BMJ Open

External Validation of the DKD Risk Score, a Risk Scoring Model for Early Diabetic Kidney Disease

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059139
Article Type:	Original research
Date Submitted by the Author:	09-Nov-2021
Complete List of Authors:	Sun, Zhenzhen; Hainan General Hospital; Nanjing University of Chinese Medicine Wang, Kun; Nanjing University of Chinese Medicine Miller, Joshua; Stony Brook University Renaissance School of Medicine Yuan, Xiaodan; Affiliated Hospital of Integrated Traditional Chinese and Western Lee, Yau-Jiunn; Lee's Clinic Lou, Qingqing; Hainan General Hospital,
Keywords:	DIABETES & ENDOCRINOLOGY, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

External Validation of the DKD Risk Score, a Risk Scoring Model for Early Diabetic Kidney Disease

Zhenzhen Sun[1,2], Kun Wang[2], Joshua D. Miller[3], Xiaodan Yuan[4], Yau-Jiunn Lee [5], Qingqing Lou[1*]

1 Endocrinology Department, Hainan General Hospital, No.19, Xiuhua Road, Xiuying District, Haikou 570311, Hainan, China

2 Nursing College, Nanjing University of Chinese Medicine, Nanjing, Jiangsu Province, China

3 Renaissance School of Medicine at Stony Brook University, Stony Brook, NY, USA

4 Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, Jiangsu Province, China

5 Lee's Clinic, No. 396, Guangdong RD, Pingtung City, Pingtung Country 900, Taiwan

*Corresponding author: Qingqing Lou

Postal address: Hainan General Hospital, No.19, Xiuhua Road, Qiuying District, Haikou 570311, Hainan, China.

Phone: +8615312019129

Fax number: +089868642548

E-mail address: 2444890144@qq.com

ORCID numbers: 0000-0002-4743-0900

Abstract

Objectives This study aims to independently and externally validate the Risk Prediction Model for Diabetic Kidney Disease (RPM-DKD) in patients with type 2 diabetes mellitus (T2DM).

Design This is a retrospective cohort study.

Setting Outpatient clinics at Lee's United Clinics, Taiwan, China.

Participants A total of 2504 patients (average age 55.44 years, SD, 7.49 years), and 4455 patients (average age 57.88 years, SD, 8.80 years) were included for analysis in the DKD prediction and progression prediction cohorts, respectively.

Exposure The predicted risk for DKD and DKD progression for each patient were all calculated using the RPM-DKD.

Primary and secondary outcome measures The primary outcome measure was overall incidence of DKD. Secondary outcomes included DKD progression. The discrimination, calibration and and precision of the RPM-DKD score were assessed.

Results The DKD prediction cohort and progression prediction cohort consisted of 2504 and 4455 T2DM patients, respectively. The RPM-DKD examined in this study showed moderately discriminative ability with AUCs ranged from 0.636 to 0.681 for the occurrence of DKD and 0.620 to 0.654 for the progression of DKD. The Hosmer-Lemeshow $\chi 2$ test indicted the RPM-DKD was not well calibrated for predicting the occurrence of DKD and over-estimated the progression of DKD. The precision for predicting the occurrence and progression of DKD were 43.2% and 42.2%, respectively.

Conclusions On external validation, the RPM-DKD cannot accurately predict the risk of DKD occurrence and progression in patients with T2DM.

Keywords External validation; diabetic kidney disease; prediction; risk assessment

Strengths and limitations of this study

- Our validation cohort was geographically different from the cohort used to derive the model and our team was not involved in model derivation, which enabled us to conduct a true independent external validation study.
- Our cohort had an average follow-up time of more than 5 years, a duration that positioned us to effectively identify the occurrence of outcome variables.
- Whilst the cohort was representative of a large cohort of over 4,000 adults, it was geographically restricted to Taiwan.
- Most patients in our cohort had better diabetes self-management behaviors, which could potentially have affected the study results and also explain why the model overestimated risk of occurrence and progression.

- The retrospective nature of our study presents an inherent limitation, although it is a simple, flexible, and low-cost method to review patient data for purposes of the present analysis

1.Introduction

Diabetic kidney disease (DKD) is one of the main microvascular complications of long-standing, uncontrolled type 2 diabetes mellitus (T2DM), and a main cause of preventable chronic and end-stage kidney disease worldwide [1]. Paradoxically, improvements in cardiovascular survival in patients with T2DM have contributed to prolonged patient survival, which in turn lengthens time at risk for developing renal impairment [2]. In China, about 20-40% of individuals with T2DM have DKD [3]. Further, progression of DKD to ESRD requiring renal replacement therapy and/or renal transplant brings economic burden and is associated with additional comorbid burden [4-6]. In light of these factors, the early intervention and study of a relevant risk prediction model for early DKD are of great clinical and societal relevance.

Clinical risk prediction models aim to estimate an individual's risk of an event based on relevant contributing information [7]. Currently, many prediction models have been developed to assess risk of incident diabetes, but few have been validated in subsequent analyses and applied to clinical practice [8-10]. For example, one T2DM risk score, the FINDRISC, is well-known in Latin America and the Caribbean, despite limited none external validation of the model [11]. A risk prediction model should not enter clinical practice unless it has been independently and externally validated and proven to perform a useful role [12, 14].

The ability to accurately predict risk of DKD would allow for earlier recognition, and perhaps intervention, in patients with long-standing T2DM. Recently, a risk prediction model for early DKD (RPM-DKD) was developed based on systematic review and meta-analysis of individual participant data from 20 cohorts of predominately white populations [15]. However, validation was limited in scope with a relatively small study size (n=380) and insufficient median follow-up time (t=2.9 years). The purpose of the current study was to independently and externally validate performance of the RPM-DKD in predicting the risk of incidence of DKD in patients with T2DM. In addition, although PRM-DKD was only used to predict the occurrence of DKD, we believe that it can predict the progress of DKD to a certain extent, with reason that the influencing factors of DKD progression and occurrence are similar. Therefore, the secondary purpose of this study is to evaluate the performance of this model in predicting the risk of DKD progression in patients with T2DM.

2.Methods

2.1 Data sources and participants

We used outpatient data from December 2006 to October 2019 from Lee's United Clinics (LUC) in Taiwan. LUC is a large ambulatory system, comprised of six clinics providing multidisciplinary care for patients with diabetes. The Taiwan Health Insurance Plan supports 4 annual follow up visits along with access to medications, diabetes supplies, diabetes self-management education DSME) clinician visitation and primary/secondary prevention screening to patients living with diabetes. This setting provided an opportune source of robust, longitudinal data in which to validate the RPM-

DKD.

Inclusion criteria for predicting the occurrence of DKD aligned with those established by the RPM-DKD [15] and included; (1) patients aged 39-75 years, and (2) patients without albuminuria (urinary albumin-to-creatinine ratio [UACR]<30mg/g or albumin excretion rate [AER]<30mg) and estimated glomerular filtration rate (eGFR)≥60mL/min/1.73 m^2 at baseline.

Inclusion criteria for predicting progression of DKD were patients aged 39-75 years with S1-S3 at baseline (The criteria for S1-S3 stage presented in diagnosis criteria part).

We excluded (1) patients with less than 3 years of longitudinal follow-up, (2) those with history of acute kidney injury, primary glomerulonephritis, urinary tract infection, urinary calculi, etc. (3) patients with missing endpoints and lost to follow-up, and (4) patients with end stage renal disease (very high DKD risk).

2.2 Diagnosis criteria

Diagnosis criteria of DKD were also consistent with foundational RPM-DKD modeling and included: (1) eGFR<60 mL/min/1.73 m^2 and/or (2) UACR≥30 mg/g (or AER≥30 mg) (3) present for≥3 months caused by diabetes [16].

Diagnostic criteria to clinical progression of DKD were [17]: (i) Patients were in a non-progression group if they maintained the same DKD stage or their condition had improved to an earlier DKD stage category. (ii) Patients were in a progression group if the DKD stage category had progressed.

The stage of DKD was classified using a combination of eGFR and ACR into four stage categories[18], i.e., (i) Low DKD risk, eGFR ≥60mL/min/1.73 m2 and ACR<30mg/g; (ii) Moderate CKD risk, eGFR between 45 and 59 mL/min/1.73 m2 and ACR<30mg/g, or eGFR ≥60mL/min/1.73 m2 and ACR between 30 and 300mg/g; (iii) High DKD risk, eGFR between 30 and 44 mL/min/1.73 m2 and ACR<30mg/g, or eGFR between 45 and 59 mL/min/1.73 m2 and ACR between 30 and 300mg/g, or eGFR ≥60mL/min/1.73 m2 and ACR>300mg/g; (iv) Very high DKD risk, eGFR≤29mL/min/1.73 m2 and ACR<30mg/g, or eGFR≤44mL/min/1.73 m^2 and ACR between 30 and 300 mg/g, or eGFR≤59mL/min/1.73 m^2 and ACR>300mg/g.

2.3 Risk score calculations

The risk score model was established by Jiang, W. et al [15], and all risk factors included in the DKD risk score model were derived from a systematic review and meta-analysis of 14 prospective and 6 retrospective cohorts. The predicted risk score for each study participant was calculated using their baseline data. The baseline variables used for the risk scores were in accordance with the model: (i) age (years) divided into three categories, 39-49 scores 0, 50–59 scores 3.0, and 60–75 scores 6.0; (ii) body mass index (BMI), which was calculated as the patient's weight divided by the square of their height (kg/m^2), divided into three categories (<25.00 scores 0, 25.00–29.99 scores 1.5, and≥30.00 scores 3.0); (iii) smoker (defined as having smoked more than 100 cigarettes in their lifetime), non-smoker scores 0 and smoker scores 4.0; (iv) diabetic retinopathy (DR), 0 if no and 3.0 if yes; (v) hemoglobin A1c(HbA1c) divided into four categories, <7.0% (<53 mmol/mol) scores 0, 7.0-7.9% (53–63 mmol/mol) scores 1.5, 8.0–8.9%

(64–74 mmol/mol) scores 3.0 and ≥9.0% (≥75 mmol/mol) scores 4.5; (vi) systolic blood pressure (SBP) divided into four categories, <130mmHg scores 0, 130-139 mmHg scores 2.0, 140-149 mmHg scores 4.0, ≥150 mmHg scores 6.0; (vii) serum high-density lipoprotein-cholesterol (HDL-C) divided into two categories, ≥1.30mmol/L scores 0, and <1.30mmol/L scores 2.5; (viii) triglycerides (TG) divided into two categories, <1.70mmol/L scores 0 and ≥1.70mmol/L scores 4.0; and (ix) UACR divided into three categories, <10mg/g scores 0, 10.00-19.99mg/g scores 2.0, 20.00-29.99mg/g scores 4.0. In addition, considering that we want to predict the progression of DKD, we continue to increase the category of UACR, that is, every increase of UACR 10mg/g, the score increases by 2 points. For example, UACR between 30.00 and 39.99mg/g scores 6.0. The coefficients in the model are shown in supplementary appendix.

Data to inform score calculation was retrieved from the LUC electronic medical record. Four risk categories include: (i) relatively low (score <12.0); (ii)moderate (score 12.0–15.5); (iii) high (score 16.0–26.5); and (iv) very high (score **>** 27.0).

2.4 Statistical analysis

The sample size needed for a validation cohort should include a minimum of 100 events and 100 non-events to detect relevant differences [19, 20].

Descriptive statistics were generated for all variables, which were stratified by the occurrence and progression of DKD. Normally distributed continuous variables were presented as means ± standard deviation (SD), and analysis of variance was used to assess inter-group comparisons. Medians (interquartile range [IQR]) were used for continuous variables that were not normally distributed, and the comparison between

groups were performed by Kruskal-Wallis H test. Categorical variables were represented as number of cases (N), and the intergroup rate (%) was compared with chi-square test.

The clinical performance of the DKD risk prediction model was assessed by means of discrimination and calibration. Model discrimination describes a model's performance in distinguishing between individuals who experience an event and those who do not[7]. Model discrimination was assessed by plotting a receiver operating characteristic (ROC) curve and calculating the area under the curve (AUC). An AUC-statistic value >0.75 was regarded to represent good discrimination. Calibration assessment of a risk prediction model describes how well predictions match observed outcomes [7]. The calibration of the risk score predictions was assessed by plotting observed versus predicted number of patients and by calculating the Hosmer-Lemeshow $\chi 2$ statistic. Groups for observed DKD events were based on deciles for the predicted probabilities. Performance was evaluated as sensitivity, specificity, and precision.

All results were presented with 95% confidence interval (CI). Any two-tailed p-values<0.05 were considered statistically significant. All satistical analyses were performed using SPSS software, version 22 (IBM Corp.).

2.5 Patient and public involvement

There was no patient or public involvement in the design and conduct of the study.

3. Results

In the DKD prediction cohort, a total of 2504 patients (average age 55.44 years, SD, 7.49 years), and 4455 patients (average age 57.88 years, SD, 8.80 years) were included for analysis in the DKD progression prediction cohort (Figure 1). The average length of follow-up was 7.37 years (SD, 3.22 years) in the DKD prediction cohort and a total of 817 (32.6%) people had DKD during the follow-up period. The mean follow-up time in the progression prediction cohort was 7.72 years (SD, 3.10 years), and the overall progression of events in this cohort was 1563 (35.1%).

3.1 DKD prediction cohort

3.1.1 Baseline characteristics

The DKD prediction cohort had an average BMI of 26.1±4.0 kg/m^2 and 54.8% were men. The proportion of smokers and drinkers were 30.7% and 25.4%, respectively. There were significant differences in the level of education (P=0.0021) and marital status (P<0.001) between patients who eventually developed DKD and those who did not. The patients who did not develop of DKD had higher rates of secondary and college-level education and lower rates of spousal loss than the patients with DKD. Furthermore, patients who eventually developed DKD had a longer diabetes duration (median 5 years [2-9 years]) and a higher level of HbA1c (median 8.4% [7.10-10.10%]) than those who did not. All patients showed normal albuminuria and renal function at baseline with median UACR of 8.64 mg/g (4.50–13.86mg/g) and median eGFR of 85.50 ml/min/1.73 m^2 (73.08–96.13 ml/min/1.73 m^2). The median systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 129mmHg (119-141mmHg)

and 77 mmHg (70-84 mmHg), respectively. Baseline characteristics of the DKD prediction cohort are displayed in Table 1.

3.1.2 External validation results for DKD prediction cohort

Of the 2504 patients, 678 (27.1%), 639 (25.5%), 1114 (44.5%) and 73 (2.9%) had risk categories of relatively low, moderate, high and very high at baseline. At the end of observation, 129 (19.0%), 175 (27.4%), 465 (41.7%), 48 (65.8%) patients in the relatively low, moderate, high and very high groups developed DKD, respectively (Figure 2).

Discrimination of the model： According to our external validation, 16 was selected as the optimal cut-off risk score value, at which the sum of sensitivity and specificity was maximal (Youden's index), which corresponded with Jiang, W. et al [14]. With a risk cut-off value of 16 points, the sensitivity would be 53.0% (95% CI 48.9–57.0), specificity would be 65.7% (95% CI 63.0–68.3). ROC curve of our external validation showed the area under the DKD risk score curve was 0.659 (95% CI 0.636-0.681).

Calibration of the model： The risk scoring model was not well calibrated for predicting the occurrence of DKD, with a Hosmer-Lemeshow $\chi 2$ statistic of 16.731 (p=0.033). The calibration plot in figure 3 shows that the comparison between observed and predicted the occurrence of DKD, indicting the over-estimation of risk occurred in tenths 1 through 10.

Precision of the model in predicting DKD： The prediction precision refers to the ratio of the actual number of patients with DKD to the number of patients predicted

to develop DKD. According to our data, patients in the DKD prediction cohort were classified as high risk if their DKD risk score ≥16 points, with precision of 43.2% (513/1187).

3.2 Progression prediction cohort

3.2.1 Baseline characteristics

The baseline clinical and biochemical characteristics of the DKD progression cohort stratified by the progression of DKD are listed in Table 1. Of the cohort, the average BMI was 26.30±4.14 kg/m^2 and 51.0% were men. The proportion of smokers and drinkers were 30.6% and 25.3%, respectively. In addition, the progression group had lower education and married level, and longer duration of diabetes than the patients in non-progression group. And patients in progression group had higher systolic blood pressure (SBP), HbA1c and UACR than the patients in non-progression group, and higher levels of diastolic blood pressure (DBP), total cholesterol than the patients in non-progression group. On DKD risk score analyses, the progression group had higher baseline risk score compared with non-progression group whatever patients with low DKD risk, moderate DKD risk or high DKD risk (Table 2).

3.2.2 External validation results for progression prediction cohort

Of the 4455 patients, 2504(56.2%), 1397 (31.4%) and 554 (12.4%) were in low, moderate and high DKD risk at baseline. At the end of observation, 589 (32.6%), 531 (36.1%) and 414 (43.5%) patients in the low, moderate and high DKD risk had progressed, respectively (Figure 4).

Discrimination of the model: ROC curve showed moderate discriminative ability of predicting the progression of DKD in progression prediction cohort, and the area under the receiver operating characteristic curve was 0.637 (95% CI 0.620-0.654). 18 was selected as the optimal cut-off risk score value with a sensitivity of 65.0% (95% CI 62.6-67.3) and a specificity of 57.0% (95% CI 55.2-58.8)

Calibration of the model: Calibration of the model for predicting the progression of DKD was no good in our external validation cohort (Hosmer-Lemeshow $\chi 2$ =23.663, P=0.003), and the over-estimation of risk occurred in tenths 1 through 10. The calibration plot in figure 5 shows that the comparison between observed and predicted the progression of DKD.

Precision of the model in predicting DKD progression: The prediction accuracy refers to the ratio of the actual number of patients whose DKD stage progressed to the number of patients predicted to progressed. According to our validation cohort, with a risk cut-off value of 18 points, the precision would be 45.0% (1016/2260). According to the model developed study [15], with a risk cut-off value of 16 points, the precision would be 42.2% (1173/2781).

4. Discussion

External validation is a mandatory step in applying a prediction model to meaningful clinical care; the process addresses the transportability of the model [21]. In this study, we evaluated the usefulness of RPM-DKD for predicting the DKD incidence and progression of DKD in patients with T2DM by assessing its discrimination, calibration and precision. The performance of the RPM-DKD

predictive potential in our validation cohort was not ideal, even when the results from the validation evaluated by the model developers were promising.

The RPM-DKD has several advantages, including easy point-of-care application, simple calculation and reliance on very few variables. Nevertheless, the RPM-DKD demonstrated moderately discriminatory ability in our cohort. With that said, the RPM-DKD was not well-calibrated for predicting the occurrence of DKD, and it over-estimated the progression of disease. When using the same foundational thresholds established by the original RPM-DKD study, precision for predicting DKD occurrence and progression in our validation cohort was low, with values of 43.2% and 42.2%, respectively. Utilizing the developers' suggested thresholds resulted in inappropriate prediction of DKD in our cohort. Even at a threshold of 18 (at which the Youden's index was maximal in our study), the precision of the model in predicting DKD progression was also low.

Overall transportability of the model was poor in our analysis., owing perhaps to the phenomenon of over-fitting. If internal validation such as bootstrap would have been performed after model developed, the phenomenon might have been foreseen [22]. Furthermore, the poor external validation performance may also be closely related to the fact that our validation cohort was vary from the model developers' cohort in terms of settings, populations and periods [23, 24].

The RPM-DKD uses cross-sectional baseline data to predict a patient's risk of DKD 5 to 10 years later; it is therefore based on the assumption that there is no significant change in relevant indicators of the patient in subsequent years – a somewhat

unrealistic expectation in a real world application. Since the occurrence and development of DKD is a relatively long process, metabolic indicators 5-, 10-years even in preceding decades can impact subsequent outcomes. However, the model, established by logistic regression, volatility of various parameters in the next few years was not considered, which results in the prediction performance was not high.

In our study, not all data specific to risk factors included in the RPM-DKD model were available (age, BMI, HbA1c, lipids, etc.); this may have contributed to poor model performance. In previous work, we found that HbA1c variability is an independent risk factor for nephropathy in patients with T2DM [25]. In addition, Viazzi et al. demonstrated that the variability of SBP and pulse pressure are also key influencing factors for the occurrence and development of DKD [26]. Thus, these parameters should be strong outcome predictors for developing DKD; and yet, the RPM-DKD does not take them into account.

The RPM-DKD model cannot predict future risk of DKD in patients with T2DM aged<39 years despite early age of diagnosis being an established risk factor for developing DKD [27]. Several groups reported an increasing incidence of youth-onset DKD[28-31]. Given the earlier onset of DKD among T2DM patients, we believe that having validated risk assessment models that include young adults may be of greater clinical use.

Strengths and limitations of this study

Our study has several strengths. First, our validation cohort was geographically different from the cohort used to derive the model; further, our team was not involved

in model derivation, which enabled us to conduct a true independent external validation study. Additionally, our cohort had an average follow-up time of more than 5 years, a duration that positioned us to effectively identify the occurrence of outcome variables.

Several limitations existed in this study. First, whilst the cohort was representative of a large cohort of over 4,000 adults, it was geographically restricted to Taiwan. Second, most patients in our cohort had better diabetes self-management behaviors, which could potentially have affected the study results and also explain why the model overestimated risk of occurrence and progression. However, diabetes self-management is a key factor for promoting better health outcomes among patients with DKD [32, 33]; longitudinally, increased awareness for the DKD burden in diabetes patients might have contributed to additional self-management behaviors with a positive effect on DKD incidence and progression. In addition, the retrospective nature of our study presents an inherent limitation, although it is a simple, flexible, and low-cost method to review patient data for purposes of the present analysis [34]; additionally, we may not have successfully captured patient data related to care that may have occurred outside of our health system.

Future research

The occurrence of DKD in our study was high (31.6%) aligning with rates reported in previous work (20% to 40%) [3]. Therefore, it is extremely significant to have an accurate prediction model that could assist clinicians in real-time evaluation of patient risk and implement primary and secondary preventive measures to delay progression of disease. However, the RPM-DKD established by logistic regression did not perform

well. Furthermore, prediction models can become obsolete with change in population demography, better therapeutic options and care pathways, and improvement in data recording [33]. In the future, it may be possible to build a DKD prediction model by deep learning methods in order to improve the prediction of DKD occurrence and progression; many studies have applied deep learning with proven success [36-40].

5. Conclusion

Our independent external validation study revealed that, in patients with T2DM, the RPM-DKD cannot accurately predict the risk of DKD occurrence and progression. The ability to accurately estimate DKD risk is critical in advancing patient care and preventing or delaying complication risk in patients with long-standing T2DM.Newer prediction models leveraging deep learning methods may prove useful for predicting risk of developing or progressing DKD.

Acknowledgments. The authors sincerely thank all participants for their help with this study.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. Q.L. conceived and designed the study. Z.S., K.W., X.Y. and Y.J.L. collected the epidemiological and clinical data. Z.S., K.W. and X.Y. drafted the manuscript. Z.S., K.W., X.Y., and Q.L. contributed to acquisition, analysis, and interpretation of data. Q.L. and J.D.M. contributed to critical revision of the manuscript for important intellectual content. All authors read, revised, and approved the final draft. Q.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding This work was supported by the National Key Research and Development Program of China (No.2021YFE0204800)

Ethics approval The present study was approved by the ethics committee of Antai Hospital, Antai Medical Association (No. : 14-055-B2)and was conducted in accordance with the ethical standards set out in the Declaration of Helsinki and its later amendments.

Disclaimer The funders had no role in the study design, data collection, or analysis, decision to publish, or preparation of the manuscript.

Patient consent for publication Not required.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information. All data requests should be submitted to the corresponding author for consideration.

References:

[1]. Afkarian, M., et al., Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 1988-2014. JAMA, 2016. 316(6): p. 602-10.

[2]. Thomas, M.C., M.E. Cooper and P. Zimmet, Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol, 2016. 12(2): p. 73-81.

[3]. Chinese guideline for the prevention and treatment of type 2 diabetes mellitus (2017 edition). Chin J Diabetes Mellitus, 2018,10(1): 4-67.

[4]. McQueen, R.B., et al., Economic burden of comorbid chronic kidney disease and diabetes. J Med Econ, 2017. 20(6): p. 585-591.

[5]. Vanholder, R., et al., Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. Nat Rev Nephrol, 2017. 13(7): p. 393-409.

[6]. Tangri, N., et al., Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure: A Meta-analysis. JAMA, 2016. 315(2): p. 164-74.

[7]. Major, R.W., et al., The Kidney Failure Risk Equation for prediction of end stage renal disease in UK primary care: An external validation and clinical impact projection cohort study. PLoS Med, 2019. 16(11): p. e1002955.

[8]. Siontis, G.C., et al., External validation of new risk prediction models is infrequent and reveals worse prognostic discrimination. J Clin Epidemiol, 2015. 68(1): p. 25-34.

[9]. Noble, D., et al., Risk models and scores for type 2 diabetes: systematic review. BMJ, 2011. 343: p. d7163.

[10]. Ayensa-Vazquez, J.A., et al., Agreement between Type 2 Diabetes Risk Scales in a Caucasian Population: A Systematic Review and Report. J Clin Med, 2020. 9(5).
[11]. Carrillo-Larco, R.M., et al., FINDRISC in Latin America: a systematic review of diagnosis and prognosis models. BMJ Open Diabetes Res Care, 2020. 8(1).
[12]. Royston, P. and D.G. Altman, External validation of a Cox prognostic model: principles and methods. BMC Med Res Methodol, 2013. 13: p. 33.
[13]. Moons, K.G., et al., Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ, 2009. 338: p. b606.
[14]. Nieboer, D., T. van der Ploeg and E.W. Steyerberg, Assessing Discriminative Performance at External Validation of Clinical Prediction Models. PLoS One, 2016. 11(2): p. e0148820.
[15]. Jiang, W., et al., Establishment and Validation of a Risk Prediction Model for Early Diabetic Kidney Disease Based on a Systematic Review and Meta-Analysis of 20 Cohorts. Diabetes Care, 2020. 43(4): p. 925-933.
[16]. Molitch, M.E., et al., Diabetic kidney disease: a clinical update from Kidney Disease: Improving Global Outcomes. Kidney Int, 2015. 87(1): p. 20-30.
[17]. Chang, Y.H., et al., Serum uric acid level as an indicator for CKD regression and progression in patients with type 2 diabetes mellitus-a 4.6-year cohort study. Diabetes Metab Res Rev, 2016. 32(6): p. 557-64
[18]. KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease. Kidney Int Suppl (2011), 2018. 8(3): p. 91-165.
[19]. Vergouwe, Y., et al., Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. J Clin Epidemiol, 2005. 58(5): p. 475-83.
[20]. Collins, G.S., E.O. Ogundimu and D.G. Altman, Sample size considerations for the external validation of a multivariable prognostic model: a resampling study. Stat Med, 2016. 35(2): p. 214-26.
[21]. Beauregard-Paultre, C., et al., External validation of clinical prediction rules for complications and mortality following Clostridioides difficile infection. PLoS One, 2019. 14(12): p. e0226672.
[22]. Steyerberg, E.W. and F.J. Harrell, Prediction models need appropriate internal, internal-external, and external validation. J Clin Epidemiol, 2016. 69: p. 245-7.
[23]. Debray, T.P., et al., A new framework to enhance the interpretation of external validation studies of clinical prediction models. J Clin Epidemiol, 2015. 68(3): p. 279-89.
[24]. Vergouwe, Y., K.G. Moons and E.W. Steyerberg, External validity of risk models: Use of benchmark values to disentangle a case-mix effect from incorrect coefficients. Am J Epidemiol, 2010. 172(8): p. 971-80.
[25]. Xue Chen., et al., Effect of glycated hemoglobin A1c variability on diabetic kidney disease in type 2 diabetes mellitus patients. Chin J Diabetes Mellitus, 2020,12(12): 993-998.
[26]. Viazzi, F., et al., Long-term blood pressure variability and development of chronic kidney disease in type 2 diabetes. Journal of Hypertension, 2019. 37(4): p. 805-813.
[27]. Koye, D.N., et al., The Global Epidemiology of Diabetes and Kidney Disease. Adv Chronic Kidney Dis, 2018. 25(2): p. 121-132.
[28]. Zeitler, P., et al., A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med, 2012. 366(24): p. 2247-56.
[29]. Dart, A.B., et al., High burden of kidney disease in youth-onset type 2 diabetes. Diabetes Care, 2012. 35(6): p. 1265-71.
[30]. Pinhas-Hamiel, O. and P. Zeitler, Acute and chronic complications of type 2 diabetes mellitus in

children and adolescents. Lancet, 2007. 369(9575): p. 1823-1831.
[31]. Thomas, M.C., M.E. Cooper and P. Zimmet, Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol, 2016. 12(2): p. 73-81.
[32]. Lin, K., et al., Effects of depression, diabetes distress, diabetes self-efficacy, and diabetes self-management on glycemic control among Chinese population with type 2 diabetes mellitus. Diabetes Res Clin Pract, 2017. 131: p. 179-186.
[33]. Lee, L.Y., et al., Predictors for self-management in older adults with type 2 diabetic nephropathy. J Clin Nurs, 2020. 29(5-6): p. 922-931.
[34]. Moons, K.G., et al., Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med, 2015. 162(1): p. W1-73.
[35]. Adderley, N.J., et al., Temporal and external validation of a prediction model for adverse outcomes among inpatients with diabetes. Diabet Med, 2018. 35(6): p. 798-806.
[36]. Elfiky, A.A., et al., Development and Application of a Machine Learning Approach to Assess Short-term Mortality Risk Among Patients With Cancer Starting Chemotherapy. JAMA Netw Open, 2018. 1(3): p. e180926.
[37]. Sun, D., M. Wang and A. Li, A multimodal deep neural network for human breast cancer prognosis prediction by integrating multi-dimensional data. IEEE/ACM Trans Comput Biol Bioinform, 2018.
[38]. Ljubic, B., et al., Predicting complications of diabetes mellitus using advanced machine learning algorithms. J Am Med Inform Assoc, 2020. 27(9): p. 1343-1351.
[39]. Yasar, H. and M. Ceylan, A novel comparative study for detection of Covid-19 on CT lung images using texture analysis, machine learning, and deep learning methods. Multimed Tools Appl, 2020: p. 1-25.
[40]. Guo, A., et al., Using electronic health records and claims data to identify high-risk patients likely to benefit from palliative care. Am J Manag Care, 2021. 27(1): p. e7-e15.

Table 1. Baseline clinical and biochemical characteristics of the study participants stratified by the occurrence and progression of DKD.

Characteristic	Occurrence of DKD				Progression of DKD			
	Total	No	Yes	P-value	Total	No	Yes	P-value
N.	2504	1687	817		4455	2892	1563	
Age (years)	55.44±7.49	55.22±7.66	55.92±7.10	0.059	57.88±8.80	56.56±8.61	60.33±8.57	<0.001
Male gender [n (%)]	991(54.8)	683(55.2)	308(53.8)	0.587	2274(51.0)	1504(52.0)	770(49.3)	0.043
BMI (kg/m^2)	26.10±4.00	25.93 ±3.86	26.44 ±3.86	0.029	26.30 ±4.14	26.24±4.07	26.43 ±4.27	0.143
Diabetes duration (years)	4(1,8)	3(1,7)	5(2,9)	<0.001	5(1,10)	4(1,8)	6(3,11)	<0.001
Education [n (%)]				0.0021				<0.001
Illiterate	182(7.3)	91(5.4)	91(11.1)		401(9.0)	205(7.1)	196(12.5)	
Literate	75(3.0)	33(2.0)	42(5.1)		132(3.0)	55(1.9)	77(4.9)	
Elementary school	678(27.1)	406(24.1)	272(33.3)		1253(28.1)	727(25.1)	526(33.7)	
Junior high school	375(15.0)	260(15.4)	115(14.1)		693(15.6)	462(16.0)	231(14.8)	
High school	738(29.5)	539(32.0)	199(24.4)		1228(27.6)	881(30.5)	347(22.2)	
College	400(16.0)	313(18.6)	87(10.6)		649(14.6)	487(16.8)	162(10.4)	
No data	56(2.2)	45(2.7)	11(1.3)		99(2.2)	75(2.6)	24(1.5)	
Marital status [n (%)]				<0.001				<0.001
Single	95(3.8)	66(3.9)	29(3.5)		181(4.1)	125(4.3)	56(3.6)	

Married	2109(84.2)	1457(86.4)	652(79.8)		3684(82.7)	2422(83.7)	1262(80.7)	
Divorced	93(3.7)	57(3.4)	36(4.4)		160(3.6)	105(3.6)	55(3.5)	
Widow or widower	171(6.8)	75(4.4)	96(11.8)		355(8.0)	181(6.3)	174(11.1)	
No data	36(1.4)	32(1.9)	4(0.5)		75(1.7)	59(2.0)	16(1.0)	
Smoking [n (%)]	769(30.7)	523(31.0)	246(30.1)	0.710	1362(30.6)	891(30.8)	471(30.1)	0.848
Drinking [n (%)]	637(25.4)	433(25.7)	204(25.0)	0.997	1124(25.2)	743(25.1)	381(24.4)	0.576
Diabetic self-management behavior								
Diet	5(4,7)	5(4,7)	5(4,7)	0.576	5(4,7)	5(4,7)	5(3,7)	0.008
Exercise	7(0,7)	7(1,7)	7(0,7)	0.821	7(1,7)	7(1,7)	6.5(0,7)	0.129
Medication	7(7,7)	7(7,7)	7(7,7)	0.229	7(7,7)	7(7,7)	7(7,7)	0.425
Monitoring	0(0,7)	0(0,7)	2(0,7)	0.408	0(0,7)	0(0,7)	1(0,7)	0.490
SBP (mmHg)	129(119,141)	128(117,139)	133(122,146)	<0.001	133(121,146)	131(120,144)	136(124,150)	<0.001
DBP (mmHg)	77(70,84)	76(69,83)	78(71,86)	<0.001	78(71,86)	77(70,85)	78(71,87)	<0.001
HbA1c (%)	7.90(6.85,9.75)	7.80(6.80,9.50)	8.40(7.10,10.10)	<0.001	8.2(7.0,10.0)	8.0(6.9,9.7)	8.5(7.1,10.5)	<0.001
TG (mg/dl)	113(83,164)	111(84,160)	120(82,168)	0.094	123(88,178)	119(86,172)	133(93,190)	<0.001
HDL-C (mg/dl)	52.00±13.51	52.44±13.98	50.73±12.38	0.038	50.75 ±13.24	51.31 ±13.41	49.71 ±12.85	<0.001
LDL-C (mg/dl)	99.41±28.56	99.09±28.55	100.10±28.60	0.401	101.23 ±29.90	101.05 ±29.87	101.55 ±29.96	0.818
eGFR (ml/min/1.73 m^2)	85.50(73.08,96.13)	87.18(74.00,96.80)	82.76(71.22,94.55)	0.002	82.01(67.88,94.93)	83.65(69.88,96.60)	77.00(65.87,91.35)	<0.001
UACR (mg/g)	8.64(4.50,13.86)	7.06(3.58,12.17)	10.95(7.14,16.32)	<0.001	17.82(7.97,50.12)	14.84(6.77,41.71)	22.72(11.05,75.23)	<0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio. Data are expressed as mean ± SD, number (%) or median (interquartile range).

Table 2 The baseline risk score of low-high DKD risk cohort stratified by the progression of DKD.

Risk stage	Non- progression group	Progression group	P-value
Low-high DKD risk	16.80±6.21	19.77±5.77	<0.001
Low DKD risk	14.48±5.61	17.83±5.74	<0.001
Moderate DKD risk	19.46±5.52	21.40±4.87	<0.001
High DKD risk	21.68±5.22	22.93±5.15	0.005

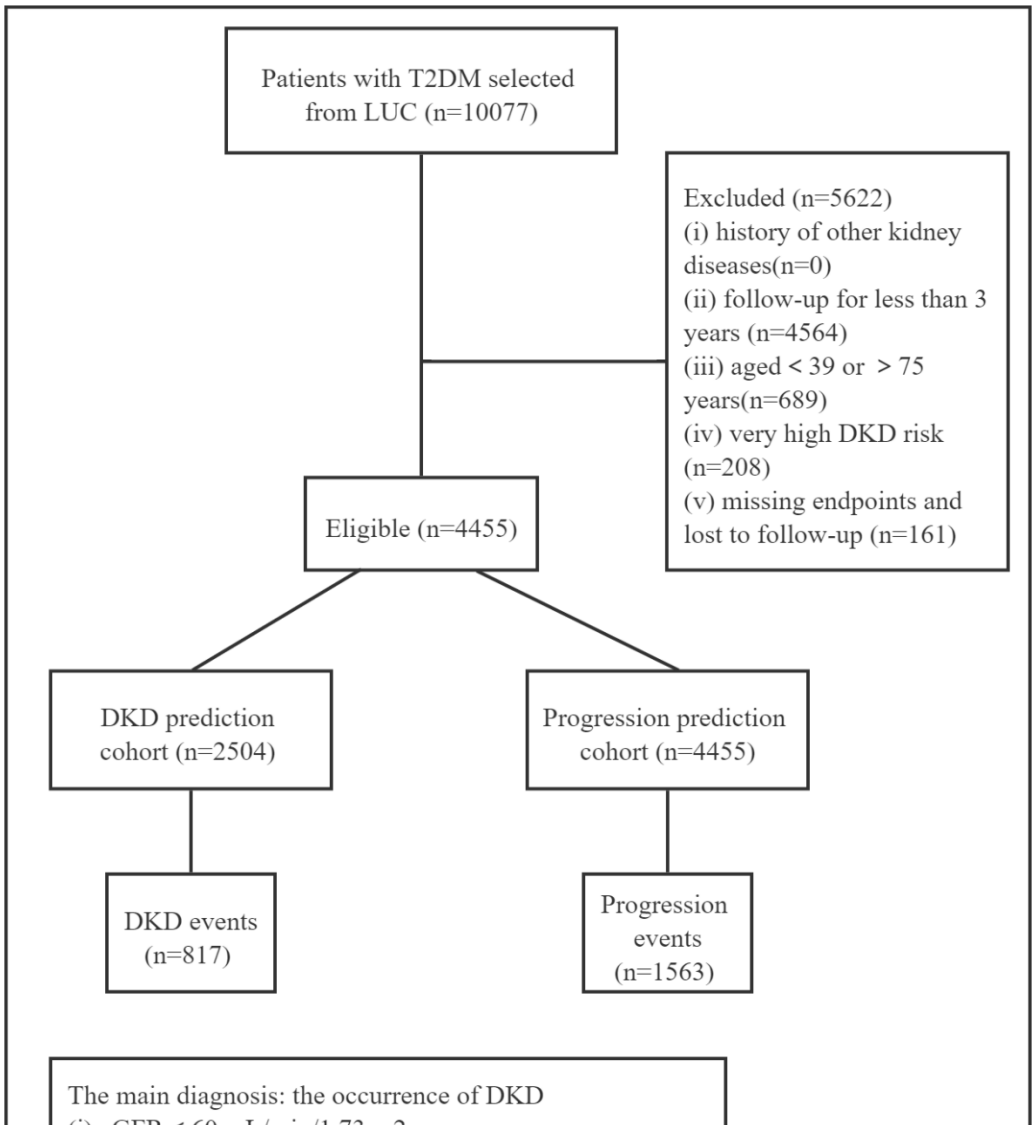

Figure 1 Flow chart of patient selection. DKD, diabetes kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; AER, albumin excretion rate.

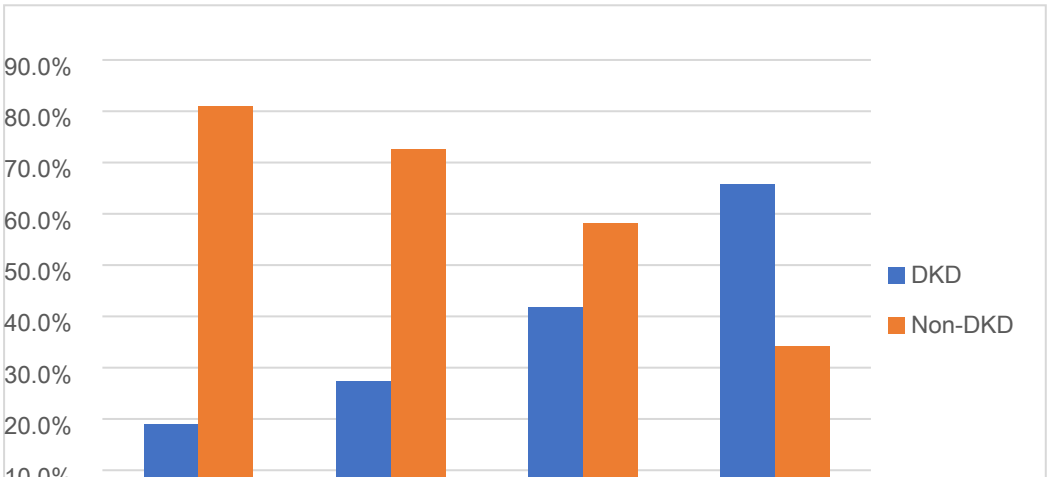

Figure 2 In the DKD prediction cohort, the final DKD, non-DKD patients' ratio stratified by DKD risk categories.

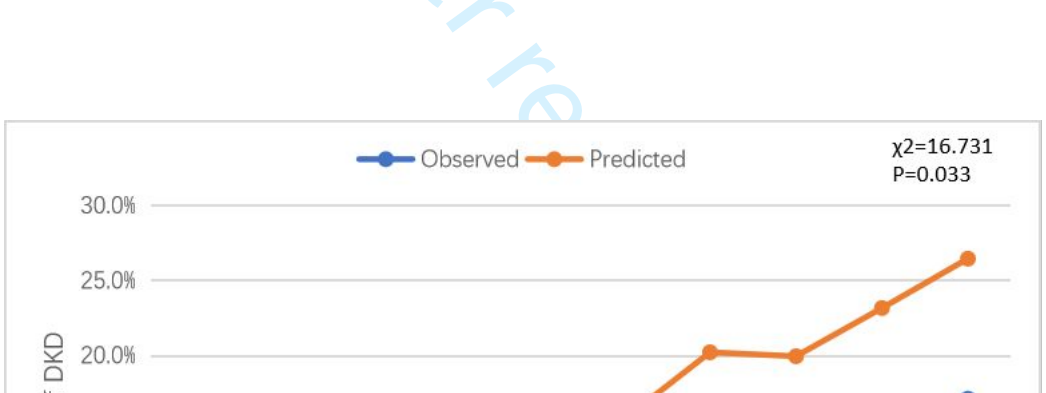

Figure 3 Observed and predicted the occurrence of DKD. Grouping method: First, calculate the predicted probability of DKD for each patient according to the DKD risk scoring model, then arrange them from small to large according to the predicted probability and divide them into 10 groups based on deciles for the predicted probabilities.

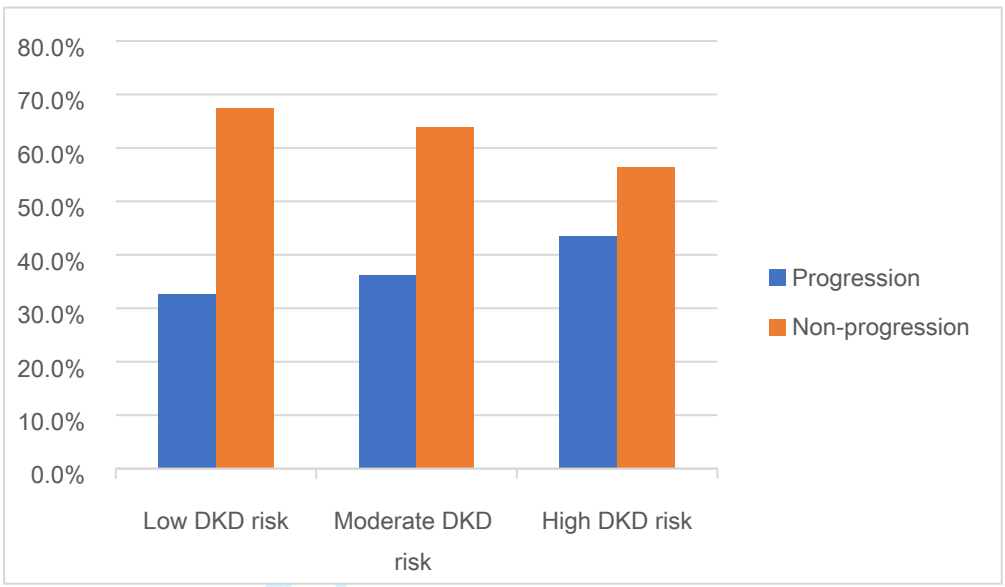

Figure 4 In the DKD progression cohort, the final progression, non-progression patients' ratio stratified by DKD stage

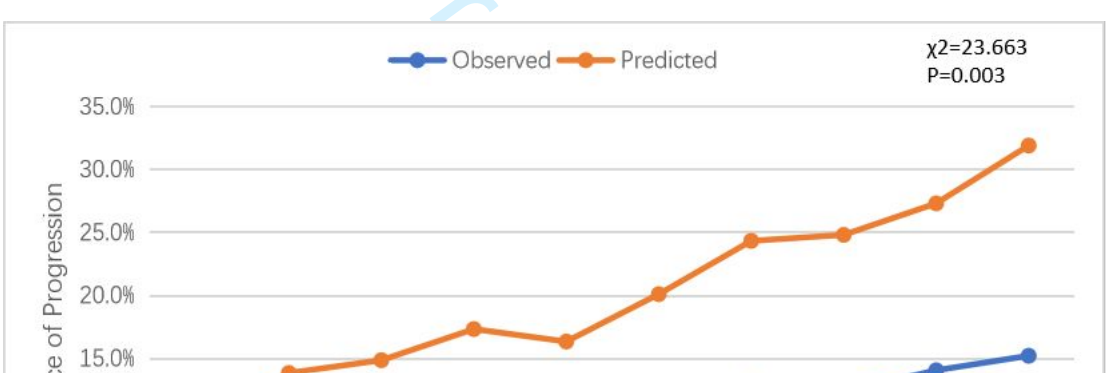

Figure 5 Observed and predicted the Progression of DKD. Grouping method: First, calculate the predicted probability of DKD for each patient according to the DKD risk scoring model, then arrange them from small to large according to the predicted probability and divide them into 10 groups based on deciles for the predicted probabilities.

Supplementary Appendix

Risk factors for DKD	RR (95%CI)	β-coefficient	Scores
Age (by 5-10 years)	1.38 (1.20-1.59)	0.32	3.0
BMI (by 5 kg/m^2)	1.16 (1.09-1.23)	0.15	1.5
Smoking(yes/no)	1.49 (1.30-1.71)	0.40	4.0
Diabetic retinopathy(yes/no)	1.31 (1.00-1 .73)	0.27	3.0
HbA1c (by 1%[11mmol/mol])	1.17 (1.09-1.26)	0.15	1.5
SBP (by 10-20mmHg)	1.21 (1.15-1.27)	0.19	2.0
HDL-C (by 1mmol/L)	0.78 (0.61-0.99)	-0.25	-2.5
TG (by 1 mmol/L)	1.42 (1.16-1.74)	0.37	4.0
UACR (by 1 mg/g)	1.13 (1.10-1.17)	0.12	1.0

Reporting checklist for prediction model development/validation.

Based on the TRIPOD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the TRIPODreporting guidelines, and cite them as:

Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement.

		Reporting Item	Page Number
Title			
	#1	Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract			
	#2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1-2
Introduction			
	#3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to	3-4

		existing models.	
	#3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods			
Source of data	#4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4-5
Source of data	#4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4-5
Participants	#5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
Participants	#5b	Describe eligibility criteria for participants.	5
Participants	#5c	Give details of treatments received, if relevant	n/a
Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5-6
Outcome	#6b	Report any actions to blind assessment of the outcome to be predicted.	5-6
Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured	6-7
Predictors	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	6-7
Sample size	#8	Explain how the study size was arrived at.	7
Missing data	#9	Describe how missing data were handled	7

		(e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	
Statistical analysis methods	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.	n/a
Statistical analysis methods	#10b	If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	n/a
Statistical analysis methods	#10c	If you are validating a prediction model, describe how the predictions were calculated.	8
Statistical analysis methods	#10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8
Statistical analysis methods	#10e	If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done	n/a
Risk groups	#11	Provide details on how risk groups were created, if done.	7
Development vs. validation	#12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	n/a The population in the development cohort was meta-analyzed and cannot be compared
Results			
Participants	#13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	9
Participants	#13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of	9

		participants with missing data for predictors and outcome.	
Participants	#13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	n/a The population in the development cohort was meta-analyzed and cannot be compared
Model development	#14a	If developing a model, specify the number of participants and outcome events in each analysis.	n/a
Model development	#14b	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	n/a
Model specification	#15a	If developing a model, present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	n/a
Model specification	#15b	If developing a prediction model, explain how to the use it.	n/a
Model performance	#16	Report performance measures (with CIs) for the prediction model.	10-12
Model-updating	#17	If validating a model, report the results from any model updating, if done (i.e., model specification, model performance).	10-12
Discussion			
Limitations	#18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	15
Interpretation	#19a	For validation, discuss the results with reference to performance in the development data, and any other validation data	12-14
Interpretation	#19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	12-14

Implications	#20	Discuss the potential clinical use of the model and implications for future research	16
Other information			
Supplementary information	#21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	17
Funding	#22	Give the source of funding and the role of the funders for the present study.	17

BMJ Open

External Validation of the Risk Prediction Model for Early Diabetic Kidney Disease in Taiwan population: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059139.R1
Article Type:	Original research
Date Submitted by the Author:	18-May-2022
Complete List of Authors:	Sun, Zhenzhen; The First Affiliated Hospital of Hainan Medical University; Nanjing University of Chinese Medicine Wang, Kun; Nanjing University of Chinese Medicine Miller, Joshua; Stony Brook University Renaissance School of Medicine Yuan, Xiaodan; Affiliated Hospital of Integrated Traditional Chinese and Western Lee, Yau-Jiunn; Lee's Clinic Lou, Qingqing; The First Affiliated Hospital of Hainan Medical University
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Renal medicine
Keywords:	DIABETES & ENDOCRINOLOGY, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

External Validation of the Risk Prediction Model for Early Diabetic Kidney Disease in Taiwan population: a retrospective cohort study

Zhenzhen Sun[1,2], Kun Wang[2], Joshua D. Miller[3], Xiaodan Yuan[4], Yau-Jiunn Lee [5], Qingqing Lou[1*]

1 Endocrinology Department, The First Affiliated Hospital of Hainan Medical University, Haikou, Hainan, China

2 Nursing College, Nanjing University of Chinese Medicine, Nanjing, Jiangsu Province, China

3 Renaissance School of Medicine at Stony Brook University, Stony Brook, NY, USA

4 Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, Jiangsu Province, China

5 Lee's Clinic, No. 396, Guangdong RD, Pingtung City, Pingtung Country 900, Taiwan

*Corresponding author: Qingqing Lou

Postal address: The First Affiliated Hospital of Hainan Medical University, No.31, Longhua Road,Haikou 570102, Hainan, China.

Phone: +8615312019129

Fax number: +089868642548

E-mail address: 2444890144@qq.com

ORCID numbers: 0000-0002-4743-0900

Abstract

Objectives This study aims to independently and externally validate the Risk Prediction Model for Diabetic Kidney Disease (RPM-DKD) in patients with type 2 diabetes mellitus (T2DM).

Design This is a retrospective cohort study.

Setting Outpatient clinics at Lee's United Clinics, Taiwan, China.

Participants A total of 2504 patients (average age 55.44 years, SD, 7.49 years), and 4455 patients (average age 57.88 years, SD, 8.80 years) were included for analysis in the DKD prediction and progression prediction cohorts, respectively.

Exposure The predicted risk for DKD and DKD progression for each patient were all

calculated using the RPM-DKD.

Primary and secondary outcome measures The primary outcome measure was overall incidence of DKD. Secondary outcomes included DKD progression. The discrimination, calibration and and precision of the RPM-DKD score were assessed.

Results The DKD prediction cohort and progression prediction cohort consisted of 2504 and 4455 T2DM patients, respectively. The RPM-DKD examined in this study showed moderately discriminative ability with AUCs ranged from 0.636 to 0.681 for the occurrence of DKD and 0.620 to 0.654 for the progression of DKD. The Hosmer-Lemeshow $\chi 2$ test indicted the RPM-DKD was not well calibrated for predicting the occurrence of DKD and over-estimated the progression of DKD. The precision for predicting the occurrence and progression of DKD were 43.2% and 42.2%, respectively.

Conclusions On external validation, the RPM-DKD cannot accurately predict the risk of DKD occurrence and progression in patients with T2DM.

Keywords External validation; diabetic kidney disease; prediction; risk assessment

Strengths and limitations of this study

- Our validation cohort was geographically different from the cohort used to derive the model and our team was not involved in model derivation, which enabled us to conduct a true independent external validation study.
- Our cohort had an average follow-up time of more than 5 years, a duration that positioned us to effectively identify the occurrence of outcome variables.
- Whilst the cohort was representative of a large cohort of over 4,000 adults, it was geographically restricted to Taiwan.
- Most patients in our cohort had better diabetes self-management behaviors, which could potentially have affected the study results and also explain why the model overestimated risk of occurrence and progression.
- The retrospective nature of our study presents an inherent limitation, although it is

a simple, flexible, and low-cost method to review patient data for purposes of the present analysis

1.Introduction

Diabetic kidney disease (DKD) is one of the main microvascular complications of long-standing, uncontrolled type 2 diabetes mellitus (T2DM), and a main cause of preventable chronic and end-stage kidney disease worldwide [1]. Paradoxically, improvements in cardiovascular survival in patients with T2DM have contributed to prolonged patient survival, which in turn lengthens time at risk for developing renal impairment [2]. In China, about 20-40% of individuals with T2DM have DKD [3]. Further, progression of DKD to ESRD requiring renal replacement therapy and/or renal transplant brings economic burden and is associated with additional comorbid burden [4-6]. In light of these factors, the early intervention and study of a relevant risk prediction model for early DKD are of great clinical and societal relevance.

Clinical risk prediction models aim to estimate an individual's risk of an event based on relevant contributing information [7]. Currently, many prediction models have been developed to assess risk of incident diabetes, but few have been validated in subsequent analyses and applied to clinical practice [8-10]. For example, one T2DM risk score, the FINDRISC, is well-known in Latin America and the Caribbean, despite limited none external validation of the model [11]. A risk prediction model should not enter clinical practice unless it has been independently and externally validated and proven to perform a useful role [12].

The ability to accurately predict risk of DKD would allow for earlier recognition,

and perhaps intervention, in patients with long-standing T2DM. Recently, a risk prediction model for early DKD (RPM-DKD) was developed based on systematic review and meta-analysis of individual participant data from 20 cohorts of predominately white populations [13]. However, validation was limited in scope with a relatively small study size (n=380) and insufficient median follow-up time (t=2.9 years). The purpose of the current study was to independently and externally validate performance of the RPM-DKD in predicting the risk of incidence of DKD in patients with T2DM. In addition, although PRM-DKD was only used to predict the occurrence of DKD, we believe that it can predict the progress of DKD to a certain extent, with reason that the influencing factors of DKD progression and occurrence are similar. Therefore, the secondary purpose of this study is to evaluate the performance of this model in predicting the risk of DKD progression in patients with T2DM.

2.Methods

2.1 Data sources and participants

We used outpatient data from December 2006 to October 2019 from Lee's United Clinics (LUC) in Taiwan. LUC is a large ambulatory system, comprised of six clinics providing multidisciplinary care for patients with diabetes. The Taiwan Health Insurance Plan supports 4 annual follow up visits along with access to medications, diabetes supplies, diabetes self-management education DSME) clinician visitation and primary/secondary prevention screening to patients living with diabetes. This setting provided an opportune source of robust, longitudinal data in which to validate the RPM-DKD.

Inclusion criteria for predicting the occurrence of DKD aligned with those established by the RPM-DKD [13] and included; (1) patients aged 39-75 years, and (2) patients without albuminuria (urinary albumin-to-creatinine ratio [UACR]<30mg/g or albumin excretion rate [AER]<30mg) and estimated glomerular filtration rate (eGFR)≥60mL/min/1.73 m^2 at baseline.

Inclusion criteria for predicting progression of DKD were patients aged 39-75 years with S1-S3 at baseline (The criteria for S1-S3 stage presented in diagnosis criteria part).

We excluded (1) patients with less than 3 years of longitudinal follow-up, (2) those with history of acute kidney injury, primary glomerulonephritis, urinary tract infection, urinary calculi, etc. (3) patients with missing endpoints and lost to follow-up, and (4) patients with end stage renal disease (very high DKD risk) at baseline.

2.2 Diagnosis criteria

Diagnosis criteria of DKD were also consistent with foundational RPM-DKD modeling and included: (1) eGFR<60 mL/min/1.73 m^2 and/or (2) UACR≥30 mg/g (or AER≥30 mg) (3) present for≥3 months caused by diabetes [14].

Diagnostic criteria to clinical progression of DKD were [15]: (i) Patients were in a non-progression group if they maintained the same DKD stage or their condition had improved to an earlier DKD stage category. (ii) Patients were in a progression group if the DKD stage category had progressed.

The stage of DKD was classified using a combination of eGFR and ACR into four stage categories[16], i.e., (i) Low DKD risk, eGFR ≥60mL/min/1.73 m2 and

ACR<30mg/g; (ii) Moderate CKD risk, eGFR between 45 and 59 mL/min/1.73 m2 and ACR<30mg/g, or eGFR ≥60mL/min/1.73 m2 and ACR between 30 and 300mg/g; (iii) High DKD risk, eGFR between 30 and 44 mL/min/1.73 m2 and ACR<30mg/g, or eGFR between 45 and 59 mL/min/1.73 m2 and ACR between 30 and 300mg/g, or eGFR ≥60mL/min/1.73 m2 and ACR>300mg/g; (iv) Very high DKD risk, eGFR≤29mL/min/1.73 m2 and ACR<30mg/g, or eGFR≤44mL/min/1.73 m^2 and ACR between 30 and 300 mg/g, or eGFR≤59mL/min/1.73 m^2 and ACR>300mg/g.

2.3 Risk score calculations

The risk score model was established by Jiang, W. et al [13], and all risk factors included in the DKD risk score model were derived from a systematic review and meta-analysis of 14 prospective and 6 retrospective cohorts. The predicted risk score for each study participant was calculated using their baseline data. The baseline variables used for the risk scores were in accordance with the model: (i) age (years) divided into three categories, 39-49 scores 0, 50–59 scores 3.0, and 60–75 scores 6.0; (ii) body mass index (BMI), which was calculated as the patient's weight divided by the square of their height (kg/m^2), divided into three categories (<25.00 scores 0, 25.00–29.99 scores 1.5, and≥30.00 scores 3.0); (iii) smoker (defined as having smoked more than 100 cigarettes in their lifetime), non-smoker scores 0 and smoker scores 4.0; (iv) diabetic retinopathy (DR), 0 if no and 3.0 if yes; (v) hemoglobin A1c(HbA1c) divided into four categories, <7.0% (<53 mmol/mol) scores 0, 7.0-7.9% (53–63 mmol/mol) scores 1.5, 8.0–8.9% (64–74 mmol/mol) scores 3.0 and ≥9.0% (≥75 mmol/mol) scores 4.5; (vi) systolic blood pressure (SBP) divided into four categories, <130mmHg scores 0, 130-139 mmHg

scores 2.0, 140-149 mmHg scores 4.0, ≥150 mmHg scores 6.0; (vii) serum high-density lipoprotein-cholesterol (HDL-C) divided into two categories, ≥1.30mmol/L scores 0, and <1.30mmol/L scores 2.5; (viii) triglycerides (TG) divided into two categories, <1.70mmol/L scores 0 and ≥1.70mmol/L scores 4.0; and (ix) UACR divided into three categories, <10mg/g scores 0, 10.00-19.99mg/g scores 2.0, 20.00-29.99mg/g scores 4.0. In addition, considering that we want to predict the progression of DKD, we continue to increase the category of UACR, that is, every increase of UACR 10mg/g, the score increases by 2 points. For example, UACR between 30.00 and 39.99mg/g scores 6.0. The coefficients in the model are shown in supplementary appendix.

Data to inform score calculation was retrieved from the LUC electronic medical record. Four risk categories include: (i) relatively low (score <12.0); (ii)moderate (score 12.0–15.5); (iii) high (score 16.0–26.5); and (iv) very high (score **>** 27.0).

2.4 Sample size and missing data

Following the simulation-based sample size calculations for external validation of clinical prediction models [17], the anticipated precisions of performance measures were estimated based on the available number of outcome events in the external validation datasets.The number of outcome events in our DKD prediction cohort were 817. When using a fixed base probability of 0.4[3], the minimum sample size used in this study should be 2043 cases.

Our validation cohort had missing information on age (1.3%), BMI (2.6%) and HbA1c(5.6%). The rest variables included in RPM-DKD model were complete. We

used multiple imputation (10 imputations) to replace missing values by using a chained equation approach based on all candidate predictors and outcomes.

2.5 Statistical analysis

Descriptive statistics were generated for all variables, which were stratified by the occurrence and progression of DKD. Normally distributed continuous variables were presented as means ± standard deviation (SD), and analysis of variance was used to assess inter-group comparisons. Medians (interquartile range [IQR]) were used for continuous variables that were not normally distributed, and the comparison between groups were performed by Kruskal-Wallis H test. Categorical variables were represented as number of cases (N), and the intergroup rate (%) was compared with chi-square test.

The clinical performance of the DKD risk prediction model was assessed by means of discrimination and calibration. Model discrimination describes a model's performance in distinguishing between individuals who experience an event and those who do not[7]. Model discrimination was assessed by plotting a receiver operating characteristic (ROC) curve and calculating the area under the curve (AUC). An AUC-statistic value >0.75 was regarded to represent good discrimination. Calibration assessment of a risk prediction model describes how well predictions match observed outcomes [7]. The calibration of the risk score predictions was assessed by plotting observed versus predicted number of patients and by calculating the Hosmer-Lemeshow $\chi 2$ statistic. Groups for observed DKD events were based on deciles for the

predicted probabilities. Performance was evaluated as sensitivity, specificity, and precision.

All results were presented with 95% confidence interval (CI). Any two-tailed p-values<0.05 were considered statistically significant. All satistical analyses were performed using SPSS software, version 22 (IBM Corp.).

2.6 Patient and public involvement

There was no patient or public involvement in the design and conduct of the study.

3. Results

In the DKD prediction cohort, a total of 2504 patients (average age 55.44 years, SD, 7.49 years), and 4455 patients (average age 57.88 years, SD, 8.80 years) were included for analysis in the DKD progression prediction cohort (Figure 1). The average length of follow-up was 7.37 years (SD, 3.22 years) in the DKD prediction cohort and a total of 817 (32.6%) people had DKD during the follow-up period. The mean follow-up time in the progression prediction cohort was 7.72 years (SD, 3.10 years), and the overall progression of events in this cohort was 1563 (35.1%).

3.1 DKD prediction cohort

3.1.1 Baseline characteristics

The DKD prediction cohort had an average BMI of 26.1±4.0 kg/m^2 and 54.8% were men. The proportion of smokers and drinkers were 30.7% and 25.4%, respectively. There were significant differences in the level of education (P=0.0021) and marital status (P<0.001) between patients who eventually developed DKD and those who did not. The patients who did not develop of DKD had higher rates of secondary and

college-level education and lower rates of spousal loss than the patients with DKD. Furthermore, patients who eventually developed DKD had a longer diabetes duration (median 5 years [2-9 years]) and a higher level of HbA1c (median 8.4% [7.10-10.10%]) than those who did not. All patients showed normal albuminuria and renal function at baseline with median UACR of 8.64 mg/g (4.50–13.86mg/g) and median eGFR of 85.50 ml/min/1.73 m^2 (73.08–96.13 ml/min/1.73 m^2). The median systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 129mmHg (119-141mmHg) and 77 mmHg (70-84 mmHg), respectively. Baseline characteristics of the DKD prediction cohort are displayed in Table 1.

3.1.2 External validation results for DKD prediction cohort

Of the 2504 patients, 678 (27.1%), 639 (25.5%), 1114 (44.5%) and 73 (2.9%) had risk categories of relatively low, moderate, high and very high at baseline. At the end of observation, 129 (19.0%), 175 (27.4%), 465 (41.7%), 48 (65.8%) patients in the relatively low, moderate, high and very high groups developed DKD, respectively (Figure 2).

Discrimination of the model：According to our external validation, 16 was selected as the optimal cut-off risk score value, at which the sum of sensitivity and specificity was maximal (Youden's index), which corresponded with Jiang, W. et al [14]. With a risk cut-off value of 16 points, the sensitivity would be 53.0% (95% CI 48.9–57.0), specificity would be 65.7% (95% CI 63.0–68.3). ROC curve of our external validation showed the area under the DKD risk score curve was 0.659 (95% CI 0.636-0.681).

Calibration of the model：The risk scoring model was not well calibrated for predicting the occurrence of DKD, with a Hosmer-Lemeshow $\chi 2$ statistic of 16.731 (p=0.033). The calibration plot in figure 3 shows that the comparison between observed and predicted the occurrence of DKD, indicting the over-estimation of risk occurred in tenths 1 through 10.

Precision of the model in predicting DKD：The prediction precision refers to the ratio of the actual number of patients with DKD to the number of patients predicted to develop DKD. According to our data, patients in the DKD prediction cohort were classified as high risk if their DKD risk score ≥16 points, with precision of 43.2% (513/1187).

3.2 Progression prediction cohort

3.2.1 Baseline characteristics

The baseline clinical and biochemical characteristics of the DKD progression cohort stratified by the progression of DKD are listed in Table 1. Of the cohort, the average BMI was 26.30±4.14 kg/m^2 and 51.0% were men. The proportion of smokers and drinkers were 30.6% and 25.3%, respectively. In addition, the progression group had lower education and married level, and longer duration of diabetes than the patients in non-progression group. And patients in progression group had higher systolic blood pressure (SBP), HbA1c and UACR than the patients in non-progression group, and higher levels of diastolic blood pressure (DBP), total cholesterol than the patients in non-progression group. On DKD risk score analyses, the progression group had higher

baseline risk score compared with non-progression group whatever patients with low DKD risk, moderate DKD risk or high DKD risk (Table 2).

3.2.2 External validation results for progression prediction cohort

Of the 4455 patients, 2504(56.2%), 1397 (31.4%) and 554 (12.4%) were in low, moderate and high DKD risk at baseline. At the end of observation, 589 (32.6%), 531 (36.1%) and 414 (43.5%) patients in the low, moderate and high DKD risk had progressed, respectively (Figure 4).

Discrimination of the model: ROC curve showed moderate discriminative ability of predicting the progression of DKD in progression prediction cohort, and the area under the receiver operating characteristic curve was 0.637 (95% CI 0.620-0.654). 18 was selected as the optimal cut-off risk score value with a sensitivity of 65.0% (95% CI 62.6-67.3) and a specificity of 57.0% (95% CI 55.2-58.8)

Calibration of the model: Calibration of the model for predicting the progression of DKD was no good in our external validation cohort (Hosmer-Lemeshow $\chi 2$ =23.663, P=0.003), and the over-estimation of risk occurred in tenths 1 through 10. The calibration plot in figure 5 shows that the comparison between observed and predicted the progression of DKD.

Precision of the model in predicting DKD progression: The prediction accuracy refers to the ratio of the actual number of patients whose DKD stage progressed to the number of patients predicted to progressed. According to our validation cohort, with a risk cut-off value of 18 points, the precision would be 45.0% (1016/2260). According

to the model developed study [15], with a risk cut-off value of 16 points, the precision would be 42.2% (1173/2781).

4. Discussion

External validation is a mandatory step in applying a prediction model to meaningful clinical care; the process addresses the transportability of the model [18]. Taiwan has established a sound universal health insurance policy supported by the government, providing a lot of reliable data for model validation. However, not all governments have established such a comprehensive universal health care policy. Hence, the limited availability of patient data, the model was not validated. In this study, we evaluated the usefulness of RPM-DKD for predicting the DKD incidence and progression of DKD in patients with T2DM by assessing its discrimination, calibration and precision. The performance of the RPM-DKD predictive potential in our validation cohort was not ideal, even when the results from the validation evaluated by the model developers were promising.

The RPM-DKD has several advantages, including easy point-of-care application, simple calculation and reliance on very few variables. Nevertheless, the RPM-DKD demonstrated moderately discriminatory ability in our cohort. With that said, the RPM-DKD was not well-calibrated for predicting the occurrence of DKD, and it over-estimated the progression of disease. When using the same foundational thresholds established by the original RPM-DKD study, precision for predicting DKD occurrence and progression in our validation cohort was low, with values of 43.2% and 42.2%, respectively. Utilizing the developers' suggested thresholds resulted in inappropriate

prediction of DKD in our cohort. Even at a threshold of 18 (at which the Youden's index was maximal in our study), the precision of the model in predicting DKD progression was also low.

Overall transportability of the model was poor in our analysis, owing perhaps to the phenomenon of over-fitting. If internal validation such as bootstrap would have been performed after model developed, the phenomenon might have been foreseen [19]. Furthermore, the poor external validation performance may also be closely related to the fact that our validation cohort was vary from the model developers' cohort in terms of settings, populations and periods [20, 21]. Moreover, a significant reason for the poor performance of DKD progression prediction is that the model was not developed to predict DKD progression. However, there is no such a simple scoring model to predict the progression of DKD at present. Most of the models that have been developed to predict the progression of DKD are complex and difficult to be widely used in clinical practice.

The RPM-DKD uses cross-sectional baseline data to predict a patient's risk of DKD 5 to 10 years later; it is therefore based on the assumption that there is no significant change in relevant indicators of the patient in subsequent years – a somewhat unrealistic expectation in a real world application. Since the occurrence and development of DKD is a relatively long process, metabolic indicators 5-, 10-years even in preceding decades can impact subsequent outcomes. However, the model, established by logistic regression, volatility of various parameters in the next few years was not considered, which results in the prediction performance was not high.

In our study, not all data specific to risk factors included in the RPM-DKD model were available (age, BMI, HbA1c.); this may have contributed to poor model performance. In previous work, we found that HbA1c variability is an independent risk factor for nephropathy in patients with T2DM [22]. In addition, Viazzi et al. demonstrated that the variability of SBP and pulse pressure are also key influencing factors for the occurrence and development of DKD [23]. Thus, these parameters should be strong outcome predictors for developing DKD; and yet, the RPM-DKD does not take them into account.

The RPM-DKD model cannot predict future risk of DKD in patients with T2DM aged<39 years despite early age of diagnosis being an established risk factor for developing DKD [24]. Several groups reported an increasing incidence of youth-onset DKD[25, 26]. Given the earlier onset of DKD among T2DM patients, we believe that having validated risk assessment models that include young adults may be of greater clinical use.

Strengths and limitations of this study

Our study has several strengths. First, our validation cohort was geographically different from the cohort used to derive the model; further, our team was not involved in model derivation, which enabled us to conduct a true independent external validation study. Additionally, our cohort had an average follow-up time of more than 5 years, a duration that positioned us to effectively identify the occurrence of outcome variables.

Several limitations existed in this study. First, whilst the cohort was representative of a large cohort of over 4,000 adults, it was geographically restricted to Taiwan.

Second, most patients in our cohort had better diabetes self-management behaviors, which could potentially have affected the study results and also explain why the model overestimated risk of occurrence and progression. However, diabetes self-management is a key factor for promoting better health outcomes among patients with DKD [27, 28]; longitudinally, increased awareness for the DKD burden in diabetes patients might have contributed to additional self-management behaviors with a positive effect on DKD incidence and progression. In addition, the retrospective nature of our study presents an inherent limitation, although it is a simple, flexible, and low-cost method to review patient data for purposes of the present analysis [29]; additionally, we may not have successfully captured patient data related to care that may have occurred outside of our health system. Apart, the scoring model was not developed to predict the progression of DKD, but we still used this scoring model to predict the progression of DKD, which may create inapplicability. However, there is no similar scoring model that can predict the progression of DKD at present.

Future research

The occurrence of DKD in our study was high (31.6%), agreeing with previous study (20% to 40%) conducted in China[3] but significantly higher than that in the United States (26.2%)[30]. Among those with diabetes, DKD prevalence varies widely between countries, with estimates ranging from 26.2% in US to 83.6% in Tanzania[31]. In general, the prevalence of DKD rate in Asia and Africa are higher than those in

Europe and the United States[32]. The insidious nature of type 2 diabetes and less accessibility of developing countries to healthcare contribute to a high proportion of undiagnosed patients[33]. The late diagnosis may partially contribute to the high prevalence of DKD in Asia and Africa. In Asia, health-care providers and nurses are not sufficiently educated about diabetes patients, about 50% lack understanding of diabetes complications[34], and self-care activities are suboptimal overall[35]. Therefore, it is extremely significant to have an accurate prediction model that could assist clinicians in real-time evaluation of patient risk and implement primary and secondary preventive measures to delay progression of disease. However, the RPM-DKD established by logistic regression did not perform well. Furthermore, prediction models can become obsolete with change in population demography, better therapeutic options and care pathways, and improvement in data recording [36]. In the future, it may be possible to build a DKD prediction model by deep learning methods in order to improve the prediction of DKD occurrence and progression; many studies have applied deep learning with proven success [37-41].

5. Conclusion

Our independent external validation study revealed that, in patients with T2DM, the RPM-DKD cannot accurately predict the risk of DKD occurrence and progression. The ability to accurately estimate DKD risk is critical in advancing patient care and preventing or delaying complication risk in patients with long-standing T2DM.Newer

prediction models leveraging deep learning methods may prove useful for predicting risk of developing or progressing DKD.

Acknowledgments. The authors sincerely thank all participants for their help with this study.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. Q.L. conceived and designed the study. Z.S., K.W., X.Y. and Y.J.L. collected the epidemiological and clinical data. Z.S., K.W. and X.Y. drafted the manuscript. Z.S., K.W., X.Y., and Q.L. contributed to acquisition, analysis, and interpretation of data. Q.L. and J.D.M. contributed to critical revision of the manuscript for important intellectual content. All authors read, revised, and approved the final draft. Q.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding This work was supported by the National Key R&D Program of China (No.2021YFE0204800) and Key R&D Program of Hainan Province (No.ZDYF2021SHFZ236)

Ethics approval The present study was approved by the ethics committee of Antai Hospital, Antai Medical Association (No.: 14-055-B2) and was conducted in accordance with the ethical standards set out in the Declaration of Helsinki and its later amendments.

Disclaimer The funders had no role in the study design, data collection, or analysis, decision to publish, or preparation of the manuscript.

Patient consent for publication Not required.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information. All data requests should be submitted to the corresponding author for consideration.

References:

[1]. Afkarian, M., et al., Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 1988-2014. JAMA, 2016. 316(6): p. 602-10.

[2]. Thomas, M.C., M.E. Cooper and P. Zimmet, Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol, 2016. 12(2): p. 73-81.

[3]. Chinese guideline for the prevention and treatment of type 2 diabetes mellitus (2017 edition). Chin J Diabetes Mellitus, 2018,10(1): 4-67.

[4]. McQueen, R.B., et al., Economic burden of comorbid chronic kidney disease and diabetes. J Med Econ, 2017. 20(6): p. 585-591.

[5]. Vanholder, R., et al., Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. Nat Rev Nephrol, 2017. 13(7): p. 393-409.

[6]. Tangri, N., et al., Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure: A Meta-analysis. JAMA, 2016. 315(2): p. 164-74.

[7]. Major, R.W., et al., The Kidney Failure Risk Equation for prediction of end stage renal disease in UK primary care: An external validation and clinical impact projection cohort study. PLoS Med, 2019. 16(11): p. e1002955.

[8]. Siontis, G.C., et al., External validation of new risk prediction models is infrequent and reveals worse prognostic discrimination. J Clin Epidemiol, 2015. 68(1): p. 25-34.

[9]. Noble, D., et al., Risk models and scores for type 2 diabetes: systematic review. BMJ, 2011. 343: p. d7163.

[10]. Ayensa-Vazquez, J.A., et al., Agreement between Type 2 Diabetes Risk Scales in a Caucasian Population: A Systematic Review and Report. J Clin Med, 2020. 9(5).

[11]. Carrillo-Larco, R.M., et al., FINDRISC in Latin America: a systematic review of diagnosis and prognosis models. BMJ Open Diabetes Res Care, 2020. 8(1).

[12]. Moons, K.G., et al., Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ, 2009. 338: p. b606.

[13]. Jiang, W., et al., Establishment and Validation of a Risk Prediction Model for Early Diabetic Kidney Disease Based on a Systematic Review and Meta-Analysis of 20 Cohorts. Diabetes Care, 2020. 43(4): p. 925-933.

[14]. Molitch, M.E., et al., Diabetic kidney disease: a clinical update from Kidney Disease: Improving Global Outcomes. Kidney Int, 2015. 87(1): p. 20-30.

[15]. Chang, Y.H., et al., Serum uric acid level as an indicator for CKD regression and progression in patients with type 2 diabetes mellitus-a 4.6-year cohort study. Diabetes Metab Res Rev, 2016. 32(6): p. 557-64

[16]. KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease. Kidney Int Suppl (2011), 2018. 8(3): p. 91-165.

[17].Snell KIE, Archer L, Ensor J, Bonnett LJ, Debray TPA, Phillips B, Collins GS, Riley RD. External validation of clinical prediction models: simulation-based sample size calculations were more reliable than rules-of-thumb. J Clin Epidemiol. 2021 Jul;135:79-89.

[18]. Beauregard-Paultre, C., et al., External validation of clinical prediction rules for complications and mortality following Clostridioides difficile infection. PLoS One, 2019. 14(12): p. e0226672.

[19]. Steyerberg, E.W. and F.J. Harrell, Prediction models need appropriate internal, internal-external,

and external validation. J Clin Epidemiol, 2016. 69: p. 245-7.
[20]. Debray, T.P., et al., A new framework to enhance the interpretation of external validation studies of clinical prediction models. J Clin Epidemiol, 2015. 68(3): p. 279-89.
[21]. Vergouwe, Y., K.G. Moons and E.W. Steyerberg, External validity of risk models: Use of benchmark values to disentangle a case-mix effect from incorrect coefficients. Am J Epidemiol, 2010. 172(8): p. 971-80.
[22]. Xue Chen., et al., Effect of glycated hemoglobin A1c variability on diabetic kidney disease in type 2 diabetes mellitus patients. Chin J Diabetes Mellitus, 2020,12(12): 993-998.
[23]. Viazzi, F., et al., Long-term blood pressure variability and development of chronic kidney disease in type 2 diabetes. Journal of Hypertension, 2019. 37(4): p. 805-813.
[24]. Koye, D.N., et al., The Global Epidemiology of Diabetes and Kidney Disease. Adv Chronic Kidney Dis, 2018. 25(2): p. 121-132.
[25]. Zeitler, P., et al., A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med, 2012. 366(24): p. 2247-56.
[26]. Dart, A.B., et al., High burden of kidney disease in youth-onset type 2 diabetes. Diabetes Care, 2012. 35(6): p. 1265-71.
[27]. Lin, K., et al., Effects of depression, diabetes distress, diabetes self-efficacy, and diabetes self-management on glycemic control among Chinese population with type 2 diabetes mellitus. Diabetes Res Clin Pract, 2017. 131: p. 179-186.
[28]. Lee, L.Y., et al., Predictors for self-management in older adults with type 2 diabetic nephropathy. J Clin Nurs, 2020. 29(5-6): p. 922-931.
[29]. Moons, K.G., et al., Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med, 2015. 162(1): p. W1-73.
[30].Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, de Boer IH. Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 1988-2014. JAMA. 2016 Aug 9;316(6):602-10.
[31].Koye DN, Magliano DJ, Nelson RG, Pavkov ME. The Global Epidemiology of Diabetes and Kidney Disease. Adv Chronic Kidney Dis. 2018 Mar;25(2):121-132.
[32].Thomas B. The Global Burden of Diabetic Kidney Disease: Time Trends and Gender Gaps. Curr Diab Rep. 2019 Mar 2;19(4):18.
[33].Ong SE, Koh JJK, Toh SES, Chia KS, Balabanova D, McKee M, Perel P, Legido-Quigley H. Assessing the influence of health systems on Type 2 Diabetes Mellitus awareness, treatment, adherence, and control: A systematic review. PLoS One. 2018 Mar 29;13(3):e0195086.
[34].Sharma PK, Rajpal N, Upadhyay S, Shaha D, Deo N. Status of diabetes control and knowledge about diabetes in patients. Endocrinol Diabetes Nutr (Engl Ed). 2021 May 10:S2530-0164(21)00102-6.
[35].Tang J, Wu T, Hu X, Gao L. Self-care activities among patients with type 2 diabetes mellitus: A cross-sectional study. Int J Nurs Pract. 2021 Dec;27(6):e12987.
[36]. Adderley, N.J., et al., Temporal and external validation of a prediction model for adverse outcomes among inpatients with diabetes. Diabet Med, 2018. 35(6): p. 798-806.
[37]. Elfiky, A.A., et al., Development and Application of a Machine Learning Approach to Assess Short-term Mortality Risk Among Patients With Cancer Starting Chemotherapy. JAMA Netw Open, 2018. 1(3): p. e180926.
[38]. Sun, D., M. Wang and A. Li, A multimodal deep neural network for human breast cancer prognosis

prediction by integrating multi-dimensional data. IEEE/ACM Trans Comput Biol Bioinform, 2018.
[39]. Ljubic, B., et al., Predicting complications of diabetes mellitus using advanced machine learning algorithms. J Am Med Inform Assoc, 2020. 27(9): p. 1343-1351.
[40]. Yasar, H. and M. Ceylan, A novel comparative study for detection of Covid-19 on CT lung images using texture analysis, machine learning, and deep learning methods. Multimed Tools Appl, 2020: p. 1-25.
[41]. Guo, A., et al., Using electronic health records and claims data to identify high-risk patients likely to benefit from palliative care. Am J Manag Care, 2021. 27(1): p. e7-e15.

Table 1. Baseline clinical and biochemical characteristics of the study participants stratified by the occurrence and progression of DKD.

Characteristic	Occurrence of DKD				Progression of DKD			
	Total	No	Yes	P-value	Total	No	Yes	P-value
N.	2504	1687	817		4455	2892	1563	
Age (years)	55.44±7.49	55.22±7.66	55.92±7.10	0.059	57.88±8.80	56.56±8.61	60.33±8.57	<0.001
Male gender [n (%)]	991(54.8)	683(55.2)	308(53.8)	0.587	2274(51.0)	1504(52.0)	770(49.3)	0.043
BMI (kg/m^2)	26.10±4.00	25.93 ±3.86	26.44 ±3.86	0.029	26.30 ±4.14	26.24±4.07	26.43 ±4.27	0.143
Diabetes duration (years)	4(1,8)	3(1,7)	5(2,9)	<0.001	5(1,10)	4(1,8)	6(3,11)	<0.001
Education [n (%)]				0.0021				<0.001
Illiterate	182(7.3)	91(5.4)	91(11.1)		401(9.0)	205(7.1)	196(12.5)	
Literate	75(3.0)	33(2.0)	42(5.1)		132(3.0)	55(1.9)	77(4.9)	
Elementary school	678(27.1)	406(24.1)	272(33.3)		1253(28.1)	727(25.1)	526(33.7)	
Junior high school	375(15.0)	260(15.4)	115(14.1)		693(15.6)	462(16.0)	231(14.8)	
High school	738(29.5)	539(32.0)	199(24.4)		1228(27.6)	881(30.5)	347(22.2)	
College	400(16.0)	313(18.6)	87(10.6)		649(14.6)	487(16.8)	162(10.4)	
No data	56(2.2)	45(2.7)	11(1.3)		99(2.2)	75(2.6)	24(1.5)	
Marital status [n (%)]				<0.001				<0.001
Single	95(3.8)	66(3.9)	29(3.5)		181(4.1)	125(4.3)	56(3.6)	

Married	2109(84.2)	1457(86.4)	652(79.8)		3684(82.7)	2422(83.7)	1262(80.7)	
Divorced	93(3.7)	57(3.4)	36(4.4)		160(3.6)	105(3.6)	55(3.5)	
Widow or widower	171(6.8)	75(4.4)	96(11.8)		355(8.0)	181(6.3)	174(11.1)	
No data	36(1.4)	32(1.9)	4(0.5)		75(1.7)	59(2.0)	16(1.0)	
Smoking [n (%)]	769(30.7)	523(31.0)	246(30.1)	0.710	1362(30.6)	891(30.8)	471(30.1)	0.848
Drinking [n (%)]	637(25.4)	433(25.7)	204(25.0)	0.997	1124(25.2)	743(25.1)	381(24.4)	0.576
Diabetic self-management behavior								
Diet	5(4,7)	5(4,7)	5(4,7)	0.576	5(4,7)	5(4,7)	5(3,7)	0.008
Exercise	7(0,7)	7(1,7)	7(0,7)	0.821	7(1,7)	7(1,7)	6.5(0,7)	0.129
Medication	7(7,7)	7(7,7)	7(7,7)	0.229	7(7,7)	7(7,7)	7(7,7)	0.425
Monitoring	0(0,7)	0(0,7)	2(0,7)	0.408	0(0,7)	0(0,7)	1(0,7)	0.490
SBP (mmHg)	129(119,141)	128(117,139)	133(122,146)	<0.001	133(121,146)	131(120,144)	136(124,150)	<0.001
DBP (mmHg)	77(70,84)	76(69,83)	78(71,86)	<0.001	78(71,86)	77(70,85)	78(71,87)	<0.001
HbA1c (%)	7.90(6.85,9.75)	7.80(6.80,9.50)	8.40(7.10,10.10)	<0.001	8.2(7.0,10.0)	8.0(6.9,9.7)	8.5(7.1,10.5)	<0.001
TG (mg/dl)	113(83,164)	111(84,160)	120(82,168)	0.094	123(88,178)	119(86,172)	133(93,190)	<0.001
HDL-C (mg/dl)	52.00±13.51	52.44±13.98	50.73±12.38	0.038	50.75 ±13.24	51.31 ±13.41	49.71 ±12.85	<0.001
LDL-C (mg/dl)	99.41±28.56	99.09±28.55	100.10±28.60	0.401	101.23 ±29.90	101.05 ±29.87	101.55 ±29.96	0.818
eGFR (ml/min/1.73 m^2)	85.50(73.08,96.13)	87.18(74.00,96.80)	82.76(71.22,94.55)	0.002	82.01(67.88,94.93)	83.65(69.88,96.60)	77.00(65.87,91.35)	<0.001
UACR (mg/g)	8.64(4.50,13.86)	7.06(3.58,12.17)	10.95(7.14,16.32)	<0.001	17.82(7.97,50.12)	14.84(6.77,41.71)	22.72(11.05,75.23)	<0.001

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio. Data are expressed as mean ± SD, number (%) or median (interquartile range).

Table 2 The baseline risk score of low-high DKD risk cohort stratified by the progression of DKD.

Risk stage	Non- progression group	Progression group	P-value
Low-high DKD risk	16.80±6.21	19.77±5.77	<0.001
Low DKD risk	14.48±5.61	17.83±5.74	<0.001
Moderate DKD risk	19.46±5.52	21.40±4.87	<0.001
High DKD risk	21.68±5.22	22.93±5.15	0.005

Figure 1 Flow chart of patient selection. DKD, diabetes kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; AER, albumin excretion rate.

Figure 2 In the DKD prediction cohort, the final DKD, non-DKD patients' ratio stratified by DKD risk categories.

Figure 3 Observed and predicted the occurrence of DKD. Grouping method: First, calculate the predicted probability of DKD for each patient according to the DKD risk scoring model, then arrange them from small to large according to the predicted probability and divide them into 10 groups based on deciles for the predicted probabilities.

Figure 4 In the DKD progression cohort, the final progression, non-progression patients' ratio stratified by DKD stage.

Figure 5 Observed and predicted the Progression of DKD. Grouping method: First, calculate the predicted probability of DKD for each patient according to the DKD risk scoring model, then arrange them from small to large according to the predicted probability and divide them into 10 groups based on deciles for the predicted probabilities.

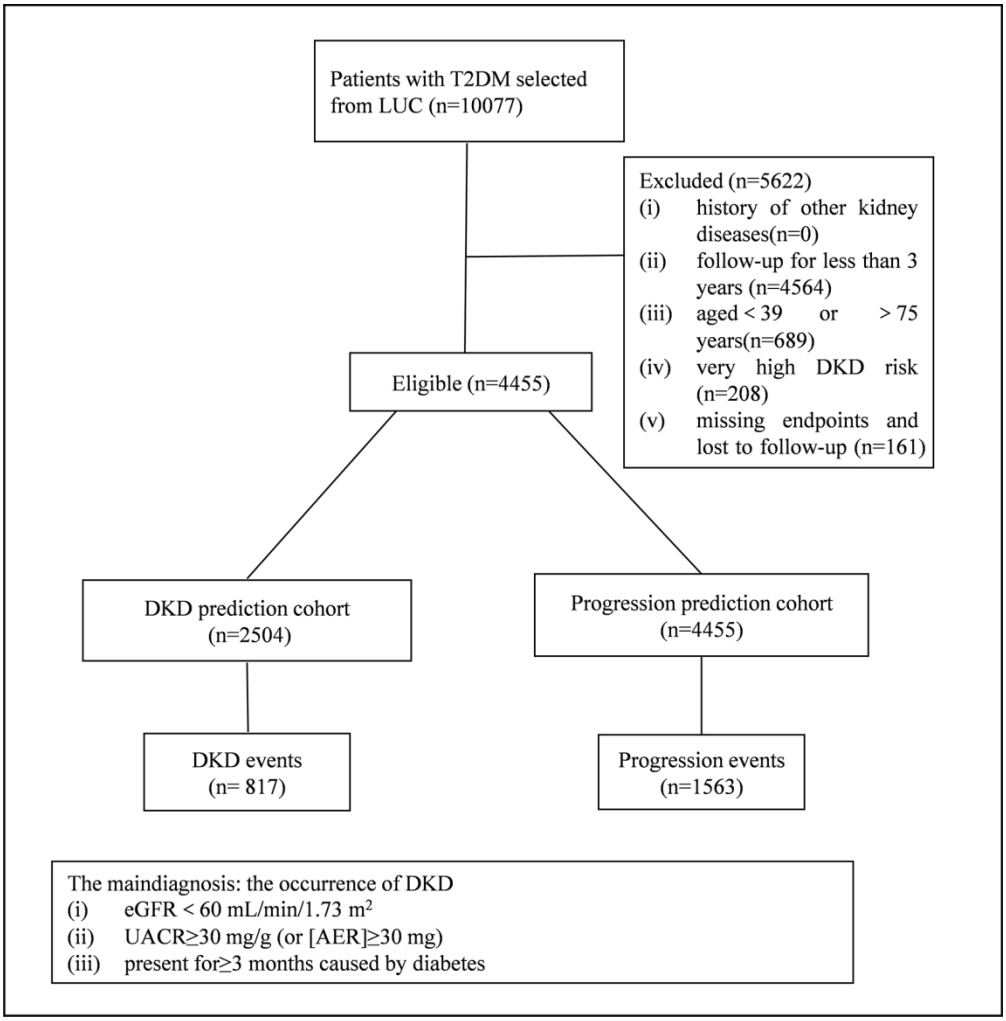

Figure 1 Flow chart of patient selection. DKD, diabetes kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; AER, albumin excretion rate.

150x151mm (300 x 300 DPI)

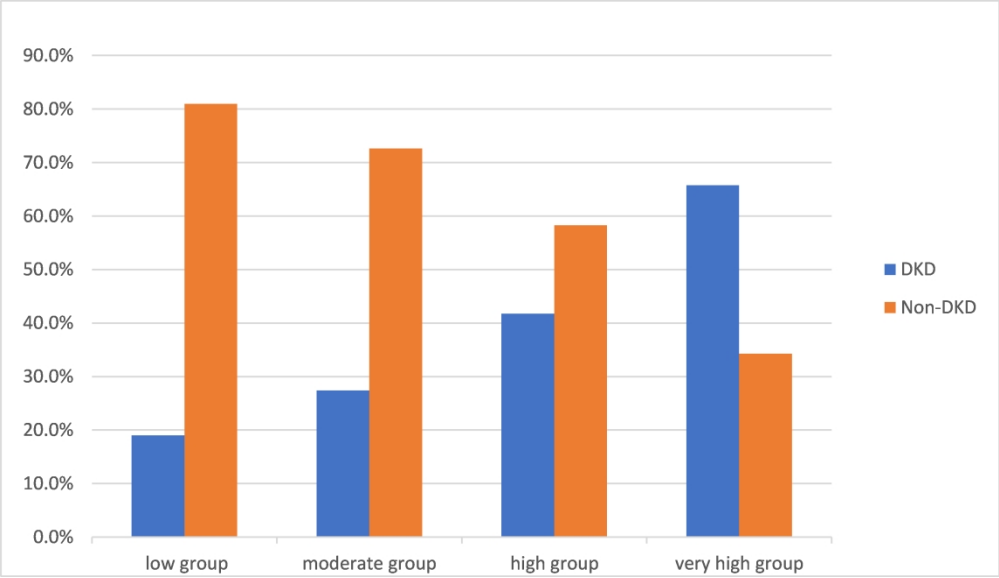

Figure 2 In the DKD prediction cohort, the final DKD, non-DKD patients' ratio stratified by DKD risk categories.

313x180mm (300 x 300 DPI)

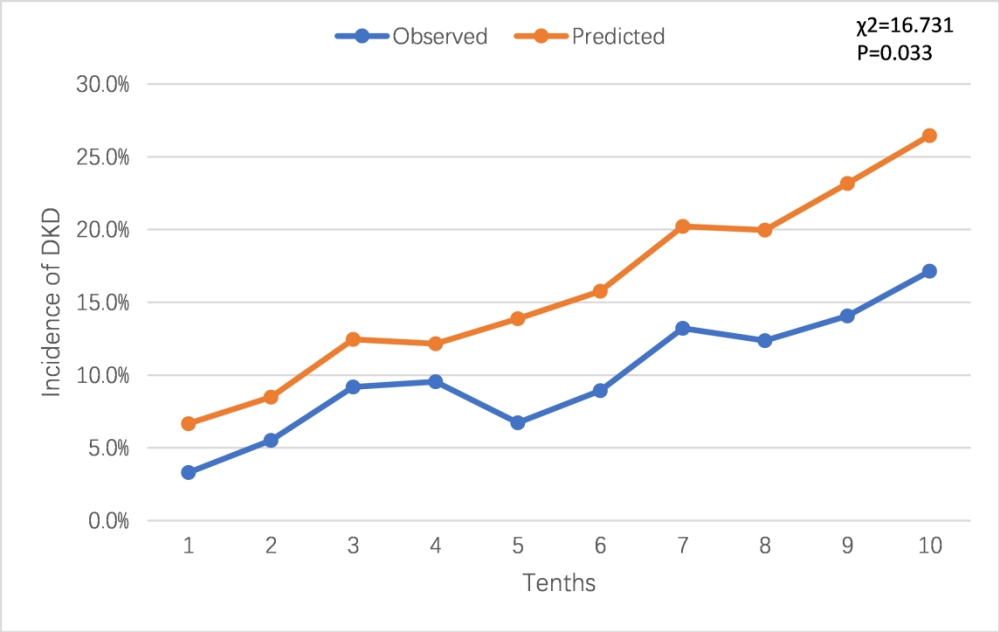

Figure 3 Observed and predicted the occurrence of DKD. Grouping method: First, calculate the predicted probability of DKD for each patient according to the DKD risk scoring model, then arrange them from small to large according to the predicted probability and divide them into 10 groups based on deciles for the predicted probabilities.

274x173mm (300 x 300 DPI)

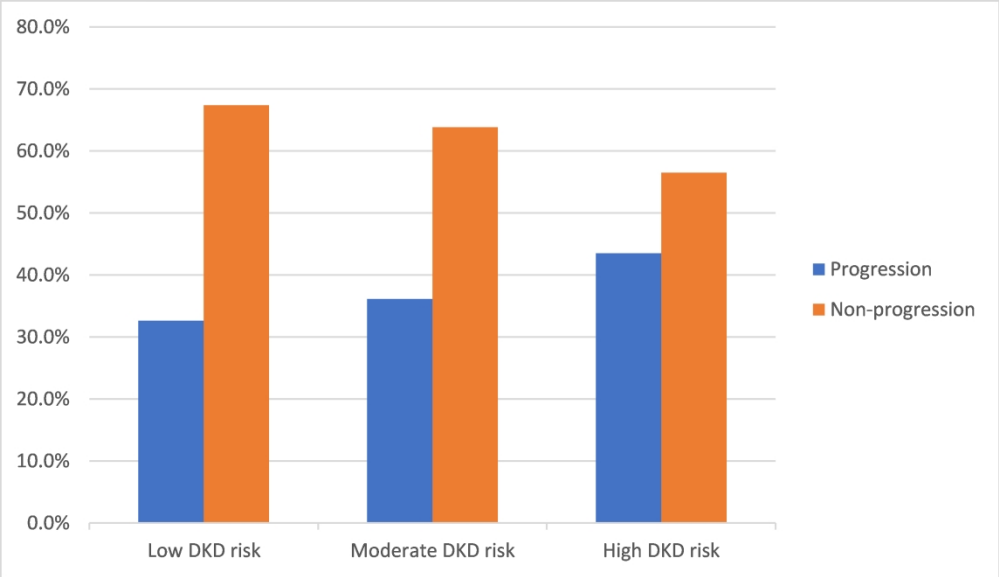

Figure 4 In the DKD progression cohort, the final progression, non-progression patients' ratio stratified by DKD stage.

296x171mm (300 x 300 DPI)

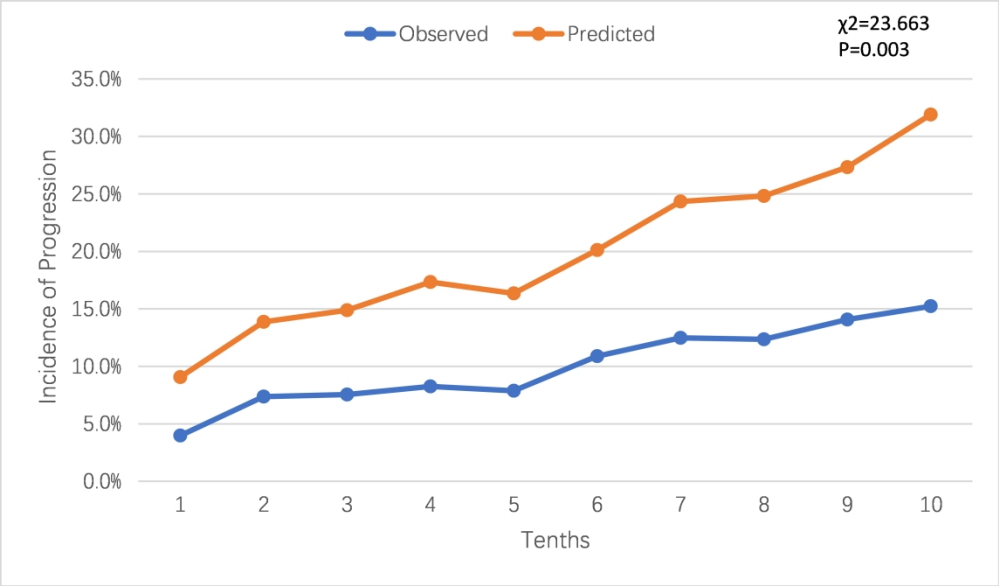

Figure 5 Observed and predicted the Progression of DKD. Grouping method: First, calculate the predicted probability of DKD for each patient according to the DKD risk scoring model, then arrange them from small to large according to the predicted probability and divide them into 10 groups based on deciles for the predicted probabilities.

291x170mm (300 x 300 DPI)

Supplementary Appendix

Risk factors for DKD	RR (95%CI)	β -coefficient	Scores
Age (by 5-10 years)	1.38 (1.20-1.59)	0.32	3.0
BMI (by 5 kg/m^2)	1.16 (1.09-1.23)	0.15	1.5
Smoking(yes/no)	1.49 (1.30-1.71)	0.40	4.0
Diabetic retinopathy(yes/no)	1.31 (1.00-1 .73)	0.27	3.0
HbA1c (by 1%[11mmol/mol])	1.17 (1.09-1.26)	0.15	1.5
SBP (by 10-20mmHg)	1.21 (1.15-1.27)	0.19	2.0
HDL-C (by 1mmol/L)	0.78 (0.61-0.99)	-0.25	-2.5
TG (by 1 mmol/L)	1.42 (1.16-1.74)	0.37	4.0
UACR (by 1 mg/g)	1.13 (1.10-1.17)	0.12	1.0

Reporting checklist for prediction model development/validation.

Based on the TRIPOD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the TRIPODreporting guidelines, and cite them as:

Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement.

		Reporting Item	Page Number
Title			
	#1	Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract			
	#2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1-2
Introduction			
	#3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to	3-4

		existing models.	
	#3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods			
Source of data	#4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4-5
Source of data	#4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4-5
Participants	#5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
Participants	#5b	Describe eligibility criteria for participants.	5
Participants	#5c	Give details of treatments received, if relevant	n/a
Outcome	#6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5-6
Outcome	#6b	Report any actions to blind assessment of the outcome to be predicted.	5-6
Predictors	#7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured	6-7
Predictors	#7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	5-6
Sample size	#8	Explain how the study size was arrived at.	7-8
Missing data	#9	Describe how missing data were handled	8

		(e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	
Statistical analysis methods	#10a	If you are developing a prediction model describe how predictors were handled in the analyses.	n/a
Statistical analysis methods	#10b	If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	n/a
Statistical analysis methods	#10c	If you are validating a prediction model, describe how the predictions were calculated.	8-9
Statistical analysis methods	#10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8
Statistical analysis methods	#10e	If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done	n/a
Risk groups	#11	Provide details on how risk groups were created, if done.	7
Development vs. validation	#12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	n/a The population in the development cohort was meta-analyzed and cannot be compared
Results			
Participants	#13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	9
Participants	#13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of	9

		participants with missing data for predictors and outcome.	
Participants	#13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	n/a The population in the development cohort was meta-analyzed and cannot be compared
Model development	#14a	If developing a model, specify the number of participants and outcome events in each analysis.	7-8
Model development	#14b	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	n/a
Model specification	#15a	If developing a model, present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	n/a
Model specification	#15b	If developing a prediction model, explain how to the use it.	n/a
Model performance	#16	Report performance measures (with CIs) for the prediction model.	9-12
Model-updating	#17	If validating a model, report the results from any model updating, if done (i.e., model specification, model performance).	9-12
Discussion			
Limitations	#18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	15-16
Interpretation	#19a	For validation, discuss the results with reference to performance in the development data, and any other validation data	13-15
Interpretation	#19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	13-15

Implications	#20	Discuss the potential clinical use of the model and implications for future research	17
Other information			
Supplementary information	#21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	18
Funding	#22	Give the source of funding and the role of the funders for the present study.	18