Bramlage Peter (Orcid ID: 0000-0003-4970-2110)
Seufert Jochen (Orcid ID: 0000-0001-5654-7310)
Danne Thomas (Orcid ID: 0000-0002-8424-3944)
Lanzinger Stefanie (Orcid ID: 0000-0002-3789-6459)

Validation of a Risk Prediction Model for Early Chronic Kidney Disease in Patients with Type 2 Diabetes: Data from the German/Austrian DPV Registry

Running title: Chronic kidney disease risk prediction model for diabetes

Stephan Kress [1], Peter Bramlage [2], Reinhard W. Holl [3,4], Christian Dominik Möller [5], Steffen Mühldorfer [6], Jörg Reindel [7], Jochen Seufert [8], Rüdiger Landgraf [9], Ludwig Merker [10], Sebastian M. Meyhöfer [4 11], Thomas Danne [12], Peter Fasching [13], Peter R. Mertens [14], Christoph Wanner [15], *Stefanie Lanzinger [3,4]*

1. Medical Clinic I, Diabetes Center, Vinzentius-Hospital, Landau, Germany; email: s.kress@vinzentius.de
2. Institute for Pharmacology and Preventive Medicine, Cloppenburg, Germany; email: peter.bramlage@ippmed.de
3. Institute for Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany; email: Reinhard.holl@uni-ulm.de; stefanie.lanzinger@uni-ulm.de
4. German Center for Diabetes Research (DZD), München-Neuherberg, Germany
5. Bürgerhospital Frankfurt am Main, Germany; email: cd.moeller@buergerhospital-ffm.de
6. Gastroenterologie, Klinikum Bayreuth, Germany; email: steffen.muehldorfer@klinikum-bayreuth.de
7. Herz- und Diabeteszentrum, Klinikum Karlsburg, Germany; email: reindel@drguth.de
8. Division of Endocrinology and Diabetology, Department of Medicine II, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; email: jochen.seufert@uniklinik-freiburg.de
9. German Diabetes Foundation, Munich, Germany; email: ruediger.landgraf@gmx.de
10. Diabetologie im MVZ am Park Ville d'Eu, Haan, Germany; email: diabetes@luckycloud.de

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11. Institute for Endocrinology & Diabetes, University of Lübeck, Lübeck, Germany; email: sebastian.meyhoefer@uni-luebeck.de

12. Kinderkrankenhaus auf der Bult, Diabeteszentrum für Kinder und Jugendliche, Hannover, Germany; email: danne@hka.de

13. 5th Medical Department for Endocrinology, Rheumatology and Acute Geriatrics, Clinic Ottakring, Vienna, Austria; email: peter.fasching@gesundheitsverbund.at

14. Clinic of Nephrology and Hypertension, Diabetes and Endocrinology, Otto-Von-Guericke University Magdeburg, Magdeburg, Germany; email: peter.mertens@med.ovgu.de

15. Division of Nephrology, Wuerzburg University Clinic, Würzburg, Germany; email: wanner_c@ukw.de

Correspondence

Prof. Dr. Peter Bramlage, MD

Institute for Pharmacology and Preventive Medicine

Bahnhofstrasse 20, 49661 Cloppenburg, Germany

Tel.: +49 3379 3147890; email: peter.bramlage@ippmed.de

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ABSTRACT

Aims: Chronic kidney disease (CKD) is characterized by impaired kidney function and/or elevated urine albumin excretion and is the major cause of end-stage kidney disease in patients with type 2 diabetes (T2D). Early detection and prevention delays disease progression. This study aimed to validate a recently proposed risk prediction model for CKD in T2D.

Materials and methods: Subjects from the German/Austrian Diabetes Prospective Follow-up (DPV) registry with T2D, normoalbuminuria, an estimated glomerular filtration rate of ≥60 mL/min/1.73 m^2, and aged 39–75 were included. Prognostic factors included age, body mass index (BMI), smoking status, and hemoglobin A1C (HbA1c). Subjects were categorized into low, moderate, high, and very high-risk groups. Outcome was CKD occurrence.

Results: Subjects (n=10,922) had mean age of 61 years, 6 years' diabetes duration, 31.7 kg/m^2 BMI, 6.9% HbA1c (52 mmol/mol); 9.1% had diabetic retinopathy; and 16.3% were smokers. After follow-up (~59 months), 37.4% subjects developed CKD. The area under the curve (AUC; unadjusted base model) was 0.58 (95% CI 0.57–0.59). After adjustment for diabetes and follow-up duration, the AUC was 0.69 (95% CI 0.68–0.70), indicating improved discrimination. After follow-up, 15.0%, 20.1%, 27.7%, and 40.2% patients in the low, moderate, high, and very high-risk groups, respectively, had developed CKD. Increasing risk score correlated with increasing cumulative risk of incident CKD over a median of 4.5 years of follow-up ($p<0.0001$).

Conclusions: The predictive model achieved moderate discrimination but good calibration in a German/Austrian T2D population suggesting that the model may be relevant for determining CKD risk.

Keywords: chronic kidney disease; type 2 diabetes mellitus; risk prediction model; Germany; Austria

INTRODUCTION

Chronic kidney disease (CKD) in type 2 diabetes (T2D) is the leading cause of end-stage kidney disease (ESKD) [1,2]. The prevalence of CKD stage 5 among patients with diabetes is predicted to increase by 3.2% per year (estimated for 2012–2025) [3], and the number of deaths from kidney disease increased by 142% between 1990 and 2019 [4,5]. Kidney disease develops in approximately 40% of individuals with T2D [6] and is defined clinically as the presence of impaired renal function (reduced estimated glomerular filtration rate [eGFR]) and/or elevated urinary albumin excretion [7].

Despite improved screening, patients at risk of kidney disease tend to be identified late and are often diagnosed only when serious complications related to kidney disease develop [8]. Early identification of individuals at high risk would help to improve the management of these patients. Previous research suggests that several factors, including hyperglycemia, hypertension, dyslipidemia, obesity, smoking, the duration of diabetes, older age, family history of nephropathy and diabetic retinopathy are associated with the development of kidney disease [6,9]. Various risk factors have been integrated into different risk prediction models for kidney disease [10-13], but their use is limited by their complexity and a lack of external validation in the target population. No specific data are available for adult patients with diabetes in Germany or Austria.

To overcome this lack of evidence and to provide a risk assessment for the German/Austrian T2DM population, we aimed to validate the risk prediction model proposed by Jiang et al. [14], which was based on a meta-analysis of several cohort studies and validated in an adult Chinese population with T2D. It is a simple, but efficient model that considers nine risk factors: age, body mass index, smoking status, diabetic retinopathy, HbA1c, systolic blood pressure, HDL-C, triglycerides and urinary albumin-to-creatinine ratio (UACR). The model revealed good discrimination between various risk populations for the combined outcome of GFR reduction and/or albuminuria.

MATERIALS AND METHODS

Study design and data sources

Patient data from the German/Austrian DPV (Diabetes Prospective Follow-up) database was used for validation [15-18]. The DPV initiative, established in 1995, collects data on patients with diabetes mellitus from centers in the German-speaking countries Germany, Austria, Switzerland, and Luxembourg (see https://www.d-p-v.eu). Anonymized data are sent to Ulm University. DPV was approved by the ethics committee of the University of Ulm (approval number 314/21), and data collection was approved by local review boards.

The study evaluated the performance of the kidney disease risk prediction model of Jiang et al. [14] when applied to patients with CKD and T2DM from the DPV database. The Jiang model predicts the risk of early CKD (defined as eGFR <60 mL/min/1.73 m^2 and/or UACR ≥30 mg/g [or AER ≥30 mg/L]) in patients with T2DM, using common clinical data. Scores are based on nine different risk factors, with a maximum total possible score of 37 points (**Supplementary Table 1**).

Patients

Patients were eligible for inclusion in the current study if they had T2D, were aged 39-75 years, had normo-albuminuria (urinary albumin creatinine ratio [UACR] <30 mg/g or albumin excretion rate [AER] <30 mg/L) and an estimated glomerular filtration rate (eGFR) of ≥60 mL/min/1.73 m^2 at baseline. Baseline was defined as the first physician – patient contact at the treating physician. GFR was estimated based on the CKD-EPI formula published by Inker et al. [19] that is independent of race. T2DM status was based on physician diagnosis, medication use, and/or laboratory tests (fasting plasma glucose (FPG) ≥126 mg/dL or HbA1c ≥6.5%). Patients with type 1 diabetes or other diabetes types and incomplete baseline data were excluded.

Patients also had to have information available for all variables required for the prognostic model of Jiang et al. [14]: age, body mass index (BMI), smoking status, diabetic retinopathy status, hemoglobin A1C (HbA1C), high-density lipoprotein cholesterol (HDL-C), triglycerides, systolic blood pressure (SBP), diastolic blood pressure (DBP), and UACR.

All prognostic factors were weighted in the score according to the original risk model study (**Supplementary Table 1**) [14].

Outcomes

The outcome of interest was the occurrence of CKD defined as eGFR <60 mL/min/1.73 m^2 and/or UACR ≥30 mg/g (or AER ≥30 mg/L). Albuminuria was determined at least twice or more at different clinical visits. Patients with only one positive test or those with an equal number of positive and negative UACR tests were disregarded.

Statistical analyses

Baseline characteristics of participants with complete data were expressed as percentages (%) for categorical variables and means with standard deviations for continuous variables. For continuous variables with a skewed distribution, the median with first and third quartiles (Q1, Q3) was reported. External validation was undertaken in accordance with guidelines for the validation and interpretation of risk prediction models [20,21]. Briefly, model performance was evaluated as follows: discrimination was assessed by concordance of C-statistics / area under receiver operator characteristic curves (ROCs), and 95% confidence intervals (CI) [22,23]; calibration, was assessed by comparing observed and predicted values. Statistical analysis was performed using SAS version 9.4 (build TS1M7) on a Windows server 2019 mainframe. A two-sided p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 693,567 subjects were identified in the DPV database. We excluded 229,732 subjects who had a diabetes diagnosis other than T2D (33.1 %), 164,646 patients because of an age at baseline below 39 years or higher than 75 years (23.7 %), 47,098 patients based on the presence of albuminuria (UACR >30 mg/g or AER >30 mg; 6.8 %), 85,586 patients based on an eGFR <60 mL/min/1.73m^2 (12.3%), and 155,583 patients with missing data for the score-related variables (age, BMI, smoking status, diabetic

retinopathy, HbA1C, HDL-C, triglycerides, SBP, DBP, UACR; 22.4 %). Consequently, 10,922 patients were included in the analysis.

Baseline characteristics

The mean age of the validation cohort at baseline was 61 years and 44.4% were female (**Table 1**). Overall, 16.3% of patients were smokers and 9.1% had diabetic retinopathy. The median diabetes duration was 6 years. Most patients tended to be obese, with a mean BMI of 31.7 kg/m^2. The median HbA1c, triglyceride, and HDL-C levels were 6.9% [52 mmol/mol], 166 mg/dL [1.90 mmol/L], and 46 mg/dL [1.19 mmol/L], respectively. The median SBP was 134 mmHg. All patients were non-albuminuric (versus a threshold of UACR ≥30 mg/g or AER ≥30 mg) at baseline, with a median AER of 1.4 mg and mean eGFR of 89.2 mL/min/1.73m^2.

Compared to the validation cohort from Jiang et al., patients in our study tended to be older (61 vs 55 years), were less likely to be smokers (16.3% vs 41.3%), had a slightly shorter duration of diabetes (6 vs 7 years), higher BMI (31.7 vs 26.6 kg/m^2), lower prevalence of diabetic retinopathy (9.1% vs 24.7%), and lower HbA1C (6.9% vs 8.5% [52 vs 69 mmol/mol]). The median duration of follow-up in our cohort was 59 months (4.9 years) compared with 2.9 years in the Jiang cohort [14].

Performance of the CKD in diabetes risk prediction model

At a median follow-up of 59 months, 4,084 patients (37.4%) had developed CKD and 6,838 (62.6%) had not. Those who developed CKD while having diabetes were older (63 vs 59 years, p<0.0001), more often female (47.0% vs 42.8%, p<0.0001), less often smokers (13.4% vs 17.9 %, p<0.0001), and had a longer diabetes duration (7 vs 6 years, p<0.0001) (**Table 1**) compared to the patients without CKD. The eGFR was already lower at baseline in those who later developed CKD (83.9 vs 92.4 mL/min/1.73 m^2, p<0.0001).

Patients who developed CKD had a higher total risk prediction score at baseline (17.2 vs 15.7 points, p<0.0001) (**Table 2**), with substantial differences (between those with and without CKD) seen in the

risk scores for age (mean 4.8 vs 4.0 points, p<0.0001), SBP (mean 2.8 vs 2.5 points, p<0.0001) and smoking (0.5 vs 0.7 points, p<0.0001).

The ROCs for the CKD risk prediction model are shown in **Figure 1**. The ROC AUC for our cohort was 0.58 (95% CI 0.57–0.59). The model adjusted for diabetes duration and follow-up duration had an AUC of 0.69 (95% CI 0.68–0.70), indicating that it provided improved discrimination.

Outcomes

Based on the data of Jiang et al. [14], patients in our cohort were categorized into the following four risk groups: low risk (score <12; n=2301), moderate risk (score 12 to 15.5; n=2741), high risk (score 16 to 26.5; n=5,611), and very high risk (score 27 to 37; n=269) (**Table 3**). The proportion of patients who developed CKD at the end of follow-up were 15.0%, 20.1%, 27.7%, and 40.2% in the four risk groups, respectively (**Supplementary Figure 1**). Kaplan-Meier curves for CKD grouped by risk scores are shown in **Figure 2**. Increasing risk score correlated with increasing cumulative risk of incident CKD over a median of 4.5 years of follow-up (Log-rank p<0.0001).

DISCUSSION

Principal findings

The aim of the current study was to validate the prediction model developed by Jiang et al. [14] for CKD in T2D risk in a German/Austrian T2DM population. The unadjusted base model showed moderate discriminative performance in the German/Austrian cohort, but discrimination improved when the model was adjusted for the duration of diabetes and follow-up, which had not been standardized during patient recruitment. In addition, a significant correlation was found between increasing risk score and the cumulative risk of CKD during follow-up. Using the model proposed by Jiang et al. we were able to identify groups of patients with different risk levels for early CKD.

Comparison with original validation cohort

The Jiang model was developed based on a meta-analysis of 20 cohort studies from Europe, Asia, and the Americas, involving 41,271 T2DM patients aged 39–75 years who were followed up for 1 to 20 years [14]. The prediction model incorporates nine risk factors, including lifestyle and clinical parameters (**Supplementary Table 1**). It was validated in an external cohort of 380 Chinese T2DM patients and was shown to have good discriminatory power for differentiating between high- and low-risk patients.

We evaluated the model in a large cohort of German/Austrian T2DM patients (n=10,922). Compared with the Chinese validation cohort, patients in our cohort tended to be older and have a higher BMI, but had a shorter duration of diabetes, a lower prevalence of diabetic retinopathy, and were less likely to smoke. The discrepancy in smoking prevalence may be explained by the different definitions applied. While Jiang defined smoker as a person that had smoked more than 100 cigarettes in their lifetime, we used the actual smoking status (yes vs. no) for the categorization of patients. This makes it likely that the higher proportion of smokers in the Jiang dataset is based on the inclusion of patients that had stopped smoking already but had smoked at least 100 cigarettes in their lifetime. In our study, 37.4% of patients developed CKD during a median follow-up of 4.9 years, compared with 25.8% of the Chinese cohort during a median follow-up of 2.9 years.

The ROC AUC in the Chinese validation cohort was 0.765 (95% CI 0.710–0.821), indicating good discrimination [14]. In contrast, the ROC AUC in our study population was 0.58 (95% CI 0.57–0.59) for the base model, indicating only moderate ability to discriminate between patients who will versus those do not develop CKD. Poorer performance of a prediction model in a new population compared with the original study is often seen, particularly when geographical or ethnical validation is being undertaken [24]. However, adjustment of models to take account of local circumstances can address relevant differences [24]. In our study, discrimination improved when the model was adjusted for diabetes duration and follow-up duration, providing an AUC of 0.69 (95% CI 0.68–0.70) which suggests potentially helpful discrimination [22]. Jiang selected a score of 16 as the optimal cutoff risk score with a higher sensitivity of 0.847 and a specificity of 0.677. When we look at Figure 3 of the manuscript though, a sensitivity of 0.847 is hardly compatible with a specificity of 0.677.

Outcomes

A significant correlation between increasing risk score and increasing cumulative risk of incident CKD was observed in German/Austrian patients, according to Kaplan-Meier curves of the actual incidence of CKD in four different risk groups based on risk scores. This is consistent with the findings of the original study published by Jiang et al. In their study, the high-risk and very high-risk groups of the validation cohort had approximately 9- and 46-fold greater risks of developing CKD compared with the low-risk group [14].

Limitations

One of the limitations of the study was a potential discrepancy in the method used to estimate eGFR between our study and the study by Jiang et al. did not specify the formula used for estimating eGFR. We elected to use a very recent formula which works well in both Caucasian people and people with other ethnicities [19]. Another limitation was that we were not able to describe the effect of drug treatment initiated between baseline and follow-up assessments, some of which could potentially affect the development of CKD (e.g. angiotensin converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors). A key strength of the study was the large sample size and the standardized data collection using a diabetes-specific electronic health record. Furthermore, the DPV initiatives can be regarded as representative for routine diabetes specialist care in Germany and Austria for adults with T2D. However, adult individuals with diabetes treated in primary care services are underrepresented.

Clinical Implications

The prerequisite of early detection of CKD is intensified monitoring of affected patients and the introduction of timely interventions to target modifiable risk factors and prevent or slow the rate of decline in renal function [9]. Several models have been developed to predict early CKD in T2D [10-12,14,25,26]. These models have incorporated a variety of clinical and laboratory parameters. The outcomes of interest have varied, for example, new microalbuminuria, new-onset macroalbuminuria, eGFR

<60mL/min/1.73 m^2, deterioration across eGFR categories, or a combination of eGFR <60mL/min/1.73 m^2 and/or UACR ≥30 mg/g (or AER ≥30 mg/L). A systematic review found that discrimination and calibration varied between models and time horizons, but individual models performed well for specific outcomes, such as albuminuria [27].

However, most of the models have not been validated outside of their original setting. It is important to assess the generalizability of prognostic models to different populations. Even models with good discriminative performance do not always perform as well for populations outside the original derivation cohort [28]. One of the few studies that has externally validated CKD risk prediction models in German populations evaluated six published CKD prediction models designed for use in a general population [29]. Most models showed fair discrimination, but only two showed good calibration; however, the overall diagnostic performance was considered suitable for identifying people at high risk for unknown CKD amongst a German general population [29].

The current study validated the risk prediction model developed by Jiang et al. [14], which focuses specifically on the risk of CKD in T2DM patients, in a German/Austrian population. The model has previously been validated in a Chinese population. The results of our study suggest that the model may also be relevant for determining risk of CKD in a German/Austrian T2DM population.

The model suggested by Jiang predicts early stage CKD in patients with type 2 diabetes based on demographic, clinical, and laboratory data. This makes it particularly useful in a routine clinical setting. This is important because prediction models that involve uncommon parameters, data that are complicated to calculate, or expensive tests are less likely to actually be used [29-31].

Conclusions

The CKD in T2D predictive model developed by Jiang et al., in which CKD in T2D is defined by a combination of reduced eGFR and/or albuminuria, achieved moderate discrimination and good calibration in a German/Austrian T2DM population. It was able to differentiate between groups with

different risk levels for early CKD in T2D. This risk model could potentially be helpful as part of a strategy of early detection and personalized intervention to prevent progression of CKD in T2D.

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Ethical approval and consent to participate

DPV was approved by the ethics committee of the University of Ulm (number 314/21), and data collection was approved by local review boards. All patients provided written informed consent.

Consent to publish

Not applicable.

Availability of data and materials

Patient consent does not include sharing original, patient-level data. However, on reasonable request, remote data access is possible.

Conflict of interest

No specific product-related competing interests. Funding by five major pharmaceutical companies is acknowledged. Funders had no influence on data collection, data analysis or the decision to publish the results.

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Authors' contributions

SK, PB, SL, and RWH were involved in the conception and design of the registry. CDM, SM, JR, JS, and TD collected the data. SL and RWH analyzed the data. SK and PB drafted the manuscript and all other

authors revised the article for important intellectual content. All authors gave final approval of the manuscript to be published.

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LEGENDS TO FIGURES

Figure 1: Receiver operating characteristic (ROC) curve for the CKD in T2D risk prediction model in the study cohort (10,992) for a) basic model; b) model adjusted for diabetes duration and follow-up duration

Legend: The area under the curve (AUC) and associated 95% confidence interval (CI) were 0.58 (0.57–0.59) for the base model and 0.69 (0.68–0.70) for the model adjusted for diabetes duration and follow-up.

Figure 2: Kaplan-Meier cumulative incidence plot for the freedom from CKD stratified by risk score

Legend: CKD, chronic kidney disease.

Supplementary Figure 1: Prevalence of CKD in four risk groups stratified by the risk score in the validation cohort

Legend: CKD defined as GFR <60 mL/min/1.73 m^2 and/or albuminuria. CKD, chronic kidney disease; GFR, glomerular filtration rate.

TABLES

Table 1: Baseline characteristics of patients in the validation cohort

		Jiang et al. [14]	DPV cohort	CKD (+)	CKD (-)	p-value
		Total (n=380)	Total (n=10,922)	(n=4,084)	(n=6,838)	
Age (years)		55 ± 9	61 ± 8.7	63 ± 8.1	59 ± 8.8	<0.0001
Female (%)		44.7	44.4	47.0	42.8	<0.0001
Smokers (%)		41.3	16.3	13.4	17.9	<0.0001
Diabetes duration (years)		7 (3, 12)	6 (2, 12)	7 (2, 12)	6 (2, 11)	<0.0001
Body mass index (kg/m^2)		26.6 ± 3.4	31.7 ± 6.2	32.0 ± 6.3	31.5 ± 6.2	0.0001
Systolic blood pressure (mmHg)		130 (120, 140)	134 (125, 144)	136 (127, 145)	133 (125, 143)	<0.0001
Diabetic retinopathy (%)		24.7	9.1	10.6	8.3	<0.0001
HbA1C	%	8.5 (7.3, 9.8)	6.9 (6.2, 8.0)	6.9 (6.2, 8.0)	6.9 (6.2, 8.0)	0.64
	mmol/mol	69 (56, 84)	52 (44, 64)	52 (44, 64)	52 (44, 64)	

TG	mmol/L	1.74 (1.18, 2.70)	1.90 (1.37, 2.69)	1.95 (1.41, 2.75)	1.85 (1.34, 2.65)	<0.0001
	mg/dL	154 (105, 239)	166 (120, 235)	171 (123, 241)	162 (117, 232)	
HDL-C	mmol/L	1.20 (1.10, 1.40)	1.19 (1.01, 1.45)	1.19 (0.98, 1.42)	1.22 (1.01, 1.45)	<0.01
	mg/dL	46 (43, 54)	46 (39, 56)	46 (38, 55)	47 (39, 56)	
Baseline UACR/AER (mg/g)		14.7 (11.9, 18.5)	1.4 (0.0, 12.0)	1.0 (0.0, 15.0)	1.5 (0.0, 11.0)	0.447
Baseline eGFR (mL/min/1.73 m^2)		99.4 ± 17.9	89.2 ± 14.7	83.9 ± 14.8	92.4 ± 13.7	<0.0001
Oral antidiabetic drugs (%)		98.7	69.3	69.4	69.3	0.86
Insulin (%)		53.9	52.3	56.1	50.5	<0.0001
Any antihypertensive drug (%)		Not reported	54.9	52.2	59.5	<0.0001
ACEi / ARB (%)		27.6	37.9	41.9	35.5	<0.0001
Statins (%)		25.0	30.7	32.4	29.6	0.0047
Follow-up, months		34.8 (24.0, 46.8)	59 (27, 98)	78 (40, 125)	43 (22, 80)	<0.0001

Legend: Data are median (IQR), mean ± SD, or %.

ACEi, angiotensin converting enzyme inhibitor; AER, albumin excretion rate; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high density-lipoprotein cholesterol; TG, triglycerides; UACR, urinary albumin creatinine ratio.

Table 2: CKD risk prediction model applied to DPV cohort patients at baseline

	DPV cohort Total (n=10,922)	**CKD (+)** (n=4,084)	**CKD (-)** (n=6,838)	**p-value**
Age	4.3 ± 2.2	4.8 ± 1.9	4.0 ± 2.2	<0.0001
Body mass index	2.2 ± 1.0	2.2 ± 1.0	2.1 ± 1.0	<0.0001
Smoker	0.7 ± 1.5	0.5 ± 1.4	0.7 ± 1.5	<0.0001
Diabetic retinopathy	0.3 ± 0.9	0.3 ± 0.9	0.2 ± 0.8	<0.0001
HbA1c	1.3 ± 1.6	1.3 ± 1.6	1.3 ± 1.6	1.000
Systolic blood pressure	2.6 ± 2.2	2.8 ± 2.2	2.5 ± 2.2	<0.0001
HDL-C	1.6 ± 1.2	1.6 ± 1.2	1.5 ± 1.2	<0.0001
Triglycerides	2.4 ± 2.0	2.5 ± 1.9	2.3 ± 2.0	<0.0001
UACR	1.1 ± 1.6	1.2 ± 1.7	1.1 ± 1.6	0.0020
Total score	16.3 ± 5.3	17.2 ± 5.1	15.7 ± 5.3	<0.0001

Legend: Values represent points from the CKD risk prediction model expressed as mean ± SD (see **Supplementary Table 1**).

CKD, chronic kidney disease; HDL-C, high density-lipoprotein cholesterol; UACR, urinary albumin creatinine ratio.

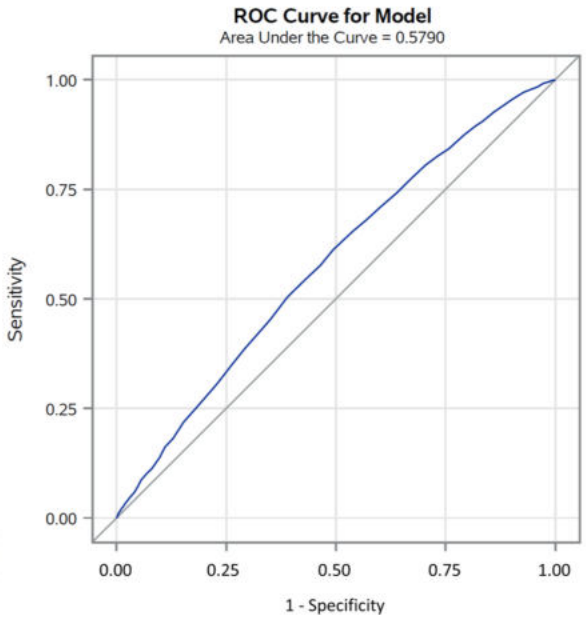
Table 3: Baseline characteristics of DPV cohort patients grouped by risk scores

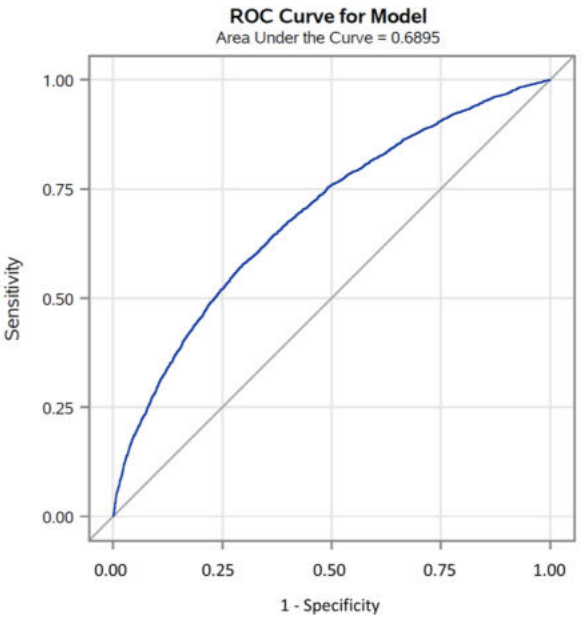
		<12	**12 – 15.5**	**16 – 26.5**	**27 – 37**	**p-value**
		(n=2,301)	(n=2,741)	(n=5,611)	(n=269)	<12 vs. 27-37
Age (years)		57.5 ± 9.5	60.4 ± 8.8	62.0 ± 8.0	64.0 ± 6.2	<0.0001
Female (%)		49.1	44.7	42.4	42.4	0.076
Smokers (%)		7.2	11.3	21.0	45.0	<0.0001
Diabetes duration (years)		4 (1, 10)	6 (2, 11)	7 (3, 13)	10 (5, 16)	<0.0001
Body mass index (kg/m^2)		29.0 ± 5.7	31.4 ± 6.2	32.8 ± 6.1	34.7 ± 5.5	<0.0001
Systolic blood pressure (mmHg)		125 (120, 133)	130 (122, 140)	140 (130, 150)	150 (140, 160)	<0.0001
Diabetic retinopathy (%)		2.0	5.2	12.7	36.1	<0.0001
HbA1C	%	6.4 (5.9, 6.9)	6.7 (6.1, 7.4)	7.3 (6.5, 8.5)	9.1 (8.0, 9.9)	<0.0001
	mmol/mol	46 (41, 52)	49 (43, 58)	57 (47, 70)	76 (64, 85)	
TG	mmol/L	1.34 (1.04, 1.63)	1.68 (1.27, 2.38)	2.22 (1.75, 3.06)	2.82 (2.13, 3.81)	<0.0001

	mg/dL	117 (91, 143)	147 (111, 208)	194 (153, 268)	247 (186, 333)	
HDL-C	mmol/L	1.42 (1.22, 1.68)	1.24 (1.03, 1.5)	1.11 (0.96, 1.29)	1.03 (0.91, 1.19)	<0.0001
	mg/dL	55 (47, 65)	48 (40, 58)	43 (37, 50)	40 (35, 46)	
Baseline UACR/AER (mg/g)		0.0 (0.0, 4.2)	0.0 (0.0, 10.0)	6.7 (0.0, 20.0)	20 (12, 20)	<0.0001
Baseline eGFR (mL/min/1.73 m^2)		92.3 ± 14.6	89.7 ± 14.5	88.0 ± 14.6	83.8 ± 15.0	<0.0001
Oral antidiabetic drugs (%)		68.0	69.9	69.7	66.9	0.71
Insulin (%)		40.6	46.9	58.6	75.1	<0.0001
Any antihypertensive drugs (%)		41.3	53.8	60.4	66.5	<0.0001
ACEi / ARB (%)		26.3	36.6	42.7	50.9	<0.0001
Statins (%)		24.8	31.3	32.4	38.7	<0.0001
Follow-up	months	59 (28, 108)	55 (27, 100)	53 (26, 95)	43 (22, 73)	<0.0001

Legend: Data are median (IQR), mean ± SD, or %.

ACEi, angiotensin converting enzyme inhibitor; AER, albumin excretion rate; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HDL-C, high density-lipoprotein cholesterol; TG, triglycerides; UACR, urinary albumin creatinine ratio.





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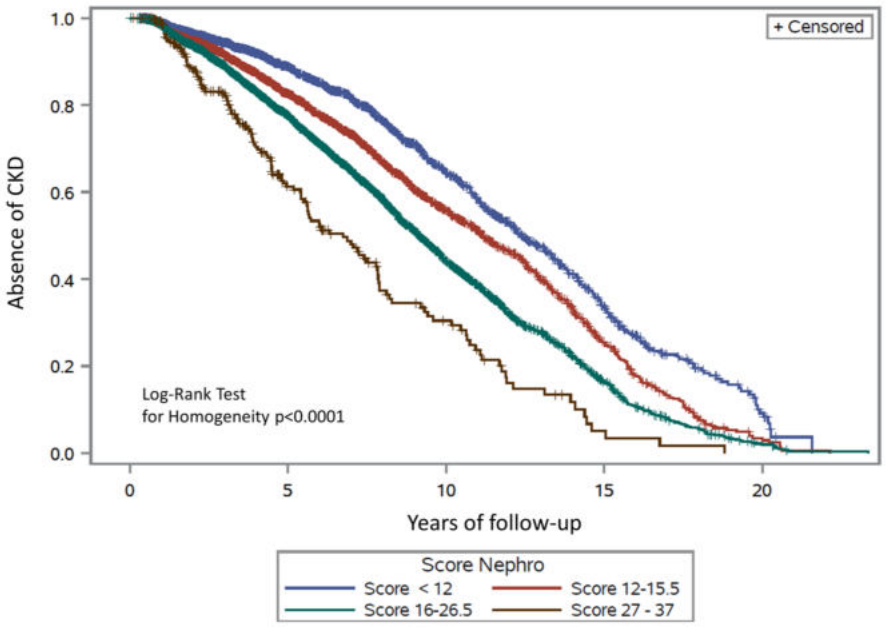

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