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ORIGINAL ARTICLE

Identification of clinical predictors of diabetic nephropathy and non-diabetic renal disease in Chinese patients with type 2 diabetes, with reference to disease course and outcome

Jiali Wang[1,2] · Qianqian Han[1] · Lijun Zhao[1] · Junlin Zhang[1] · Yiting Wang[1] · Yucheng Wu[1] · Tingli Wang[1] · Rui Zhang[1] · Premesh Grung[1] · Huan Xu[3] · Fang Liu[1]

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Abstract

Aims To determine the prevalence of diabetic nephropathy (DN) and non-diabetic renal disease (NDRD) in patients with type 2 diabetes mellitus (T2DM), and the important clinical predictors of renal outcome and clinical course.

Methods We conducted a retrospective analysis of clinical, laboratory, and histopathologic data from T2DM patients with renal involvement confirmed by renal biopsy ($n=505$). The outcome was defined as the progression to end-stage renal disease (ESRD).

Results Renal biopsy revealed that 302 patients (59.8%) had DN, 174 (34.5%) had NDRD, and 29 (5.7%) had NDRD superimposed on DN. In multivariate analysis, the absence of diabetic retinopathy (DR) (odds ratio (OR) 4.171, 95% confidence interval (CI) 1.810–9.612; $P=0.001$), absence of hypertension (OR 2.412, 95% CI 1.095–5.315; $P=0.029$), shorter duration of diabetes (OR 1.015, 95% CI 1.008–1.022; $P<0.001$), lower-risk chronic kidney disease (CKD) heat map category (green, yellow and orange) (OR 3.885, 95% CI 1.289–11.707; $P=0.016$) and lower glycated hemoglobin (HbA1c) (OR 1.339, 95% CI 1.114–1.610; $P=0.002$) were significant clinical predictors of NDRD. Patients with DN had a poorer 5-year renal outcome than those with NDRD, and multivariate analysis identified DN as an independent risk factor for progression to ESRD, when adjusted for important clinical variables ($P<0.05$).

Conclusions This study has identified the absence of DR and hypertension, lower-risk CKD heat map category, shorter duration of diabetes, and lower HbA1c as useful clinical predictors of NDRD. Renal biopsy is recommended for patients with T2DM and renal disease to obtain an accurate diagnosis and determine timely disease-specific treatment, which should increase the chance of a good renal outcome.

Keywords Diabetic nephropathy · Non-diabetic renal disease · Clinical predictor · Disease course · Outcome · End-stage renal disease

Introduction

Diabetic nephropathy (DN) is now the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide [1–3], and in China DN accounts for approximately 16.4% of all cases of ESRD [4, 5]. DN is usually diagnosed clinically, but renal biopsy is recommended

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Jiali Wang and Qianqian Han contributed equally to the work and both are first authors.

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✉ Fang Liu
liufangfh@163.com

[1] Division of Nephrology, West China Hospital of Sichuan University, No. 37, Guoxue Alley, Chengdu 610041, Sichuan, China

[2] Division of Nephrology, Mianyang Central Hospital, Mianyang 621000, China

[3] Division of Pathology, West China Hospital of Sichuan University, Chengdu 610041, Sichuan, China

for patients with atypical presentations. However, patients with DN can manifest various degrees of renal insufficiency and albuminuria, with a high degree of heterogeneity in the clinical and pathologic features, especially in those with type 2 diabetes mellitus (T2DM) [6]. Previous studies have suggested that the incidence of non-diabetic renal diseases (NDRD), such as IgA nephropathy (IgAN) and membranous nephropathy (MN), in patients with T2DM and renal disease, varies between 17 and 85% [7–12], which implies a high degree of heterogeneity in patients with T2DM and renal disease, as well as a lack of conformity between the clinical characteristics and the final diagnosis.

The clinical features that have previously been shown to predict NDRD in diabetic patients are a rapid increase in proteinuria, a rapid decline in renal function, the presence of proteinuria without retinopathy or neuropathy, a short duration of DM, and obvious glomerular hematuria [13–16]. Renal biopsy is recommended for atypical patients with T2DM and renal involvement, because the differentiation of NDRD from DN using non-invasive clinical parameters poses a significant challenge.

In this study, we determined the clinical features, renal pathologic changes, and renal outcome in T2DM patients with renal biopsy-diagnosed DN or NDRD, to identify the clinical predictors of DN and NDRD in patients with T2DM and renal disease, and to identify appropriate indications for renal biopsy in such patients.

Materials and methods

Patient inclusion and exclusion criteria

A total of 505 patients were considered to be eligible and were enrolled in the study. Diagnoses of T2DM were made using the criteria of the American Diabetes Association [17]. The indications for renal biopsy in this study were T2DM patients with renal damage who lacked absolute contraindications, especially T2DM patients without DR or those with obvious glomerular hematuria and/or a short diabetic duration, sudden onset overt proteinuria, rapidly declined renal function or rapidly increased proteinuria [8]. The inclusion criteria were as follows: (1) age $\geq$ 18 years old, (2) a diagnosis of T2DM, (3) a diagnosis of DN or NDRD proven by renal biopsy, and (4) estimated glomerular filtration rate(e-GFR, calculated by the CKD-EPI formula) > 15 mL/min/1.73 m^2. The included patients were followed up for at least a year. The exclusion criteria were other types of diabetes (diagnosed using patient history and assays of serum glutamic acid decarboxylase and insulinoma antigen-2 autoantibodies to exclude type 1 diabetes mellitus), a history of kidney transplantation, incomplete data, commencement of dialysis before renal biopsy, and follow-up < 1 year. All renal biopsies were performed with the consent of the patient. The study protocol was reviewed and approved by the hospital ethics committee. The renal outcome was ESRD, which was considered to require treatment using dialysis. Patients who died were not included in the outcome measurement.

Assessment of renal histopathology

For each biopsy specimen, routine light microscopy, immunofluorescence, and electron microscopy were performed by the same group of pathologists. Patients were then divided into three groups according to the pathology present: those with DN, those with NDRD superimposed on DN (mixed lesions), and those with NDRD, according to the pathological classification published by the Renal Pathology Society in 2010 [18].

Clinical and laboratory data

The following baseline clinical characteristics were assessed at the time of renal biopsy: age, sex, systolic/diastolic blood pressure, duration of T2DM, 24-h urinary protein, blood urea nitrogen, serum creatinine, glycated hemoglobin (HbA1c), total cholesterol, and eGFR, which was calculated using the CKD-EPI equation. DR lesions were also recorded at the time of biopsy after ophthalmoscopic examination by experienced ophthalmologists. In several patients, definitive diagnoses were made using optical coherence tomography and fundus color.

In the present study, the CKD heat map categories recommended by Kidney Disease-Improving Global Outcomes 2012 [19] were used to evaluate the prognosis of patients with T2DM and renal disease using four colors: green, yellow, orange, and red. Those in the red category have the highest proteinuria and lowest GFR, and carry the poorest prognosis. Due to the limited number of cases, patients who were categorized in the green, yellow, and orange groups were allocated to a single category in this study [20]. Thus, all the patients were categorized into either a lower-risk CKD heat map category [green, yellow, and orange (G&Y&O)] or a higher-risk CKD heat map category (Red).

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, NY, USA). For continuous variables, data are presented as the mean ± standard deviation or median with range. Differences between groups were assessed using Student's *t* test or analysis of variance for continuous variables, or with Fisher's exact test or the Chi square test for categorical variables. Multiple logistic regression using a forward stepwise method was performed to determine the independent predictors of DN and NDRD, including

all covariates with a $P < 0.05$ in the univariate analysis. Receiver operating characteristic (ROC) curves were constructed for significant predictors of NDRD and DN by plotting sensitivity vs. 1 − specificity, and the areas under the ROC curves (AUC) were calculated to determine the sensitivity and specificity of the predictors. A Kaplan–Meier analysis was used to compare the unadjusted renal outcomes. Univariate and multivariate Cox hazard analyses were used to determine the independent predictors of renal prognosis in T2DM patients.

Results

Clinical and pathologic characteristics and use of medication

A total of 505 T2DM patients with renal disease were eligible and enrolled in the present study. Renal biopsy revealed that 302 patients (59.8%) had DN, 174 (34.5%) had NDRD, and 29 (5.7%) had NDRD superimposed on DN. Primary glomerulonephritis (GN) was more frequent than secondary GN among patients with NDRD. MN was the most common type of primary NDRD lesion (56 patients; 32.2%), followed by IgAN (38 patients; 21.8%). Details of the NDRD present in the study sample are shown in Table 1.

The baseline clinical features of the patients with DN, NDRD, or NDRD superimposed on DN are listed in Table 2. Of the 505 patients, 310 were male (61.4%) and 195 were female (38.6%). At the time of renal biopsy, the median T2DM duration was 60 months (range 1–360 months) and the median follow-up period was 26 months (range 12–107 months). There were no differences in the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antihyperlipidemic drugs, or insulin among the three groups. However, immunosuppressive treatment, such as steroids and immunosuppressants, was most common in patients with NDRD.

Identification of clinical predictors of DN and NDRD in patients with T2DM

Multivariate logistic regression analysis was used to determine the clinical predictors of DN and NDRD (Table 3). For NDRD, these were identified to be the absence of DR (OR 4.171, 95% CI 1.810–9.612; $P = 0.001$), the absence of hypertension (OR 2.412, 95% CI 1.095–5.315; $P = 0.029$), a shorter history of diabetes (OR 1.015, 95% CI 1.008–1.022; $P < 0.001$), being categorized in the lower-risk CKD heat map category (G&Y&O) (OR 3.885, 95% CI 1.289–11.707; $P = 0.016$), and lower HbA1c (OR 1.339, 95% CI 1.114–1.610; $P = 0.002$).

ROC analysis was used to evaluate the sensitivity and specificity of the predictors of DN and NDRD (Table 4). For DN, a history of diabetes of > 5 years was associated with the largest AUC, followed by being categorized in the higher-risk CKD heat map category (Red), the presence of DR, the presence of hypertension, and higher HbA1c. However, a history of diabetes of > 10 years was not associated with the highest AUC, but rather being categorized in the higher-risk CKD heat map category. For NDRD, a duration of diabetes of < 5 years was associated with the largest AUC, followed by being categorized in the lower-risk CKD heat map category, the absence of DR, the absence of hypertension, and lower HbA1c. Of these, being categorized in the lower-risk CKD heat map category was associated with the largest AUC. The AUCs of the predictors for NDRD are shown in the supplementary data (Supplementary Fig. 1).

Table 1 Pathological findings of type of glomerular lesions in NDRD group

Type of NDRD	NDRD group ($n = 174$)	NDRD + DN group ($n = 29$)	ALL ($n = 203$)
Membranous nephropathy	56 (32.2)	10 (34.5)	66 (32.5)
IgA nephropathy	38 (21.8)	11 (37.9)	49 (24.1)
Minimal change disease	29 (16.7)	2 (6.9)	31 (15.3)
Focal segmental glomerular sclerosis	15 (8.6)	2 (6.9)	17 (8.4)
Amyloid nephropathy	2 (1.1)	0	2 (1.0)
Hypertensive nephropathy	5 (2.9)	0	5 (2.5)
Purpura nephritis	5 (2.9)	0	5 (2.5)
Lupus nephritis	3 (1.7)	1 (3.4)	4 (2.0)
Mesangial proliferative glomerulonephritis	6 (3.4)	2 (6.9)	8 (3.9)
ANCA associated glomerulonephritis	3 (1.7)	0	3 (1.5)
Membranoproliferative glomerulonephritis	2 (1.1)	0	2 (1.0)
Proliferative sclerosis nephritis	4 (2.3)	0	4 (2.0)
Obesity related glomerulopathy	2 (1.1)	0	2 (1.0)
Others	4 (2.3)	1 (3.4)	5 (2.5)

Table 2 Baseline clinical features and drug treatment of patients in the DN group, NDRD group and NDRD superimposed on DN group

	Total ($n=505$)	DN group ($n=302$)	NDRD group ($n=174$)	NDRD + DN group ($n=29$)	P
Male (%)	310 (61.4)	201 (66.6)	90 (51.7)[a]	19 (65.5)	0.005
Age (years)	51.01 ± 10.11	51.46 ± 9.68	50.32 ± 10.65	50.45 ± 11.35	0.474
Diabetic retinopathy (%)	166 (32.9)	138 (45.7)	26 (14.9)[a]	2 (6.9)[b]	< 0.001
Hypertension (%)	368 (72.9)	259 (85.8)	92 (52.9)[a]	17 (58.6)[b]	< 0.001
Duration of diabetes (m)	60 (1–360)	84 (1–360)	12 (1–240)[a]	61 (1–132)[b]	< 0.001
SBP (mmHg)	140.65 ± 23.10	146.10 ± 23.88	132.38 ± 19.21[a]	133.83 ± 20.18[b]	< 0.001
DBP (mmHg)	85.11 ± 13.25	86.74 ± 13.44	82.84 ± 12.75[a]	81.79 ± 11.88[b]	0.003
eGFR (mL/min/1.73 m^2)	78.01 ± 40.27	66.50 ± 33.16	98.36 ± 45.88[a]	87.99 ± 28.76[b]	< 0.001
Serum creatinine (mg/dL)	1.39 ± 0.91	1.59 ± 0.97	1.09 ± 0.75[a]	1.13 ± 0.43[b]	< 0.001
BUN (mmol/L)	8.68 ± 6.61	9.26 ± 5.66	7.95 ± 8.27[a]	7.13 ± 3.12[b]	0.049
UA (mmol/L)	378.12 ± 88.18	385.12 ± 81.88	365.37 ± 96.62[a]	381.70 ± 93.0	0.061
Triglycerides (mmol/L)	2.52 ± 2.81	2.19 ± 1.77	2.88 ± 3.89[a]	3.72 ± 3.43[b]	0.002
Cholesterol (mmol/L)	5.75 ± 2.19	5.31 ± 1.72	6.38 ± 2.56[a]	6.52 ± 2.95[b]	< 0.001
LDL-C (mmol/L)	3.39 ± 1.68	3.12 ± 1.37	3.82 ± 2.00[a]	3.70 ± 1.94[b]	< 0.001
HDL-C (mmol/L)	1.43 ± 0.61	1.36 ± 0.53	1.60 ± 0.75[a]	1.26 ± 0.33[b]	< 0.001
HbA1c (%)	7.40 ± 2.02	7.43 ± 1.98	7.10 ± 1.84	8.76 ± 2.87	0.002
Proteinuria (g/24 h)	4.4 (0.02–29.60)	4.4 (0.04–27.00)	3.8 (0.02–29.60)	5.0 (0.14–20.70)	0.612
Hematuria (%)	320 (63.4)	182 (60.3)	120 (69.0)	18 (62.1)	0.163
CKD heat map category					
Lower-risk CKD heat map categories (G&Y&O) (%)	321 (63.6)	148 (49.0)	149 (85.6)	24 (82.8)	< 0.001
Higher-risk CKD heat map categories (red) (%)	184 (36.4)	154 (51.0)	25 (14.4)[a]	5 (17.2)[b]	< 0.001
Use of ACEI/ARB (%)	385 (76.2)	240 (79.5)	125 (71.8)	20 (69.0)	0.108
Immunosuppressive treatment (%)	46 (9.1)	0 (0.0)	40 (23.0)[a]	6 (20.7)[b]	< 0.001
Use of hypolipidemic drugs (%)	272 (53.9)	172 (57.0)	85 (48.9)	15 (51.7)	0.226
Use of insulin (%)	342 (67.7)	213 (70.5)	110 (63.2)	19 (65.5)	0.251

Data are presented as the mean ± standard deviation, the median with range or counts and percentages

$P < 0.05$ (analysis of variance for continuous variables and Fisher's exact test or Chi square test for categorical variables)

SBP systolic blood pressure, *DBP* diastolic blood pressure, *e-GFR* estimated glomerular filtration rate, *BUN* blood urea nitrogen, *UA* uric acid, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker; immunosuppressive treatment, use of steroids and/or immunosuppressants

[a]Significant difference between the DN group and the NDRD group

[b]Significant difference between the DN group and the NDRD superimposed on DN group

Table 3 Multivariate logistic regression analysis of diabetic nephropathy and of non-diabetic renal disease

Indicator	*b*-Estimate	Standard error	*P* value	Odds ratio	95% Confidence interval
Diabetic retinopathy	1.428	0.426	0.001	4.171	1.810–9.612
Hypertension	0.881	0.403	0.029	2.412	1.095–5.315
Duration of diabetes (years)	0.015	0.003	< 0.001	1.015	1.008–1.022
CKD heat map categories	1.357	0.563	0.016	3.885	1.289–11.707
HbA1c (%)	0.292	0.09	0.002	1.339	1.114–1.610

Renal outcomes

Survival curves for the renal outcome in the NDRD and DN groups are shown in Fig. 1. The Kaplan–Meier survival analysis yielded an overall percentage of patients not progressing to ESRD over 5 years of 80.5%. Patients with NDRD and DN had 5-year percentages of 96.0% and 71.5%, respectively, which were significantly different ($P < 0.001$).

Univariate Cox analysis showed that compared with NDRD patients, patients with DN had a higher renal mortality (hazard ratio (HR) 9.676, 95% CI 4.671–20.045;

Table 4 Sensitivity, specificity, positive and negative predictive values of significant variables in the prediction of diabetic nephropathy and of non-diabetic renal disease

Variable	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*P* value
For DN						
Diabetic retinopathy (yes vs. no)	0.680	45.70	85.06	84.15	47.44	< 0.001
Hypertension (yes vs. no)	0.664	85.76	47.13	73.79	65.60	< 0.001
Duration of diabetes (> 5 years) (yes vs. no)	0.705	64.57	77.01	82.98	55.60	< 0.001
Higher-risk CKD heat map categories (Red) (yes vs. no)	0.683	50.99	85.63	86.03	50.17	< 0.001
HbA1c (> 7%) (yes vs. no)	0.590	51.95	66.40	74.07	42.78	0.005
For NDRD						
Diabetic retinopathy (no vs. yes)	0.680	47.44	84.15	85.06	45.70	< 0.001
Hypertension (no vs. yes)	0.664	65.60	73.79	47.13	85.76	< 0.001
Duration of diabetes (< 5 years) (yes vs. no)	0.705	55.60	82.98	77.01	64.57	< 0.001
Lower-risk CKD heat map categories (G&Y&O) (yes vs. no)	0.683	50.17	86.03	85.63	50.99	< 0.001
HbA1c (< 7%) (yes vs. no)	0.590	42.78	74.07	66.40	51.95	0.005

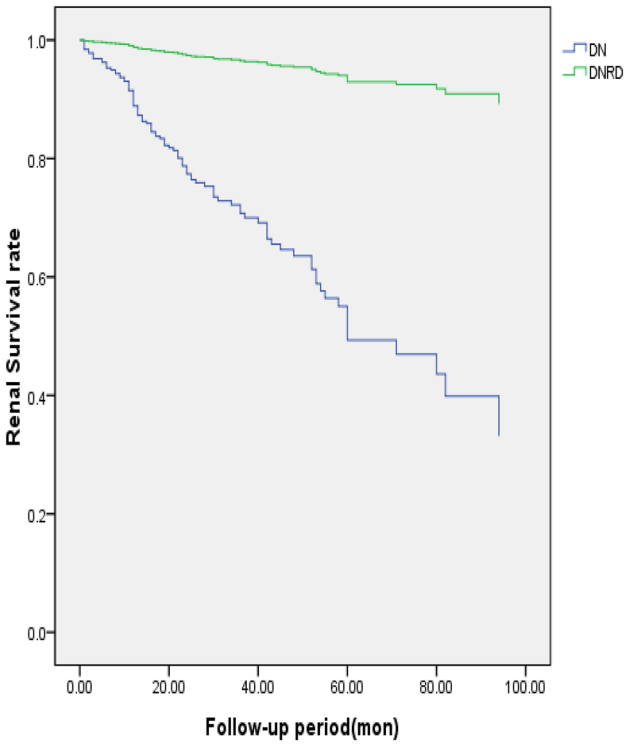

Fig. 1 Renal survival rate in univariate analysis in DN and NDRD group

$P < 0.001$; Fig. 2). In models 1, 2, and 3, the HRs for the DN group were significantly higher than those for the NDRD group.

Discussion

In this study, we have assessed the clinicopathologic features and renal outcomes of T2DM patients with concurrent renal disease and identified clinical predictors of DN and NDRD in these patients. The main findings were that NDRD is common in T2DM patients with renal disease, as previously reported [8], and that a lower incidence of DR, lower incidence of hypertension, being categorized in the lower-risk CKD heat map category (G&Y&O), a shorter duration of diabetes, and lower HbA1c, are clinical predictors of NDRD. A duration of diabetes of < 5 years had the highest predictive power, followed by being categorized in the lower-risk CKD heat map category, the absence of DR, the absence of hypertension, and lower HbA1c. In contrast, a duration of diabetes of > 5 years had the highest predictive power for DN, followed by being categorized in the higher-risk CKD heat map category, the presence of DR, the presence of hypertension, and higher HbA1c.

The reported prevalence of the various types of NDRD varies among previous studies. In accordance with the report by Liu [21], our study found that the most frequent NDRD was MN, which accounted for 32.2% of all NDRD, followed by IgAN (21.8%). In contrast, Shree et al. reported that the most frequent pathologic diagnosis was focal segmental glomerulosclerosis [22]. The large variation in the reported prevalence of NDRD is probably the result of the different criteria used for renal biopsy, but may also be due to geographic and ethnic differences [23–26].

DN is one of the chronic microvascular complications of diabetes, developing 5–10 years after the onset of diabetes. In the present study, we found a longer duration of diabetes, of > 5 or > 10 years, to be a significant clinical predictor of DN, and a shorter duration of diabetes, of < 5 or < 10 years, to be a significant predictor of NDRD. Consistent with this,

Factor	HR	95%CI	P-value
Univariate			
DN	9.676	4.671-20.045	<0.001
Model 1			
DN	5.374	2.134-13.533	<0.001
Hypertension	1.059	0.539-2.078	0.868
Diabetic retinopathy	1.001	0.629-1.594	0.996
Duration of diabetes	1.002	0.999-1.005	0.239
CKD heat map category	4.691	2.684-8.197	<0.001
HbA1c	0.972	0.864-1.093	0.636
Model 2			
DN	6.687	3.137-14.258	0.001
Proteinuria	1.046	1.008-1.086	0.018
eGFR	0.971	0.963-0.979	<0.001
Model 3			
DN	8.297	3.319-20.742	<0.001
Male	1.03	0.646-1.643	0.901
Serum creatinine	1.861	1.643-2.11	<0.001
Triglyceride	0.991	0.873-1.125	0.891
Cholesterol	1.054	0.934-1.188	0.394
Immunosuppresive treatment	0.858	0.162-4.536	0.857

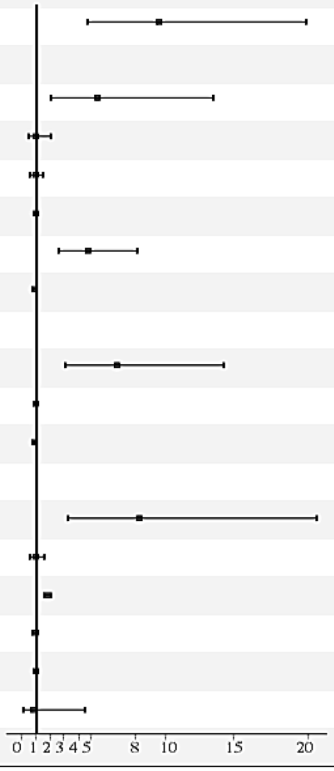

Fig. 2 HRs of progression to ESRD for the patients with DN vs. NDRD in the cohort study using univariate/multivariate COX hazard analysis

Kritmetapak et al. reported that a short duration of diabetes (< 8 years) is associated with a high likelihood of NDRD, rather than DN alone [27], and Horvatic et al. found that a longer duration of diabetes (> 7-year cut-off value determined using ROC analysis) is a significant predictor of DN using a multivariate analysis [28]. The sensitivity and specificity of a longer history of diabetes prior to biopsy for the prediction of DN in the present study were 64.57% and 77.01%, respectively, which are lower than those calculated in the study by Horvatic et al., in which the values were 78.43% and 82.76% [28]. In the present study, the sensitivity and specificity of a shorter history of diabetes prior to biopsy for the prediction of NDRD were 55.60% and 82.98%, respectively, which are consistent with the established view that a longer duration of diabetes in T2DM patients with renal disease confers a greater risk of DN, whereas a shorter duration of diabetes is associated with a greater likelihood of NDRD being present. The Chinese participants studied here had a significantly shorter history of diabetes at biopsy than previously studied groups from Thailand, Croatia, and Korea [12, 27, 28]. The variation in the sensitivity and specificity of the duration of diabetes may also be due to variations in the time of screening and treatment of diabetes and diabetes with renal disease in these different countries.

The CKD heat map was established to help determine the prognosis of CKD, and this applies equally to DN. The sensitivity and specificity of being categorized in the higher-risk CKD heat map category (Red) for the prediction of DN in the present study were 50.99% and 85.63%, respectively, and the equivalent values for the lower-risk CKD category (G&Y&O) for the prediction of NDRD were 50.17% and 86.03%. These findings are consistent with the accepted view that if T2DM patients with renal disease are in a high-risk group for CKD, then DN should be suspected, whereas those in lower-risk groups are more likely to have NDRD.

In multivariate analysis, the presence of DR was found to be a significant independent predictor of DN, whereas the absence of DR was a significant independent predictor of NDRD. The absence of DR has been reported to be a significant predictor of NDRD in the majority of previous studies and has been accepted as an important clinical indication for renal biopsy in T2DM patients with renal disease [22, 29], although some other studies have not found the absence of DR to be a significant predictor of NDRD [30]. In the present study, the sensitivity and specificity of the absence of DR in the prediction of NDRD were 47.44% and 84.15%, respectively, whereas Horvatic et al. calculated values of 73.47% and 77.42% [12]. The sensitivity and specificity of the presence of DR in the prediction of DN in our study were 45.70% and 85.06%, respectively, which are lower than those calculated by Horvatic et al. (58.82% and 96.55%) [28], and by Erdogmus et al. (75.00% and 91.00%) [31]. In our study,

the patients with diabetes and renal disease had a significantly shorter history of diabetes at the time of renal biopsy than the patients in the other studies, and DR did not show a high sensitivity and specificity in the prediction of DN.

Blood pressure control is important for the prevention of progression of both diabetic and non-diabetic renal lesions. In our study, the frequency of hypertension in the DN group was significantly higher than in the NDRD group, which is consistent with the findings of Zhou et al. [32] and Wong et al. [26]. This suggests that the presence of hypertension is a significant clinical predictor of DN, which may be linked to the high dietary intake of salt in China [21, 33]. The sensitivity and specificity of the presence of hypertension for the prediction of DN in the present study were 85.76% and 47.13%, respectively, and the values for the absence of hypertension for the prediction of NDRD were 65.60% and 73.79%. However, we could not find any previously reported sensitivity or specificity data for comparison with published studies.

Serum HbA1c was also found to be a significant predictor of DN in the present study, as in the study by Zhou et al. [32]. The sensitivity and specificity of the presence of an HbA1c > 7% for the prediction of DN in our study were 51.95% and 66.40%, and the equivalent values for the presence of an HbA1c < 7% for the prediction of NDRD were 42.78% and 74.07%. Therefore, once again, the present findings are consistent with the accepted view that higher HbA1c in T2DM patients with renal disease means that DN is more likely, whereas lower HbA1c is more likely to be associated with NDRD.

It is generally thought that DN outcomes are worse than those of NDRD [29]. This emphasizes the importance of confirming the diagnosis of NDRD in diabetic patients, including through renal biopsy, as well as the use of immunosuppressive treatment, such as with immunosuppressants or glucocorticoids.

A few limitations of the present study are worthy of comment. Firstly, it was a retrospective study performed in a single center, which implies sampling bias, and selection bias is inevitable in any biopsy-based study. Secondly, the role of unmeasured confounding factors, such as smoking status, that could have influenced the observed associations cannot be entirely ruled out. Thirdly, only 29 (5.7%) of the included patients had NDRD superimposed on DN and, finally, we did not control for all the therapeutic interventions that were used, such as erythropoiesis stimulating agents.

In conclusion, renal biopsy should be recommended for T2DM patients with atypical nephropathy, because a considerable number may have NDRD, especially those who do not have DR or hypertension, have a shorter history of diabetes, or are in the higher-risk CKD heat map category. Large, multicenter, randomized prospective studies are required to fully identify the preliminary changes in T2DM patients to distinguish those with NDRD from those with NDRD superimposed on DN at an early stage, which should help with the initiation of specific treatment, improve renal prognosis, and reduce the prevalence of renal involvement in T2DM patients.

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Compliance with ethical standards

Conflict of interest The authors have no conflicting interests that are relevant to this article.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (West China Hospital of Sichuan University Biomedical Research Ethics Committee, 2013R01) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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