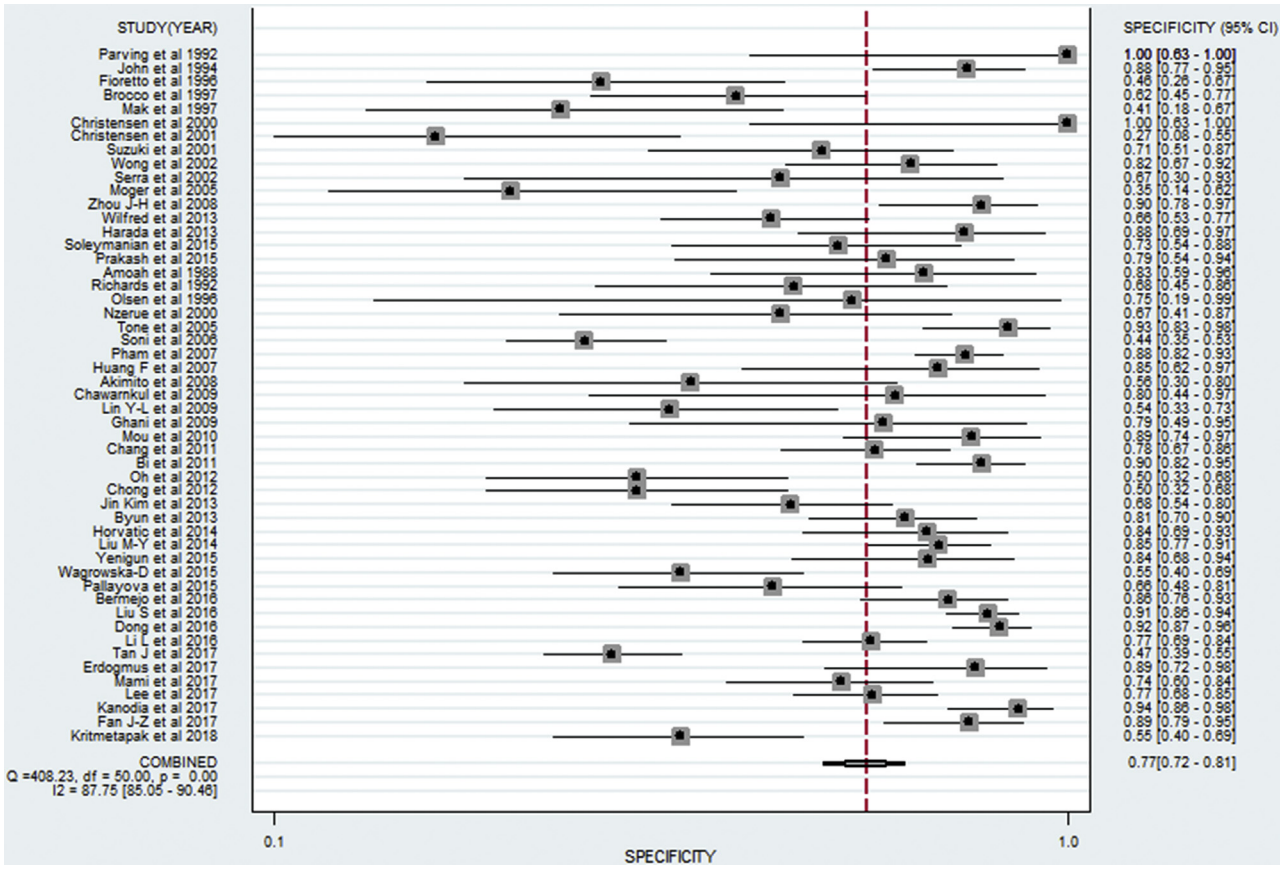

Figure 3. Specificity of diabetic retinopathy for the diagnosis of diabetic kidney disease, which shows that the overall pooled specificity is 0.77 (95% CI: 0.72, 0.81).

Pooled diagnostic accuracy of proliferative DR predicting DKD

Only 4 studies evaluated DR graded as simple or PDR (4,49,58,59). PDR demonstrated a sensitivity of 0.25 (95% CI 0.16 to 0.35) and a specificity of 0.98 (95% CI 0.92 to 1.00) for DKD. The summary receiver operating characteristic curve showed an AUC of 0.99. There was obvious heterogeneity in sensitivity (I^2=85.3%; p<0.01) and specificity (I^2=93.2%; p<0.01) among the studies.

Publication bias

The Deeks test was performed to evaluate the potential of publication bias in overall studies (Supplementary Figure 2), which suggested no publication bias (p=0.478).

Discussion

There was an increasing number of patients worldwide with type 2 diabetes who developed nephropathy, including DKD and NDRD with or without DKD, but DKD was still the primary cause of ESRD, so it is urgent to detect DKD (63). Considering the simplicity and noninvasiveness of DR evaluation, DR may be a good choice to identify DKD compared to renal biopsy with its invasive nature (8).

There is a meta-analysis from 2012 that aimed to determine the predictive value of DR in differentiating DKD from NDRD in patients with type 2 diabetes and renal disease (11). The author and colleagues concluded that DR is not as successful as expected in discriminating between DKD and NDRD, and PDR may be a highly specific indicator for DR, which differed from our hypothesis. (Differences are shown in the fourth paragraph of the Discussion.) In addition, likelihood ratios and post-test probabilities are also relevant for clinicians in clinical practice because they provide information about the likelihood that a patient with a positive or negative test of DR actually has DKD or does not, a test they did not perform. Furthermore, there was significant heterogeneity (11), but they did not perform subgroup analysis or metaregression to further explore potential sources. Finally, there have been many new studies of this subject since the publication of the meta-analysis, and our understanding of DR is still developing. Based on the above, re-evaluation is advisable.

In the current meta-analysis of 51 studies involving 4,900 participants with type 2 diabetes and renal disease from multiple centres throughout the world, the selected studies were considered to have low risk of bias and moderately good quality, according to the Quality Assessment of Diagnostic Accuracy Studies-2 criteria. In the overall analysis, the pooled sensitivity and specificity of DR for indicating DKD in people with type 2 diabetes and kidney disease were 0.67 and 0.77, respectively. Meanwhile, the pooled PLR and NLR were 2.86 and 0.43, and the AUC was 0.78, indicating DR is not good at detecting DKD; PLR above 5 and NLR below 0.2 have been noted to give strong diagnostic evidence (16). In addition, analysis indicated significant heterogeneity in sensitivity (I^2=86.20; p<0.01) and specificity (I^2=87.05; p<0.01) in included studies, but no evidence of publication bias was detected by analyzing with the Deeks regression test. Then we suspected that these potential variables (study design, race, year of publication and indications for renal biopsy) have been the sources of heterogeneity. We performed subgroup analysis and meta-regression based on the above variables; a value of I^2 was >50% in each subgroup analysis, and all values of p were >0.05 in metaregression, indicating that none of those variables contributed to interstudy heterogeneity. Finally, we performed the Fagan nomogram, and we found that the clinical

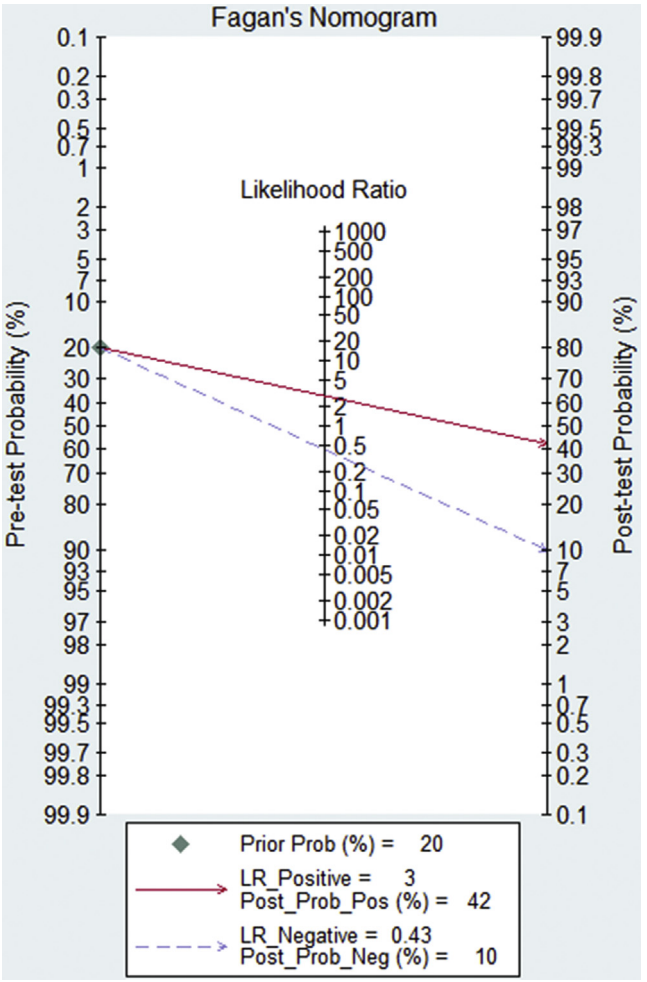

Figure 4. Fagan nomogram for diabetic retinopathy (DR) shows post-test probability (Prob) of diabetic kidney disease (DKD) in type 2 diabetes with kidney disease, which shows that if the test for DR is negative (Neg), the probability of DKD will decrease to 10%, but if the test for DR is positive (Pos), the probability will increase only to 42%, indicating that DR lacks adequate evidence to improve the prediction of DKD. *T2DM,* type 2 diabetes.

application of DR in diabetes was not obvious. Our results showed that if the test for DR is negative, the probability of DKD would decrease to 10%, but if the test for DR is positive, the probability of DKD would increase only to 42%.

Based on the above analysis, we concluded that DR lacks adequate evidence either to verify DKD or to exclude NDRD, which differs from the previous meta-analysis. The conclusion could be supported by a recent study (64) that performed a cluster analysis of a large group of patients older than 18 years of age. They clearly demonstrated that DR was associated with insulin deficiency, whereas DKD was associated with insulin resistance; this result showed that patients who developed DR did not necessarily have DKD (64).

However, in the subgroup analysis of the Mongolian group, the predictive value was higher than in the Caucasian group and in the overall group. The p value was close to 0.05 in the metaregression based on different races; therefore, we could not rashly draw the conclusion that race was not a potential source of interstudy heterogeneity. In the meantime, it has been reported that the prevalence of DR was associated with race (65,66).

Additionally, the pooled sensitivity and specificity of PDR for indicating DKD in people with type 2 diabetes and kidney disease were 0.25 and 0.98, respectively, leaving the pooled AUC as 0.99. These results show that the severity of DR might not correlate with the presence of DKD in individuals with type 2 diabetes, combined with the overall DR diagnostic accuracy. This conclusion also differs from the previous meta-analysis.

After performing subgroup analysis and meta-regression, there was still significant interstudy heterogeneity, which might be interpreted by several following limitations: 1) there were different categories of renal pathology among the studies; most studies divided patients into 2 groups (the DKD group and the NDRD group), whereas others divided patients into 3 groups (the DKD group, the NDRD group and the DKD group overlapping with the NDRD group), and these overlapping groups were classified in the NDRD groups; 2) the duration of diabetes was different in the included studies, which may have influenced the results, because it has been reported that longer duration of diabetes is strongly associated with DR in patients with diabetes (67); 3) hyperglycemia, hypertension and dyslipidemia also had effects on DR (67), but we could not explore their influence on the basis of the included data; 4) baseline proteinuria was not uniform, whereas proteinuria has been proven to be an independent risk predictor for the progression of DKD (68); 5) only studies in English were included in this meta-analysis; and 6) the sample size of patients with DR (and also DKD) in most of the included studies was low.

In conclusion, evaluating DR may lack adequate evidences either to verify DKD or to exclude NDRD in patients with type 2 diabetes and renal disease. In addition, the severity of DR may be not correlated with the presence of DKD in people with type 2 diabetes because it has much lower diagnostic accuracy than that of DR in distinguishing NDRD from DKD, although advanced DR may provide very high specificity for diagnosis of DKD.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Diabetes* at https://www.canadianjournalofdiabetes.com.

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Author Disclosures

Conflicts of interest: None.

Author Contributions

Daijin Ren and Wenling Kang reviewed articles, performed the meta-analysis and wrote the manuscript. Gaosi Xu designed the analysis and revised the manuscript. All authors have read and approved this manuscript.

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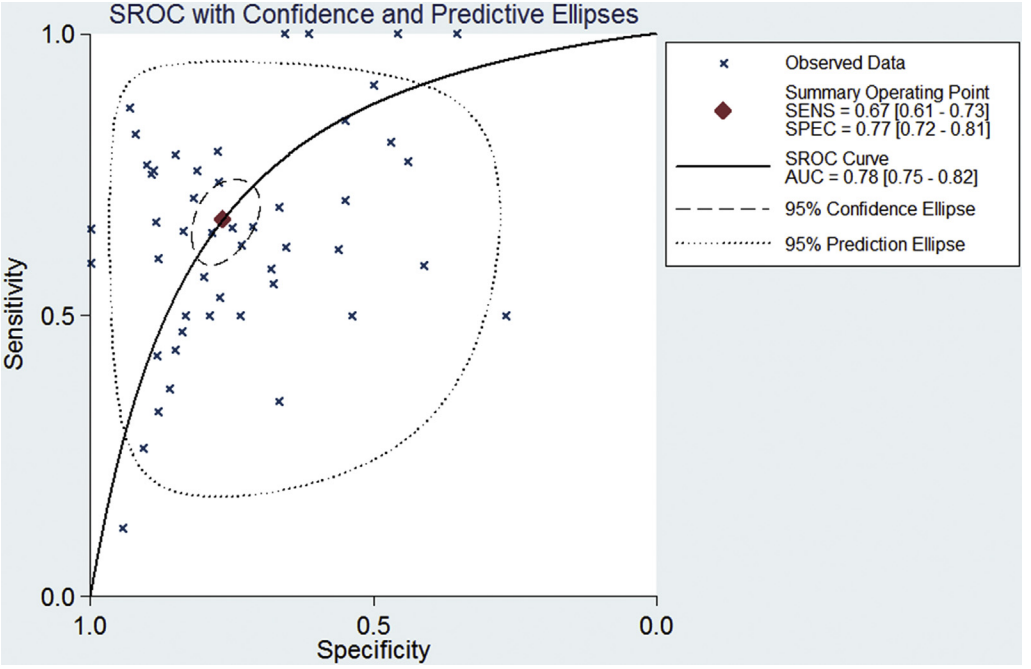
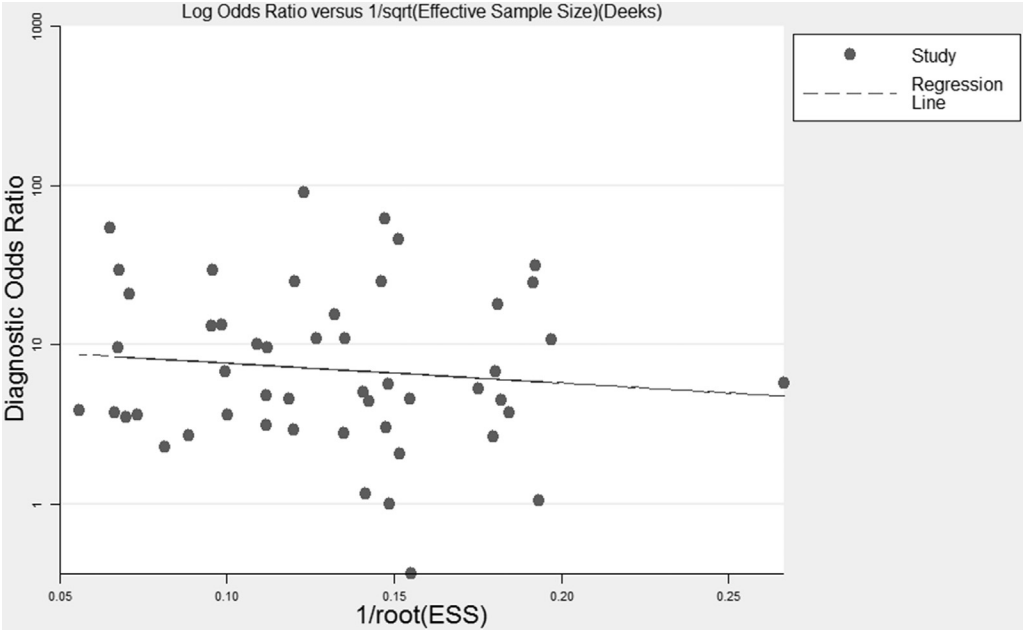


Supplementary Figure 1. Summary receiver operating characteristic (SROC) curve with pooled estimates of area under the curve (AUC), which shows that the overall pooled AUC is 0.78 (95% CI 0.75 to 0.82). *SENS*, sensitivity; *SPEC*, specificity.



Supplementary Figure 2. Graph of Deeks funnel plot asymmetry test, which shows no publication bias (p=0.478). *ESS*, effective sample size.

Supplementary Table 1
Quality assessment of the studies included in the systematic review according to the QUADAS-2 tool, which shows the majority of the studies are ranked as having moderately high quality

Study	Patient selection		Index test		Reference standard		Flow and timing
	Risk of bias	Applicability concerns	Risk of bias	Applicability concerns	Risk of bias	Applicability concerns	Risk of bias
Kritmetapak et al, 2018 (18)	Unclear	Low	Low	Low	Unclear	Low	Low
Fan J-Z et al, 2018 (19)	Unclear	Low	Low	Low	Unclear	Low	Low
Kanodia et al, 2017 (20)	Unclear	Low	Low	Low	High	Low	Low
Lee et al, 2017 (21)	Unclear	Low	Low	Low	Unclear	Low	Low
Mami et al, 2017 (22)	Unclear	Low	Low	Low	Unclear	Low	Low
Erdogmus et al, 2017 (23)	High	Low	Low	Unclear	Unclear	Low	Low
Tan J et al, 2017, (24)	Low	Low	Low	Unclear	Low	Low	High
Li L et al, 2016 (25)	High	Low	Low	Unclear	Unclear	Low	Low
Dong Z-Y et al, 2016 (26)	High	High	Low	Low	High	Low	Low
Liu S et al, 2016 (27)	Unclear	Low	Low	Unclear	High	Low	Low
Bermejo et al, 2016 (28)	Low	Low	Low	Unclear	Unclear	Low	Low
Pallayova et al, 2015 (29)	Unclear	High	Low	Unclear	Unclear	Low	Low
Wagrowska-D et al, 2015 (30)	Unclear	Low	Low	Unclear	Unclear	Low	Low
Yenigun et al, 2015 (31)	Unclear	Low	Low	Low	Unclear	Low	Low
Liu M-Y et al, 2014 (32)	Unclear	High	Low	Unclear	High	Low	Low
Horvatic et al, 2014 (33)	Low	Low	Low	Low	Unclear	Low	Low
Byun et al, 2013 (34)	Unclear	Low	Low	Low	Unclear	Low	Low
Jin Kim et al, 2013 (35)	Low	Low	Low	Unclear	Unclear	Low	High
Chong et al, 2012 (5)	Low	Low	Low	Unclear	Unclear	Low	High
Oh et al, 2012, (36)	Unclear	Low	Low	Low	Unclear	Low	High
Bi et al, 2011, (37)	Low	Low	Low	Low	Unclear	Low	Low
Chang et al, 2011 (38)	High	Low	Low	Low	Unclear	Low	Low
Mou et al, 2010 (39)	High	Low	Low	Low	Unclear	Low	Low
Ghani et al, 2009 (40)	Unclear	Low	Low	Low	Unclear	Low	Low
Lin Y-L et al, 2009 (41)	Unclear	Low	Low	Low	Unclear	Low	Low
Chawarnkul et al, 2009 (42)	Low	Unclear	Low	Low	Low	Low	Low
Akimito et al, 2008 (43)	Unclear	Low	Low	Low	Unclear	Low	Low
Huang F et al, 2007 (44)	Low	Low	Low	Low	Low	Low	Low
Pham et al, 2007 (45)	Unclear	Low	Low	Unclear	Unclear	Low	Low
Soni et al, 2006 (46)	Unclear	Low	Low	Unclear	Unclear	Low	Low
Tone et al, 2005 (47)	Unclear	Low	Low	Low	Unclear	Low	High
Nzerue et al, 2000 (48)	High	Low	Low	Low	Unclear	Low	Low
Olsen et al, 1996 (49)	Low	Low	Low	Unclear	Unclear	Low	Low
Richards et al, 1992 (50)	Low	Low	Low	NR	Unclear	Low	Low
Amoah et al, 1988 (3)	Low	Unclear	Low	Low	Unclear	Low	Low
Prakash et al, 2015 (51)	Unclear	Low	Low	Low	Low	Low	Low
Soleymanian et al, 2015 (52)	Unclear	Low	Low	Low	Unclear	Low	Low
Harada et al, 2013 (6)	Unclear	Low	Low	Low	Unclear	Low	Low
Wilfred et al, 2013 (53)	High	Low	Low	Unclear	Low	Low	Low
Zhou J-H et al, 2008 (54)	Low	Low	Low	Unclear	Unclear	Low	Low
Moger et al, 2005 (55)	High	Low	Low	Unclear	Unclear	Low	Low
Serra et al, 2002 (56)	High	Low	Low	Low	Unclear	Low	Low
Wong et al, 2002 (10)	Low	Low	Low	Low	Low	Low	Low
Suzuki et al, 2001 (57)	Low	Low	Low	Low	Unclear	Low	Low
Christensen et al, 2001 (58)	Low	Low	Low	Low	Low	Low	Low
Christensen et al, 2000 (59)	Low	Low	Low	Low	Low	Low	Low
Mak et al, 1997 (60)	Low	Low	Low	Low	Unclear	Low	Low
Brocco et al, 1997 (4)	Low	Low	Low	Low	Unclear	Low	Low
Fioretto et al, 1996 (61)	Low	Low	Low	Low	Unclear	Low	Low
John et al, 1994 (9)	Unclear	High	Low	Low	Unclear	Low	High
Parving et al, 1992 (62)	High	Low	Low	Low	Low	Low	High

QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies Tool-2.

Supplementary Table 2
Subgroup analysis of diabetic retinopathy as a predictor of diabetic kidney disease based on study design, race, publication time and indications of retinal biopsy

Covariate	N (studies)	Independent estimates (95% CI)				AUC
		Sensitivity	I^2 (%)	Specificity	I^2 (%)	
All studies	51	0.67 (0.61–0.73)	86.2	0.77 (0.72–0.81)	87.75	0.78
Study design						
Prospective studies	16	0.64 (0.59, 0.69)	70.6	0.72 (0.68, 0.76)	80.5	0.75
Retrospective studies	35	0.64 (0.62, 0.66)	90.0	0.77 (0.75, 0.79)	89.2	0.79
Race						
Mongoloid	24	0.69 (0.66, 0.71)	85.3	0.81 (0.79, 0.83)	83.7	0.81
Caucasian	27	0.56 (0.53, 0.60)	86.8	0.70 (0.67, 0.73)	87.7	0.71
Publication time						
Before 2010	24	0.61 (0.57, 0.64)	75.6	0.72 (0.69, 0.75)	85.9	0.73
After 2010 (including 2010)	27	0.66 (0.63, 0.68)	91.0	0.78 (0.76, 0.80)	88.4	0.81
Indications for renal biopsy						
Different degrees of proteinuria	10	0.70 (0.66, 0.75)	80.2	0.80 (0.76, 0.84)	89.2	0.82
Suspected NDRD	41	0.63 (0.61, 0.65)	88.1	0.75 (0.74, 0.77)	87.1	0.77

AUC, area under the curve; *CI*, confidence interval; *NDRD*, nondiabetic renal disease.
Note: I^2>50% is considered to indicate heterogeneity.