Nomogram to Predict Rapid Kidney Function Decline in Population at Risk of Cardiovascular Disease

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Abstract

Background

To develop a simple model to predict risk of rapid kidney function decline (RKFD) in population at risk of cardiovascular disease.

Methods

8455 subjects aged ≥ 65 years or complicated diabetes or hypertension undergoing community annual health examinations between January 2015 and December 2020 were included. All participants were randomly assigned to a development cohort and a validation cohort in a 2:1 ratio. Rapid kidney function decline was defined as the reduction of estimated glomerular filtration rate (eGFR) $\geq 40\%$ during follow-up period. Cox regression analysis and stepwise approach were used to identify the risk factors. A nomogram based on these predictors was then developed, and discrimination, calibration and decision curve analysis were assessed.

Results

During the median follow-up period of 3.72 years, the incidence of rapid kidney function decline was 11.96% (n = 1011), 11.98% (n = 676) and 11.92% (n = 335) in the entire cohort, development cohort and validation cohort, respectively. Age, eGFR, hemoglobin, systolic blood pressure, and diabetes were identified as predictors for RKFD. The nomogram demonstrated a good discriminative power with the 5-year AUCs of 0.763 and 0.740 in the development and the validation cohort, respectively. Calibration plots also demonstrated a good fitness between the observed and predicted risk in both cohorts.

Conclusions

Risk stratification for rapid kidney function decline is achievable using a risk prediction nomogram based on clinical factors that are readily accessible in primary care. The utility of this nomogram in identifying individuals at high risk of RKFD in the community needs further investigation.

Introduction

Chronic kidney disease (CKD) is growing a critical global public health problem(1), there was an increase of 70% of persons worldwide had reduced estimated glomerular filtration rate (eGFR) in 2016 compared with 1990(2)². Rapid kidney function decline (RKFD) is associated with an increased risk of cardiovascular disease (CVD)(3), incidence CKD(4) and all-cause mortality(5). On the other hand, individuals with one or more risk factors of cardiovascular disease are often need to take medicines for multiple comorbidities, such as antihypertension medicine, antidiabetic drugs or antithrombotic agents,

these drugs may increase the burden on the kidney. Therefore, early identifying the individuals at high risk of RKFD may decrease the incidence of cardiovascular events in the population at risk of cardiovascular disease(6).

Risk predicted tools could be used to identify those at increased risk of RKFD. Many previous studies mainly focused on the risk of incident CKD which mainly defined as estimated glomerular filtration rate less than 60 ml/min/1.73m² (7–8). Risk model for predicting incident CKD just could be used in the individuals without CKD. Once those patients had progressed to CKD, these risk models were no more available. So, risk model for predicting RKFD, it could be used not only to predict the risk of rapid renal function decline in population without CKD, but also to predict the risk of deterioration of renal function in patients who have developed CKD. However, there were little previous work had focused on the risk model of RKFD. In the present study, data from a south Chinese cohort including population with one or more risk factors of cardiovascular disease was used to develop a risk prediction model to quickly identify individuals at high risk of RKFD.

Methods

Study Design and Participants

An ambispective cohort study was conducted among participants who underwent annual community physical examination in Guangzhou, Guangdong between January 2015 and December 2020. We retrospectively collected the data of the previous examination reports of participants from the primary medical institution, and we prospectively conducted the study from January 2020. Subjects aged ≥ 65 years or aged ≥ 35 years complicating diabetes or hypertension were enrolled in the analysis. The exclusion criteria included: 1) pre-existing end-stage kidney disease (estimated glomerular filtration rate < 15 mL/min/1.73m²), and 2) missing follow-up creatinine data. The Ethics Committee of the Nanfang Hospital has approved this study. And the written informed consents were obtained from participants enrolled prospectively. All the participants were randomly assigned to a development cohort and a validation cohort in a 2:1 ratio (Figure 1).

Procedures

The Modification of Diet in Renal Disease (MDRD) equation was used to calculate estimated glomerular filtration rate(9). Serum creatinine was measured by enzyme method. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, or use of antihypertensive medications. Diabetes mellitus was defined as random blood glucose level ≥ 11.1 mmol/L or fasting plasma glucose level ≥ 7.0 mmol/L or hemoglobin A1c (HbA1c) $\geq 6.5\%$. Body mass index (BMI) values calculated by the body weight and height of each participant as the follow equation: BMI = weight (kg)/[height (m)]². Smoking was classified as ever smoking vs never smoking. Exercise was divided into four categories according the frequency: never, once a week, few times a week and daily.

Endpoint

The endpoint of this study was rapid kidney function decline, defined as the reduction of estimated glomerular filtration rate $\geq 40\%$ during follow-up period. And participants without RKFD during the whole follow-up period were defined as event-free. After enrollment, laboratory measures and medical history were annually performed and collected during the follow-up period.

Patient and Public Involvement

The study was an ambispective cohort study. The retrospective data range from 2015 to 2019 was obtained from the electronic health records in primary medical institution. In 2020 year, we conducted face-to-face follow-up in the communities. And the results of our study had been send to participants with their examination reports. And we thanks all participants for their valuable contribution.

Sample size calculation and statistical analysis

Determination of minimum sample size

Use pmsampsize package of R(10-11) to calculate the minimum sample size required for developing a multivariable prediction model with a survival outcome using 5 candidate predictors. We hypothesis an AUC value of 0.72, so we selected the related predicted value of R^2D was 0.294 from table 1 in the work of Jinks et al(12) according to this AUC. The mean follow-up of the entire cohort was 3.72 years, and overall event rate was 0.1196. We select a timepoint of interest for prediction using the newly developed model of 5 years. Therefore, the events per candidate predictor parameter (EPP) was 11.3. In the development cohort, the minimum sample size required 945 participants. And because of the proportion of development cohort and validation group is 2:1, so the validation cohort need at least 473 participants.

Statistical Analysis

The unpaired, 2-tailed t test was used to analyse quantitative variables that were normally distributed and homoscedastic, this type of variables were summarized by mean $\pm$ SD. The Wilcoxon rank-sum test was used to analyse quantitative variables that were non-normally distributed or not homoscedastic, and this type of variables were summarized by median (interquartile range). Qualitative variables such as gender, comorbidities, life style, and medication situation were compared using the χ^2 test or Fisher's exact test and are expressed as percentages.

The multivariable Cox regression analysis was used to determine the risk factors of rapid eGFR decline. Variables with no more than 15% missing values and were imbalanced between groups in the development cohort or that are clinically important were included in the univariable Cox regression analysis. Variables with significance in the univariate analysis were preliminarily screened out and to be included in the multivariable Cox regression analysis. For the determination of significance variables, $p < 0.05$ was the threshold for identification. And we manually investigated the contribution of the remaining variables to determine the final predictors. Then, the risk prediction nomogram was formulated

based on the results and by using the rms package of R. To form the nomogram, each regression coefficient in the multivariable Cox regression was proportionally converted into a 0- to 100-point scale. The variable with the highest β coefficient (absolute value) was assigned 100 points. The points are added across each variable to calculate the total points, which are finally converted to predicted probabilities.

The nomogram was evaluated in both the training and validation cohorts. Discriminative ability was assessed using the concordance index (C-index) and the area under the time-dependent receiver operating characteristic curve (AUC). Calibration was assessed using a bootstrap approach with 1000 resamples to compare the predicted event rate with the observed one in the study. The entire cohort was also divided into low-risk group (≤ 150 points) and high-risk group (>150 points), and the event rate was also compared between groups. Missing data were not imputed. In all analyses, $P < 0.05$ was considered statistically significant. All analyses were conducted with R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) and SPSS (version 26.0).

Results

Population Characteristics

The study design and participants are shown in the Figure 1. After the exclusion of those missing follow-up creatinine data ($n=6166$) and the baseline eGFR $\leq 15\text{mL/min/1.73m}^2$ ($n=11$), 8455 high CVD risk participants were included in the study. 5645 and 2810 participants were categorized into the development and validation cohorts, respectively (Table S1). During the median of 3.72 years follow-up, the incidence of RKFD was 11.96% ($n = 1011$), 11.98% ($n=676$) and 11.92% ($n=335$) in the entire cohort, development cohort and validation cohort, respectively. Participants developed RKFD approximately two-third were female (68.8%), and the mean age was 67.66 ± 6.70 years. No significant differences were identified between the development and validation cohorts.

Table 1 shows the basic characteristics of the study participants. Compared with those without RKFD, the participants who developed RKFD were likely to be female and to have a history of type 2 DM and hypertension, to be taking metformin for DM. They also were older and had a higher SBP but not a higher DBP. As for laboratory examinations, lower hemoglobin and serum creatinine and cholesterol and uric acid (UA), and higher eGFR were found among those developing RKFD. Whereas they were less likely to be ever smokers or drinkers.

Predicting Nomogram Development

The results of univariable COX regression analysis are detailed in Table S2. Through multivariable COX regression analysis and a backward stepwise approach, age (HR: 1.056, 95% CI: 1.044-1.068), eGFR (HR: 1.022, 95% CI: 1.019-1.025), hemoglobin (HR: 0.985, 95% CI: 0.98-0.989), SBP (HR: 1.007, 95% CI: 1.004-1.011), and diabetes (HR: 1.902, 95% CI: 1.606-2.252) were selected as predictors of RKFD (Table 2). The nomogram for predicting 5-year RKFD risk was then built based on these five variables (Figure 2).

Validation of the Predicting Nomogram

In both cohorts, the nomogram demonstrated good discriminative power with C-index of 0.73 in the development cohort and 0.71 in the validation cohort, respectively. The 5-year AUCs were 0.763 in the development cohort and 0.74 in the validation cohort (Figure 3, A,B).

The calibration plots for the 5-year RKFD indicated that there was good agreement between the actual observations and predictions made using the nomogram in both the development cohort and the validation cohort (Figure 3, C, D).

Risk Stratification of RKFD Based on the Nomogram Scores

Based on the predicted 5-year incidence of RKFD in relation to different total nomogram scores, we further divided the participants into 2 score categories: low-risk group (scores ≤ 150 , 5-year risk = 11.90%), and high-risk group (scores > 150 , 5-year risk = 47.98%). The predicted rates of RKFD in the validation cohort were closed to those in the development cohort inside both of the risk groups (Supplement figure 1). And Kaplan-Meier curves of RKFD for patients in the low- and high-risk groups shown that this risk classification system had a good discriminative power, the incidence of RKFD was significantly increased in the high-risk group (Figure 4).

Discussion

The present study maybe the first to develop a nomogram for the prediction of 5-year risk of RKFD. By examined predictors of rapid kidney function decline among individuals at high cardiovascular disease risk in the community, we developed a simple nomogram including the predictors: age, eGFR, hemoglobin, SBP, and diabetes. The risk prediction model demonstrates good discrimination and calibration. And the entire cohort was divided to low-risk group (≤ 150 points) and high-risk group (> 150 points). It is enables us to identify individuals at high risk of RKFD readily.

Rapid declining kidney function associates with higher risk for myocardial infarction (MI), heart failure (HF), stroke, and peripheral arterial disease (PAD) among patients with or without CKD(13). Especially for the elderly adults who are likely to suffer from cardiovascular disease (CVD) and CKD. The elderly and the adults with the hypertension or/and diabetes are the key groups of primary health care. How to quickly identify individuals with rapidly declining renal function in this population is very meaningful, which is expected to reduce the occurrence of cardiovascular disease events and improve the quality of life. About how to define the “rapid declining kidney function”, some studies choose the define of annual eGFR declines of 3 ml/min per 1.73m²(13–14) or 5 ml/min per 1.73m²(15). But, recently, a Japanese study among healthy subjects reported that the eGFR decline non-linearly altered according to age(16). Compared with these absolute values, the percentage decrease of eGFR seems to be a more personalized indication of the decline of renal function. And there was a large cohort study included 13,029 participants of ARIC showed that annual decline (annual decline $\geq 5.65\%$) in eGFR was at significantly greater risk for coronary heart disease(3). In 2014 year, the NKF and FDA published a series articles to

suggest that eGFR declines of 40% decline could be an effective surrogate endpoint in the clinical trials(17).

In this study, predict factors of RKFD included 5 variables: age, baseline eGFR, hemoglobin concentration, SBP, and diabetes. This finding was partly consistent with those of prior studies(4, 8, 18–21). In a community-based retrospective cohort study among 51,938 adults who underwent annual medical examinations between 1999 and 2013, it observed older age, higher SBP, proteinuria, and smoking were related to faster loss of kidney function(19). A prospective observational cohort study - KNOW-CKD Study(20) and a study based on Chinese population(15) also found that SBP had a greater association with adverse kidney outcomes than DBP. These results clearly emphasize that SBP is an important correlated factor for faster loss of kidney function. Anemia is also an independent risk factor for progression of kidney function among the middle-aged and elderly population(21). As we all known, CKD often complicated anemia mainly due to iron deficiency and erythropoietin deficiency(22–23). On the contrary, anemia could also contribute to kidney function decline, the mainly relevant mechanism is hypoxia and/or increased oxidative stress(24). Anemia decrease the oxygen delivery to tissues and thus affects organ function including kidney and cardiac function(21). For the baseline eGFR, the stage of baseline eGFR has been added to the risk prediction equation for incident CKD(8, 25), and we found the baseline eGFR also contributed to the rapid eGFR decline (HR = 1.022, 95%CI 1.019–1.025), this further confirmed that the baseline value of eGFR is a predictor for rapid kidney function decline(26). There is no doubt that diabetes is an independent risk factor for kidney function decline. Two-thirds of those with type-2 diabetes have or will develop CKD mainly derived from altered metabolic transcriptional networks and mitochondrial functional deficits(27).

Strengths And Limitations

To our knowledge, this might be the first study to develop a nomogram for the prediction of 5-year risk of RKFD in a high CVD risk population. Our nomogram derived from clinical factors that are readily accessible in primary care. And it with good discriminative power enables us to identify individuals at high risk of RKFD readily and take action in time. Compared to the traditional hard end point such as chronic kidney disease or end stage renal disease, eGFR declining more than 40% shows the dynamic change of the kidney function among individuals with or without CKD, it is more meaningful for the primary care.

This study has several limitations. First, majority of participants lack of albuminuria data at baseline. Positive proteinuria is related to increasing risk of kidney disease and death(28). However, there is a large proportion of people have kidney disease without albuminuria(29). And for the community primary care, proteinuria is often measured in patients with DM, so our nomogram maybe more available for the community health institution. Second, the nomogram developed in our study just incorporated routinely collected data, its predictive accuracy could be enhanced by adding newly identified biomarkers or genotype data of RKFD(30). Third, there was no external validation of our model, although it shows good C-index and AUCs in the internal validation cohort.

Conclusions

By using the demographic, clinical and laboratory variables from electronic health records, it is clinically applicable and simple to use, and it's easier to promote the predict nomogram in primary health care. Compared to only preventing incident CKD in the non-CKD population, early identifying the high-risk individuals of rapid kidney decline in the population with CKD or without CKD will be helpful for more persons. And we further defined the optimal cutoff value as 150 to be the risk stratification point. However, further external validations are needed before clinical generalization.

Declarations

Ethical Statement

The study was approved by the Ethics Committee of the Nanfang Hospital, Southern Medical University.

Consent for publication

Written informed consent for publication was obtained from all participants who needed to receive prospective data collection.

Competing Interests

None of authors declared potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' Contributions

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. ZQX and XJC contributed to the conception or design of the work. ZQX, LJY, LL, LGD, LXQ, ASL, LHB, ZJY, LY, CYD, PJZ, CYJ, LXX, LXB and ZSY contributed to the acquisition, analysis, or interpretation of data for the work. ZQX drafted the manuscript. ZQX, LL, LJY, XJC and ZXL critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Availability of data and materials

Data relevant to this study are available upon reasonable request to the corresponding authors.

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Tables

Table 1
Baseline characteristics of participants with and without follow-up RKFD in the study cohort.

Variables	Missing data (%)	RKFD (n = 676)	Non-RKFD (n = 4969)	P value
Age,y	0 (0.00)	68.31 ± 6.84	67.57 ± 6.67	< 0.010
Female, n (%)	0 (0.00)	465 (68.8)	3003 (60.4)	< 0.001
Height (cm)	0 (0.05)	154.31 ± 7.44	156.10 ± 8.08	< 0.001
Weight (kg)	4 (0.07)	58.80 ± 10.49	59.61 ± 10.31	0.058
BMI (kg/m ²)	4 (0.07)	24.64 ± 3.73	24.42 ± 3.57	0.128
Waist (cm)	27(0.48)	84.96 ± 9.03	84.94 ± 9.46	0.954
SBP (mmHg)	11 (0.19)	150.41 ± 20.72	145.62 ± 20.29	< 0.001
DBP (mmHg)	15 (0.27)	81.21 ± 11.58	81.79 ± 11.29	0.217
Diabetes mellitus, n (%)	0 (0.00)	196 (29.1)	894 (18.6)	< 0.001
Hypertension, n (%)	0 (0.00)	557 (82.4)	3675 (74.0)	< 0.001
Ever smoking, n (%)	1 (0.02)	79 (11.7)	926 (18.6)	< 0.001
Ever drinking, n (%)	0 (0.00)	48 (7.1)	630 (12.7)	< 0.001
Exercise	4 (0.07)			< 0.001
Never, n (%)		356 (52.7)	2239 (45.1)	
Once a week, n (%)		152 (22.5)	727 (14.6)	
Few times a week, n (%)		28 (4.1)	261 (5.3)	
Daily, n (%)		140 (20.7)	1738 (35.0)	

Abbreviations: Values are mean ± standard deviation or n (%); RKFD, rapid kidney function decline; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; RBC, red blood cell; WBC, white blood cell; PLT, platelet; ALT, alanine aminotransferase; BUN, urea nitrogen ; Scr, serum creatinine; eGFR, estimated glomerular filtration rate ; ACEI, angiotensin-converting enzyme inhibitor ; ARB, angiotensin receptor antagonists; CCB, calcium channel blocker.

Variables	Missing data (%)	RKFD (n = 676)	Non-RKFD (n = 4969)	P value
Laboratory examination				
Fasting glucose (mmol/L)	6 (0.11)	4.72 [4.26, 5.52]	4.88 [4.43, 5.50]	0.003
RBC (10 ¹² /L)	90 (0.16)	4.63 [4.28, 5.08]	4.64 [4.33, 5.01]	0.790
Hemoglobin (g/L)	57(1.01)	134.00 [124.00, 143.00]	137.00 [127.00, 146.00]	< 0.001
WBC (10 ⁹ /L)	27 (0.48)	6.60 [5.70, 7.60]	6.59 [5.60, 7.70]	0.357
PLT (10 ⁹ /L)	150 (2.66)	209.00 [174.25, 247.00]	211.00 [177.00, 250.00]	0.259
ALT (U/L)	10(0.18)	23.60 [17.80, 32.65]	22.50 [17.20, 30.20]	0.001
BUN (mmol/L)	23 (0.41)	5.10 [4.40, 6.20]	5.50 [4.60, 6.40]	< 0.001
Cholesterol (mmol/L)	13 (0.41)	5.20 [4.46, 5.91]	5.35 [4.64, 6.11]	< 0.001
Triglyceride (mmol/L)	11 (0.19)	1.38 [0.96, 2.02]	1.42 [0.99, 2.08]	0.262
Uric acid (umol/L)	1146(20.3)	323.90 [261.30, 404.00]	375.15 [304.72, 452.10]	< 0.001
Scr (umol/L)	0 (0.00)	54.45 [45.80, 68.10]	67.70 [56.40, 81.80]	< 0.001
eGFR (mL/min/1.73m ²)	0 (0.00)	112.82 [91.70, 136.01]	90.60 [76.12, 106.36]	< 0.001
Medications				
ACEI/ARB, n (%)	321 (5.69)	57 (8.8)	395 (8.4)	0.803
CCB, n (%)	322 (5.7)	61 (9.4)	491 (10.5)	0.450
β-blocker, n (%)	322(5.7)	14 (2.2)	167 (3.6)	0.084
Diuretics, n (%)	322(5.7)	5 (0.8)	42 (0.9)	0.927
Metformin, n (%)	199 (3.5)	34 (5.2)	168 (3.5)	0.043
Abbreviations: Values are mean ± standard deviation or n (%); RKFD, rapid kidney function decline; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; RBC, red blood cell; WBC, white blood cell; PLT, platelet; ALT, alanine aminotransferase; BUN, urea nitrogen ; Scr, serum creatinine; eGFR, estimated glomerular filtration rate ; ACEI, angiotensin-converting enzyme inhibitor ; ARB, angiotensin receptor antagonists; CCB, calcium channel blocker.				

Table 2
Univariable and Multivariable Cox Regression Analysis of Rapid Kidney Function Decline.

Variables	Univariable analysis		Multivariable analysis	
	Adjusted HR (95%CI)	P value	Adjusted HR (95%CI)	P value
Age, years	1.04 (1.03–1.05)	< 0.001	1.056 (1.044–1.068)	< 0.001
Female	0.72(0.61–0.85)	< 0.001		
Height, cm	0.98 (0.97–0.99)	< 0.001		
BMI, kg/m ²	1.00 (0.99–1.03)	0.600		
SBP, mmHg	1.01 (1.00-1.01)	< 0.001	1.007 (1.004–1.011)	0.002
Diabetes mellitus	1.99 (1.69–2.35)	< 0.001	1.902 (1.606–2.252)	0.002
Hypertension	1.56 (1.28–1.90)	< 0.001		
eGFR, mL/min/1.73m ²	1.02 (1.02–1.02)	< 0.001	1.022 (1.019–1.025)	< 0.001
Ever smoking	0.65 (0.52–0.83)	< 0.001		
Ever drinking	0.65 (0.49–0.87)	0.002		
Hemoglobin	0.98 (0.97–0.99)	< 0.001	0.985 (0.98–0.989)	0.002
Cholesterol	0.89 (0.83–0.96)	< 0.010		
Uric acid	1.00 (1.00-1.01)	< 0.001		
ALT	1.00 (1.00–1.00)	0.500		
BUN	0.99 (0.97–1.01)	0.400		
Metformin	2.04 (1.44–2.88)	< 0.001		
Abbreviations: HR: hazard ratio; BMI: body mass index; SBP: systolic blood pressure; eGFR: estimated glomerular filtration rate; ALT: alanine aminotransferase, BUN: blood urea nitrogen.				

Figures

Figure 1

Flow chart of study design and participants. eGFR: estimated glomerular filtration rate.

Figure 2

Nomogram to predict the 5-year risk of rapid kidney function decline (RKFD). To use the nomogram, find the position of each variable on the relative axis, draw a line to the points axis for the number of points, add the points derived from all the variables together, and refer to the total points axis to determine the 5-year of RKFD probabilities. eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure.

Figure 3

Receiver operating characteristic curves and predictive value validation of the nomogram. The 5-year AUC in the development cohort (A) and in the validation cohort (B). Validity of the predictive value in the development cohort (C) and in the validation cohort (D) of the 5-year CKD probability. AUC: area under the curve.

Figure 4

Kaplan-Meier curves of incident rapid kidney function decline for patients in the low- and high-risk groups stratified by total score of 150 points calculated from nomogram. Low-risk group (scores ≤ 150), high-risk group (scores > 150).

Supplementary Files

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- [Supplementalmaterial.pdf](#)