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

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4 **External Validation of the DKD Risk Score, a Risk Scoring Model for**  
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6 **Early Diabetic Kidney Disease**  
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43  
44 **Abstract**

45  
46 **Objectives** This study aims to independently and externally validate the Risk  
47 Prediction Model for Diabetic Kidney Disease (RPM-DKD) in patients with type 2  
48 diabetes mellitus (T2DM).  
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50  
51 **Design** This is a retrospective cohort study.  
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54 **Setting** Outpatient clinics at Lee's United Clinics, Taiwan, China.  
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57 **Participants** A total of 2504 patients (average age 55.44 years, SD, 7.49 years), and  
58 4455 patients (average age 57.88 years, SD, 8.80 years) were included for analysis in  
59 the DKD prediction and progression prediction cohorts, respectively.  
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4 **Exposure** The predicted risk for DKD and DKD progression for each patient were all  
5 calculated using the RPM-DKD.  
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7 **Primary and secondary outcome measures** The primary outcome measure was  
8 overall incidence of DKD. Secondary outcomes included DKD progression. The  
9 discrimination, calibration and and precision of the RPM-DKD score were assessed.  
10

11 **Results** The DKD prediction cohort and progression prediction cohort consisted of  
12 2504 and 4455 T2DM patients, respectively. The RPM-DKD examined in this study  
13 showed moderately discriminative ability with AUCs ranged from 0.636 to 0.681 for  
14 the occurrence of DKD and 0.620 to 0.654 for the progression of DKD. The Hosmer-  
15 Lemeshow  $\chi^2$  test indicted the RPM-DKD was not well calibrated for predicting the  
16 occurrence of DKD and over-estimated the progression of DKD. The precision for  
17 predicting the occurrence and progression of DKD were 43.2% and 42.2%, respectively.  
18

19 **Conclusions** On external validation, the RPM-DKD cannot accurately predict the risk  
20 of DKD occurrence and progression in patients with T2DM.  
21

22 **Keywords** External validation; diabetic kidney disease; prediction; risk assessment  
23

### 24 **Strengths and limitations of this study**

- 25 ● Our validation cohort was geographically different from the cohort used to derive  
26 the model and our team was not involved in model derivation, which enabled us to  
27 conduct a true independent external validation study.  
28
- 29 ● Our cohort had an average follow-up time of more than 5 years, a duration that  
30 positioned us to effectively identify the occurrence of outcome variables.  
31
- 32 ● Whilst the cohort was representative of a large cohort of over 4,000 adults, it was  
33 geographically restricted to Taiwan.  
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- 35 ● Most patients in our cohort had better diabetes self-management behaviors, which  
36 could potentially have affected the study results and also explain why the model  
37 overestimated risk of occurrence and progression.  
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- 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].

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4 The ability to accurately predict risk of DKD would allow for earlier recognition,  
5  
6 and perhaps intervention, in patients with long-standing T2DM. Recently, a risk  
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8 prediction model for early DKD (RPM-DKD) was developed based on systematic  
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10 review and meta-analysis of individual participant data from 20 cohorts of  
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12 predominately white populations [15]. However, validation was limited in scope with  
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14 a relatively small study size (n=380) and insufficient median follow-up time (t=2.9  
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16 years). The purpose of the current study was to independently and externally validate  
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18 performance of the RPM-DKD in predicting the risk of incidence of DKD in patients  
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20 with T2DM. In addition, although PRM-DKD was only used to predict the occurrence  
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22 of DKD, we believe that it can predict the progress of DKD to a certain extent, with  
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24 reason that the influencing factors of DKD progression and occurrence are similar.  
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26 Therefore, the secondary purpose of this study is to evaluate the performance of this  
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28 model in predicting the risk of DKD progression in patients with T2DM.  
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## 37 **2.Methods**

### 38 **2.1 Data sources and participants**

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41 We used outpatient data from December 2006 to October 2019 from Lee's United  
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43 Clinics (LUC) in Taiwan. LUC is a large ambulatory system, comprised of six clinics  
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45 providing multidisciplinary care for patients with diabetes. The Taiwan Health  
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47 Insurance Plan supports 4 annual follow up visits along with access to medications,  
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49 diabetes supplies, diabetes self-management education (DSME) clinician visitation and  
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51 primary/secondary prevention screening to patients living with diabetes. This setting  
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53 provided an opportune source of robust, longitudinal data in which to validate the RPM-  
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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) $\geq$ 60mL/min/1.73 m<sup>2</sup> 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<sup>2</sup> and/or (2) UACR $\geq$ 30 mg/g (or AER $\geq$ 30 mg) (3) present for $\geq$ 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.



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4 The stage of DKD was classified using a combination of eGFR and ACR into four  
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6 stage categories[18], i.e., (i) Low DKD risk, eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> and  
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8 ACR < 30 mg/g; (ii) Moderate CKD risk, eGFR between 45 and 59 mL/min/1.73 m<sup>2</sup> and  
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10 ACR < 30 mg/g, or eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> and ACR between 30 and 300 mg/g; (iii)  
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12 High DKD risk, eGFR between 30 and 44 mL/min/1.73 m<sup>2</sup> and ACR < 30 mg/g, or  
13  
14 eGFR between 45 and 59 mL/min/1.73 m<sup>2</sup> and ACR between 30 and 300 mg/g, or  
15  
16 eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> and ACR > 300 mg/g; (iv) Very high DKD risk,  
17  
18 eGFR  $\leq 29$  mL/min/1.73 m<sup>2</sup> and ACR < 30 mg/g, or eGFR  $\leq 44$  mL/min/1.73 m<sup>2</sup> and ACR  
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20 between 30 and 300 mg/g, or eGFR  $\leq 59$  mL/min/1.73 m<sup>2</sup> and ACR > 300 mg/g.  
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### 27 2.3 Risk score calculations

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30 The risk score model was established by Jiang, W. et al [15], and all risk factors  
31  
32 included in the DKD risk score model were derived from a systematic review and meta-  
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34 analysis of 14 prospective and 6 retrospective cohorts. The predicted risk score for each  
35  
36 study participant was calculated using their baseline data. The baseline variables used  
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38 for the risk scores were in accordance with the model: (i) age (years) divided into three  
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40 categories, 39-49 scores 0, 50-59 scores 3.0, and 60-75 scores 6.0; (ii) body mass index  
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42 (BMI), which was calculated as the patient's weight divided by the square of their  
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44 height (kg/m<sup>2</sup>), divided into three categories (<25.00 scores 0, 25.00-29.99 scores 1.5,  
45  
46 and  $\geq 30.00$  scores 3.0); (iii) smoker (defined as having smoked more than 100 cigarettes  
47  
48 in their lifetime), non-smoker scores 0 and smoker scores 4.0; (iv) diabetic retinopathy  
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50 (DR), 0 if no and 3.0 if yes; (v) hemoglobin A1c (HbA1c) divided into four categories,  
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52 <7.0% (<53 mmol/mol) scores 0, 7.0-7.9% (53-63 mmol/mol) scores 1.5, 8.0-8.9%  
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(64–74 mmol/mol) scores 3.0 and  $\geq 9.0\%$  ( $\geq 75$  mmol/mol) scores 4.5; (vi) systolic blood pressure (SBP) divided into four categories,  $<130$  mmHg scores 0, 130–139 mmHg scores 2.0, 140–149 mmHg scores 4.0,  $\geq 150$  mmHg scores 6.0; (vii) serum high-density lipoprotein-cholesterol (HDL-C) divided into two categories,  $\geq 1.30$  mmol/L scores 0, and  $<1.30$  mmol/L scores 2.5; (viii) triglycerides (TG) divided into two categories,  $<1.70$  mmol/L scores 0 and  $\geq 1.70$  mmol/L scores 4.0; and (ix) UACR divided into three categories,  $<10$  mg/g scores 0, 10.00–19.99 mg/g scores 2.0, 20.00–29.99 mg/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 10 mg/g, the score increases by 2 points. For example, UACR between 30.00 and 39.99 mg/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  $\pm$  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

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4 groups were performed by Kruskal-Wallis H test. Categorical variables were  
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6 represented as number of cases (N), and the intergroup rate (%) was compared with chi-  
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8 square test.  
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11 The clinical performance of the DKD risk prediction model was assessed by means  
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13 of discrimination and calibration. Model discrimination describes a model's  
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15 performance in distinguishing between individuals who experience an event and those  
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17 who do not[7]. Model discrimination was assessed by plotting a receiver operating  
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19 characteristic (ROC) curve and calculating the area under the curve (AUC). An AUC-  
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21 statistic value  $>0.75$  was regarded to represent good discrimination. Calibration  
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23 assessment of a risk prediction model describes how well predictions match observed  
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25 outcomes [7]. The calibration of the risk score predictions was assessed by plotting  
26  
27 observed versus predicted number of patients and by calculating the Hosmer-  
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29 Lemeshow  $\chi^2$  statistic. Groups for observed DKD events were based on deciles for the  
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31 predicted probabilities. Performance was evaluated as sensitivity, specificity, and  
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33 precision.  
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43 All results were presented with 95% confidence interval (CI). Any two-tailed p-  
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45 values  $<0.05$  were considered statistically significant. All statistical analyses were  
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47 performed using SPSS software, version 22 (IBM Corp.).  
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## 50 **2.5 Patient and public involvement**

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53 There was no patient or public involvement in the design and conduct of the study.  
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## 56 **3. Results**

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4 In the DKD prediction cohort, a total of 2504 patients (average age 55.44 years,  
5 SD, 7.49 years), and 4455 patients (average age 57.88 years, SD, 8.80 years) were  
6 included for analysis in the DKD progression prediction cohort (Figure 1). The average  
7 length of follow-up was 7.37 years (SD, 3.22 years) in the DKD prediction cohort and  
8 a total of 817 (32.6%) people had DKD during the follow-up period. The mean follow-  
9 up time in the progression prediction cohort was 7.72 years (SD, 3.10 years), and the  
10 overall progression of events in this cohort was 1563 (35.1%).  
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### 22 **3.1 DKD prediction cohort**

#### 23 **3.1.1 Baseline characteristics**

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27 The DKD prediction cohort had an average BMI of  $26.1 \pm 4.0$  kg/m<sup>2</sup> and 54.8%  
28 were men. The proportion of smokers and drinkers were 30.7% and 25.4%, respectively.  
29  
30 There were significant differences in the level of education ( $P=0.0021$ ) and marital  
31 status ( $P<0.001$ ) between patients who eventually developed DKD and those who did  
32 not. The patients who did not develop of DKD had higher rates of secondary and  
33 college-level education and lower rates of spousal loss than the patients with DKD.  
34  
35 Furthermore, patients who eventually developed DKD had a longer diabetes duration  
36 (median 5 years [2-9 years]) and a higher level of HbA1c (median 8.4% [7.10-10.10%])  
37 than those who did not. All patients showed normal albuminuria and renal function at  
38 baseline with median UACR of 8.64 mg/g (4.50–13.86mg/g) and median eGFR of  
39 85.50 ml/min/1.73 m<sup>2</sup> (73.08–96.13 ml/min/1.73 m<sup>2</sup>). The median systolic blood  
40 pressure (SBP) and diastolic blood pressure (DBP) were 129mmHg (119-141mmHg)  
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4 and 77 mmHg (70-84 mmHg), respectively. Baseline characteristics of the DKD  
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6 prediction cohort are displayed in Table 1.  
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### 9 **3.1.2 External validation results for DKD prediction cohort**

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11 Of the 2504 patients, 678 (27.1%), 639 (25.5%), 1114 (44.5%) and 73 (2.9%) had  
12  
13 risk categories of relatively low, moderate, high and very high at baseline. At the end  
14  
15 of observation, 129 (19.0%), 175 (27.4%), 465 (41.7%), 48 (65.8%) patients in the  
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17 relatively low, moderate, high and very high groups developed DKD, respectively  
18  
19 (Figure 2).  
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25 **Discrimination of the model** : According to our external validation, 16 was  
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27 selected as the optimal cut-off risk score value, at which the sum of sensitivity and  
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29 specificity was maximal (Youden's index), which corresponded with Jiang, W. et al  
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31 [14]. With a risk cut-off value of 16 points, the sensitivity would be 53.0% (95% CI  
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33 48.9–57.0), specificity would be 65.7% (95% CI 63.0–68.3). ROC curve of our external  
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35 validation showed the area under the DKD risk score curve was 0.659 (95% CI 0.636-  
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37 0.681).  
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43 **Calibration of the model** : The risk scoring model was not well calibrated for  
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45 predicting the occurrence of DKD, with a Hosmer-Lemeshow  $\chi^2$  statistic of 16.731  
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47 ( $p=0.033$ ). The calibration plot in figure 3 shows that the comparison between observed  
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49 and predicted the occurrence of DKD, indicating the over-estimation of risk occurred in  
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51 tenths 1 through 10.  
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56 **Precision of the model in predicting DKD** : The prediction precision refers to  
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58 the ratio of the actual number of patients with DKD to the number of patients predicted  
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4 to develop DKD. According to our data, patients in the DKD prediction cohort were  
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6 classified as high risk if their DKD risk score  $\geq 16$  points, with precision of 43.2%  
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9 (513/1187).

## 11 **3.2 Progression prediction cohort**

### 13 **3.2.1 Baseline characteristics**

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17 The baseline clinical and biochemical characteristics of the DKD progression  
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19 cohort stratified by the progression of DKD are listed in Table 1. Of the cohort, the  
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21 average BMI was  $26.30 \pm 4.14$  kg/m<sup>2</sup> and 51.0% were men. The proportion of smokers  
22  
23 and drinkers were 30.6% and 25.3%, respectively. In addition, the progression group  
24  
25 had lower education and married level, and longer duration of diabetes than the patients  
26  
27 in non-progression group. And patients in progression group had higher systolic blood  
28  
29 pressure (SBP), HbA1c and UACR than the patients in non-progression group, and  
30  
31 higher levels of diastolic blood pressure (DBP), total cholesterol than the patients in  
32  
33 non-progression group. On DKD risk score analyses, the progression group had higher  
34  
35 baseline risk score compared with non-progression group whatever patients with low  
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37 DKD risk, moderate DKD risk or high DKD risk (Table 2).  
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### 45 **3.2.2 External validation results for progression prediction cohort**

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48 Of the 4455 patients, 2504(56.2%), 1397 (31.4%) and 554 (12.4%) were in low,  
49  
50 moderate and high DKD risk at baseline. At the end of observation, 589 (32.6%), 531  
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52 (36.1%) and 414 (43.5%) patients in the low, moderate and high DKD risk had  
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54 progressed, respectively (Figure 4).  
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4       **Discrimination of the model:** ROC curve showed moderate discriminative ability  
5  
6 of predicting the progression of DKD in progression prediction cohort, and the area  
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8 under the receiver operating characteristic curve was 0.637 (95% CI 0.620-0.654). 18  
9  
10 was selected as the optimal cut-off risk score value with a sensitivity of 65.0% (95%  
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12 CI 62.6-67.3) and a specificity of 57.0% (95% CI 55.2-58.8)  
13  
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16       **Calibration of the model:** Calibration of the model for predicting the progression  
17  
18 of DKD was no good in our external validation cohort (Hosmer-Lemeshow  $\chi^2 = 23.663$ ,  
19  
20  $P=0.003$ ), and the over-estimation of risk occurred in tenths 1 through 10. The  
21  
22 calibration plot in figure 5 shows that the comparison between observed and predicted  
23  
24 the progression of DKD.  
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30       **Precision of the model in predicting DKD progression:** The prediction accuracy  
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32 refers to the ratio of the actual number of patients whose DKD stage progressed to the  
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34 number of patients predicted to progressed. According to our validation cohort, with a  
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36 risk cut-off value of 18 points, the precision would be 45.0% (1016/2260). According  
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38 to the model developed study [15], with a risk cut-off value of 16 points, the precision  
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40 would be 42.2% (1173/2781).  
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#### 45 46 **4. Discussion**

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48       External validation is a mandatory step in applying a prediction model to  
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50 meaningful clinical care; the process addresses the transportability of the model [21].  
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52 In this study, we evaluated the usefulness of RPM-DKD for predicting the DKD  
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54 incidence and progression of DKD in patients with T2DM by assessing its  
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56 discrimination, calibration and precision. The performance of the RPM-DKD  
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4 predictive potential in our validation cohort was not ideal, even when the results from  
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6 the validation evaluated by the model developers were promising.  
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9 The RPM-DKD has several advantages, including easy point-of-care application,  
10  
11 simple calculation and reliance on very few variables. Nevertheless, the RPM-DKD  
12  
13 demonstrated moderately discriminatory ability in our cohort. With that said, the  
14  
15 RPM-DKD was not well-calibrated for predicting the occurrence of DKD, and it over-  
16  
17 estimated the progression of disease. When using the same foundational thresholds  
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19 established by the original RPM-DKD study, precision for predicting DKD occurrence  
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21 and progression in our validation cohort was low, with values of 43.2% and 42.2%,  
22  
23 respectively. Utilizing the developers' suggested thresholds resulted in inappropriate  
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25 prediction of DKD in our cohort. Even at a threshold of 18 (at which the Youden's  
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27 index was maximal in our study), the precision of the model in predicting DKD  
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29 progression was also low.  
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38 Overall transportability of the model was poor in our analysis., owing perhaps to  
39  
40 the phenomenon of over-fitting. If internal validation such as bootstrap would have  
41  
42 been performed after model developed, the phenomenon might have been foreseen [22].  
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44 Furthermore, the poor external validation performance may also be closely related to  
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46 the fact that our validation cohort was vary from the model developers' cohort in terms  
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48 of settings, populations and periods [23, 24].  
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53 The RPM-DKD uses cross-sectional baseline data to predict a patient's risk of  
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55 DKD 5 to 10 years later; it is therefore based on the assumption that there is no  
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57 significant change in relevant indicators of the patient in subsequent years – a somewhat  
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4 unrealistic expectation in a real world application. Since the occurrence and  
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6 development of DKD is a relatively long process, metabolic indicators 5-, 10-years  
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8 even in preceding decades can impact subsequent outcomes. However, the model,  
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10 established by logistic regression, volatility of various parameters in the next few years  
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12 was not considered, which results in the prediction performance was not high.  
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17 In our study, not all data specific to risk factors included in the RPM-DKD model  
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19 were available (age, BMI, HbA1c, lipids, etc.); this may have contributed to poor model  
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21 performance. In previous work, we found that HbA1c variability is an independent risk  
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23 factor for nephropathy in patients with T2DM [25]. In addition, Viazzi et al.  
24  
25 demonstrated that the variability of SBP and pulse pressure are also key influencing  
26  
27 factors for the occurrence and development of DKD [26]. Thus, these parameters  
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29 should be strong outcome predictors for developing DKD; and yet, the RPM-DKD does  
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31 not take them into account.  
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38 The RPM-DKD model cannot predict future risk of DKD in patients with T2DM  
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40 aged <39 years despite early age of diagnosis being an established risk factor for  
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42 developing DKD [27]. Several groups reported an increasing incidence of youth-onset  
43  
44 DKD [28-31]. Given the earlier onset of DKD among T2DM patients, we believe that  
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46 having validated risk assessment models that include young adults may be of greater  
47  
48 clinical use.  
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#### 52 53 *Strengths and limitations of this study*

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56 Our study has several strengths. First, our validation cohort was geographically  
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58 different from the cohort used to derive the model; further, our team was not involved  
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4 in model derivation, which enabled us to conduct a true independent external validation  
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6 study. Additionally, our cohort had an average follow-up time of more than 5 years, a  
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8 duration that positioned us to effectively identify the occurrence of outcome variables.  
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12 Several limitations existed in this study. First, whilst the cohort was representative  
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14 of a large cohort of over 4,000 adults, it was geographically restricted to Taiwan.  
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16 Second, most patients in our cohort had better diabetes self-management behaviors,  
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18 which could potentially have affected the study results and also explain why the model  
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20 overestimated risk of occurrence and progression. However, diabetes self-management  
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22 is a key factor for promoting better health outcomes among patients with DKD [32, 33];  
23  
24 longitudinally, increased awareness for the DKD burden in diabetes patients might have  
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26 contributed to additional self-management behaviors with a positive effect on DKD  
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28 incidence and progression. In addition, the retrospective nature of our study presents an  
29  
30 inherent limitation, although it is a simple, flexible, and low-cost method to review  
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32 patient data for purposes of the present analysis [34]; additionally, we may not have  
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34 successfully captured patient data related to care that may have occurred outside of our  
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36 health system.  
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#### 45 *Future research*

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48 The occurrence of DKD in our study was high (31.6%) aligning with rates reported  
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50 in previous work (20% to 40%) [3]. Therefore, it is extremely significant to have an  
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52 accurate prediction model that could assist clinicians in real-time evaluation of patient  
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54 risk and implement primary and secondary preventive measures to delay progression  
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56 of disease. However, the RPM-DKD established by logistic regression did not perform  
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4 well. Furthermore, prediction models can become obsolete with change in population  
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6 demography, better therapeutic options and care pathways, and improvement in data  
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8 recording [33]. In the future, it may be possible to build a DKD prediction model by  
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10 deep learning methods in order to improve the prediction of DKD occurrence and  
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12 progression; many studies have applied deep learning with proven success [36-40].  
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## 16 17 **5. Conclusion**

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19 Our independent external validation study revealed that, in patients with T2DM,  
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21 the RPM-DKD cannot accurately predict the risk of DKD occurrence and progression.  
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23 The ability to accurately estimate DKD risk is critical in advancing patient care and  
24  
25 preventing or delaying complication risk in patients with long-standing T2DM. Newer  
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27 prediction models leveraging deep learning methods may prove useful for predicting  
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29 risk of developing or progressing DKD.  
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36

37  
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40  
41 **Author Contributions.** Q.L. conceived and designed the study. Z.S., K.W., X.Y. and Y.J.L.  
42  
43 collected the epidemiological and clinical data. Z.S., K.W. and X.Y. drafted the manuscript. Z.S.,  
44  
45 K.W., X.Y., and Q.L. contributed to acquisition, analysis, and interpretation of data. Q.L. and J.D.M.  
46  
47 contributed to critical revision of the manuscript for important intellectual content. All authors read,  
48  
49 revised, and approved the final draft. Q.L. is the guarantor of this work and, as such, had full access  
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51 to all the data in the study and takes responsibility for the integrity of the data and the accuracy of  
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53 the data analysis.  
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**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.

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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	2292	1563	
Age (years)	55.44±7.49	55.22±7.66	55.92±7.10	0.059	57.88±8.80	56.55±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 <sup>2</sup> )	26.10±4.00	25.93 ±3.86	26.44 ±3.86	0.029	26.30 ±4.14	26.23 ±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)	207(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)	122(4.3)	56(3.6)	

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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)	103(3.6)	55(3.5)	
Widow or widower	171(6.8)	75(4.4)	96(11.8)		355(8.0)	187(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(0,7)	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	101.00±29.87	101.55 ±29.96	0.818
eGFR (ml/min/1.73 m <sup>2</sup> )	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(6.7,41.71)	22.72(11.05,75.23)	<0.001

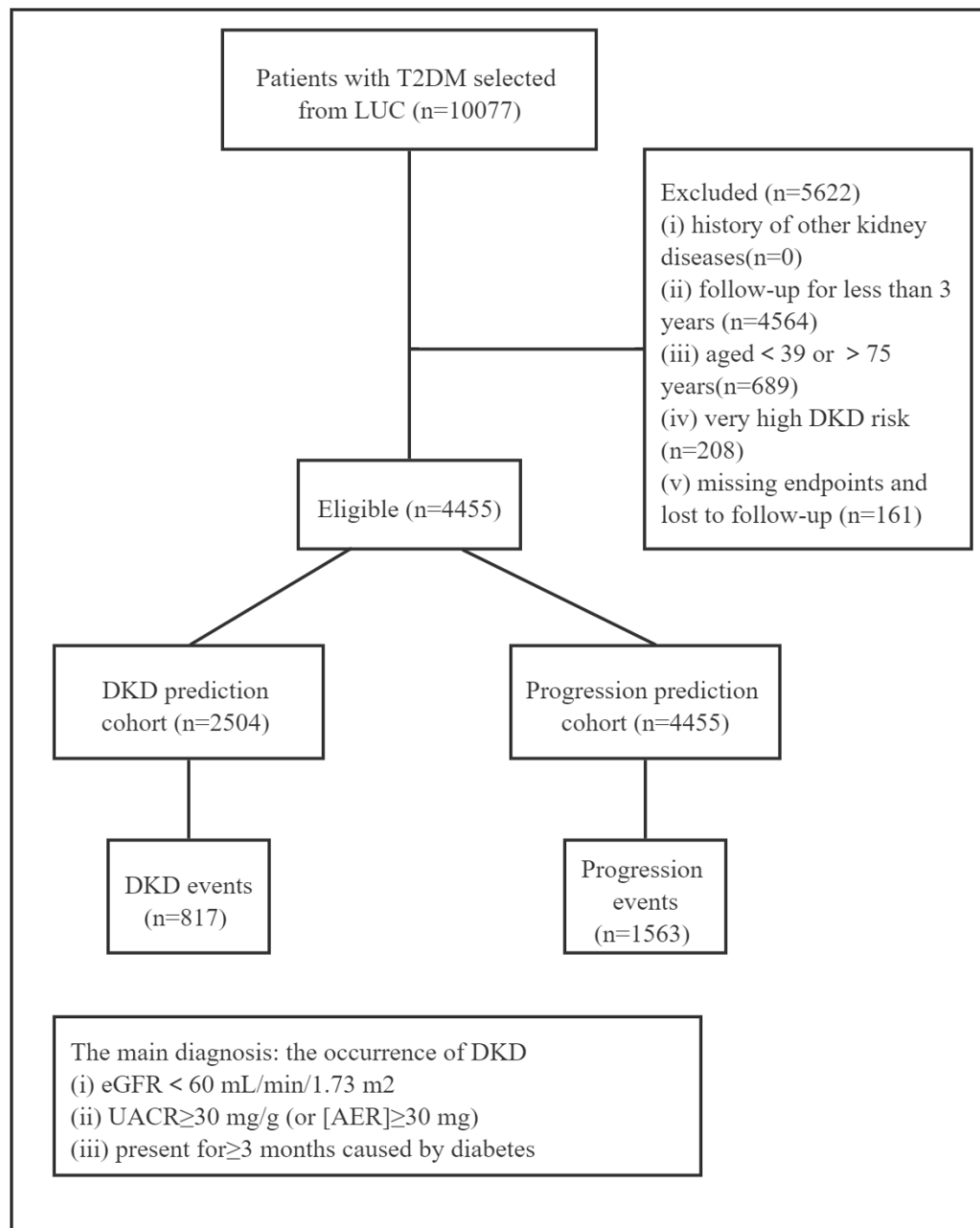


Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine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

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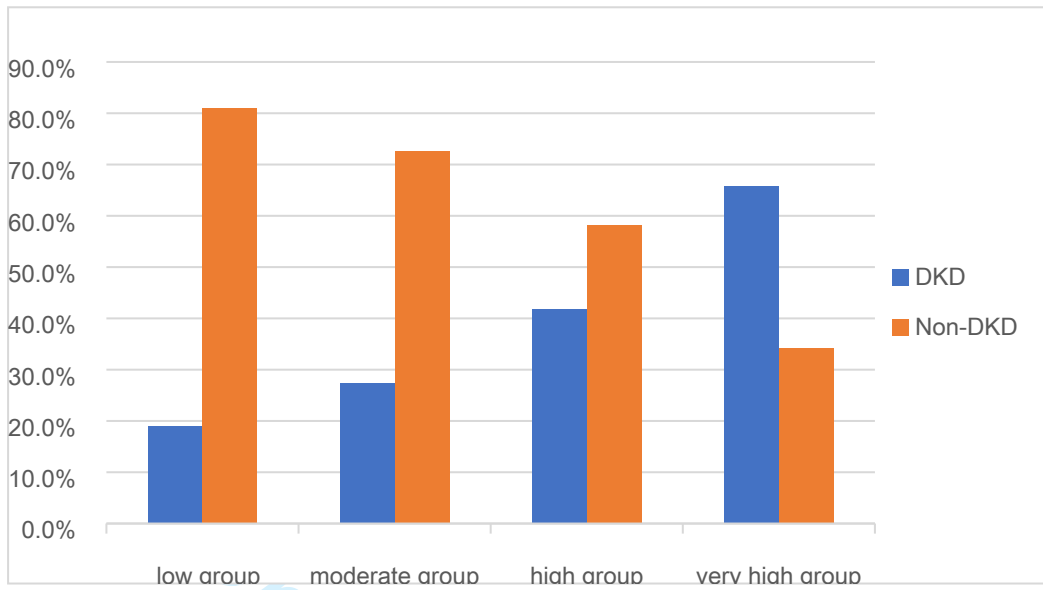
**Table 2 The baseline risk score of low-high DKD risk cohort stratified by the progression of DKD.**

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

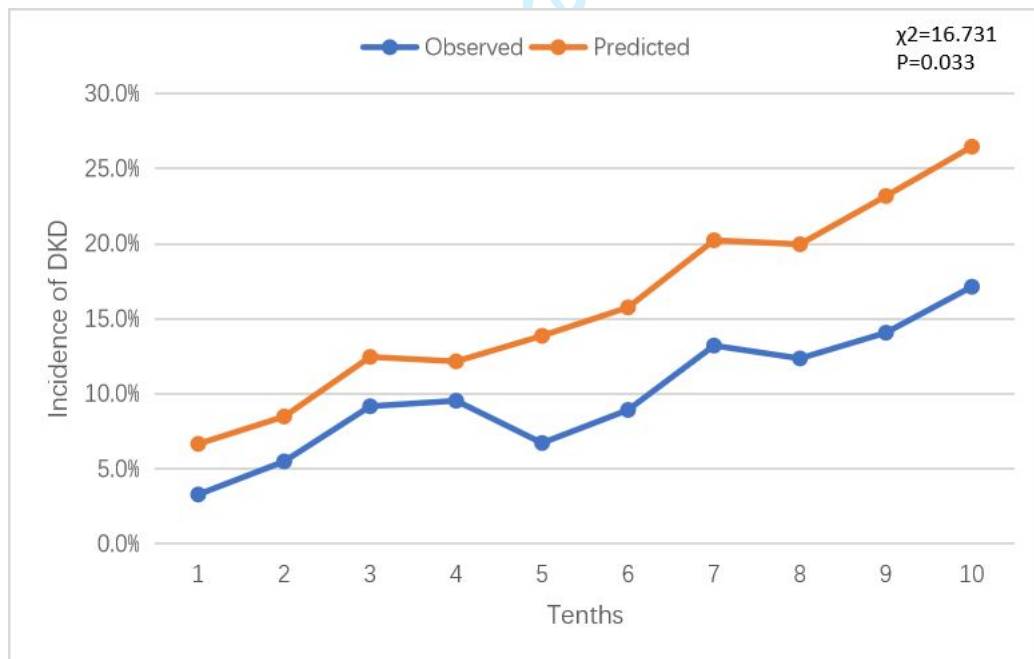


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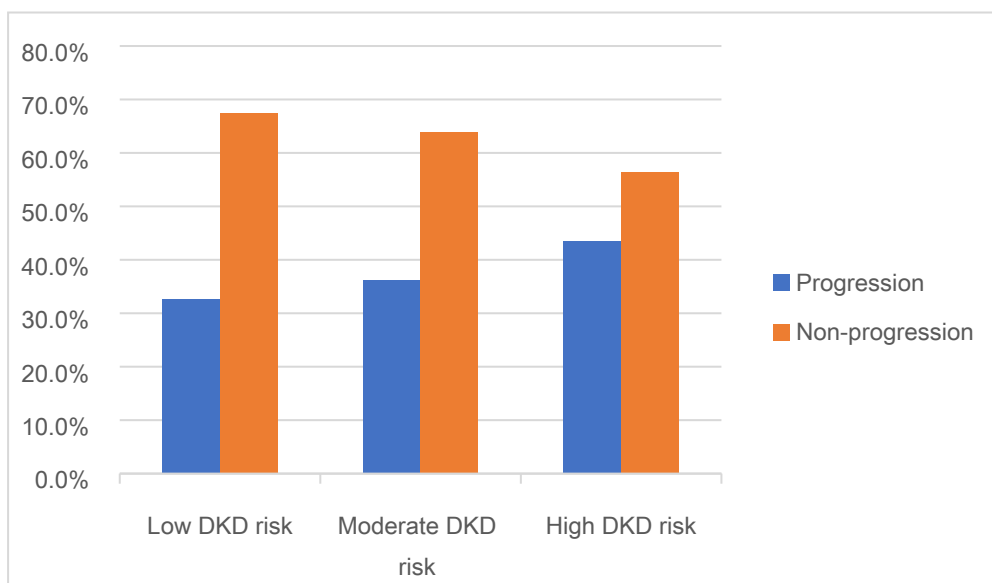
**Figure 1** Flow chart of patient selection. DKD, diabetes kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; AER, albumin excretion rate.



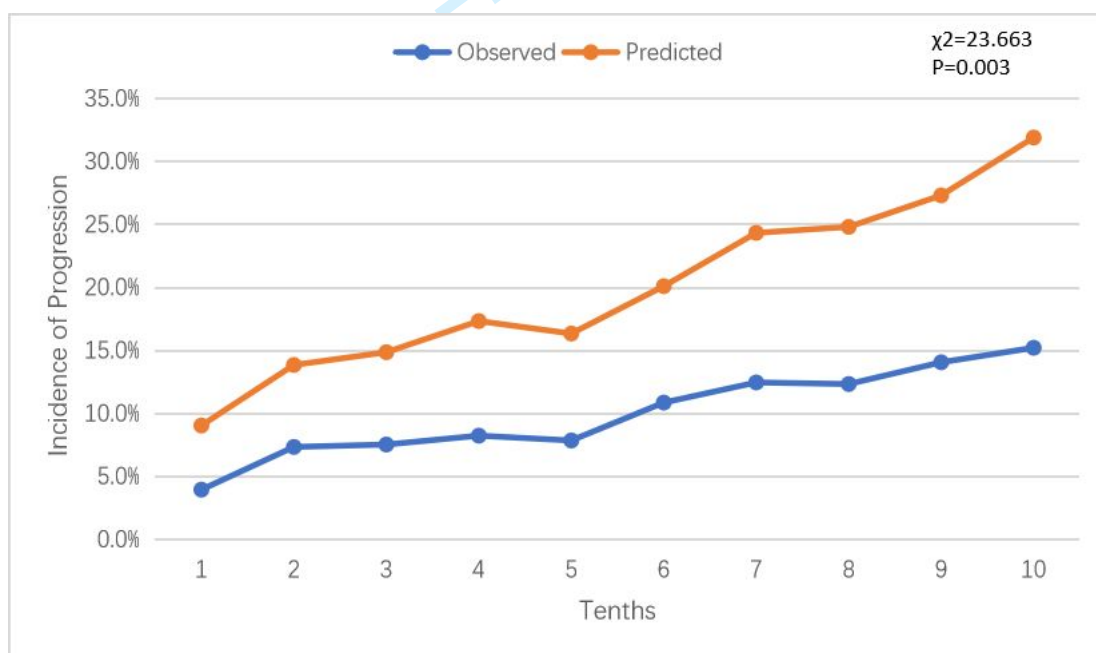
**Figure 2** In the DKD prediction cohort, the final DKD, non-DKD patients' ratio stratified by DKD risk categories.



**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)	$\beta$ -coefficient	Scores
Age (by 5-10 years)	1.38 (1.20-1.59)	0.32	3.0
BMI (by 5 kg/m <sup>2</sup> )	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.

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

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	Reporting Item	Page Number
<b>Title</b>		
	<a href="#">#1</a> Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
<b>Abstract</b>		
	<a href="#">#2</a> Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1-2
<b>Introduction</b>		
	<a href="#">#3a</a> 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.

1				
2				
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4				
5	Statistical	<a href="#">#10a</a>	If you are developing a prediction model	n/a
6	analysis methods		describe how predictors were handled in the	
7			analyses.	
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10	Statistical	<a href="#">#10b</a>	If you are developing a prediction model,	n/a
11	analysis methods		specify type of model, all model-building	
12			procedures (including any predictor selection),	
13			and method for internal validation.	
14				
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17	Statistical	<a href="#">#10c</a>	If you are validating a prediction model,	8
18	analysis methods		describe how the predictions were calculated.	
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21	Statistical	<a href="#">#10d</a>	Specify all measures used to assess model	8
22	analysis methods		performance and, if relevant, to compare	
23			multiple models.	
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27	Statistical	<a href="#">#10e</a>	If you are validating a prediction model,	n/a
28	analysis methods		describe any model updating (e.g.,	
29			recalibration) arising from the validation, if	
30			done	
31				
32				
33	Risk groups	<a href="#">#11</a>	Provide details on how risk groups were	7
34			created, if done.	
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36				
37	Development vs.	<a href="#">#12</a>	For validation, identify any differences from	n/a
38	validation		the development data in setting, eligibility	The population in the
39			criteria, outcome, and predictors.	development cohort was
40				meta-analyzed and
41				cannot be compared
42				
43				
44	<b>Results</b>			
45				
46	Participants	<a href="#">#13a</a>	Describe the flow of participants through the	9
47			study, including the number of participants	
48			with and without the outcome and, if	
49			applicable, a summary of the follow-up time. A	
50			diagram may be helpful.	
51				
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54	Participants	<a href="#">#13b</a>	Describe the characteristics of the participants	9
55			(basic demographics, clinical features,	
56			available predictors), including the number of	
57				
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		participants with missing data for predictors and outcome.	
Participants	<a href="#">#13c</a>	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	<a href="#">#14a</a>	If developing a model, specify the number of participants and outcome events in each analysis.	n/a
Model development	<a href="#">#14b</a>	If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome.	n/a
Model specification	<a href="#">#15a</a>	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	<a href="#">#15b</a>	If developing a prediction model, explain how to the use it.	n/a
Model performance	<a href="#">#16</a>	Report performance measures (with CIs) for the prediction model.	10-12
Model-updating	<a href="#">#17</a>	If validating a model, report the results from any model updating, if done (i.e., model specification, model performance).	10-12
<b>Discussion</b>			
Limitations	<a href="#">#18</a>	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	15
Interpretation	<a href="#">#19a</a>	For validation, discuss the results with reference to performance in the development data, and any other validation data	12-14
Interpretation	<a href="#">#19b</a>	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	12-14

1	Implications	<a href="#">#20</a>	Discuss the potential clinical use of the model	16
2			and implications for future research	
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5	<b>Other</b>			
6	<b>information</b>			
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9	Supplementary	<a href="#">#21</a>	Provide information about the availability of	17
10	information		supplementary resources, such as study	
11			protocol, Web calculator, and data sets.	
12				
13				
14	Funding	<a href="#">#22</a>	Give the source of funding and the role of the	17
15			funders for the present study.	
16				
17				

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# BMJ Open

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

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

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**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

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4 calculated using the RPM-DKD.

5 **Primary and secondary outcome measures** The primary outcome measure was  
6 overall incidence of DKD. Secondary outcomes included DKD progression. The  
7 discrimination, calibration and and precision of the RPM-DKD score were assessed.  
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10 **Results** The DKD prediction cohort and progression prediction cohort consisted of  
11 2504 and 4455 T2DM patients, respectively. The RPM-DKD examined in this study  
12 showed moderately discriminative ability with AUCs ranged from 0.636 to 0.681 for  
13 the occurrence of DKD and 0.620 to 0.654 for the progression of DKD. The Hosmer-  
14 Lemeshow  $\chi^2$  test indicted the RPM-DKD was not well calibrated for predicting the  
15 occurrence of DKD and over-estimated the progression of DKD. The precision for  
16 predicting the occurrence and progression of DKD were 43.2% and 42.2%, respectively.  
17  
18

19 **Conclusions** On external validation, the RPM-DKD cannot accurately predict the risk  
20 of DKD occurrence and progression in patients with T2DM.  
21  
22

23 **Keywords** External validation; diabetic kidney disease; prediction; risk assessment  
24  
25

### 26 **Strengths and limitations of this study**

- 27 ● Our validation cohort was geographically different from the cohort used to derive  
28 the model and our team was not involved in model derivation, which enabled us to  
29 conduct a true independent external validation study.
- 30 ● Our cohort had an average follow-up time of more than 5 years, a duration that  
31 positioned us to effectively identify the occurrence of outcome variables.
- 32 ● Whilst the cohort was representative of a large cohort of over 4,000 adults, it was  
33 geographically restricted to Taiwan.
- 34 ● Most patients in our cohort had better diabetes self-management behaviors, which  
35 could potentially have affected the study results and also explain why the model  
36 overestimated risk of occurrence and progression.
- 37 ● The retrospective nature of our study presents an inherent limitation, although it is  
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4 a simple, flexible, and low-cost method to review patient data for purposes of the  
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6 present analysis  
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## 10 **1.Introduction**

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12  
13 Diabetic kidney disease (DKD) is one of the main microvascular complications of  
14  
15 long-standing, uncontrolled type 2 diabetes mellitus (T2DM), and a main cause of  
16  
17 preventable chronic and end-stage kidney disease worldwide [1]. Paradoxically,  
18  
19 improvements in cardiovascular survival in patients with T2DM have contributed to  
20  
21 prolonged patient survival, which in turn lengthens time at risk for developing renal  
22  
23 impairment [2]. In China, about 20-40% of individuals with T2DM have DKD [3].  
24  
25 Further, progression of DKD to ESRD requiring renal replacement therapy and/or renal  
26  
27 transplant brings economic burden and is associated with additional comorbid burden  
28  
29 [4-6]. In light of these factors, the early intervention and study of a relevant risk  
30  
31 prediction model for early DKD are of great clinical and societal relevance.  
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39  
40 Clinical risk prediction models aim to estimate an individual's risk of an event  
41  
42 based on relevant contributing information [7]. Currently, many prediction models have  
43  
44 been developed to assess risk of incident diabetes, but few have been validated in  
45  
46 subsequent analyses and applied to clinical practice [8-10]. For example, one T2DM  
47  
48 risk score, the FINDRISC, is well-known in Latin America and the Caribbean, despite  
49  
50 limited none external validation of the model [11]. A risk prediction model should not  
51  
52 enter clinical practice unless it has been independently and externally validated and  
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54 proven to perform a useful role [12].  
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60 The ability to accurately predict risk of DKD would allow for earlier recognition,



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4 and perhaps intervention, in patients with long-standing T2DM. Recently, a risk  
5  
6 prediction model for early DKD (RPM-DKD) was developed based on systematic  
7  
8 review and meta-analysis of individual participant data from 20 cohorts of  
9  
10 predominately white populations [13]. However, validation was limited in scope with  
11  
12 a relatively small study size (n=380) and insufficient median follow-up time (t=2.9  
13  
14 years). The purpose of the current study was to independently and externally validate  
15  
16 performance of the RPM-DKD in predicting the risk of incidence of DKD in patients  
17  
18 with T2DM. In addition, although PRM-DKD was only used to predict the occurrence  
19  
20 of DKD, we believe that it can predict the progress of DKD to a certain extent, with  
21  
22 reason that the influencing factors of DKD progression and occurrence are similar.  
23  
24 Therefore, the secondary purpose of this study is to evaluate the performance of this  
25  
26 model in predicting the risk of DKD progression in patients with T2DM.  
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## 35 **2.Methods**

### 36 **2.1 Data sources and participants**

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39 We used outpatient data from December 2006 to October 2019 from Lee's United  
40  
41 Clinics (LUC) in Taiwan. LUC is a large ambulatory system, comprised of six clinics  
42  
43 providing multidisciplinary care for patients with diabetes. The Taiwan Health  
44  
45 Insurance Plan supports 4 annual follow up visits along with access to medications,  
46  
47 diabetes supplies, diabetes self-management education (DSME) clinician visitation and  
48  
49 primary/secondary prevention screening to patients living with diabetes. This setting  
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51 provided an opportune source of robust, longitudinal data in which to validate the RPM-  
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60 DKD.

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4 Inclusion criteria for predicting the occurrence of DKD aligned with those  
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6 established by the RPM-DKD [13] and included; (1) patients aged 39-75 years, and (2)  
7  
8 patients without albuminuria (urinary albumin-to-creatinine ratio [UACR]<30mg/g or  
9  
10 albumin excretion rate [AER]<30mg) and estimated glomerular filtration rate  
11  
12 (eGFR) $\geq$ 60mL/min/1.73 m<sup>2</sup> at baseline.  
13  
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16  
17 Inclusion criteria for predicting progression of DKD were patients aged 39-75  
18  
19 years with S1-S3 at baseline (The criteria for S1-S3 stage presented in diagnosis criteria  
20  
21 part).  
22  
23

24  
25 We excluded (1) patients with less than 3 years of longitudinal follow-up, (2) those  
26  
27 with history of acute kidney injury, primary glomerulonephritis, urinary tract infection,  
28  
29 urinary calculi, etc. (3) patients with missing endpoints and lost to follow-up, and (4)  
30  
31 patients with end stage renal disease (very high DKD risk) at baseline.  
32  
33  
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## 35 **2.2 Diagnosis criteria**

36  
37 Diagnosis criteria of DKD were also consistent with foundational RPM-DKD  
38  
39 modeling and included: (1) eGFR<60 mL/min/1.73 m<sup>2</sup> and/or (2) UACR $\geq$ 30 mg/g (or  
40  
41 AER $\geq$ 30 mg) (3) present for $\geq$ 3 months caused by diabetes [14].  
42  
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45  
46 Diagnostic criteria to clinical progression of DKD were [15]: (i) Patients were in  
47  
48 a non-progression group if they maintained the same DKD stage or their condition had  
49  
50 improved to an earlier DKD stage category. (ii) Patients were in a progression group if  
51  
52 the DKD stage category had progressed.  
53  
54

55  
56 The stage of DKD was classified using a combination of eGFR and ACR into four  
57  
58 stage categories[16], i.e., (i) Low DKD risk, eGFR  $\geq$ 60mL/min/1.73 m<sup>2</sup> and  
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4 ACR<30mg/g; (ii) Moderate CKD risk, eGFR between 45 and 59 mL/min/1.73 m<sup>2</sup> and  
5  
6 ACR<30mg/g, or eGFR ≥60mL/min/1.73 m<sup>2</sup> and ACR between 30 and 300mg/g; (iii)  
7  
8 High DKD risk, eGFR between 30 and 44 mL/min/1.73 m<sup>2</sup> and ACR<30mg/g, or  
9  
10 eGFR between 45 and 59 mL/min/1.73 m<sup>2</sup> and ACR between 30 and 300mg/g, or  
11  
12 eGFR ≥60mL/min/1.73 m<sup>2</sup> and ACR>300mg/g; (iv) Very high DKD risk,  
13  
14 eGFR≤29mL/min/1.73 m<sup>2</sup> and ACR<30mg/g, or eGFR≤44mL/min/1.73 m<sup>2</sup> and ACR  
15  
16 between 30 and 300 mg/g, or eGFR≤59mL/min/1.73 m<sup>2</sup> and ACR>300mg/g.  
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### 22 **2.3 Risk score calculations**

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24  
25 The risk score model was established by Jiang, W. et al [13], and all risk factors  
26  
27 included in the DKD risk score model were derived from a systematic review and meta-  
28  
29 analysis of 14 prospective and 6 retrospective cohorts. The predicted risk score for each  
30  
31 study participant was calculated using their baseline data. The baseline variables used  
32  
33 for the risk scores were in accordance with the model: (i) age (years) divided into three  
34  
35 categories, 39-49 scores 0, 50-59 scores 3.0, and 60-75 scores 6.0; (ii) body mass index  
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37 (BMI), which was calculated as the patient's weight divided by the square of their  
38  
39 height (kg/m<sup>2</sup>), divided into three categories (<25.00 scores 0, 25.00-29.99 scores 1.5,  
40  
41 and≥30.00 scores 3.0); (iii) smoker (defined as having smoked more than 100 cigarettes  
42  
43 in their lifetime), non-smoker scores 0 and smoker scores 4.0; (iv) diabetic retinopathy  
44  
45 (DR), 0 if no and 3.0 if yes; (v) hemoglobin A1c(HbA1c) divided into four categories,  
46  
47 <7.0% (<53 mmol/mol) scores 0, 7.0-7.9% ( 53-63 mmol/mol) scores 1.5, 8.0-8.9%  
48  
49 (64-74 mmol/mol) scores 3.0 and ≥9.0% (≥75 mmol/mol) scores 4.5; (vi) systolic blood  
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51 pressure (SBP) divided into four categories, <130mmHg scores 0, 130-139 mmHg  
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4 scores 2.0, 140-149 mmHg scores 4.0,  $\geq 150$  mmHg scores 6.0; (vii) serum high-density  
5 lipoprotein-cholesterol (HDL-C) divided into two categories,  $\geq 1.30$ mmol/L scores 0,  
6 and  $< 1.30$ mmol/L scores 2.5; (viii) triglycerides (TG) divided into two categories,  
7  $< 1.70$ mmol/L scores 0 and  $\geq 1.70$ mmol/L scores 4.0; and (ix) UACR divided into three  
8 categories,  $< 10$ mg/g scores 0, 10.00-19.99mg/g scores 2.0, 20.00-29.99mg/g scores 4.0.  
9  
10 In addition, considering that we want to predict the progression of DKD, we continue  
11 to increase the category of UACR, that is, every increase of UACR 10mg/g, the score  
12 increases by 2 points. For example, UACR between 30.00 and 39.99mg/g scores 6.0.  
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14 The coefficients in the model are shown in supplementary appendix.  
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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

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4 used multiple imputation (10 imputations) to replace missing values by using a chained  
5  
6 equation approach based on all candidate predictors and outcomes.  
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## 9 **2.5 Statistical analysis**

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11 Descriptive statistics were generated for all variables, which were stratified by the  
12  
13 occurrence and progression of DKD. Normally distributed continuous variables were  
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15 presented as means  $\pm$  standard deviation (SD), and analysis of variance was used to  
16  
17 assess inter-group comparisons. Medians (interquartile range [IQR]) were used for  
18  
19 continuous variables that were not normally distributed, and the comparison between  
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21 groups were performed by Kruskal-Wallis H test. Categorical variables were  
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23 represented as number of cases (N), and the intergroup rate (%) was compared with chi-  
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25 square test.  
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32  
33 The clinical performance of the DKD risk prediction model was assessed by means  
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35 of discrimination and calibration. Model discrimination describes a model's  
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37 performance in distinguishing between individuals who experience an event and those  
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39 who do not[7]. Model discrimination was assessed by plotting a receiver operating  
40  
41 characteristic (ROC) curve and calculating the area under the curve (AUC). An AUC-  
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43 statistic value  $>0.75$  was regarded to represent good discrimination. Calibration  
44  
45 assessment of a risk prediction model describes how well predictions match observed  
46  
47 outcomes [7]. The calibration of the risk score predictions was assessed by plotting  
48  
49 observed versus predicted number of patients and by calculating the Hosmer-  
50  
51 Lemeshow  $\chi^2$  statistic. Groups for observed DKD events were based on deciles for the  
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4 predicted probabilities. Performance was evaluated as sensitivity, specificity, and  
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6 precision.  
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9 All results were presented with 95% confidence interval (CI). Any two-tailed p-  
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11 values<0.05 were considered statistically significant. All statistical analyses were  
12  
13 performed using SPSS software, version 22 (IBM Corp.).  
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## 16 **2.6 Patient and public involvement**

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18  
19 There was no patient or public involvement in the design and conduct of the study.  
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21

## 22 **3. Results**

23  
24 In the DKD prediction cohort, a total of 2504 patients (average age 55.44 years,  
25  
26 SD, 7.49 years), and 4455 patients (average age 57.88 years, SD, 8.80 years) were  
27  
28 included for analysis in the DKD progression prediction cohort (Figure 1). The average  
29  
30 length of follow-up was 7.37 years (SD, 3.22 years) in the DKD prediction cohort and  
31  
32 a total of 817 (32.6%) people had DKD during the follow-up period. The mean follow-  
33  
34 up time in the progression prediction cohort was 7.72 years (SD, 3.10 years), and the  
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36 overall progression of events in this cohort was 1563 (35.1%).  
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### 42 **3.1 DKD prediction cohort**

#### 43 **3.1.1 Baseline characteristics**

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46 The DKD prediction cohort had an average BMI of 26.1±4.0 kg/m<sup>2</sup> and 54.8%  
47  
48 were men. The proportion of smokers and drinkers were 30.7% and 25.4%, respectively.  
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50  
51 There were significant differences in the level of education (P=0.0021) and marital  
52  
53 status (P<0.001) between patients who eventually developed DKD and those who did  
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55 not. The patients who did not develop of DKD had higher rates of secondary and  
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4 college-level education and lower rates of spousal loss than the patients with DKD.  
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6 Furthermore, patients who eventually developed DKD had a longer diabetes duration  
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8 (median 5 years [2-9 years]) and a higher level of HbA1c (median 8.4% [7.10-10.10%])  
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10 than those who did not. All patients showed normal albuminuria and renal function at  
11  
12 baseline with median UACR of 8.64 mg/g (4.50–13.86mg/g) and median eGFR of  
13  
14 85.50 ml/min/1.73 m<sup>2</sup> (73.08–96.13 ml/min/1.73 m<sup>2</sup>). The median systolic blood  
15  
16 pressure (SBP) and diastolic blood pressure (DBP) were 129mmHg (119-141mmHg)  
17  
18 and 77 mmHg (70-84 mmHg), respectively. Baseline characteristics of the DKD  
19  
20 prediction cohort are displayed in Table 1.  
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### 26 27 **3.1.2 External validation results for DKD prediction cohort**

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30 Of the 2504 patients, 678 (27.1%), 639 (25.5%), 1114 (44.5%) and 73 (2.9%) had  
31  
32 risk categories of relatively low, moderate, high and very high at baseline. At the end  
33  
34 of observation, 129 (19.0%), 175 (27.4%), 465 (41.7%), 48 (65.8%) patients in the  
35  
36 relatively low, moderate, high and very high groups developed DKD, respectively  
37  
38 (Figure 2).  
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43 **Discrimination of the model** : According to our external validation, 16 was  
44  
45 selected as the optimal cut-off risk score value, at which the sum of sensitivity and  
46  
47 specificity was maximal (Youden's index), which corresponded with Jiang, W. et al  
48  
49 [14]. With a risk cut-off value of 16 points, the sensitivity would be 53.0% (95% CI  
50  
51 48.9–57.0), specificity would be 65.7% (95% CI 63.0–68.3). ROC curve of our external  
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53 validation showed the area under the DKD risk score curve was 0.659 (95% CI 0.636-  
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55 0.681).  
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4       **Calibration of the model** : The risk scoring model was not well calibrated for  
5  
6 predicting the occurrence of DKD, with a Hosmer-Lemeshow  $\chi^2$  statistic of 16.731  
7  
8 (p=0.033). The calibration plot in figure 3 shows that the comparison between observed  
9  
10 and predicted the occurrence of DKD, indicating the over-estimation of risk occurred in  
11  
12 tenths 1 through 10.  
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17       **Precision of the model in predicting DKD** : The prediction precision refers to  
18  
19 the ratio of the actual number of patients with DKD to the number of patients predicted  
20  
21 to develop DKD. According to our data, patients in the DKD prediction cohort were  
22  
23 classified as high risk if their DKD risk score  $\geq 16$  points, with precision of 43.2%  
24  
25 (513/1187).  
26  
27  
28

## 29 30 **3.2 Progression prediction cohort**

### 31 32 **3.2.1 Baseline characteristics**

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34  
35       The baseline clinical and biochemical characteristics of the DKD progression  
36  
37 cohort stratified by the progression of DKD are listed in Table 1. Of the cohort, the  
38  
39 average BMI was  $26.30 \pm 4.14$  kg/m<sup>2</sup> and 51.0% were men. The proportion of smokers  
40  
41 and drinkers were 30.6% and 25.3%, respectively. In addition, the progression group  
42  
43 had lower education and married level, and longer duration of diabetes than the patients  
44  
45 in non-progression group. And patients in progression group had higher systolic blood  
46  
47 pressure (SBP), HbA1c and UACR than the patients in non-progression group, and  
48  
49 higher levels of diastolic blood pressure (DBP), total cholesterol than the patients in  
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51 non-progression group. On DKD risk score analyses, the progression group had higher  
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4 baseline risk score compared with non-progression group whatever patients with low  
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6 DKD risk, moderate DKD risk or high DKD risk (Table 2).  
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### 9 **3.2.2 External validation results for progression prediction cohort**

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11 Of the 4455 patients, 2504(56.2%), 1397 (31.4%) and 554 (12.4%) were in low,  
12  
13 moderate and high DKD risk at baseline. At the end of observation, 589 (32.6%), 531  
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15 (36.1%) and 414 (43.5%) patients in the low, moderate and high DKD risk had  
16  
17 progressed, respectively (Figure 4).  
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22 **Discrimination of the model:** ROC curve showed moderate discriminative ability  
23  
24 of predicting the progression of DKD in progression prediction cohort, and the area  
25  
26 under the receiver operating characteristic curve was 0.637 (95% CI 0.620-0.654). 18  
27  
28 was selected as the optimal cut-off risk score value with a sensitivity of 65.0% (95%  
29  
30 CI 62.6-67.3) and a specificity of 57.0% (95% CI 55.2-58.8)  
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35 **Calibration of the model:** Calibration of the model for predicting the progression  
36  
37 of DKD was no good in our external validation cohort (Hosmer-Lemeshow  $\chi^2 = 23.663$ ,  
38  
39  $P=0.003$ ), and the over-estimation of risk occurred in tenths 1 through 10. The  
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41 calibration plot in figure 5 shows that the comparison between observed and predicted  
42  
43 the progression of DKD.  
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48 **Precision of the model in predicting DKD progression:** The prediction accuracy  
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50 refers to the ratio of the actual number of patients whose DKD stage progressed to the  
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52 number of patients predicted to progressed. According to our validation cohort, with a  
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54 risk cut-off value of 18 points, the precision would be 45.0% (1016/2260). According  
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4 to the model developed study [15], with a risk cut-off value of 16 points, the precision  
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6 would be 42.2% (1173/2781).  
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#### 8 9 **4. Discussion**

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11 External validation is a mandatory step in applying a prediction model to  
12 meaningful clinical care; the process addresses the transportability of the model [18].  
13  
14 Taiwan has established a sound universal health insurance policy supported by the  
15 government, providing a lot of reliable data for model validation. However, not all  
16 governments have established such a comprehensive universal health care policy.  
17 Hence, the limited availability of patient data, the model was not validated. In this study,  
18 we evaluated the usefulness of RPM-DKD for predicting the DKD incidence and  
19 progression of DKD in patients with T2DM by assessing its discrimination, calibration  
20 and precision. The performance of the RPM-DKD predictive potential in our validation  
21 cohort was not ideal, even when the results from the validation evaluated by the model  
22 developers were promising.  
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40 The RPM-DKD has several advantages, including easy point-of-care application,  
41 simple calculation and reliance on very few variables. Nevertheless, the RPM-DKD  
42 demonstrated moderately discriminatory ability in our cohort. With that said, the RPM-  
43 DKD was not well-calibrated for predicting the occurrence of DKD, and it over-  
44 estimated the progression of disease. When using the same foundational thresholds  
45 established by the original RPM-DKD study, precision for predicting DKD occurrence  
46 and progression in our validation cohort was low, with values of 43.2% and 42.2%,  
47 respectively. Utilizing the developers' suggested thresholds resulted in inappropriate  
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4 prediction of DKD in our cohort. Even at a threshold of 18 (at which the Youden's  
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6 index was maximal in our study), the precision of the model in predicting DKD  
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8 progression was also low.  
9

10  
11 Overall transportability of the model was poor in our analysis, owing perhaps to  
12  
13 the phenomenon of over-fitting. If internal validation such as bootstrap would have  
14  
15 been performed after model developed, the phenomenon might have been foreseen [19].  
16  
17 Furthermore, the poor external validation performance may also be closely related to  
18  
19 the fact that our validation cohort was vary from the model developers' cohort in terms  
20  
21 of settings, populations and periods [20, 21]. Moreover, a significant reason for the poor  
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23 performance of DKD progression prediction is that the model was not developed to  
24  
25 predict DKD progression. However, there is no such a simple scoring model to predict  
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27 the progression of DKD at present. Most of the models that have been developed to  
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29 predict the progression of DKD are complex and difficult to be widely used in clinical  
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31 practice.  
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40 The RPM-DKD uses cross-sectional baseline data to predict a patient's risk of  
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42 DKD 5 to 10 years later; it is therefore based on the assumption that there is no  
43  
44 significant change in relevant indicators of the patient in subsequent years – a somewhat  
45  
46 unrealistic expectation in a real world application. Since the occurrence and  
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48 development of DKD is a relatively long process, metabolic indicators 5-, 10-years  
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50 even in preceding decades can impact subsequent outcomes. However, the model,  
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52 established by logistic regression, volatility of various parameters in the next few years  
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54 was not considered, which results in the prediction performance was not high.  
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4 In our study, not all data specific to risk factors included in the RPM-DKD model  
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6 were available (age, BMI, HbA1c.); this may have contributed to poor model  
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8 performance. In previous work, we found that HbA1c variability is an independent risk  
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10 factor for nephropathy in patients with T2DM [22]. In addition, Viazzi et al.  
11  
12 demonstrated that the variability of SBP and pulse pressure are also key influencing  
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14 factors for the occurrence and development of DKD [23]. Thus, these parameters  
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16 should be strong outcome predictors for developing DKD; and yet, the RPM-DKD does  
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18 not take them into account.  
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25 The RPM-DKD model cannot predict future risk of DKD in patients with T2DM  
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27 aged <39 years despite early age of diagnosis being an established risk factor for  
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29 developing DKD [24]. Several groups reported an increasing incidence of youth-onset  
30  
31 DKD [25, 26]. Given the earlier onset of DKD among T2DM patients, we believe that  
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33 having validated risk assessment models that include young adults may be of greater  
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35 clinical use.  
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#### 40 *Strengths and limitations of this study*

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43 Our study has several strengths. First, our validation cohort was geographically  
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45 different from the cohort used to derive the model; further, our team was not involved  
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47 in model derivation, which enabled us to conduct a true independent external validation  
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49 study. Additionally, our cohort had an average follow-up time of more than 5 years, a  
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51 duration that positioned us to effectively identify the occurrence of outcome variables.  
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55 Several limitations existed in this study. First, whilst the cohort was representative  
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57 of a large cohort of over 4,000 adults, it was geographically restricted to Taiwan.  
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4 Second, most patients in our cohort had better diabetes self-management behaviors,  
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6 which could potentially have affected the study results and also explain why the model  
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8 overestimated risk of occurrence and progression. However, diabetes self-management  
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10 is a key factor for promoting better health outcomes among patients with DKD [27, 28];  
11  
12 longitudinally, increased awareness for the DKD burden in diabetes patients might have  
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14 contributed to additional self-management behaviors with a positive effect on DKD  
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16 incidence and progression. In addition, the retrospective nature of our study presents an  
17  
18 inherent limitation, although it is a simple, flexible, and low-cost method to review  
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20 patient data for purposes of the present analysis [29]; additionally, we may not have  
21  
22 successfully captured patient data related to care that may have occurred outside of our  
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24 health system. Apart, the scoring model was not developed to predict the progression  
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26 of DKD, but we still used this scoring model to predict the progression of DKD, which  
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28 may create inapplicability. However, there is no similar scoring model that can predict  
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30 the progression of DKD at present.  
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#### 48 *Future research*

49 The occurrence of DKD in our study was high (31.6%), agreeing with previous  
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51 study (20% to 40%) conducted in China[3] but significantly higher than that in the  
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53 United States (26.2%)[30]. Among those with diabetes, DKD prevalence varies widely  
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55 between countries, with estimates ranging from 26.2% in US to 83.6% in Tanzania[31].  
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57 In general, the prevalence of DKD rate in Asia and Africa are higher than those in  
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4 Europe and the United States[32]. The insidious nature of type 2 diabetes and less  
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6 accessibility of developing countries to healthcare contribute to a high proportion of  
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8 undiagnosed patients[33]. The late diagnosis may partially contribute to the high  
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10 prevalence of DKD in Asia and Africa. In Asia, health-care providers and nurses are  
11  
12 not sufficiently educated about diabetes patients, about 50% lack understanding of  
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14 diabetes complications[34], and self-care activities are suboptimal overall[35].  
15  
16 Therefore, it is extremely significant to have an accurate prediction model that could  
17  
18 assist clinicians in real-time evaluation of patient risk and implement primary and  
19  
20 secondary preventive measures to delay progression of disease. However, the RPM-  
21  
22 DKD established by logistic regression did not perform well. Furthermore, prediction  
23  
24 models can become obsolete with change in population demography, better therapeutic  
25  
26 options and care pathways, and improvement in data recording [36]. In the future, it  
27  
28 may be possible to build a DKD prediction model by deep learning methods in order to  
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30 improve the prediction of DKD occurrence and progression; many studies have applied  
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32 deep learning with proven success [37-41].  
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## 48 **5. Conclusion**

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50 Our independent external validation study revealed that, in patients with T2DM,  
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52 the RPM-DKD cannot accurately predict the risk of DKD occurrence and progression.  
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54 The ability to accurately estimate DKD risk is critical in advancing patient care and  
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56 preventing or delaying complication risk in patients with long-standing T2DM. Newer  
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4 prediction models leveraging deep learning methods may prove useful for predicting  
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6 risk of developing or progressing DKD.  
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10

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12

13  
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15  
16 collected the epidemiological and clinical data. Z.S., K.W. and X.Y. drafted the manuscript. Z.S.,  
17  
18 K.W., X.Y., and Q.L. contributed to acquisition, analysis, and interpretation of data. Q.L. and J.D.M.  
19  
20 contributed to critical revision of the manuscript for important intellectual content. All authors read,  
21  
22 revised, and approved the final draft. Q.L. is the guarantor of this work and, as such, had full access  
23  
24 to all the data in the study and takes responsibility for the integrity of the data and the accuracy of  
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26 the data analysis.  
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35  
36

37 **Ethics approval** The present study was approved by the ethics committee of Antai Hospital, Antai  
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39 Medical Association (No.: 14-055-B2) and was conducted in accordance with the ethical standards  
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41 set out in the Declaration of Helsinki and its later amendments.  
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45 **Disclaimer** The funders had no role in the study design, data collection, or analysis, decision to  
46  
47 publish, or preparation of the manuscript.  
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50 **Patient consent for publication** Not required.  
51

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53 **Data availability statement** Data are available on reasonable request. All data relevant to the study  
54  
55 are included in the article or uploaded as online supplemental information. All data requests should  
56  
57 be submitted to the corresponding author for consideration.  
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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	2292	1563	
Age (years)	55.44±7.49	55.22±7.66	55.92±7.10	0.059	57.88±8.80	56.55±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 <sup>2</sup> )	26.10±4.00	25.93 ±3.86	26.44 ±3.86	0.029	26.30 ±4.14	26.23 ±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)	207(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)	122(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)	103(3.6)	55(3.5)	
Widow or widower	171(6.8)	75(4.4)	96(11.8)		355(8.0)	187(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(0,7)	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	101.00±29.87	101.55 ±29.96	0.818
eGFR (ml/min/1.73 m <sup>2</sup> )	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(6.7,41.71)	22.72(11.05,75.23)	<0.001

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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  $\pm$  SD, number (%) or median (interquartile range).

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**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

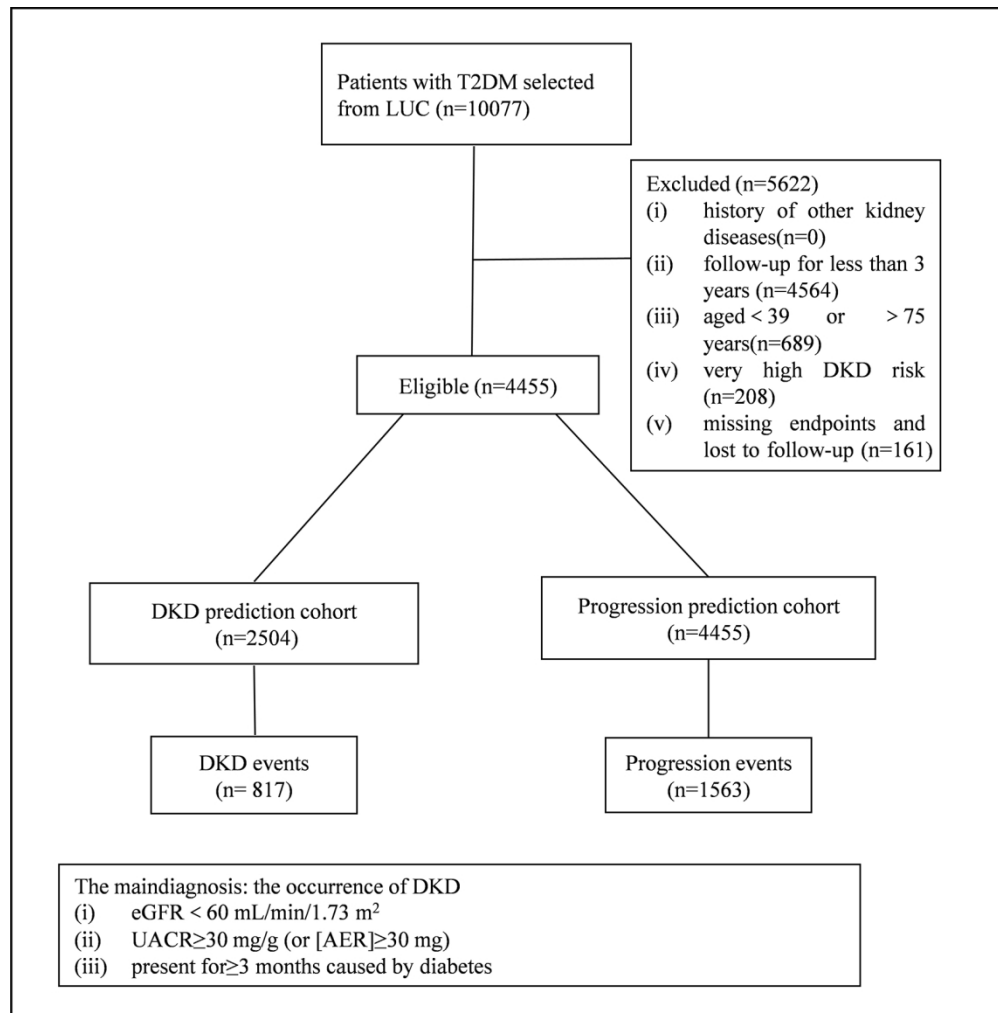
**Figure 1** Flow chart of patient selection. DKD, diabetes kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; AER, albumin excretion rate.

**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.



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

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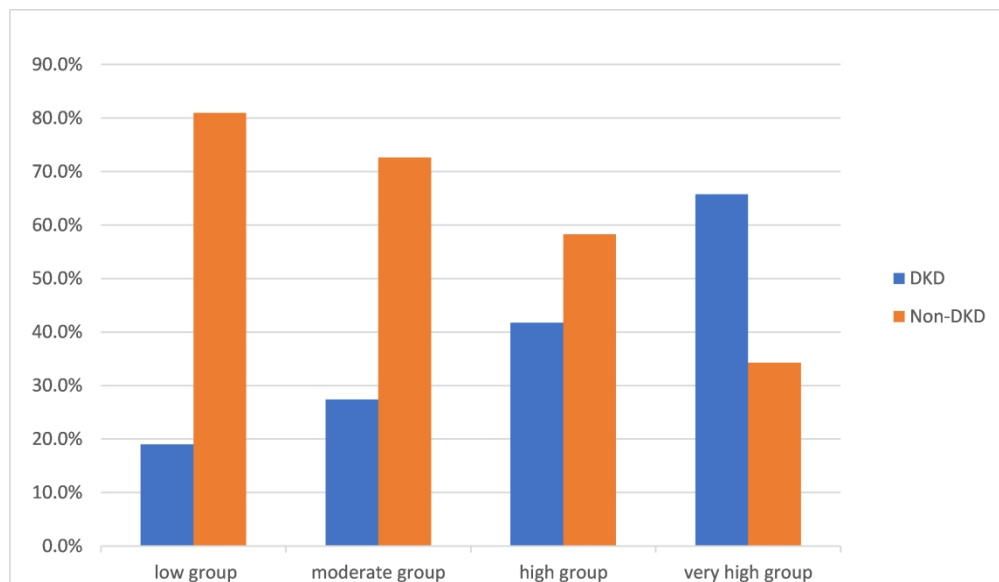


Figure 2 In the DKD prediction cohort, the final DKD, non-DKD patients' ratio stratified by DKD risk categories.

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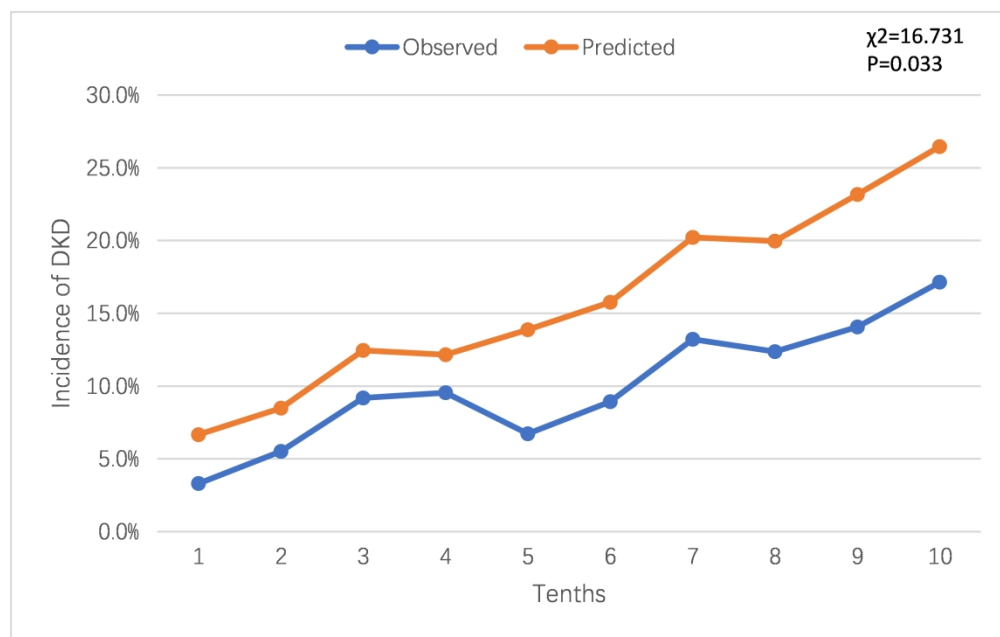


Figure 3 Observed and predicted the occurrence of DKD. Grouping method: First, calculate the predicted probability of DKD for each patient according to the DKD risk scoring model, then arrange them from small to large according to the predicted probability and divide them into 10 groups based on deciles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

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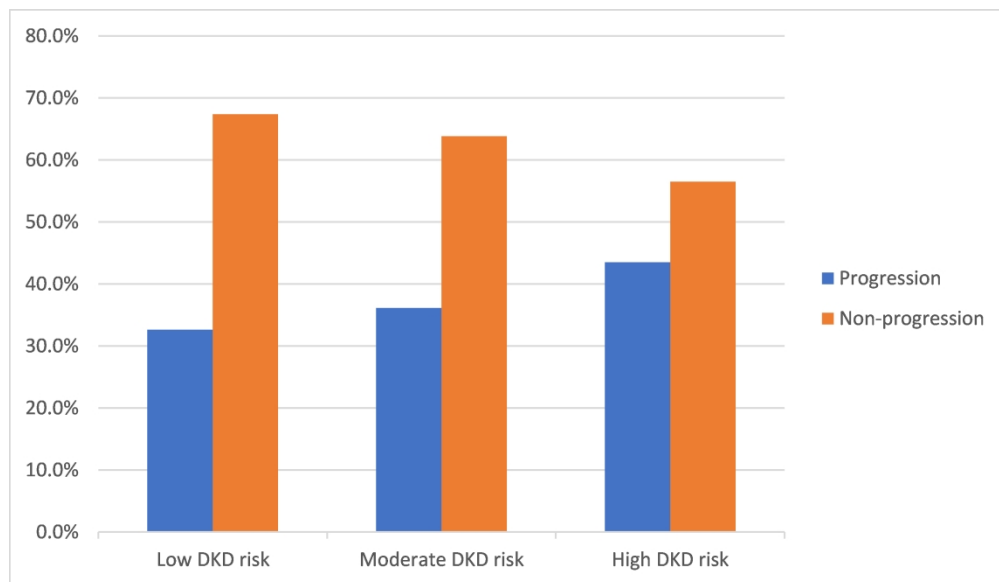


Figure 4 In the DKD progression cohort, the final progression, non-progression patients' ratio stratified by DKD stage.

296x171mm (300 x 300 DPI)

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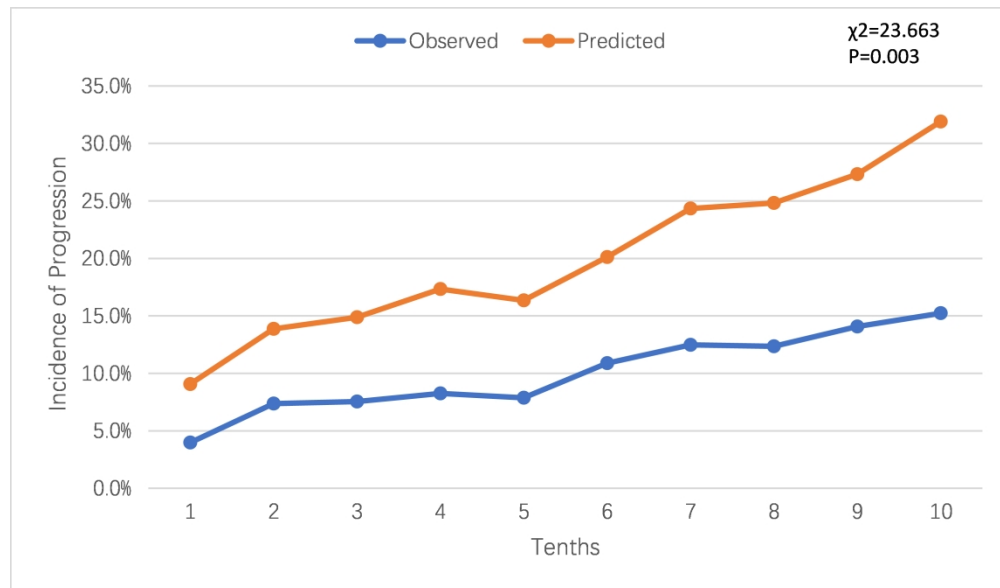


Figure 5 Observed and predicted the Progression of DKD. Grouping method: First, calculate the predicted probability of DKD for each patient according to the DKD risk scoring model, then arrange them from small to large according to the predicted probability and divide them into 10 groups based on deciles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

291x170mm (300 x 300 DPI)

**Supplementary Appendix**

Risk factors for DKD	RR (95%CI)	$\beta$ -coefficient	Scores
Age (by 5-10 years)	1.38 (1.20-1.59)	0.32	3.0
BMI (by 5 kg/m <sup>2</sup> )	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 TRIPOD reporting 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
<b>Title</b>		
	<a href="#">#1</a> Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
<b>Abstract</b>		
	<a href="#">#2</a> Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1-2
<b>Introduction</b>		
	<a href="#">#3a</a> 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.

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5	Statistical	<a href="#">#10a</a>	If you are developing a prediction model	n/a
6	analysis methods		describe how predictors were handled in the	
7			analyses.	
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10	Statistical	<a href="#">#10b</a>	If you are developing a prediction model,	n/a
11	analysis methods		specify type of model, all model-building	
12			procedures (including any predictor selection),	
13			and method for internal validation.	
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17	Statistical	<a href="#">#10c</a>	If you are validating a prediction model,	8-9
18	analysis methods		describe how the predictions were calculated.	
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21	Statistical	<a href="#">#10d</a>	Specify all measures used to assess model	8
22	analysis methods		performance and, if relevant, to compare	
23			multiple models.	
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27	Statistical	<a href="#">#10e</a>	If you are validating a prediction model,	n/a
28	analysis methods		describe any model updating (e.g.,	
29			recalibration) arising from the validation, if	
30			done	
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33	Risk groups	<a href="#">#11</a>	Provide details on how risk groups were	7
34			created, if done.	
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37	Development vs.	<a href="#">#12</a>	For validation, identify any differences from	n/a
38	validation		the development data in setting, eligibility	The population in the
39			criteria, outcome, and predictors.	development cohort was
40				meta-analyzed and
41				cannot be compared
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44	<b>Results</b>			
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46	Participants	<a href="#">#13a</a>	Describe the flow of participants through the	9
47			study, including the number of participants	
48			with and without the outcome and, if	
49			applicable, a summary of the follow-up time. A	
50			diagram may be helpful.	
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54	Participants	<a href="#">#13b</a>	Describe the characteristics of the participants	9
55			(basic demographics, clinical features,	
56			available predictors), including the number of	
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1		participants with missing data for predictors	
2		and outcome.	
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4	Participants	<a href="#">#13c</a> For validation, show a comparison with the	n/a The population in the
5		development data of the distribution of	development cohort was
6		important variables (demographics, predictors	meta-analyzed and
7		and outcome).	cannot be compared
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11	Model	<a href="#">#14a</a> If developing a model, specify the number of	7-8
12	development	participants and outcome events in each	
13		analysis.	
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16	Model	<a href="#">#14b</a> If developing a model, report the unadjusted	n/a
17	development	association, if calculated between each	
18		candidate predictor and outcome.	
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21	Model	<a href="#">#15a</a> If developing a model, present the full	n/a
22	specification	prediction model to allow predictions for	
23		individuals (i.e., all regression coefficients, and	
24		model intercept or baseline survival at a given	
25		time point).	
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30	Model	<a href="#">#15b</a> If developing a prediction model, explain how	n/a
31	specification	to the use it.	
32			
33	Model	<a href="#">#16</a> Report performance measures (with CIs) for	9-12
34	performance	the prediction model.	
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37	Model-updating	<a href="#">#17</a> If validating a model, report the results from	9-12
38		any model updating, if done (i.e., model	
39		specification, model performance).	
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43	<b>Discussion</b>		
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45	Limitations	<a href="#">#18</a> Discuss any limitations of the study (such as	15-16
46		nonrepresentative sample, few events per	
47		predictor, missing data).	
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50	Interpretation	<a href="#">#19a</a> For validation, discuss the results with	13-15
51		reference to performance in the development	
52		data, and any other validation data	
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55	Interpretation	<a href="#">#19b</a> Give an overall interpretation of the results,	13-15
56		considering objectives, limitations, results from	
57		similar studies, and other relevant evidence.	
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1	Implications	<a href="#">#20</a>	Discuss the potential clinical use of the model	17
2			and implications for future research	
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5	<b>Other</b>			
6	<b>information</b>			
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9	Supplementary	<a href="#">#21</a>	Provide information about the availability of	18
10	information		supplementary resources, such as study	
11			protocol, Web calculator, and data sets.	
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14	Funding	<a href="#">#22</a>	Give the source of funding and the role of the	18
15			funders for the present study.	
16				
17				

18 None The TRIPOD checklist is distributed under the terms of the Creative Commons Attribution  
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