

# A Multifactorial Risk Score System for the Prediction of Diabetic Kidney Disease in Patients with Type 2 Diabetes Mellitus

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**Purpose:** In-depth investigations of risk factors for the identification of diabetic kidney disease (DKD) in type 2 diabetes mellitus (T2DM) are rare. We aimed to investigate the risk factors for developing DKD from multiple types of clinical data and conduct a comprehensive risk assessment for individuals with diabetes.

**Methods:** We carried out a case-control study, enrolling 958 patients to identify the risk factors for developing DKD in T2DM patients from a database established from inpatient electronic medical records. Multivariable logistic regression was applied to develop a prediction model and the performance of the model was evaluated using the area under the curve (AUC) and calibration curve. A multifactorial risk score system was established according to the Framingham Study risk score.

**Results:** DKD accounted for 34.03% of eligible patients in total. Twelve risk factors were selected in the final prediction model, including age, duration of diabetes, duration of hypertension, fasting blood glucose, fasting C-peptide, insulin use, systolic blood pressure, low-density lipoprotein,  $\gamma$ -glutamyl transpeptidase, platelet, uric acid, and thyroid stimulating hormone; and one protective factor, serum albumin. The prediction model showed an AUC of 0.862 (95% Confidence Interval (CI) 0.834–0.890) with an accuracy of 81.5% in the derivation dataset and an AUC of 0.876 (95% CI 0.825–0.928) in the validation dataset. The calibration curves were excellent and the estimated probability of DKD was more than 80% when the cumulative score for risk factors reached 17 points.

**Conclusion:** Newly recognized risk factors were applied to assess the development of DKD in T2DM patients and the established risk score system was a reliable and feasible tool for assisting clinicians to identify patients at high risk of DKD.

**Keywords:** diabetic kidney disease, multifactorial, prediction model, risk factors, type 2 diabetes

## Introduction

Diabetic kidney disease (DKD) increases as the prevalence of diabetes mellitus (DM) rises dramatically.<sup>1</sup> Publications based on epidemiology have indicated that DKD in developed countries is 20%–40%, and the overall frequency in China is 21.8% and showed geographical and gender variation.<sup>2,3</sup> Moreover, nearly 50% of DKD patients would progress to end-stage renal disease, bringing an enormous cost burden to public healthcare systems.<sup>4</sup> Early identification and intervention of DKD may offer the best opportunity for halting the disease progression. Consequently, efforts should be made to better understand routine risk factors in the development of DKD in patients with type 2 DM (T2DM).

Current studies have proposed two categories of risk factor associated with DKD, one for non-modifiable risk factors and the other for modifiable risk factors.<sup>5,6</sup> However, most of the studies only focus on finding and identification of risk factors for DKD, failing to give more in-depth insight into their role in the development of DKD.<sup>7,8</sup> For example, little is known about the desired target values of risk factors in predicting or intervening in the development of DKD. Previous

studies have indicated that strict management of one modifiable factor, such as hyperglycemia, still inevitably promotes DKD progress.<sup>9</sup> Recently, from the Steno-2 and J-DOIT3 studies, it was found that reduced macroalbuminuria and beneficial kidney function in DKD was achieved by the interaction of multiple factors.<sup>10–12</sup> This indicates that the complex and multifactorial characteristics of DKD cannot be accurately explained by a single factor or a limited number of factors. The data from our study is based on patient electronic medical records, and is an example of a real-world study, may be able to compensate for the diversity of patients selected that randomized controlled studies cannot achieve, offering new perspectives for the recognition and management of the disease.

In the present study, we aimed to explore increased information concerning the risk factors for associated with the prediction of DKD in the T2DM population by using a dataset extracted from inpatient medical electronic records. In addition, we comprehensively assessed risk factors to establish a prediction model and then converted it into a risk score system as a simple and easy tool for clinical application.

## Materials and Methods

### Study Population

This was a retrospective case-control study, enrolling 958 patients who were hospitalized in the Department of Endocrinology or Nephrology at Shanxi provincial people's hospital, Taiyuan, China between January 2017 and December 2021. The inclusion criteria were patients diagnosed with T2DM or first diagnosis of DKD at ages 18–75 years. Exclusion criteria were as follows: (1) patients with type 1 diabetes or secondary diabetes; (2) patients with acute complications of diabetes (hyperosmolar hyperglycemia syndrome, diabetic ketoacidosis, lactic acidosis), or the presence of diabetic retinopathy (DR); (3) presence of severe infection or autoimmune diseases, or malignant tumors; (4) patients with mental disease or genetic diseases; (5) patients complicated by urinary tract infection, acute/chronic nephritis and taking nephrotoxic drugs or drugs having an effect on the urinary protein excretion rate; or (6) patients with chronic kidney disease (CKD) stage 4 or stage 5 or having renal replacement therapy. The flowchart depicting our study design is shown in [Supplementary Figure 1](#), and the study was reviewed and approved by the Institutional Review Board of the Shanxi provincial people's hospital, Taiyuan, China ([2021] Provincial Medical Opinions No.354). As this study was conducted using medical records obtained from patient's prior clinical procedures, their informed consent was waived. We ensured patient data confidentiality and patient privacy was protected, and the study was also in compliance with the Declaration of Helsinki and it followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement.<sup>13</sup>

### Data Collection and Pre-Processing

The data were extracted from the clinical research platform at the Kidney Disease Data Center in Shanxi provincial people's hospital, which included patient hospitalization medical records, outpatient medical records and others. We searched for the main diagnosis of T2DM and/or DKD (diagnosed according to the International Classification of Disease (ICD) –10 codes) from inpatient electronic medical records in the platform. Based on the purpose and inclusion and exclusion criteria, 958 patients were eligible to take part, of which 632 patients had T2DM and 326 patients had DKD. Initially, 70 variables were extracted, including demographic characteristics, previous medical history, previous drug use, glucose-related parameters, and laboratory examinations (blood routine items, liver function, thyroid function, renal function). After data cleaning, 22 variables with missing values of more than 40% were eliminated. Since the missing rate of the else variables were less than 15%, it was imputed using the median. Considering the recent research progress and clinical practice, 48 parameters were finally used for analysis in this study. The details of these variables are shown in [Supplementary Table 1](#). The overall quality of the input data was assessed by two experienced physicians.

### Definitions

The diagnosis of T2DM was according to the 1999 World Health Organization diagnostic criteria:<sup>14</sup> a fasting plasma glucose  $\geq 126$  mg/dL (7.0 mmol/L), or a random plasma glucose  $\geq 200$  mg/dL (11.1 mmol/L), or HbA1c  $\geq 6.5\%$  with typical symptoms of diabetes, or the use of glucose-lowering agents. The diagnosis of DKD was based on urinary albumin-to-creatinine (UACR)  $\geq 30$  mg/g, and/or an estimated glomerular filtration rate (eGFR) of less than 60 mL/min

per  $1.73 \text{ m}^2$  within 3 months or more with absence of other primary causes of kidney damage in patients with T2DM.<sup>15</sup> Hypertension was considered as systolic pressure  $\geq 140 \text{ mmHg}$  and/or a diastolic pressure  $\geq 90 \text{ mmHg}$  or taking medication for hypertension.<sup>16</sup> Macrovascular complications were defined as the middle and upper artery atherosclerosis caused by diabetes, including cerebral arteries, aorta, coronary arteries, and peripheral arteries. Peripheral vascular disease refers to stenosis or occlusion of the lower limb arteries caused by diabetes, resulting in intermittent claudication, and a more severe stage of limb amputation and death. Diabetic peripheral neuropathy was defined as damage to the nervous system caused by chronic hyperglycemia and various pathophysiological changes. Smoking was defined as those who had smoked for at least 6 months or had at least 100 cigarettes in their lifetime. Family history referred to first-degree relatives who had suffered from diabetes, hypertension, or both in their medical records.

## Statistical Analysis

Analyses were performed using SPSS 26.0 (SPSS Inc., USA). The continuous variables were expressed as median and interquartile interval [M (QL, QU)] due to the non-normal distribution, using Mann–Whitney *U*-test. Categorical variables were expressed as frequencies (%) and compared by using Chi-square test. *P*-values  $< 0.05$  with two-tailed were considered as a statistically significant level. Significant parameters ( $P < 0.05$ ) were used for univariate and multivariate regression analysis to considerate the candidate variables (Shown in [Supplementary Table 2](#)). The multicollinearity test indicates the absence of multicollinearity among the covariates that the maximum variance inflation factor (VIF) was less than 2. Candidate variables were determinate by using a stepwise forward selection procedure and multivariable logistic regression equation modelling was used to develop the model for predicting DKD.

## Prediction Model and Risk Score Development

The data were randomly allocated into training data sets (80%) for developing the model and validation data sets (20%) for validating the model's performance. We used cut-off value determined by the receiver operating characteristic (ROC) curve to transform the continuous candidate variables into dichotomous variables and the results of variable conversions are shown in [Supplementary Table 3](#). All candidate variables were initially included in a multivariable logistic regression model and screened by forward stepwise regression to get the best performance for the model. Next, we rechecked other excluded parameters at this stage and estimated them where necessary. Finally, twelve risk factors and one protective factor were identified after adjusting many times. Then, a forward stepwise logistic regression was used to develop a prediction model and its validation in the internal database. The performance of the model was evaluated using the area under the ROC curve and calibration curve. An area under the curve (AUC)  $> 0.8$  was considered as excellent discrimination. Calibration was determined by a visual calibration plot comparing the predicted probability and the observed proportion of the occurrence of DKD. The calibration ability of the prediction model was evaluated by Hosmer–Lemeshow goodness-of-fit test. The established equation for predicting DKD was converted into a risk score system by using the estimated regression coefficients with reference to the Framingham Study risk score.<sup>17</sup> After that, we also obtained an estimated probability at different risk scores.

## Results

### General Characteristics of the Patients

There were 958 patients included in the analysis, and the proportion of DKD patients was 34.03% (326/958) in total. The study population was randomly divided into a derivation set ( $n = 780$ ) and a validation set ( $n = 178$ ) by 8:2, and patient characteristics of both cohorts are shown in [Tables 1](#) and [Table 2](#). All quantitative variables were tested and confirmed to a non-normal distribution ( $P < 0.05$ ). In the derivation dataset, the mean ages for patients with T2DM was 51.36 (45.00, 59.00) years, and in DKD patients it was 53.98 (46.75, 64.00) years. Males were the main gender, and the ratio of males to females was 1.78:1 in total. The mean Scr was 66.03 (56.22, 74.64)  $\mu\text{mol/L}$  in T2DM patients and 76.28 (58.41, 83.97)  $\mu\text{mol/L}$  in DKD patients. After non parametric tests and Chi-square tests, factors with significant differences ( $P < 0.05$ ) were determined, including age, body mass index (BMI), smoking, duration of diabetes, hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), duration of hypertension, peripheral vascular disease, antidiabetic agents, antihypertension agents, lipid-lowering agents, aspirin, fasting

**Table I** Clinical Characteristics of the Patients

	Training Cohort			Validation Cohort		
	T2DM (n=514)	DKD (n=266)	P	T2DM (n=118)	DKD (n=60)	P
Age (years)	51.36 (45.00, 59.00)	53.98 (46.75, 64.00)	<0.001	51.47 (43.75, 60.25)	55.57 (51.00, 65.00)	0.021
Gender			0.747			0.732
Male (%)	62.84	67.29		68.64	71.67	
Female (%)	33.86	32.71		31.36	28.33	
BMI (kg/m <sup>2</sup> )	25.38 (23.32, 27.22)	26.32 (23.43, 29.00)	0.001	26.07 (23.34, 27.91)	24.52 (23.05, 27.80)	0.897
Smoker (%)	41.24	48.87	0.048	44.92	46.67	0.874
Drinking (%)	33.85	36.84	0.428	36.44	41.67	0.518
Family history			0.227			0.054
None (%)	46.50	42.11		50.00	36.67	
Diabetes (%)	32.30	33.83		35.59	31.67	
Hypertension (%)	10.50	15.04		7.63	16.67	
Hypertension & Diabetes (%)	10.70	9.02		6.78	15.00	
Duration of diabetes (years)	6.26 (1.00, 10.00)	9.14 (3.00, 14.00)	<0.001	5.86 (1.00, 9.00)	8.14 (1.00, 12.50)	0.018
Hypertension (%)	31.27	65.04	<0.001	31.36	73.33	<0.001
SBP (mmHg)	126.81 (120.00, 130.00)	134.45 (125.00, 141.25)	<0.001	125.08 (120.00, 130.00)	131.63 (124.00, 148.00)	<0.001
DBP (mmHg)	78.27 (72.00, 81.00)	82.06 (74.00, 89.00)	<0.001	77.54 (72.00, 81.00)	83.46 (74.00, 90.00)	0.004
Duration of hypertension (years)	2.46 (0.00, 2.00)	6.49 (0.00, 10.00)	<0.001	2.66 (0.00, 2.00)	8.52 (0.00, 15.00)	<0.001
Dyslipidemias (%)	7.60	10.41	0.179	9.32	6.67	0.588
Duration of dyslipidemia (years)	0.47 (0.00, 0.00)	0.68 (0.00, 0.00)	0.078	0.46 (0.00, 0.00)	0.78 (0.00, 0.00)	0.544
Peripheral neuropathy (%)	69.12	63.16	0.108	71.19	65.00	0.925
Peripheral macrovascular (%)	28.79	30.08	0.740	31.36	36.67	0.504
Peripheral vascular (%)	21.01	32.71	<0.001	22.88	28.33	0.464
Antidiabetic agents			<0.001			0.054
None (%)	24.90	12.41		21.19	18.33	
Insulin use (%)	9.34	25.56		10.17	21.67	
Oral agents and Insulin use (%)	13.23	23.31		16.94	25.00	
Oral agents (%)	52.53	38.72		51.69	35.00	
Anti-hypertension agents			<0.001			<0.001
None (%)	82.49	40.60		71.19	33.33	
ACEI (%)	5.64	8.27		6.78	15.00	
ARB (%)	4.86	13.16		10.17	36.67	
Others (%)	7.01	37.97		11.86	15.00	
Lowering-Lipid agent (%)	6.81	15.04	<0.001	6.78	16.67	0.063
Aspirin (%)	4.28	10.53	0.001	7.63	13.33	0.281

plasma glucose (FPG), glycated hemoglobin (HbA1c), white blood cells (WBC), hematocrit (HCT), platelet (PLT), aspartate aminotransferase (AST), serum albumin (ALB),  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GGT), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), serum creatinine (Scr), total serum bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), fasting C-peptide (FCP), fasting insulin (FINS), and thyroid stimulating hormone (TSH). In the validation dataset, the mean age in T2DM patients was 51.47 (43.75, 60.25) years and 55.57 (51.00, 65.00) years in the DKD patients. Males again represented most populous gender, and the ratio of men to women was 2.30:1 overall. Significantly different factors ( $P < 0.05$ ) were age, duration of diabetes, hypertension, duration of hypertension, SBP, DBP, antihypertension agents, HCT, ALB, TG, Scr, and TSH.

## Candidate Variables Selection

To attain the potentially valuable predictors, we first screened out 29 variables by using univariate logistic regression analysis, and then imputed 28 variables into the multivariate logistic regression model to further ascertain 12 significant variables after adjustment. Due to the collinearity between hemoglobin (Hb) and HCT, we did not include HCT for analysis, and the result details are shown in [Supplementary Table 2](#). We then reconfirmed the excluded predictors and whether they could be involved in a multivariable logistic analysis. At this stage, we converted the continuous variables

**Table 2** Laboratory Characteristics of the Patients

	Training Cohort			Validation Cohort		
	T2DM (n=514)	DKD (n=266)	P	T2DM (n=118)	DKD (n=60)	P
FPG (mmol/L)	8.87 (6.84, 10.33)	10.29 (7.01, 12.96)	<0.001	8.75 (6.61, 10.46)	9.90 (7.07, 11.74)	0.058
HbA1c (%)	8.59 (7.10, 9.80)	9.05 (7.50, 10.50)	0.001	8.54 (6.80, 9.70)	8.84 (7.25, 9.98)	0.308
WBC ( $\times 10^9/L$ )	6.50 (5.32, 7.36)	7.10 (5.67, 8.31)	<0.001	6.41 (5.26, 7.13)	6.51 (5.13, 7.45)	0.417
RBC ( $\times 10^{12}/L$ )	4.56 (4.37, 5.06)	4.52 (4.18, 5.06)	0.397	4.66 (4.46, 5.11)	4.53 (4.31, 5.05)	0.101
Hb (g/L)	144.49 (134, 155)	141.31 (130, 155)	0.096	145.61 (135.00, 157.00)	142.58 (131.00, 155.75)	0.172
HCT (%)	0.431 (0.400, 0.460)	0.420 (0.390, 0.460)	0.037	0.433 (0.391, 0.455)	0.420 (0.400, 0.464)	0.030
RDW-CV (fl)	12.95 (12.50, 13.30)	13.36 (12.40, 13.40)	0.971	13.05 (12.50, 13.50)	12.84 (12.43, 13.28)	0.199
RDW-SD (fl)	41.48 (39.70, 42.90)	41.49 (39.58, 41.53.30)	0.878	41.69 (40.15, 43.30)	41.34 (39.48, 42.85)	0.209
PLT ( $\times 10^9/L$ )	198.27 (157.00, 229.25)	224.81 (177.00, 262.00)	<0.001	197.35 (155.00, 227.25)	207.45 (160.25, 242.00)	0.274
AST (IU/L)	22.00 (15.29, 23.21)	23.53 (15.63, 25.16)	0.037	21.17 (14.74, 24.55)	24.99 (15.18, 26.09)	0.665
ALT (IU/L)	28.65 (15.31, 32.74)	30.00 (14.98, 33.23)	0.922	29.70 (14.95, 35.44)	31.25 (14.28, 29.19)	0.530
Alb (g/L)	41.85 (39.46, 43.93)	34.48 (25.98, 42.55)	<0.001	42.27 (39.75, 44.56)	39.14 (37.16, 42.15)	<0.001
$\gamma$ -GGT (IU/L)	35.45 (17.16, 39.76)	42.93 (20.13, 44.73)	<0.001	34.99 (18.87, 42.36)	52.59 (20.05, 42.09)	0.499
TG (mmol/L)	2.27 (1.14, 2.52)	2.52 (1.24, 2.81)	0.010	2.18 (1.17, 2.45)	3.15 (1.37, 3.48)	0.011
TC (mmol/L)	4.46 (3.81, 5.02)	4.74 (3.84, 5.40)	0.021	4.54 (3.75, 5.08)	4.43 (4.10, 5.38)	0.488
LDL-C (mmol/L)	2.71 (2.29, 3.12)	2.96 (2.39, 3.47)	<0.001	2.68 (2.26, 3.12)	2.76 (2.24, 3.32)	0.592
HDL-C (mmol/L)	1.02 (0.86, 1.14)	1.08 (0.83, 1.17)	0.950	1.05 (0.88, 1.17)	1.01 (0.83, 1.14)	0.238
UA ( $\mu$ mol/L)	309.26 (249.62, 359.82)	345.48 (273.04, 411.31)	<0.001	323.59 (241.08, 399.17)	347.32 (276.78, 426.93)	0.243
Scr ( $\mu$ mol/L)	66.03 (56.22, 74.64)	76.28 (58.41, 83.97)	<0.001	65.67 (56.72, 72.99)	80.64 (60.75, 94.04)	0.001
TBIL ( $\mu$ mol/L)	14.77 (10.95, 17.70)	13.61 (9.94, 15.96)	0.002	14.75 (11.51, 17.05)	15.22 (10.68, 17.96)	0.849
DBIL ( $\mu$ mol/L)	2.61 (1.88, 3.01)	2.36 (1.73, 2.90)	0.004	2.58 (1.86, 3.00)	2.73 (1.79, 3.09)	0.808
IBIL ( $\mu$ mol/L)	12.03 (8.79, 14.44)	11.22 (8.30, 13.05)	0.018	12.21 (9.73, 14.43)	12.44 (8.45, 14.38)	0.501
FCP (ng/mL)	1.89 (1.20, 2.46)	2.24 (1.49, 2.98)	<0.001	2.09 (1.37, 2.77)	2.19 (1.49, 3.01)	0.553
FINS ( $\mu$ U/mL)	10.24 (5.43, 12.44)	13.30 (7.43, 14.34)	<0.001	11.23 (5.53, 13.86)	12.80 (6.46, 16.68)	0.155
TSH ( $\mu$ U/mL)	2.48 (1.45, 2.88)	3.47 (1.77, 4.17)	<0.001	2.53 (1.49, 3.51)	3.14 (2.12, 3.56)	0.022

into binary terms to obtain valuable predictors without omitting a single circumstance, as shown in [Supplementary Table 3](#). Finally, we selected age, duration of diabetes, duration of hypertension, FPG, FCP, insulin use, SBP, TSH, UA, PLT,  $\gamma$ -GGT, LDL-C, and peripheral vascular disease as the 13 risk factors, and ALB as a protective factor for DKD.

## Development of the Risk Score

The final prediction model was developed by using a stepwise multivariable logistic regression, including two continuous variables of age and duration of hypertension, others being dichotomy variables. The model showed an accuracy of 81.5%, sensitivity of 77.1%, and specificity of 82.5%. The detailed DKD risk prediction model was established as follows: age (1.026, 95% confidence interval (CI) [1.006, 1.047]); duration of diabetes (1.694, [1.040, 2.761]); FPG (4.215, [2.775, 6.402]); FCP (2.972, [1.878, 4.703]); Insulin use (3.171, [2.086, 4.821]); duration of hypertension (1.074, [1.040, 1.109]); SBP (2.628, [1.751, 3.945]); LDL -C (2.756, [1.718, 4.419]); UA (3.833, [2.444, 6.013]); TSH (2.433, [1.641, 3.607]);  $\gamma$ -GGT (1.829, [1.231, 2.751]); PLT (1.916, [1.285, 2.856]); and ALB (0.941, [0.901, 0.984]) (Shown in [Table 3](#)). The cumulative total score was 51 points in the transformed risk score chart, of which the probability of predicting DKD was more than 80% when the cumulative score reached 17 points (Shown in [Table 4](#)).

## Performance and Validation of the Risk Score

In the derivation cohort, the AUC for the risk prediction model was 0.862 (95% CI: 0.834–0.890); and the AUC was 0.876 (95% CI: 0.825–0.928) in the validation cohort. The ROC curve is shown in [Figure 1](#). The Hosmer-Lemeshow goodness-of-fit test showed that Hosmer-Lemeshow (derivation cohort:  $\chi^2 = 9.285$ ,  $P = 0.319$ ; validation cohort:  $\chi^2 = 5.357$ ,  $P = 0.719$ ) revealed no significance between the predicted probability and the observed proportion ([Figure 2A](#) and [Figure 2B](#)). We also

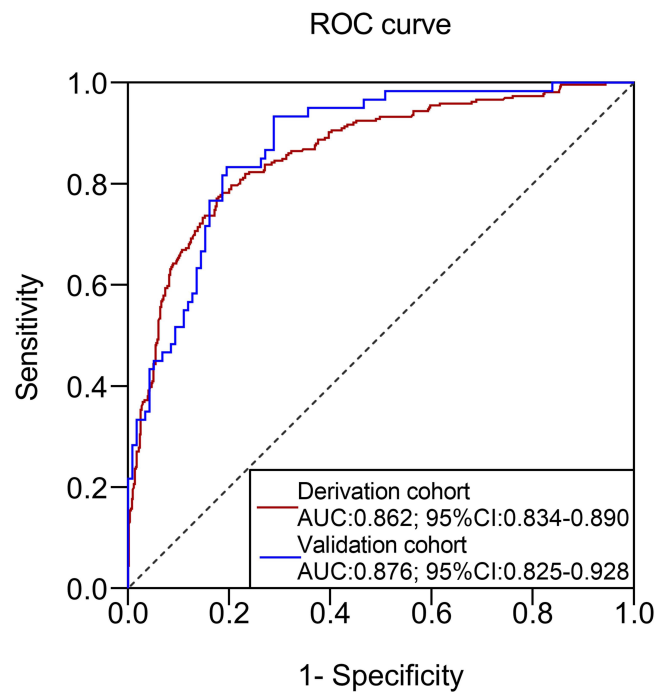
**Table 3** Variables in the DKD Prediction Model

Factors	$\beta$ -Coefficient	S. E	P value	OR (95% CI)
Age (years)	0.026	0.010	0.010	1.026 (1.006, 1.047)
Duration of diabetes (>10 years)	0.527	0.249	0.034	1.694 (1.040, 2.761)
FPG (>10.41 mmol/L)	1.439	0.213	<0.001	4.215 (2.775, 6.402)
FCP (>1.41 ng/mL)	1.089	0.234	<0.001	2.972 (1.878, 4.703)
Insulin use (yes)	1.154	0.214	<0.001	3.171 (2.086, 4.821)
Duration of hypertension (years)	0.071	0.016	<0.001	1.074 (1.040, 1.109)
SBP (>130 mmHg)	0.966	0.207	<0.001	2.628 (1.751, 3.945)
LDL-C (>3.4 mmol/L)	1.014	0.241	<0.001	2.756 (1.718, 4.419)
UA (>385.48 $\mu$ mol/L)	1.344	0.230	<0.001	3.833 (2.444, 6.013)
TSH (>2.10 $\mu$ IU/mL)	0.889	0.201	<0.001	2.433 (1.641, 3.607)
$\gamma$ -GGT (>23.43 IU/L)	0.604	0.202	0.003	1.829 (1.231, 2.751)
PLT (>187.5 $\times 10^9$ /L)	0.650	0.204	0.001	1.916 (1.285, 2.856)
ALB (>44.34 g/L)	-0.060	0.023	0.008	0.941 (0.901, 0.984)

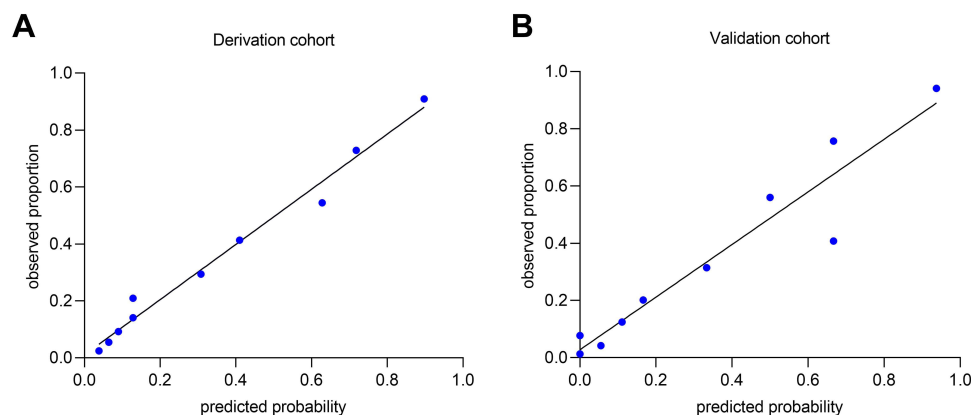
**Table 4** Risk Score System for DKD and Prediction Probability

Predictors	Categories	Points	Total Score	Estimated Risk
Age (years)	$\leq 60$	0	0	0.0591
	61–65	3	1	0.0746
	66–70	3	2	0.0938
	71–75	4	3	0.1173
Duration of diabetes (years)	$\leq 10$	0	4	0.1457
	>10	2	5	0.1797
FPG (mmol/L)	$\leq 10.41$	0	6	0.2195
	>10.41	6	7	0.2653
FCP (ng/mL)	$\leq 1.41$	0	8	0.3168
	>1.41	4	9	0.3732
Insulin use	No	0	10	0.4333
	Yes	5	11	0.4954
Duration of hypertension (years)	$\leq 1$	0	12	0.5576
	1–5	1	13	0.6181
	6–10	2	14	0.6751
	11–15	4	15	0.7274
	16–20	5	16	0.7741
	>20	8	17	0.8148
SBP (mmHg)	$\leq 130$	0	18	0.8496
	>130	4	19	0.8788
LDL-C (mmol/L)	$\leq 3.40$	0	20	0.903
	>3.40	4	21	0.9228
UA ( $\mu$ mol/L)	$\leq 385.48$	0	22	0.9389
	>385.48	5	$\geq 23$	0.9517
TSH ( $\mu$ IU/mL)	$\leq 2.10$	0		
	>2.10	4		
PLT ( $\times 10^9$ /L)	$\leq 187.5$	0		
	>187.5	3		
$\gamma$ -GGT (IU/L)	$\leq 23.43$	0		
	>23.43	2	Total: 51 points	





**Figure 1** Receiver operating characteristic (ROC) curve of the derivation and validation cohort. The solid red line represented the derivation cohort, which the AUC and its 95% confidence interval (CI) were 0.862 (0.834–0.890); the solid blue line represented the validation cohort, which the AUC and its 95% CI were 0.876 (0.825–0.928).



**Figure 2** The calibration curves for the risk score system in the derivation and validation cohort. The calibration plot showed the agreement between the predicted probability (x-axis) and the observed proportion (y-axis) of the risk of the study outcomes. **(A)** The calibration curve of the derivation cohort; **(B)** the calibration curve of the validation cohort.

calculated the probability of predicting the occurrence of DKD at different scores, ranging from the least at 5% to more than 90%.

## Discussion

Seeking risk factors for DKD in patients with T2DM is a basic and crucial issue, which will promote better understanding of the disease pathophysiology and improve the ability to identify high-risk populations. In this study, we demonstrated that risk factors not only referred to the well-known modifiable indicators of hyperglycemia, hypertension, dyslipidemia, but also involved some newly recognized factors, such as FCP, insulin use, UA, TSH, PLT, and  $\gamma$ -GGT. These findings provided multiple levels of information related to DKD development, which might pave the way for new ideas to further elucidate the disease mechanism. Unlike previous studies, the continuous variables of risk factors in the

prediction model were converted into dichotomous variables with cut-off values determined by ROC curves, to increase the clinical interpretability. The established multifactorial risk score system showed excellent predictive performance both in the derivation and the internal validation datasets. Moreover, the system strengthens its contribution for predicting DKD compared to single variables, making it dependable for clinicians to apply in clinical practice.

Patients with a diagnosis of DKD accounted for 34.03% (326/958) in our study, which indicated a high frequency of DKD requiring the implementation of effective interventions to prevent or delay the progression. Our findings demonstrated that two nonmodifiable factors of old age (>60 years) and duration of diabetes (>10 years) were closely related to the development of DKD, and this is consistent with previous studies.<sup>8,18</sup> However, their efficacy at predicting DKD was not so clear when considering the simultaneous effect of multiple factors or their interactions. As is known, hypertension plays an important role in DKD development and progression.<sup>19,20</sup> However, our study adopted hypertension duration instead of the presence of hypertension as a predictor after adjustment of covariates. Through stratification analysis of the hypertension duration, we found that the risk score for predicting DKD increased approximately two-fold with a duration of hypertension increment of 5 years. This provided a quantifiable indicator to better assess the role of hypertension.

Hyperglycemia is a widely accepted modifiable risk factor for the initiation and promotion of DKD, especially in people with poor glycemic control. Our study showed that the cut-off value of FPG was 10.41 mmol/L for predicting DKD, which might provide new ideas for treating patients with poor glycemic control. However, how to set appropriate targets for patients with different physiological conditions need further study. In addition, the results underline the importance of controlling FPG for the reduction of DKD risk. Though HbA1c was a key indicator in clinical diagnosis, and its importance was eliminated after several adjustments using multivariate regression analysis. This might be the reason for its role in the progression of DKD to ESRD,<sup>21</sup> not for the development of DKD. Fasting C-peptide is a stable indicator for the assessment of endogenous secretion of insulin and contributes to the occurrence of diabetic microvascular complications.<sup>22</sup> A cross-sectional real-world study demonstrated that C-peptide might promote the incidence of DKD, and this relationship followed a U-style curve when C-peptide  $\geq 1.71$  ng/mL.<sup>23</sup> Similarly, the threshold for the C-peptide was 1.41 ng/mL for the prediction of DKD in our study with an increased risk of 3.0 times. Moreover, our study showed that insulin use was more frequent in the DKD patients than in the T2DM patients. This demonstrated that unsatisfactory glycemic control was more common in the DKD population. Therefore, a comprehensive analysis of fasting blood glucose, pancreatic function and timing of insulin use would be beneficial to reduce the development of DKD.

Elevated blood pressure and dyslipidemia were identified as other major modifiable risk factors associated with the development and progression of DKD in individuals with T2DM.<sup>24</sup> We found that SBP > 130 mmHg positively increased the risk of DKD, indicating that it was an attractive target for patients to reduce complications. A previous study from the UK Prospective Diabetes Study showed that triglycerides and LDL cholesterol were independent risk factors for DKD progression.<sup>25</sup> However, studies on the relationship between lipoprotein and DKD were inconsistent and heterogeneous. Moreover, it remains to be determined which type of lipoprotein affects the occurrence of DKD and to what extent. In the present study, we suggest that LDL-C was an independent risk factor for predicting DKD at a level higher than 3.4 mmol/L, which might provide management targets in T2DM patients.

Concerning uric acid (UA), an observational analysis from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study showed that increased UA strongly predicted higher risk of hypertension and DKD.<sup>26</sup> In our study, we found that the risk of DKD can be recognized when the value of UA is greater than 385.48  $\mu\text{mol/L}$  in the prediction model, without gender distinction. TSH is the earliest and most sensitive indicator of thyroid function. Several studies confirmed that high TSH levels were related to increased incidence of DKD, particularly in cases of macroalbuminuria.<sup>27</sup> Our results found that the increased risk of DKD was identified when the TSH level was higher than 2.10 U/mL. However, a recent study indicated that TSH negatively correlated with UA, and the mechanism might involve the regulation of UA metabolism in early-stage DKD patients.<sup>28</sup> The relationship between UA, TSH and hypertension warrants further study to elucidate the mechanism of their role in the occurrence of DKD.

Studies looking at the relationship PLT,  $\gamma$ -GGT and ALB and the onset of DKD are scarce. Our study showed that PLT with a borderline value of  $187.5 \times 10^9/\text{L}$  was associated with an increased risk of DKD. This mechanism may be related to spontaneous platelet aggregation, and blood in a high coagulated state, resulting in renal micro-thrombosis and ultimately glomerulosclerosis.<sup>29,30</sup>  $\gamma$ -GGT is a metabolic biomarker for liver dysfunction and excessive alcohol intake



and can promote the development of T2DM in a nonlinear dose-response pattern.<sup>31</sup> Recent evidence has suggested that  $\gamma$ -GGT has extra-hepatic implications for the application of in risk stratification related to cardiovascular disease and cognitive impairment.<sup>32,33</sup> Our results demonstrated that  $\gamma$ -GGT levels higher than 23.43 IU/L would increase the risk of DKD by 1.8-times. The two identified variables suggested that we can understand the pathophysiological changes in DKD from the aspects of hemodynamic and metabolic transformation. Albumins participate in maintaining homeostasis, supply nutrients to the body and regulate important physiological processes. Recently, a retrospective study showed that decreased ALB levels below 39.3 g/L was an independent risk indicator of DKD in T2DM patients.<sup>34</sup> This result was consistent with our study showing that high levels of ALB was a protective factor in DKD patients. From the above, we recommended that screening for ALB might contribute to protect the kidney from hyperglycemia.

Based on previous studies, we analyzed and obtained multiple risk factors associated with the development of DKD from the available medical data from hospitalized patients. Those predictors not only included three well-known modified factors (hyperglycemia, hypertension, and dyslipidemia), but also pointed out the linkage between DKD and liver function, thyroid function, or hemostasis. Thus, this represents a comprehensive understanding of the risk factors for DKD in T2DM patients. We also determined the cut-off value of the continuous variables in the risk factors, which might strengthen knowledge of the disease and promote the management of T2DM patients. Finally, the established risk score was more reliable and feasible for clinicians to utilize and enhances the ability to identify high-risk populations. There were several limitations of our present study. Since we carried out a retrospective study, the causality between risk factors and DKD could not be elucidated. Furthermore, there was a bias in patient selection, which needs to be confirmed in different populations. We also excluded patients complicated with diabetic retinopathy as this represented an additional microvascular complication. Finally, the lack of any external validation reduces the applicability of the DKD risk score.

## Conclusion

We found that the identified risk factors associated with the development of DKD in T2DM patients covered blood glucose, blood pressure, blood lipids, thyroid function, liver function and hemostasis. For patients with T2DM, strict control of the above factors would be beneficial for the delay or prevention of DKD. The established multifactorial risk score system can be applied to detect and predict T2DM patients with a high risk of DKD, and to better understand the disease pathophysiology and help promote diabetes management. In addition, it is easy for clinicians to implement during their clinical practice.

## Data Sharing Statement

The data in favor of the findings of this study cannot be disclosed due to the protection of patient privacy, but are available from the corresponding author Dr. Zhou [zhouxiaoshuang@sxmu.edu.cn].

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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