ORIGINAL ARTICLE

Predicting the Risk of Chronic Kidney Disease Among Type 2 Diabetes Mellitus Patients in a Primary Care Setting: An Evaluation of the QKidney Model

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ABSTRACT

Introduction: Diabetes mellitus is a major risk factor for chronic kidney disease (CKD). Thus, making routine screening among the diabetic group is necessary in order to reduce the burden of the disease. As such, various risk prediction models including QKidney model have been developed for early detection of CKD. However, the Qkidney model has not been validated in Malaysia. This study aimed to evaluate the performance of QKidney model in predicting a 5-year risk of developing CKD in a cohort of type 2 diabetes mellitus (T2DM) patients in the primary care setting. **Methods:** A total of 377 T2DM patients attended the primary care clinic at the town of Rawang, aged 30-74 years old, and free of CKD outcomes at baseline were recruited and followed-up for 5 years. Their CKD risk was calculated using the QKidney model. The predictive performance of QKidney model was assessed through discrimination and calibration analyses. **Results:** At the end of the 5-year follow-up, a total median QKidney score was 3.9% (IQR: 5.9). The median QKidney score of male participants (7.3%) was significantly higher than that of the females (3.0%) ($p < 0.001$). The QKidney model has a moderate discrimination in which the area under the receiver operating characteristic curve was 0.748, with good calibration ($\chi^2 = 13.039$, $p = 0.111$). **Conclusion:** It was found that the QKidney model had a moderate discriminative ability with good calibration. When taken together, it was suggested that the QKidney model could be utilized to predict a moderate-to-severe CKD risk in Malaysians with T2DM.

Keywords: Chronic kidney disease, Diabetes mellitus, Risk prediction, QKidney model

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INTRODUCTION

The prevalence of chronic kidney disease (CKD) is increasing globally, making it a major public health concern. Of note, type 2 diabetes mellitus (T2DM) is one of the major risk factors for CKD, in which the global prevalence of CKD among T2DM patients were reported between 30.0% and 40.0% (1, 2). As such, early detection and identification of diabetic population at risk of developing CKD via risk prediction model is vital to improve patient's care through preventive interventions (3). Patient's involvement in disease prevention can also improve their health status.

To date, various risk models have been developed to predict the onset of CKD such as Rotterdam-Hoorn (4), SCORED (5), PREVEND (6), and ADVANCE (7) scores. Nevertheless, a majority of these models, including QKidney model have not undergone validation process outside the population they were established (8).

The QKidney model is a multivariable risk model that has been developed in the UK to predict a 5-year risk of developing moderate-to-severe CKD in a primary care setting (9). Based on previous validation studies, the discrimination of QKidney model ranged from 0.837 to 0.910; positive predictive value = 0.147; sensitivity = 0.870; specificity = 0.805 (9, 10).

Among the above CKD predicting models, the QKidney model was selected for the current validation due to its high performance in the discrimination analysis, hence, giving a higher optimism of its utilization in a Malaysia context. In addition, it has been derived from a large cohort consists of 1.6 million participants from the general practices, as compared to other risk models which derivation populations were rather small. Without the needs of blood parameters in its risk calculation, the QKidney could potentially be a preferred model to be utilized by public health personnel to identify the high-risk group for CKD, especially during health promotion programs or outreach activities without an access to blood analyzers or blood test kits. Last but not least, the QKidney is able to compute the 5-year CKD risk development in a multiracial community like Malaysia, thanks to its derivative population which consists of

various ethnicities, including Chinese, Indian, and other Asians.

Despite a good discriminative performance with a high positive predictive value, specificity, and sensitivity, the QKidney model has not been validated in the Malaysia population, specifically among T2DM patients. Hence, in the absence of a local CKD risk prediction model, we aimed to assess the performance of QKidney model in a primary care setting in Malaysia.

MATERIALS AND METHODS

Study Design and Study Population

This was a retrospective cohort study. There were more than 35,000 patients in the patient registries across 13 GP clinics in the Rawang district. The T2DM patients attended one of these GP clinics in Rawang within the baseline period of 1 January 2010 until 30 June 2013, and those who regularly did follow-ups for at least 5 years were selected via a universal sampling method.

Sample Size Calculation

As a validation study of prognostic model, a minimum of 100 outcomes (i.e. moderate-to-severe CKD and ESRD) were required (11). Given a 30-40% prevalence of CKD among diabetic patients, a sample size of 500 T2DM participants will be satisfactory for this analysis. With a 10% estimated rate of incomplete information, the estimated sample size was 550.

Among the 35,000 patients, 550 T2DM patients were selected via universal sampling. We excluded 73 patients because they did not possess the complete variables necessary to calculate the CKD risk (Table 1). Twenty-five patients were excluded as their CKD status cannot be ascertained at the time of selection. As a result, 452 patients were eligible for analysis. Out of the number, 75 patients did not complete a 5-year follow-up. Finally, a total of 377 patients were validated as fit to be included in current analysis.

Data Collection

Baseline data such as patients' socio-demographic characteristics and clinical information on their first entry to the GP clinics were extracted from the patients' registries. These included the patient's age, gender, ethnicity, body mass index (BMI), smoking status, systolic blood pressure, status of hypertension and T2DM, histories of CVD, peripheral vascular disease, congestive cardiac failure and rheumatoid arthritis, as well as family history of renal disease. It is not a usual practice of GP clinics to gather such robust and detailed data as mentioned above in view of limited consultation time. This is especially true if the patients present with trivial complaints such as cough, cold, and back pain. However, such information is mandatory to be noted by the consulting doctors from an ethical point of view, with priority given to those patients who complaint of more serious medical illnesses such as chest pain and chronic joint pain or suspected for CVD, rheumatoid arthritis, and renal disease. These above variables are essential to compute the "predicted outcomes" (5-year risk of developing moderate-to-severe CKD) using the QKidney model.

Even though the data were extracted manually from patients' registry, they were not necessarily comprehensive. Patients with missing or incomplete data of any variable required for calculating the QKidney score were interviewed at the clinics or through phone calls. If the patients were deceased, their family members were called instead. Patients who were unreachable through phone calls or whose missing data cannot be retrieved were excluded.

Predictors of QKidney Model

Socio-demographic data, clinical information, and other variables of each patient (Table I) were keyed-in manually into the QKidney online risk engine to generate the "predicted outcomes" (i.e. development of moderate-to-severe CKD) for each individual.

Based on the above predictors, the QKidney model was utilized to compute the risk of developing CKD outcomes within 5 years in the form of percentage, ranging from 0 – 100%. A higher percentage signified a greater likelihood of developing CKD in 5 years.

Table I: Predictors of the QKidney Model

Predictors Entered to QKidney Model
• Age
• Body mass index
• Systolic blood pressure (mmHg)
• Smoking status (non-smoker, ex-smoker; current smokers)
• Ethnicity
• Diagnosed of T1DM
• Diagnosed of T2DM
• Diagnosed of rheumatoid arthritis
• Diagnosed of hypertension and under treatment
• Diagnosed of CVD
• Diagnosed of congestive cardiac failure
• Diagnosed of peripheral vascular disease
• Diagnosed of systemic lupus erythematosis
• Diagnosed of renal calculi
• Positive family history of renal diseases

Outcomes of the QKidney Model

The presence or absence of "observed outcomes" (i.e. actual development of moderate-to-severe CKD in 5 years) of each patient was acknowledged after 5-year following up, as recorded in the patients' registries. "Moderate-to-severe CKD" will be identified if the GFR was less than 45 mL/min/1.73m2 (Stage IIIB, Stage IV, and Stage V CKD), or in the presence of proteinuria, recorded renal transplant, dialysis, or diagnosis of nephropathy.

Handling of Data

All data from the patients' registries were manually extracted. Patients with missing or incomplete data (27.7%) were interviewed through phone calls. If the

patients were deceased, their family members were called instead upon an inform consent. Electronic records of patients with outlier values (e.g. systolic blood pressure, height, weight) were traced from the registries. However, those who were unreachable through phone calls (n = 74) and refused to be interviewed (n = 1) were excluded. The response rate was 83.4%.

Statistical Analysis

All statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS Version 22). Descriptive data were reported in means and percentages. Differences in socio-demographic and clinical characteristics at baseline between male and female patients were compared. Chi-Square test was used for categorical variables but independent t-test was for continuous variables. Due to the fact that the QKidney scores were found to be heavily skewed, the median scores were reported for male, female, and all participants instead of the mean values. Any significant difference between the medians were tested via non-parametric test. The ability and accuracy of the risk model in predicting the outcomes were determined using discrimination and calibration analyses.

Discrimination is defined as "the ability of the risk prediction model in distinguishing patients who are suffering from a CKD outcomes from those who do not, using an overall c-index" (12). The c-index is represented by the area under the receiver operating characteristic curve (ROC). The observed outcomes (y-axis) were plotted against the predicted outcomes (x-axis) in the ROC curve. Hence, the discrimination of a risk model is considered satisfactory if the c-index was close to 1, while a c-index of 0.5 and below indicates that the risk score tool is no better than chance. For the current research, 0.75 was the cut-off point for "good discrimination". The QKidney model was confirmed to have a moderate discrimination if the c-index fell between the range of 0.51 to 0.74 (13).

Calibration was employed to examine whether or not the "observed outcomes" differed significantly from the "predicted outcomes". The calibration of the QKidney model was determined using Hosmer-Lemeshow test (14). Poor calibration was indicated if the chi-square value and p-value of the QKidney model were greater than 20 and less than 0.05, respectively.

Ethics Approval

Study approval was granted by the UMMC Ethics Committee (MREC ID No: 2018711-6477), and all participants were provided informed consent. Prior to current study, a permission from all involved GP clinics was also granted.

RESULTS

A total of 377 patients' records from baseline were amounted into the analysis. Table II shows the socio-demographic data of the patient cohort. Female patients made up 58.4% of the population. The study population consisted of 37.1%, 32.4%, and 30.5% of Indians, Chinese, and Malays patients, respectively. The mean age was 58.65 ± 8.3 years at baseline. In terms of gender, there was no significant difference in baseline characteristics between males and females patients.

Table II: Sociodemographic characteristics of participants at baseline

	Male (n= 157)	Female (n = 220)	Total (n = 377)	P-value*
Age, year (mean ± SD)	59.23 ± 8.2	58.23 ± 8.4	58.65 ± 8.3	0.602
Age group (n, %)				
35 – 44	7 (4.5)	16 (7.3)	23 (6.1)	0.574
45 – 54	30 (19.1)	51 (23.2)	81 (21.5)	
55 – 64	76 (48.4)	100 (45.5)	176 (46.7)	
65 – 74	44 (28.0)	53 (24.1)	97 (25.7)	
Ethnicity (n, %)				
Malay	35 (22.3)	80 (36.4)	115 (30.5)	0.244
Chinese	58 (36.9)	64 (29.1)	122 (32.4)	
Indian	64 (40.8)	76 (34.6)	140 (37.1)	

*Independent t-test was used to compare the mean between male and female patients

Generally, the cohort was found to be overweight, evident by a mean BMI of 27.2 ± 4.5 kg/m2 (Table III). The blood pressure control was unsatisfactory for the patients in this age group, with a mean systolic blood pressure of 141.77 ± 47.2 mmHg. Majority of the population were non-smokers (83.3%), with slightly more than 10% were active smokers (10.1%), while 6.1% were ex-smokers.

The prevalence of congestive cardiac failure, peripheral vascular disease, rheumatoid arthritis, systemic lupus erythematous, and renal calculi was low in this cohort, that the prevalence rate was less than 2%. However, hypertension with treatment was highly prevalent, indicated by a prevalence rate of 68.7%. Of note, 2.7% of the patients had family history of renal diseases.

In terms of gender, male patients had significantly greater weight, proportion of smokers, prevalence of myocardial infarction, angina, stroke, or transient ischaemic attack, as well as family history of renal diseases compared to female counterpart.

Table IV shows the median score, calculated from QKidney model. The QKidney score was found to be heavily skewed to the left, that the median score was 3.9% with a skewness of 3.32. The median QKidney score of male participants (7.3%) was significantly higher than that of the female (3.0%), in which $p < 0.001$. The inter-quartile range was 3.8 – 8.2%.

In general, the area under the receiver operating

Table III: Lifestyle and clinical characteristics of participants at baseline

	Male (n = 157)	Female (n = 220)	Total (n = 377)	P –value*
Height, m (mean)	1.65 ± 0.1	1.54 ± 0.1	1.59 ± 0.1	0.107
Weight, kg (mean)	73.1 ± 14.4	65.2 ± 11.4	68.45 ± 13.3	0.025
BMI, kg/m^2 (mean)	26.7 ± 4.5	27.5 ± 4.5	27.20 ± 4.5	0.742
Systolic Blood Pressure, mmHg (mean)	144.0 ± 70.3	140.2 ± 17.2	141.77 ± 47.2	0.289
Smoking Status (n, %)				
Current smoker	36 (22.9)	4 (1.8)	40 (10.6)	<0.001
Non-smoker	99 (63.1)	215 (97.7)	314 (83.3)	
Ex-smoker	22 (14.0)	1 (4.3)	23 (6.1)	
Congestive Cardiac Failure (n, %)	0 (0.0)	1 (0.5)	1 (0.3)	0.398
Peripheral Vascular Disease (n, %)	1 (0.6)	2 (0.9)	3 (0.8)	0.769
Hypertension Under Treatment (n, %)	112 (71.3)	147 (66.8)	259 (68.7)	0.351
Rheumatoid Arthritis (n, %)	3 (1.9)	2 (0.9)	5 (1.3)	0.402
Systemic Lupus Erythematous (n, %)	1 (0.6)	1 (0.5)	2 (0.5)	0.810
Cardiovascular Disease (including myocardial infarction, angina, stroke, or transient ischaemic attack) (n, %)	31 (19.7)	21 (9.5)	52 (13.8)	0.005
Renal Calculi (n, %)	1 (0.6)	3 (1.4)	4 (1.1)	0.497
Family History of Renal Disease (n, %)	6 (3.8)	4 (1.8)	10 (2.7)	0.233

*Independent t-test was used to compare the mean between male and female patients

Table IV: QKidney scores of male, female and all participants

	Median Score,% (IQR)	P-value*
Male (n = 157)	7.3 (8.2)	<0.001
Female (n = 220)	3.0 (3.8)	
Total (N = 377)	3.9 (5.9)	

*Non-parametric test was used to compare median between male and female patients

characteristic curve (aROC) for QKidney model was 0.748, showing a moderate discrimination (Table V). The calibration for the model was good as the Hosmer-Lemeshow test result was $\chi^2 = 13.039$, p = 0.111 (Table VI).

Table V: Discrimination analysis of QKidney Score

	Male	Female	Total
aROC (95% CI)	0.784 (0.704 – 0.864)	0.755 (0.684 – 0.825)	0.748 (0.692 – 0.804)
P-value	<0.001	<0.001	<0.001
Discrimination	Moderate	Moderate	Moderate

Table VI: Calibration with Hosmer-Lemeshow Test

	Male	Female	Total
Chi-Square	9.111	9.800	13.039
P-value	0.333	0.279	0.111
Calibration	Good	Good	Good

DISCUSSION

To the best of our knowledge, this was the first validation of the QKidney model in a Malaysian T2DM population, who were initially free of CKD.

The total median QKidney score was 3.9%. The median QKidney score of male participants was significantly higher than that of the female. This result was in agreement with previous research that male patients showed a substantially higher prevalence of CKD than female patients (15, 16). Such gender discrepancy in CKD progression was related to a higher prevalence of hypertension (17, 18), hyperglycemia (19), albuminuria (20), dyslipidemia (21), body mass index (22), smoking (23), and sex hormones (24) among the male patients.

Importantly, the QKidney model seemingly predicted the moderate-to-severe CKD risk moderately in both genders, as evident by a moderate discrimination and good calibration analyses. The QKidney model did not seem to underestimate or overestimate the risk of CKD development among our patients, despite that they were exclusively diabetic and had a higher prevalence of hypertension (68.7%), as compared to the original QKidney cohort whose prevalence of T2DM and hypertension were only 4.2% and 12.4%, respectively. This was due to the calculation of QKidney score was not solely based on diabetes and hypertension status of the patients, but it took various predictors into account, hence, giving its robustness. Of note, the prevalence of cardiac failure (0.3%), peripheral vascular disease (0.8%), and renal calculi (1.1%) in this current cohort were comparable to those of the original QKidney cohort. Also, it is worth mentioning that the proportion of smokers in this cohort (10.6%) was relatively small compared to the original QKidney cohort (21.9%). When these predictors were taken together, the QKidney model was able to average out the effects of all predictors, thus, predicting the CKD risk accurately.

It is well known that renal filtration rate will decrease with age (25). Although the decline in GFR begins as early as the age of 30 to 40 years old, such decline is most apparent or drastic after the age of 60 to 70 years old due to a disproportionate fall in renal plasma flow (26). This was important evidence in our current research as the mean age of our patients was 58.65 years old at baseline, similar to the QKidney population whom was also younger than 60 years old (i.e. mean age of 47.3 years old at baseline). As the patients' ages from this cohort as well as the original QKidney population were below the 60-year-old cut-off point, the rate of GFR decline of the two cohorts was expected to be equal. Hence, the proportion of our patients ended up with CKD outcome at the end of 5 years will be similar to

that in QKidney derivative population.

As reported by the Malaysia Clinical Practice Guideline in Management of Hypertension, only 37.4% of the hypertensive patients achieved blood pressure control (i.e. less than 140/90 mmHg) (27). Not surprisingly, the patients in this cohort, who were diabetic, showed equally poor control of blood pressure as the original QKidney cohort. This similarity (i.e. an uncontrollably high systolic blood pressure) gave rise to a rather accurate prediction of the QKidney model in CKD development in Malaysia. According to Peralta et al., both systolic blood pressure and pulse pressure were significantly associated with kidney function even in subjects with presumably normal kidney function, by creatinine-based measures (28). This was agreed by Lee et al. whom reported that poorly controlled hypertension significantly increased as CKD progressed, mainly associated with the increase in pulse pressure (29). To date, however, the relationship between hypertension control and risk of CKD could not be clearly quantified (i.e. how many percents of CKD risk can be reduced with every 10 mmHg decrement in systolic blood pressure).

As a country that embraces the concept of "universalism" (i.e. health care as human right for all), the primary health care is easily accessible throughout Malaysia. Such primary care system is comparative to the National Health Service (NHS) in the United Kingdom where the derivation population was recruited. With the recent achievement of Universal Health Care (UHC) in Malaysia, every citizen is able to access a basic health care without any financial burden (30). With such a wide coverage of primary health care, more people are able to undergo screening tests at the local GP clinics. With the increment of screening tests and improved efficacy in diagnosis, it is unsurprising that most CKD outcomes are captured in the clinics' registries, giving a prediction that they are as accurate as that in the original QKidney cohort in the United Kingdom.

Although it was lower than the previous validation studies elsewhere, the discrimination, assessed by AUC under the ROC curve was found to be moderate in the QKidney model (aROC = 0.748) (9, 31). In other words, QKidney has a satisfactory ability to distinguish patients who suffered from CKD outcomes from those who did not. Furthermore, the QKidney model demonstrated a good calibration (χ^2 = 13.039, p = 0.111). This signified that the "observed outcomes" did not differ significantly from the "predicted outcomes".

The present study has several strengths. Firstly, our study was conducted in a primary care setting where the CKD risk profiles were more representative of the diabetic community compared to secondary and tertiary health care settings, where patients were usually presented at a later stage of CKD and manifested with more comorbidities.

Secondly, the current validation of QKidney model was not invasive as parameters such as serum creatinine and serum albumin were not required for validation purposes. As all information for the validation can be obtained during a routine general practice appointment without the need of blood sampling, this approach is less time and cost consuming. Hence, it is more patient-friendly with less ethical concerns raised.

From the perspective of cost-effectiveness, such non-invasive study has provided important insights to future validation studies, in view of limited resources and the rapidly growing burden of CKD.

We were able to establish the temporal sequence between exposures and CKD outcomes, as a retrospective cohort design was applied. Although it was not as strong as a prospective cohort study, such design was still more superior to a cross-sectional study in terms of identifying temporality.

Nevertheless, a few limitations were identified in the current study. Similar to other epidemiological studies, misclassification bias may occur when patients were incorrectly categorised with respect to their exposure status or outcome. Some of the patients were unable or unwilling to provide accurate or honest answers during the interviews (information bias). Some patients experienced difficulty to recall information regarding their exposure in the past (e.g. presence or absence of family history of renal disease, renal calculi) upon questioned (recall bias). This, however, was unavoidable due to the nature of retrospective cohort study.

In addition, the systolic blood pressure was measured by different personnel and via different sphygmomanometers across the GP clinics. Such unstandardized measurements can be explained by the fact that the original measurement of blood pressure was not intended for research purposes, but rather, for the purposes of clinical evaluation. All the above misclassification biases tended to reduce the discriminative power of the QKidney model (9).

The ethnic minorities were not included in our study. Unlike the original QKidney cohort which included 4.9% of minorities (e.g. Pakistani, Bangladeshi, Caribbean, Black African, and other Asians), our study mainly focused on Malaysian citizens, mainly consisted of the Malay, Chinese, and Indian communities (9).

Besides that, our sample size (N = 377) was small in comparison with other studies (9, 31). Although the number of patients in the GP clinic registry was large, many patients did not have sufficient data for the CKD risk calculation. With the constraints of time and funding, many of these patients cannot be contacted and traced for their missing data. This resulted in a huge exclusion of patients from our cohort.

Owing to majority of the patients were from GP clinics in the town of Rawang, the participants in this study may not fully representative of the entire population of individuals with T2DM in Malaysia. This limited the generalizability and extrapolation of our findings to other populations.

CONCLUSION

In summary, the purpose of this research was to assess the QKidney model with respect to its ability to predict CKD outcomes in a multiethnic, diabetic population in Malaysia. We observed that the male participants had greater weight and a larger proportion of smokers than females. They also had higher prevalence of CVD and CKD than the female counterpart. We also found that the QKidney model moderately estimated the CKD risks in T2DM patients, whereby its discriminative ability was found to be moderate, while its calibration was considered as good. When taken together, our analysis suggested that the QKidney model could be used to predict moderate-to-severe CKD risk in Malaysian with T2DM, albeit its limitations. In future studies, we recommended the development of a local and diabetes-specific risk model to predict the risk of CKD among patients with T2DM, which may provide a more accurate estimation of the outcomes in the context of Malaysian CKD patients.

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