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ORIGINAL RESEARCH

Development and External Validation of a Nomogram and a Risk Table for Prediction of Type 2 Diabetic Kidney Disease Progression Based on a Retrospective Cohort Study in China

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Purpose: Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease worldwide. Risk assessment provides information about patient prognosis, contributing to the risk stratification of patients and the rational allocation of medical resources. We aimed to develop a model for individualized prediction of renal function decline in patients with type 2 DKD (T2DKD).

Patients and Methods: In a retrospective observational study, we followed 307 T2DKD patients and evaluated the determinants of 1) risk of doubling in serum creatinine (Scr), 2) risk of eGFR<15 mL/min/1.73m^2 using potential risk factors at baseline. A prediction model represented by a nomogram and a risk table was developed using Cox regression and externally validated in another cohort with 206 T2DKD patients. The discrimination and calibration of the prediction model were evaluated by the concordance index (C-index) and calibration curve, respectively.

Results: Four predictors were selected to establish the final model: Scr, urinary albumin/creatinine ratio, plasma albumin, and insulin treatment. The nomogram achieved satisfactory prediction performance, with a C-index of 0.791 [95% confidence interval (CI) 0.762–0.820] in the derivation cohort and 0.793 (95% CI 0.746–0.840) in the external validation cohort. Then, all predictors were scored according to their weightings. A risk table with the highest score of 11.5 was developed. The C-index of the risk table was 0.764 (95% CI: 0.731–0.797), which was similar to the external validation cohort (0.763; 95% CI: 0.714–0.812). Additionally, the patients were divided into two groups based on the risk table, and significant differences in the probability of outcome events were observed between the high-risk (score >2) and low-risk (score ≤2) groups in the derivation and external validation cohorts ($P < 0.001$).

Conclusion: The nomogram and the risk table using readily available clinical parameters could be new tools for bedside prediction of renal function decline in T2DKD patients.

Keywords: diabetic kidney disease, type 2 diabetes, estimated glomerular filtration rate, progression, prediction model

Introduction

Diabetes mellitus (DM) is a global health challenge and has reached alarming levels.[1] Diabetic kidney disease (DKD) is a major microvascular complication of DM, occurring in approximately half of all patients with type 2 DM (T2DM) and one-third with type 1 DM (T1DM).[2] DKD is defined as an estimated glomerular filtration rate (eGFR)<60 mL/min/1.73m^2 and/or urinary albumin/creatinine ratio (UACR)≥30 mg/g for more than three months caused by diabetes,[3,4] which accounts for approximately 1/3 of the whole disease burden of chronic kidney disease (CKD) worldwide.[5] In the past few decades, China has witnessed a dramatic increase in diabetes prevalence from an estimation of 0.67% in 1980 to 10.9% in 2013.[6,7] Since 2011, the percentage of DKD in China has exceeded CKD related to glomerulonephritis, and the gap is growing.[8] Despite advances over the past two decades in postponing the progression of DKD, it has become evident that DKD constitutes the leading cause

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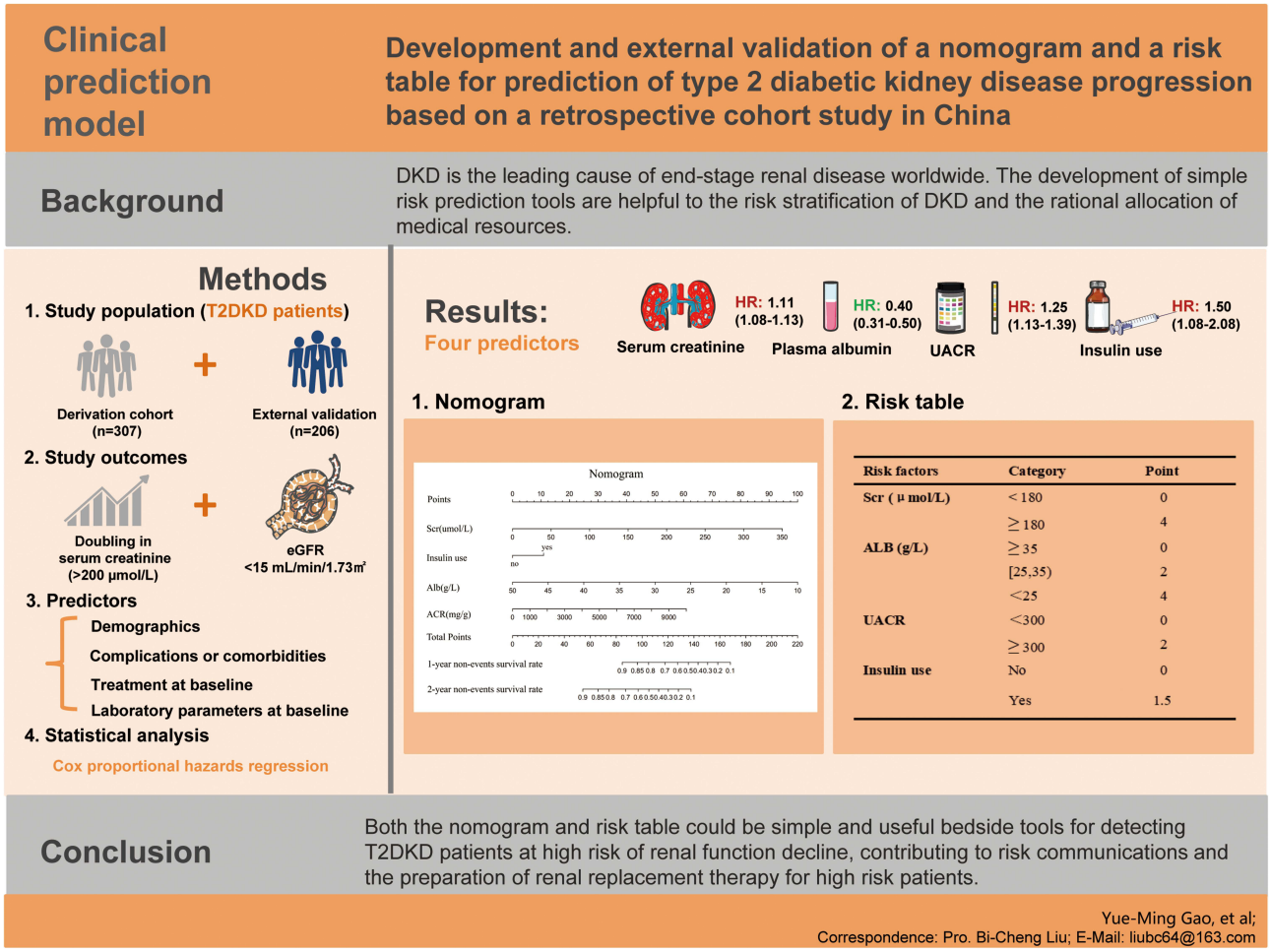
Graphical Abstract



of end-stage renal disease (ESRD) in many populations,[9] which also contributes significantly to the excess all-cause and cardiovascular mortality in T2DM patients.[10]

Predicting kidney disease progression in DKD patients remains a significant clinical challenge. Although eGFR is a well-established prognostic biomarker for predicting ESRD and cardiovascular events in DKD patients, it is insufficient to predict disease progression in the early stages. Albuminuria also strongly predicts the progression of DKD, but it lacks specificity and sensitivity for predicting ESRD and eGFR decline.[11,12] Moreover, albuminuria was reported to follow a remission/regression trajectory rather than a linearly progressive process, which might reduce its prognostic value.[13] Furthermore, recent studies have produced an explosion of novel assay-based risk biomarkers for DKD, but their clinical use remains limited because of instability and high cost.[14] Clearly, it is necessary to strengthen the risk assessment of type 2 DKD (T2DKD) progression, which will contribute to making clinical decisions and reasonably allocating medical resources.

In general, previous studies have proposed a vast number of risk factors for progressive DKD in T2DM patients.[15–22] Given that a patient may have multiple risk factors. Thus, the establishment of multifactorial prediction models is of great significance to simplify T2DKD prognostication. Several prediction models were established to predict DKD progression in T2DM patients. Elley et al[15] developed five Cox proportional hazards models to predict fatal or nonfatal ESRD events in patients with T2DM from the New Zealand Diabetes Cohort Study. These models included sex, ethnicity, age, diabetes duration, albuminuria, Scr, systolic blood pressure (SBP), glycosylated hemoglobin (HbA1c), smoking status, and

previous cardiovascular disease status, with the highest C-index of 0.89. Jardine et al[16] published an equation predicting the risk of major kidney-related events, including seven predictors: eGFR, UACR, SBP, HbA1c, diabetic retinopathy, sex, and educational attainment, with a C-index of 0.847. Wan et al[18] developed new gender-specific models to provide a more accurate 5-year ESRD risk prediction for Chinese patients with T2DM than other existing models, which included 11–12 predictors. However, these models were aimed at patients with T2DM instead of DKD. Moreover, these models were presented in the form of complex equations, which may be difficult to be applied in routine clinical practice.

This retrospective observational study aimed to develop and externally validate a model to predict renal function decline in Chinese patients with T2DKD. The prediction model was represented by a nomogram and a risk table, which could be easily applied in clinical practice by using readily available clinical parameters.

Patients and Methods

Study Design

This observational, retrospective cohort study was conducted in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement.[23]

Study Population

In this retrospective cohort study, patients with T2DKD who were hospitalized in the Institute of Nephrology, Zhongda Hospital, Southeast University School of Medicine (baseline from June 2013 to June 2017) were screened. The inclusion criteria included: (1) eGFR<60 mL/min/1.73m^2 and/or UACR≥30 mg/g for more than three months caused by T2DM; (2) the follow-up time was more than six months. The exclusion criteria included: (1) patients with eGFR<15 mL/min/1.73m^2 or with renal replacement treatment; (2) patients with nondiabetic renal diseases, such as IgA nephropathy or membranous nephropathy; (3) patients with other systemic diseases involving the kidney, such as multiple myeloma, allergic purpura, vasculitis, or systemic lupus erythematosus; (4) baseline data were incomplete. Finally, 307 T2DKD patients were included as the derivation cohort. The flowchart for the selection of patients in the derivation cohort was shown in Supplement Figure 1. Another 206 hospitalized T2DKD patients in the First Hospital Affiliated with Zhengzhou University from January 2018 to January 2020 were enrolled as the external validation cohort. For each patient, the start of observation (origin) was the date of the first hospitalization. This study was approved by the Ethics Committee of Zhongda Hospital, Southeast University (2019ZDSYLL057-P01) and was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

Study Outcomes

The primary endpoint was defined as the doubling of Scr or eGFR<15 mL/min/1.73m^2 up to January 2021 (end date), whatever came first. Doubling of Scr was defined as an increase of 100% and to at least 177 μmol/L, as suggested previously.[24] For patients without outcomes, the end date was defined as the time of the latest hospitalization or the latest clinic visit. The follow-up time for each patient was calculated as the number of days between the origin and end date. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was chosen to calculate eGFR based on different Scr values, age, and sex.[25,26]

Predictors

Predictors were prespecified according to the clinical experience and current literature on established and potential predictors in the progression of DKD.[14] Clinical characteristics, including age, sex, body mass index (BMI), SBP, diastolic blood pressure (DBP), duration of DM, smoking, family history of DM, medical history of diabetic retinopathy, hypertension, coronary heart disease (CHD) and stroke, and insulin and renin-angiotensin-aldosterone system inhibitor (RAASi) treatment were collected. Laboratory parameters considered were Scr, eGFR, hemoglobin, plasma albumin (ALB), fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, HbA1c, blood urea nitrogen (BUN), serum uric acid, serum cystatin C, 24-h urine protein, and UACR.

Data Collection

Baseline demographics, complications or comorbidities, treatment, laboratory parameters, and outcomes were collected in detail from electronic medical records of these patients. Data were extracted by two trained physicians (Yue-Ming Gao and Song-Tao Feng) and checked by the third experienced physician (Bin Wang). Patients were also contacted via telephone if there were missing data.

Statistical Analysis

Analyses were performed using R software, version 3.5.3 (R Project for Statistical Computing). We used the means ± standard deviation (SD) or medians [interquartile range (IQR)] to express continuous variables, whereas categorical variables were presented as frequencies (%). Continuous variables were compared using the independent sample *t*-test or the Mann–Whitney *U*-test, while categorical variables were compared using the chi-square or Fisher's exact tests. *P*-values<0.05 (two-sided) were considered significant. Missing data were imputed using random forests-based missing data imputation (R package missForest).[27]

Cox proportional hazards regression was used to establish the prediction model. The backward step method was used to select the independent variables of the model. A restricted cubic spline (RCS) curve and a minimum *p*-value method were used to determine the optimal cut-off value of the continuous variables, which were then transformed into categorical variables. A nomogram and a risk table were used to illustrate the model.

The performance of the prediction model was assessed by discrimination and calibration.[28] Discrimination was determined by the area under the receiver operating characteristic (ROC) curve (AUC), which ranged from 0.5 (no discrimination) to 1 (perfect discrimination).[29] Calibration was determined by a visual calibration plot comparing the predicted and actual probability of T2DKD progression. In addition, patients were categorized into two risk groups based on the risk table, including low- and high-risk. Furthermore, a Kaplan–Meier curve was generated for each risk group to evaluate the predictive power of the risk table.

Results

Study Population and Outcomes

The derivation cohort consisted of 307 eligible patients with a median follow-up of 29 months, and there were 198 outcomes (64.50%). The baseline clinical data of the derivation cohort are shown in Table 1. Compared to patients without outcome, patients with outcomes had higher levels of SBP, DBP, Scr, BUN, total cholesterol, LDL-C, serum uric acid, serum cystatin C, 24-h urine protein and UACR, lower levels of eGFR, hemoglobin and plasma ALB, a higher proportion of insulin treatment, and lower proportion of RAASi treatment. Another 206 eligible patients with a median follow-up of 18 months were chosen as the external validation cohort, and there were 97 outcomes (47%).

Selected Factors for Model

The hazard ratio (HR) and *p*-value (<0.1) of univariate regression analysis were used to select the potential risk factors (Table 2). Patients with higher levels of SBP (HR, 1.012; 95% CI, 1.005–1.019; $p=0.001$), total cholesterol (HR, 1.170; 95% CI, 1.078–1.269; $p<0.001$), serum uric acid (HR, 1.002; 95% CI, 1.001–1.003; $p=0.001$), Scr (HR, 1.010; 95% CI, 1.008–1.013; $p<0.001$) and UACR (HR, 1.029; 95% CI, 1.020–1.037; $p<0.001$), and a history of insulin use (HR, 1.490; 95% CI, 1.080–2.055; $p=0.015$) had a higher risk of renal function decline. Additionally, patients with higher levels of hemoglobin (HR, 0.976; 95% CI, 0.970–0.983; $p<0.001$) and eGFR (HR, 0.975; 95% CI, 0.968–0.982; $p<0.001$), and a history of RAASi use (HR, 0.576; 95% CI, 0.432–0.768; $p<0.001$) had a lower risk of progression. Other predictors, including DBP, LDL-C, BUN, 24-h urine protein, and serum cystatin C, are also statistically significant in univariate Cox regression analysis. Independent variables were selected by a backward stepwise multivariate Cox regression method with a *p*-value threshold of 0.05 (Figure 1A). Four variables, including the insulin treatment (HR, 1.50; 95% CI, 1.08–2.08; $p=0.016$), plasma ALB (HR, 0.40; 95% CI, 0.31–0.50; $p<0.001$), Scr (HR, 1.11; 95% CI, 1.08–1.13; $p<0.001$), and UACR (HR, 1.25; 95% CI, 1.13–1.39; $p<0.001$), were incorporated in the final model.

Table 1 Baseline Clinical Characteristics of the Derivation Cohort

Characteristics	Overall (n = 307)	Patients without Outcome (n = 109)	Patients with Outcome (n = 198)	*P*-value
Demographics				
Age (years)	66.00 (55.00, 75.00)	68.00 (56.00, 77.00)	65.00 (55.00, 74.75)	0.306
Female sex (%)	59.93	60.55	59.60	0.967
BMI (kg/m^2)	25.97 (23.63, 28.89)	25.39 (23.29, 28.34)	26.30 (23.73, 28.95)	0.074
SBP (mmHg)	147.00 (133.00, 160.00)	140.00 (130.00, 150.00)	150.00 (138.00, 160.00)	0.007
DBP (mmHg)	80.00 (72.00, 88.50)	80.00 (74.00, 80.00)	80.00 (71.25, 90.00)	0.032
Duration of DM (months)	120 (78, 240)	120 (60, 240)	120 (96, 225)	0.082
Smoking history (%)	24.43	24.77	24.24	1.000
Family history of DM (%)	11.07	12.84	10.10	0.587
Complications or Comorbidities				
Diabetic retinopathy (%)	46.58	41.28	49.49	0.207
Hypertension (%)	89.25	86.24	90.91	0.284
CHD (%)	23.13	21.10	24.24	0.629
Stroke (%)	33.55	30.28	35.35	0.438
Treatment at baseline				
Insulin (%)	66.45	51.38	74.75	< 0.001
RAASi (%)	44.63	55.96	38.38	0.004
Laboratory parameters at baseline				
Scr (μmol/L)	126.00 (95.00, 184.00)	102.00 (83.00, 142.00)	143.50 (109.00, 204.75)	< 0.001
eGFR (mL/min/1.73m^2)	46.72 (28.83, 64.90)	56.33 (41.34, 76.47)	37.88 (25.42, 57.23)	< 0.001
Hemoglobin (g/L)	118.18 ± 23.55	126.94 ± 22.43	113.35 ± 22.80	< 0.001
Plasma ALB (g/L)	34.20 (29.00, 39.00)	38.00 (34.00, 41.00)	32.85 (27.00, 37.00)	< 0.001
FPG (mmol/L)	6.92 (5.53, 8.71)	6.89 (5.67, 8.78)	6.94 (5.42, 8.62)	0.630
Total cholesterol (mmol/L)	4.81 (4.07, 5.80)	4.50 (3.98, 5.23)	5.01 (4.20, 6.24)	0.001
LDL-C (mmol/L)	2.94 (2.36, 3.66)	2.70 (2.32, 3.16)	3.09 (2.40, 3.84)	0.001
HDL-C (mmol/L)	1.19 (1.02, 1.40)	1.14 (0.99, 1.37)	1.21 (1.06, 1.42)	0.101
Triglyceride (mmol/L)	1.78 (1.27, 2.50)	1.67 (1.26, 2.47)	1.82 (1.28, 2.50)	0.417
HbA1c (%)	7.40 (6.50, 8.80)	7.30 (6.60, 8.70)	7.45 (6.30, 8.80)	0.822
BUN (mmol/L)	8.40 (6.20, 11.40)	7.20 (5.40, 9.30)	9.30 (6.73, 12.80)	< 0.001
Serum uric acid (μmol/L)	376.00 (310.50, 454.00)	360.00 (299.00, 406.00)	391.00 (317.75, 480.25)	0.017
Serum cystatin C (mg/L)	1.77 (1.33, 2.42)	1.37 (1.18, 1.78)	2.02 (1.57, 2.65)	< 0.001
24-h urine protein (g)	1.92 (0.70, 4.44)	0.72 (0.36, 1.89)	3.19 (1.44, 5.81)	< 0.001
UACR (mg/g)	628.90 (215.24, 1133.38)	228.07 (50.20, 740.40)	785.54 (402.29, 1237.60)	< 0.001

Note: Variables are expressed as frequency (%), mean ± standard deviation, or median (IQR).

Abbreviations: IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; CHD, coronary heart disease; RAASi, renin-angiotensin-aldosterone system inhibitor; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; ALB, albumin; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; BUN, blood urea nitrogen; UACR, urinary albumin/creatinine ratio.

A Nomogram of the Final Prediction Model

A nomogram predicting the risk of renal function decline in T2DKD patients is shown in Figure 2. Four predictors, including Scr, insulin treatment, plasma ALB, and UACR, were incorporated in the nomogram. The total score could be calculated by adding up the assigned number of points for each predictor in the nomogram. A higher total score indicated a worse prognosis for each patient. For example, a patient with a normal Scr level (73 μmol/L), lower plasma ALB level (32 g/L), higher UACR level (256 mg/g), and insulin treatment would have a total score of 77.2, indicating a predicted one-year or two-year event-free survival rates of 89% and 78.6%, respectively.

A Risk Table of the Final Prediction Model

Predictors selected in the final model included three continuous variables (Scr, ALB, and UACR) and one categorical variable (insulin treatment). First, we used a minimum *p*-value approach to evaluate the optimal cut-off value of event-

Table 2 Predictors Identified by Univariate Cox Regression Analysis

Variables	Univariate Cox Regression	
	HR (95% CI)	*P*-value
SBP (incremented by 1 mmHg)	1.012 (1.005–1.019)	0.001
DBP (incremented by 1 mmHg)	1.016 (1.003–1.030)	0.016
Insulin treatment	1.490 (1.080–2.055)	0.015
RAASi treatment	0.576 (0.432–0.768)	< 0.001
Hemoglobin (incremented by 1 g/L)	0.976 (0.970–0.983)	< 0.001
Plasma ALB (incremented by 1 g/L)	0.890 (0.869–0.911)	< 0.001
Total cholesterol (incremented by 1 mmol/L)	1.170 (1.078–1.269)	< 0.001
LDL-C (incremented by 1 mmol/L)	1.110 (1.048–1.174)	< 0.001
Serum uric acid (incremented by 1μmol/L)	1.002 (1.001–1.003)	0.001
BUN (incremented by 1 mmol/L)	1.010 (1.005–1.016)	< 0.001
Scr (incremented by 1μmol/L)	1.010 (1.008–1.013)	< 0.001
Serum cystatin C (incremented by 1 mmol/L)	2.607 (2.205–3.083)	< 0.001
eGFR (incremented by 1 mL/min/1.73m^2)	0.975 (0.968–0.982)	< 0.001
24-h urine protein (incremented by 1 g)	1.235 (1.189–1.284)	< 0.001
UACR (incremented by 100 mg/g)	1.029 (1.020–1.037)	< 0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; RAASi, renin-angiotensin-aldosterone system inhibitor; ALB, albumin; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; UACR, urinary albumin/creatinine ratio.

free survival to categorize continuous variables. Additionally, the linearity assumption in continuous variables was examined using RCS curves (Figure 3). Combined with the results of the minimum *p*-value method and RCS curves, and fully considering the convenience of clinical application, we categorized the above three continuous variables as follows: Scr (μmol/L; <180 or ≥180), plasma ALB (g/L; ≥35, [25–35), or < 25), UACR (mg/g; < 300 or ≥300). The multivariate regression results after continuous variables were transformed into categorical variables are shown in Figure 1B. Next, the score of each variable was assigned according to the HR (Supplement Table 1). Finally, each category was assigned a score, and a risk table was developed as follows: Scr (μmol/L; <180 scores 0 and ≥180 scores 4), plasma ALB (g/L; ≥35 scores 0, 25–35 scores 2, and <25 scores 4), UACR (mg/g; <300 scores 0 and ≥300 scores 2), insulin treatment (no scores 0 and yes scores 1.5), and the highest score was 11.5 (Table 3).

Performance of the Nomogram and the Risk Table

Based on the ROC analysis, the nomogram showed robust discrimination, with an AUC of 0.791 (95% CI 0.762–0.820) in the derivation cohort and 0.793 (95% CI 0.746–0.840) in the validation cohort (Figure 4A). Calibration curves of the nomogram showed that the 24-month risk of the study outcomes predicted by the nomogram was well consistent with the actual probabilities both in the derivation (Figure 5A) and the validation cohort (Figure 5B). The risk table also showed robust discrimination, with an AUC of 0.764 (95% CI 0.731–0.797) in the derivation cohort and 0.763 (95% CI 0.714–0.812) in the validation cohort (Figure 4B). Calibration curves of the risk table showed that the 24-month risk of the outcomes predicted by the risk table was well consistent with the actual probabilities both in the derivation (Figure 5C) and the validation cohort (Figure 5D).

Risk Stratification of Risk Table

Based on the risk table, we used the minimum *p*-value method to separate the total scores and fully considered the clinical application. Patients were finally categorized into two risk groups, including low- (score≤2) and high-risk (score>2). In the low-risk group, the probability of patients who had outcome events was 30.6% in the derivation cohort and 27.7% in the validation cohort, which increased to 69.4% and 72.3% in the high-risk group, respectively (Figure 6C). The prevalence of the event-free survival rate was calculated, and a Kaplan–Meier curve was generated in each risk

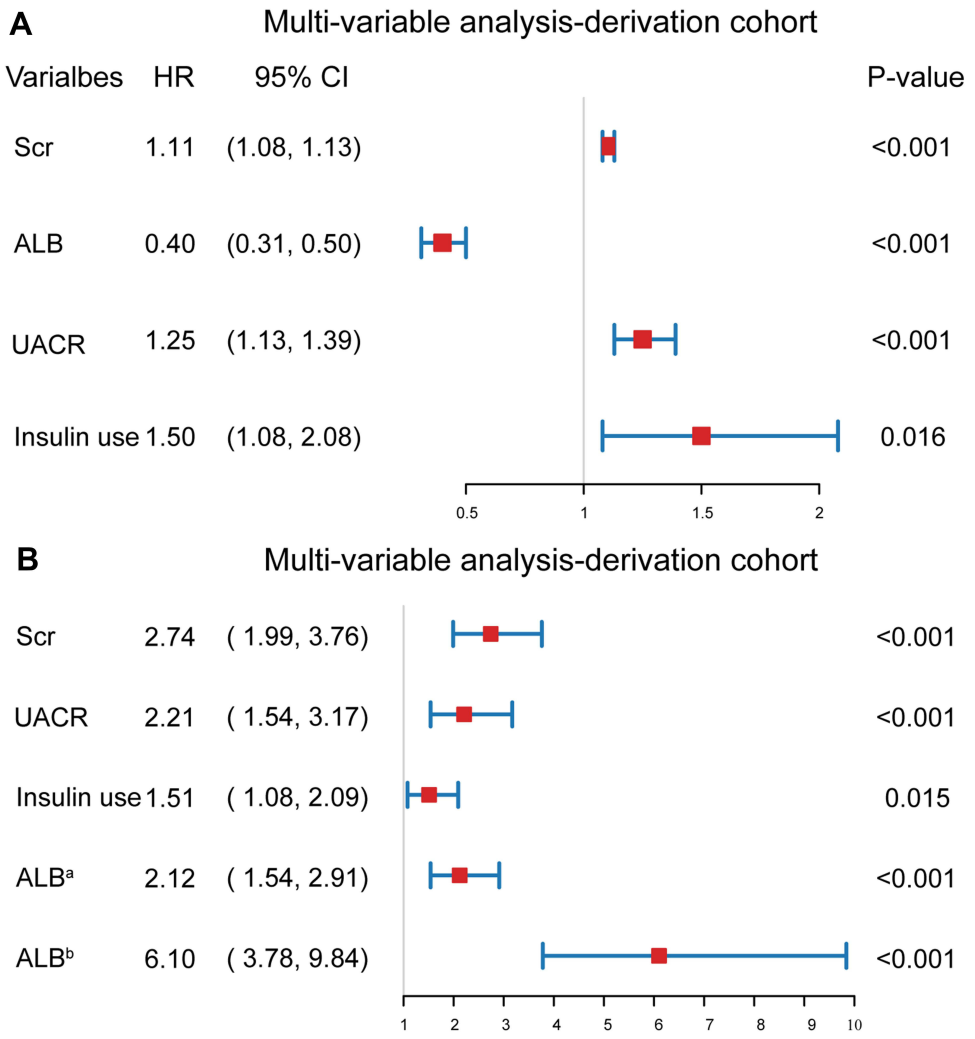


Figure 1 Forest plots of the predictors selected by multivariate Cox analysis in the derivation cohort. (**A**) Results of the multivariate Cox regression analysis of the derivation cohort; (**B**) the multivariate regression results after continuous variables transformed into categorical variables in the derivation cohort. [a]Represented the level of ALB was between 25 and 35 g/L; [b]represented the level ALB level was less than 25 g/L. Red squares and horizontal bars represent the overall estimates and 95% CIs.
Abbreviations: HR, hazard ratio; CI, confidence interval; Scr, serum creatinine; ALB, albumin; UACR, urinary albumin/creatinine ratio.

group both in the derivation (Figure 6A) and the validation cohort (Figure 6B). Compared with the low-risk group, the high-risk group had significantly lower event-free survival rates. Compared with the low-risk group, the HRs of the probability of outcome events in the high-risk group were 3.87 (95% CI: 2.63–5.68) in the derivation cohort and 5.90 (95% CI: 2.73–12.73) in the validation cohort, respectively (p<0.001).

Discussion

In recent years, risk prediction for CKD progression has raised significant attention, and several prediction instruments were developed to guide risk stratification using either traditional regression or novel statistical methods.[30–35] However, these prediction models focused on the general CKD population, not on patients with DKD. Due to the much higher risk of progressing to ESRD in DKD patients than other types of CKD,[2] the performance of these models is needed to be further elucidated, and prediction models aimed at evaluating the risk of DKD progression are needed.

In this study, we demonstrated that the higher UACR level, the lower plasma ALB level, the higher Scr level and insulin treatment significantly increased the risk of renal function decline in patients with T2DKD. Using these predictors, we developed and externally validated a nomogram and a risk table containing variables obtained routinely in clinical practice, which could serve as practicable bedside tools to identify T2DKD patients at high risk of renal

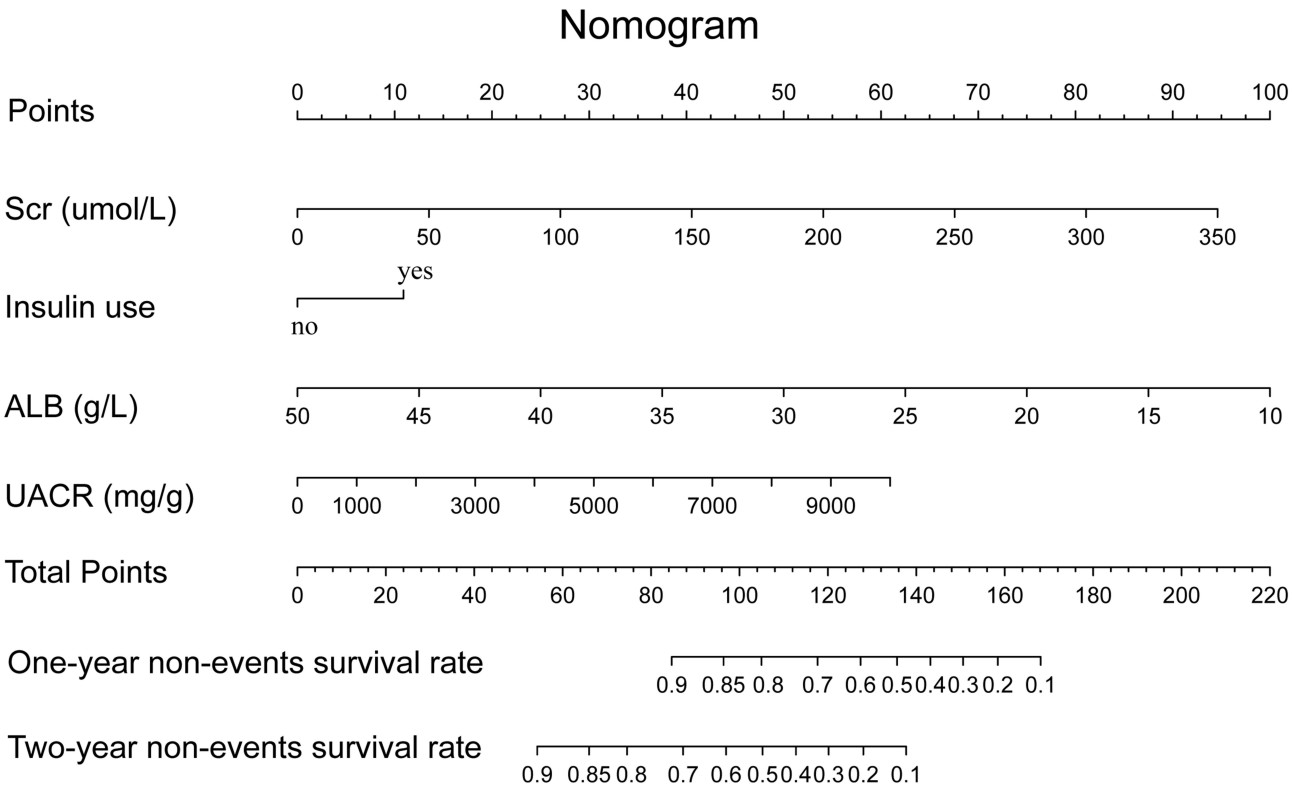


Figure 2 A nomogram of the final prediction model.
Abbreviations: Scr, serum creatinine; ALB, albumin; UACR, urinary albumin/creatinine ratio.

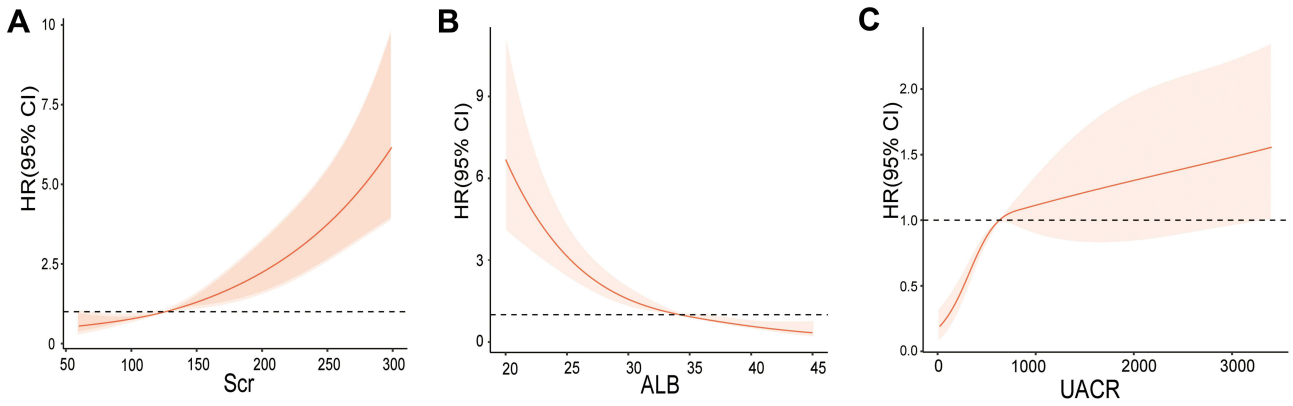


Figure 3 Restricted cubic spline (RCS) curves of the continuous variables involved in the final model.
Abbreviations: Scr, serum creatinine; ALB, albumin; UACR, urinary albumin/creatinine ratio.

function decline. Moreover, based on the risk table, we could easily divide T2DKD patients into different risk categories, which would be helpful to guide clinical decision making.

Albuminuria is a traditional marker of DKD progression. In predicting the risk of progression to hard renal endpoints, studies based on large cohorts have included albuminuria as an essential predictor in their prediction models. In a retrospective analysis based on the results of the large multicenter New Zealand Diabetes Cohort Study, Elley et al[15] developed a series of renal risk models to predict the 5-year risk of ESRD in T2DM patients (baseline median eGFR of 75 mL/min/1.73m^2), and they found albuminuria was a strong predictor. In addition, based on the results of the ADVANCE study, Jardine et al[16] established a risk score for major kidney-related events in T2DM patients (mean eGFR was 74.6 mL/min/1.73m^2), and UACR was one of the most important predictors in the final model. In the Chinese population, Wan et al[18]

Table 3 A Simple Risk Table of the Final Prediction Model

Risk Factors	Category	Points
Scr (μmol/L)	< 180	0
	≥ 180	4
Plasma ALB (g/L)	≥ 35	0
	[25,35)	2
	<25	4
UACR (mg/g)	<300	0
	≥ 300	2
Insulin treatment	No	0
	Yes	1.5

Abbreviations: Scr, serum creatinine; ALB, albumin; UACR, urinary albumin/creatinine ratio.

developed a gender-specific 5-year ESRD risk prediction model among 149,333 adults with T2DM, and UACR was identified as an important predictor. Through the Cox regression analysis, we also confirmed the importance of UACR in predicting hard renal endpoints. It is noteworthy that the previous studies were focused on T2DM patients with a preserved renal function instead of DKD. However, we included patients with T2DKD (median eGFR of 46.72 mL/min/1.73m^2) in our derivation cohort, which could better characterize renal function decline in T2DKD patients.

Previous studies also investigated risk factors for eGFR decline in T2DM patients. In a prospective observational cohort study, Zoppini et al[17] followed 1682 Caucasian patients with T2DM and preserved kidney function and identified that albuminuria was the strongest predictor of annual eGFR decline. Additionally, Lorenzo et al[36] also reported that albuminuria was the strongest predictor of faster annual eGFR decline in 153 Caucasian T2DM patients with moderate to advanced CKD. According to the results of a World Health Organization multinational study, the incidence of proteinuria was higher in Chinese diabetic patients when compared with other populations.[37,38] Therefore, our study provides further evidence that albuminuria is an essential risk factor of renal function decline in Chinese patients with T2DKD. The results of our study emphasized the importance of UACR in predicting renal function decline in T2DKD patients, which

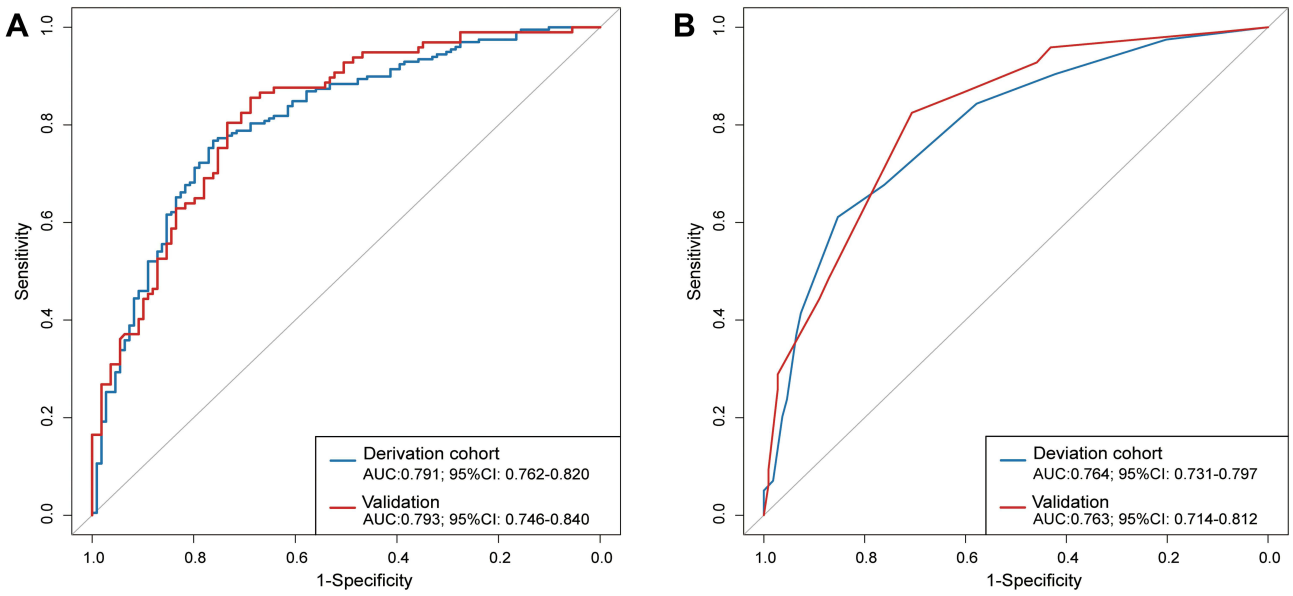


Figure 4 Receiver operating characteristic (ROC) curve for the nomogram and the risk table. The solid blue line represented the derivation cohort, and the solid red line represented the validation cohort. (**A**) ROC curve for the nomogram. The AUC and its 95% CI were 0.791 (0.762–0.820) in the derivation cohort and 0.793 (0.746–0.840) in the validation cohort; (**B**) ROC curve for the risk table. The AUC and its 95% CI were 0.764 (0.731–0.797) in the derivation cohort and 0.763 (0.714–0.812) in the validation cohort.

Abbreviations: ROC, receiver operating characteristic; AUC, area under the ROC curve; CI, confidence interval.

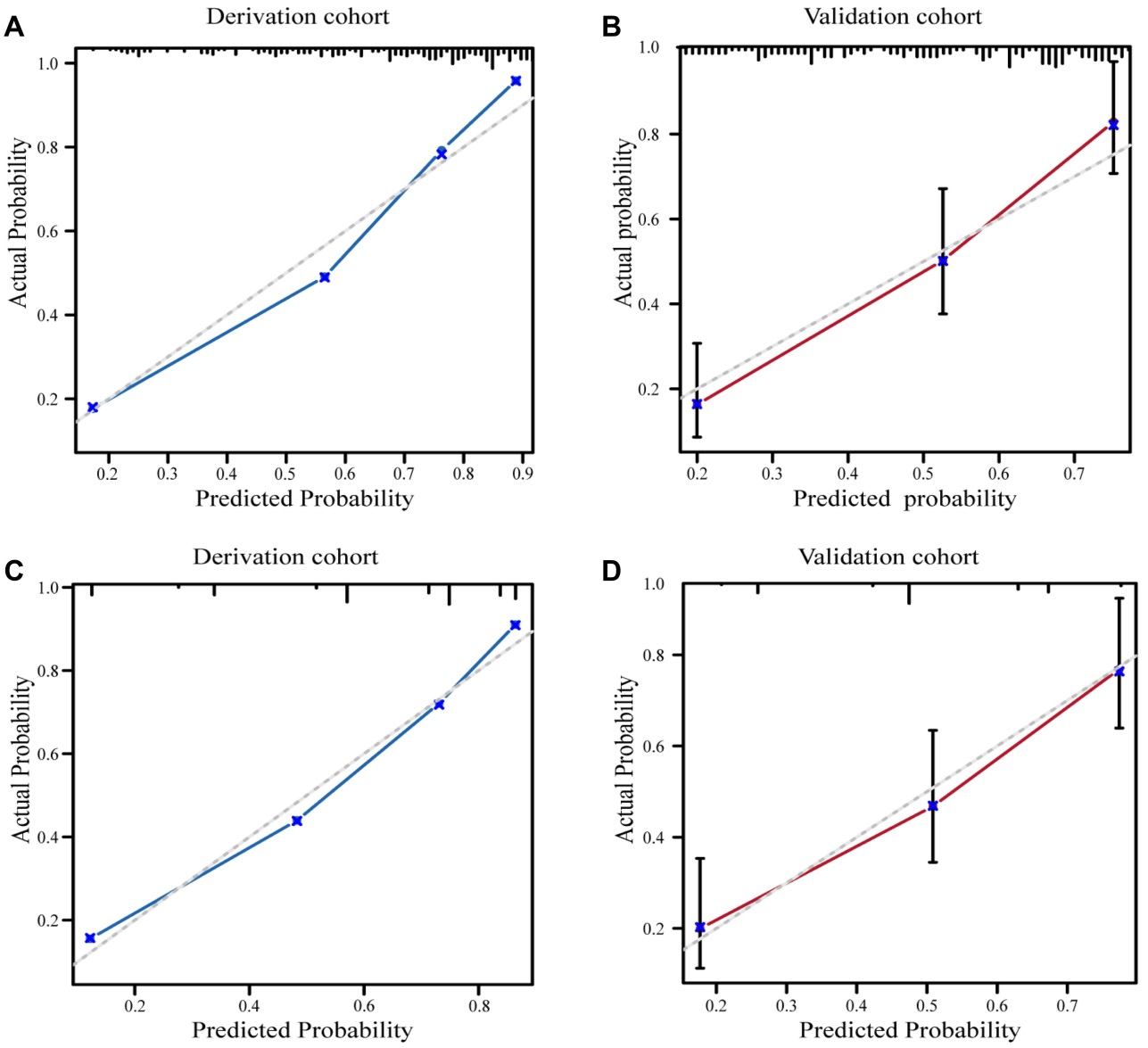


Figure 5 The calibration curves for the nomogram and the risk table in the derivation and validation cohort. (**A**) The calibration curves for the nomogram in the derivation cohort; (**B**) the calibration curves for the nomogram in the validation cohort; (**C**) the calibration curves for the risk table in the derivation cohort; (**D**) the calibration curves for the risk table in the validation cohort. The calibration plot showed the agreement between the predicted probability (x-axis) and the actual probability (y-axis) of the 24-month risk of the study outcomes. A perfect prediction would correspond to the 45° grey dotted line. Spike histograms on the top of each picture reflected the number of T2DKD patients with a predicted probability corresponding to the x-axis value.

indicates that regular UACR assessment should be recommended as part of the routine test for identifying high-risk patients.

Our study also demonstrated that risk factors including hypoalbuminemia and increase of Scr in addition to albuminuria predicted renal function decline in T2DKD patients. Although correlated with each other, every factor is irreplaceable and indispensable in our final model, and one could not be fully predicted by the others. Previously, serum albumin was reported as a predictor of ESRD in T2DM patients with nephropathy in the RENAAL study,[39] and it was independent of and complementary to albuminuria in the final risk score. However, the risk score derived from the RENAAL study was lack of discrimination statistics and external validation. Our study evaluated the discrimination determined by the AUC and then validated our model in an external cohort, further confirming the irreplaceable role of serum albumin in predicting renal function decline in T2DKD patients.

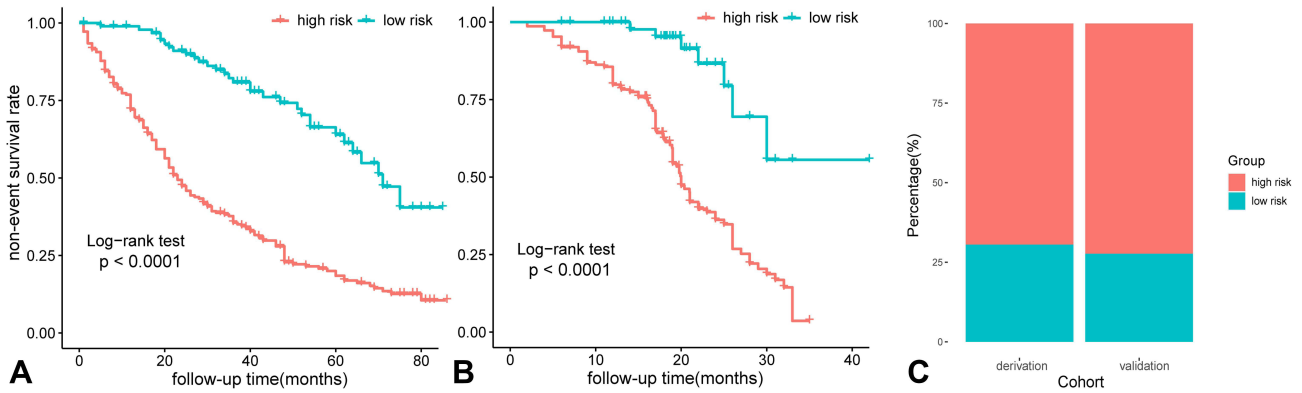


Figure 6 Risk stratification and Kaplan–Meier curve of each risk group in the derivation and validation cohort. (**A**) Kaplan–Meier curve in the derivation cohort; (**B**) Kaplan–Meier curve in the validation cohort; (**C**) risk stratification based on the risk table in the derivation and the validation cohort.

Insulin treatment was also identified as an independent risk factor for T2DKD progression. Previous studies suggested that patients with worse glycemic control were more likely to initiate insulin therapy, and insulin users were inclined to suffer from longer duration of DM, greater incidence of cardiovascular disease, CKD, macroalbuminuria, as well as obesity and dyslipidemia.[40,41] Our finding also indicated relatively poorer glycemic control among insulin users compared to patients without insulin treatment (median HbA1c 7.80% IQR [6.60, 9.30] % vs 6.90% IQR [6.13, 8.20] %, Z=−3.197, p=0.001). This finding was in consistent with a previous study conducted in 729 Japanese T2DM patients with preserved kidney function and normoalbuminuria, which demonstrated that the degree of chronic hyperglycemia plays a vital role in aggravating the rapid decline of annual eGFR during a 3-year follow-up period.[42] Our results further indicated that insulin treatment might be a risk factor for renal function decline in T2DKD, even with advanced CKD.

Concerning the clinical utility of this model, we developed a nomogram to predict the one-year and two-year event-free survival rates. The nomogram behaved good performance with a C-index of 0.791 in the derivation cohort and 0.793 in the external validation cohort, showing good discriminatory performance, and the calibration was good as well. Then, we transformed the model into a simple risk table. For the continuous variables included in the model, the cut-off values were confirmed by a minimum p-value method and RCS curves, taking into full consideration the significance of the clinical practice. Although with some inevitable loss of precision, the performance remained satisfactory.

There are several limitations to this study. Firstly, although our model was externally validated in another center in China with satisfactory performance, the sample size is relatively small with a relatively short follow-up period. Future studies should include a more extensive study population with a longer follow-up time. Secondly, our study may suffer from bias in report and selection due to the retrospective study design. Research with a prospective study design in the future is warranted. Finally, DKD was mainly clinically diagnosed in our participants with diabetes. Future studies could optimize the inclusion criteria and stratify renal function to achieve a more accurate prediction.

Conclusion

Based on a retrospective cohort study, we developed a risk prediction model for T2DKD progression that integrates four easily accessible clinical risk factors (Scr, ALB, UACR, and insulin treatment) to form a practicable nomogram and risk table. Both the nomogram and risk table showed satisfactory prediction performance in the derivation and the external validation cohort. They could serve as quickly useful bedside tools for predicting the risk of renal function decline, thereby making a more rational clinical decision for patients with T2DKD.

Data Sharing Statement

The datasets used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Zhongda Hospital, Southeast University (2019ZDSYLL057-P01) and was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

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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 report no conflicts of interest in this work.

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