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A risk scoring system for the decreased glomerular filtration rate in Chinese general population

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Abstract

Objective: The aim of this study was to establish a risk scoring system for the decreased glomerular filtration rate (GFR) in Chinese general population.

Methods: Totally 781 participants who underwent a health checkup in The First Affiliated Hospital of Nanjing Medical University from January to September 2017 were involved in the study. Significant variables chosen by multivariable logistic regression analysis were allocated the integral scores in proportion to its odds ratio (OR), and then the risk of decreased GFR was assessed based on the scores.

Results: The people with abnormal homocysteine (Hcy) level (OR: 1.534, 95% confidential interval [CI]: 1.075-2.190, P = .018), males (OR: 2.054, 95%CI: 1.365-3.092, P < .001), and those at the age of 46-52 years (OR: 2.943, 95%CI: 1.546-5.605, P = .001), 52-59 years (OR: 3.664, 95%CI: 1.937-6.931, P < .001) and ≥59 years (OR: 13.452, 95%CI: 7.339-24.657, P < .001) were subjected to GFR reduction. These three variables were allocated the integral scores in proportion to its OR, and four risk categories were divided according to the scores. The prevalence of the decreased GFR in people with low (score 0-4, n = 8), below the average (score 4-6, n = 37), above the average (score 6-13, n = 47), and high risks (score ≥ 13, n = 103) was 5.26%, 16.89%, 22.93% and 50.24%, respectively, and this prevalence raised with the increase of scores (P < .001).

Conclusions: A risk scoring system is developed in this study, which may offer a specific risk stratification for GFR reduction in Chinese general population.

KEYWORDS

Chinese population, chronic kidney disease, glomerular filtration rate, homocysteine, risk score

1 | INTRODUCTION

Chronic kidney disease (CKD), characterized by high prevalence, low awareness rate, poor prognosis, and high medical costs, has become a global public health problem. It is defined as either kidney damage or reduced kidney function (decreased glomerular filtration rate, GFR) for three or more months and is associated with an increased risk of all-cause and cardiovascular mortality as well as end-stage renal disease (ESRD).[1,2] The prevalence of CKD was estimated to be 14.3% in general populations and 36.1% in high-risk populations

from low- and middle-income countries.[3] A cross-sectional survey from China indicated that the prevalence of CKD was 16.9% and 18.3%, respectively, in the north and southwest regions.[4] The main outcomes of CKD include complications of reduced kidney function, progression to kidney failure and cardiovascular disease.[5] The studies have displayed that early screening and intervention are conductive to preventing or delaying some adverse outcomes for CKD patients at the early stage.[6,7]

Glomerular filtration rate is considered as the best measuring indicator for overall kidney function in disease and health.[8] It varies greatly based on the age, gender, race, and body size. The normal GFR usually ranges from 120 to 130 mL/min per 1.73 m^2 and decreases with age.[9-11] The prevalence of CKD complications will increase if the GFR is <60 mL/min per 1.73 m^2.[5] The decreased GFR is reported to be associated with a variety of complications, including neuropathy,[12] anemia,[13] hypertension,[14] bone mineral metabolism,[15] and so on. In the elderly, a decline in GFR has become an independent predictive factor for adverse outcomes,[16-18] such as cardiovascular disease and death. However, this decreased GFR can be improved or prevented by treatments at an early stage. It is thus of great importance to establish a risk scoring system for the decreased GFR.

Until now, the risk models for incident CKD have been determined in American general population,[19,20] but these risk models may be inappropriate to assess the risk in Asian population due to different risk factors.[21] Therefore, in this study, the risk factors related to the decreased GFR were investigated in Chinese general population, and a risk scoring system for the decreased GFR was established based on these risk factors.

2 | MATERIALS AND METHODS

2.1 | Study population

This was a retrospective study involving 781 participants who underwent a health checkup in The First Affiliated Hospital of Nanjing Medical University from January to September 2017. All the participants were informed consent, and voluntarily participated in the study. This study was approved by the Institutional Review Board of The First Affiliated Hospital of Nanjing Medical University (approval No.: 2018-SR-181).

Inclusion criteria were as follows: (a) people above 40 years old; (b) healthy people or those with stable diseases, such as hypertensive patients with the blood pressure controlled in the range of 140/90 mm Hg by adjusting the lifestyles or using drugs; (c) people with the fasting blood glucose (FBG) <7.0 mmol/L, glycosylated hemoglobin <7%, aspartate aminotransferase (AST) <40 U/L, alanine aminotransferase (ALT) <40 U/L, blood urea nitrogen (BUN) of 1.8-7.5 mmol/L, and serum creatinine (Scr) of 0.49-1.54 mg/dL; (d) hemoglobin of 110-176 g/L, with the hematocrit value of 0.37-0.47 for females and 0.40-0.52 for males; (e) normal results of the routine

urine test; (f) people with emotional stability and a certain learning and memory capabilities, as well as those without mental disorders. Exclusion criteria were as follows: (a) previous history of malignant tumors and severe organic diseases that can affect the activity of daily living; (b) people with severe pleural effusion or ascites, serious edema or malnutrition, skeletal muscle atrophy, amputation and ketoacidosis; (c) people who took trimethoprim, cimetidine or angiotensin receptor inhibitors or angiotensin-converting enzyme inhibitors, and those who were treated with hemodialysis and glucocorticoids.

2.2 | Collection of basic information

A survey questionnaire was designed and was filled in by the participants with the assistance of trained nurses. The contents of the questionnaire included the age, gender, body weight, body height, occupation, dietary habits, history of various diseases, and so on. The body height and weight of participants without shoes were measured to ensure the accuracy. The body mass index (BMI) was calculated according to the formula of the body weight in kilograms/ body height in meters squared.

The blood pressure in the right arm of participants in a sitting position was measured and recorded at least 3 times using an automatic sphygmomanometer. The interval of each measurement was at least 2 minutes, and the difference of blood pressure between two measurements was not more than 4 mm Hg. The average value of three measurements was taken finally.

2.3 | Detection of blood samples

Venous blood was drawn from the fasting participants in the morning after an overnight of 8-12 hours and then were centrifuged 10 minutes at 3000 r/min. The serum was separated timely. The blood biochemical indicators were detected using an automatic biochemical analyzer (type AU5800; Beckman Coulter, Inc.). Scr level was measured by enzymic method. The plasma homocysteine (Hcy) level was detected using fluorescent quantitation detection method, with the kits provided by Jinan Xingen Biotechnology Co., Ltd. The normal reference value of Hcy was set as 0-15 μmol/L.

2.4 | Assessment on the decreased GFR

Based on NKFK/DOQI clinical practice guidelines,[22] GFR < 90 mL/min per 1.73 m^2 was set as the decreased GFR in this study. The GFR was estimated by chronic kidney disease-epidemiology collaboration (CKD-EPI) equation in 2009: (1) female, Scr ≤ 0.7 mg/dL, GFR = 144 × (Scr/0.7)$^{-0.329}$ × (0.993)^{Age}; (2) female, Scr > 0.7 mg/dL, GFR = 144 × (Scr/0.7)$^{-1.209}$ × (0.993)^{Age}; (3) male, Scr ≤ 0.9 mg/dL, GFR = 141 × (Scr/0.9)$^{-0.411}$ × (0.993)^{Age}; (4) male, Scr > 0.9 mg/dL, GFR = 141 × (Scr/0.7)$^{-1.209}$ × (0.993)^{Age}.[23]

2.5 | Clinical risk scoring system

Based on the risk scoring system made by Takagi et al,[24] a risk scoring system for the decreased GFR was established by logistic regression analysis. Significant variables were chosen using a multivariable logistic regression model and were allocated the integral scores in proportion to its odds ratio (OR). Four risk categories were determined based on the quartile of total scores, including the low risk (score 0-4), the risk below the average (score 4-6), the risk above the average (score 6-13), and the high risk (score ≥13).

2.6 | Statistical analysis

SPSS 22.0 software (SPSS Inc) was adopted to analyze the data. The data with normal distribution were expressed as the mean ± standard deviation ($\overline{x} \pm s$) by t test, whereas those with abnormal distribution were manifested as the median and quartile (M[Q25, Q75]) using rank-sum test. The enumeration data were presented as n (%) with chi-square test. The multivariable logistic regression model was used to analyze the factors with significant differences through the univariate analysis. According to the OR scores of relevant risk factors, a risk scoring system for the decreased GFR was established, and the receiver operating characteristic (ROC) curve was drawn to assess the predictive value of this system. The value of $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Basic information of participants

A total of 781 participants including 547 males and 234 females were involved in the study. They were at the age of 40-89 years, with the

TABLE 1 Univariate analysis of the decreased GFR (n, %)

Variables	Normal GFR group (n = 586)	Decreased GFR group (n = 195)	χ^2/Z	P
Gender			5.870	.015
Male	397 (67.75)	150 (76.92)		
Female	189 (32.25)	45 (23.08)		
Age (y)			9.592	<.001
<46	180 (30.72)	15 (7.69)		
46-52	154 (26.28)	36 (18.46)		
52-59	150 (25.60)	41 (21.03)		
≥59	102 (17.41)	103 (52.82)		
BMI (kg/m^2)			-0.315	.753
<18.5	9 (1.54)	4 (2.05)		
18.5-23.9	192 (32.76)	65 (33.33)		
>23.9	385 (65.70)	126 (64.62)		
Hcy (μmol/L)			12.233	<.001
Abnormal	255 (43.52)	113 (57.95)		
Normal	331 (56.48)	82 (42.05)		
TC (mmol/L)			0.254	.614
Abnormal	135 (22.80)	47 (24.10)		
Normal	457 (77.20)	148 (75.90)		
TG (mmol/L)			0.340	.560
Abnormal	131 (22.35)	52 (26.67)		
Normal	455 (77.65)	143 (73.33)		
HDL-C (mmol/L)			0.320	.572
Abnormal	169 (28.84)	81 (41.54)		
Normal	417 (71.16)	114 (58.46)		
LDL-C (mmol/L)			0.585	.444
Abnormal	230 (39.25)	93 (47.69)		
Normal	356 (60.75)	102 (52.31)		

Note: Homocysteine (Hcy) reference value: 0-15 μmol/L; total cholesterol (TC) reference value: 2.9-6.0 mmol/L; triglyceride (TG) reference value: 0.2-2.0 mmol/L; low-density lipoprotein cholesterol (LDL-C) reference value: 1.55-3.35 mmol/L; high-density lipoprotein cholesterol (HDL-C) reference value: 1.1-1.7 mmol/L.

mean age of (53.22 ± 9.92) years. According to the level of estimated glomerular filtration rate (eGFR), the participants were assigned into the decreased GFR group (eGFR <90 mL/min per 1.73 m², n = 195) and normal GFR group (eGFR ≥90 mL/min per 1.73 m², n = 586). In the decreased GFR group, the participants including 150 males and 45 females were at the age of 40-89 years, with the mean age of (60.87 ± 11.77) years, while those containing 397 males and 189 females in control group were at the age of 40-77 years, with the mean age of (50.67 ± 7.70) years.

3.2 | Analysis of risk factors for the decreased GFR

Univariate analysis of the decreased GFR was presented in Table 1. The differences were pronounced between the decreased GFR group and normal GFR group regarding the age, gender, and Hcy level (P < .05), but no significant differences were shown in the BMI, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels (P > .05).

Multivariate Logistic regression analysis in Table 2 revealed that the people with abnormal Hcy level (OR: 1.534, 95% confidential interval [CI]: 1.075-2.190, P = .018) and males (OR: 2.054, 95%CI: 1.365-3.092, P < .001) were prone to suffer GFR reduction; when compared with the people aged <46 years, those at the age of 46-52 years (OR: 2.943, 95%CI: 1.546-5.605, P = .001), 52-59 years

(OR: 3.664, 95%CI: 1.937-6.931, P < .001), and ≥59 years (OR: 13.452, 95%CI: 7.339-24.657, P < .001) were subjected to a decline of GFR.

3.3 | Model scoring

Multivariate logistic regression analysis found that Hcy, age, and gender were three significant predictive factors for GFR reduction. These three variables were allocated the integral scores in proportion to its OR, which were listed in Table 2.

The scores of study population ranged 0-17. The prevalence of the decreased GFR was 0 (score 0), 3.77% (score 2), 13.79% (score 3), 15.32% (score 4), 18.52% (score 5), 20.93% (score 6), 20.34% (score 7), 28.33% (score 8), 32.56% (score 13), 46.84% (score 15), and 62.65% (score 17), respectively (Figure 1).

In the prediction of the decreased GFR, the sensitivity, specificity, and the area under the curve (AUC) of this risk scoring system were 65.1%, 72.4%, and 0.749, respectively (Figure 2).

3.4 | Association between different scores and the decreased GFR

As shown in Table 3, significant difference was presented between the decreased GFR group and normal GFR group regarding the

TABLE 2 Multivariate logistic analysis of the decreased GFR

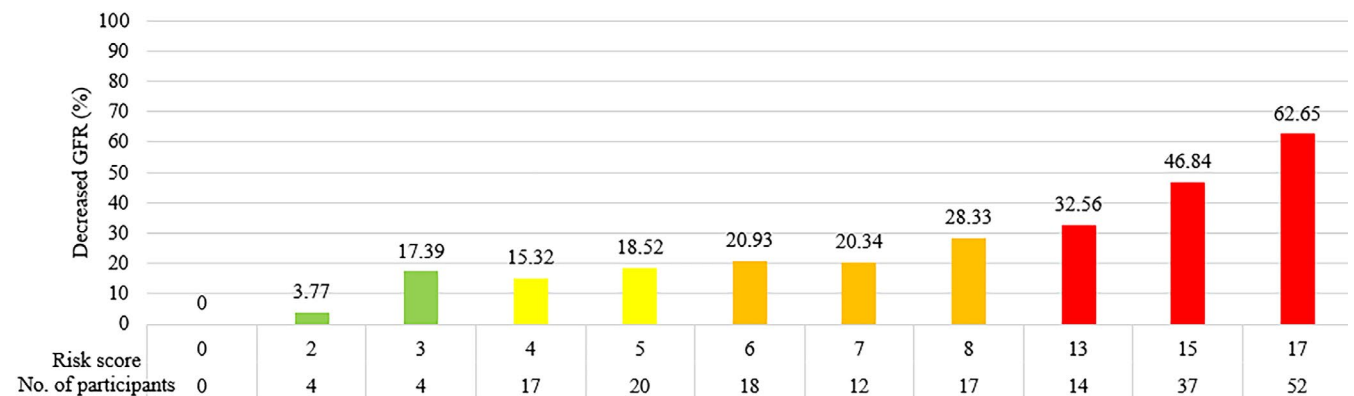| Variables	β	SE	Wald	P	OR	95%CI Lower	Upper	Assigned score
Constant	−3.293	0.336	96.161	<.001	–	–	–	–
Abnormal Hcy (μmol/L)	0.428	0.182	5.554	.018	1.534	1.075	2.190	2
Age (46-52 y)	1.080	0.329	10.792	.001	2.943	1.546	5.605	3
Age (52-59 y)	1.299	0.325	15.940	<.001	3.664	1.937	6.931	4
Age (≥59 y)	2.599	0.309	70.679	<.001	13.452	7.339	24.657	13
Gender (male)	0.720	0.209	11.917	<.001	2.054	1.365	3.092	2

Abbreviation: Hcy, homocysteine.

FIGURE 1 Prevalence changes of the decreased GFR with the increase of scores

different scores ($P < .001$), and the prevalence of decreased GFR raised with the increase of scores ($P < .001$).

In this study, four risk categories were divided according to the scores, including the low risk (score 0-4, n = 8), the risk below the average (score 4-6, n = 37), the risk above the average (score 6-13, n = 47), and the high risk (score ≥13, n = 103). As indicated in Figure 3, the prevalence of the decreased GFR was 5.26% in the low-risk population, 16.89% in the population with the risk below
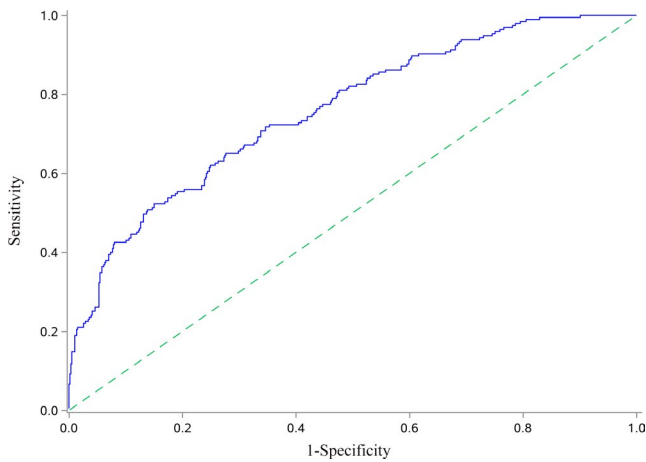
the average, 22.93% in the population with the risk above the average and 50.24% in the high-risk population, respectively.

4 | DISCUSSION

In this study, a risk scoring system for the decreased GFR was established in Chinese general population. Through multivariate logistic regression analysis, three predictive factors including Hcy, gender, and age were identified and indicated an evidence association with a decline of GFR. Meanwhile, four risk categories were classified according to the scores, which offered a specific risk stratification for GFR reduction in Chinese general population.

Hcy, a sulfur-containing amino acid with the cytotoxic effect and an intermediate product in the metabolic process of methionine,[25] can promote the generation of oxygen free radicals and peroxides, induce the oxidative stress, vascular endothelial injury and dysfunction, consequently leading to the occurrence of various diseases.[26-28] Hcy is toxic to the kidney tissue.[29] In terms of Hcy-induced glomerular injury, it was found that Hcy could promote Erk activity in mesangial cells via the calcium-dependent mechanism to enhance activator protein-1 binding and DNA synthesis, as well as to induce endoplasmic reticulum stress,[30] and meanwhile, it could provoke the ceramide-mediated redox signaling and facilitate the expression of monocyte chemoattractant protein-1 in the kidney through nuclear factor-kappaB activation.[31,32] Previous

FIGURE 2 ROC curve for the scoring system in the prediction of the decreased GFR

TABLE 3 Association between different scores and the decreased GFR (n, %)

Scores	Normal GFR group (n = 586)	Decreased GFR group (n = 195)	χ^2	P_1	P_2
0-4	144 (94.74)	8 (5.26)	109.488	<.001	<.001
4-6	182 (83.11)	37 (16.89)			
6-13	158 (77.07)	47 (22.93)			
≥13	102 (49.76)	103 (50.24)			

Note: P_1 represents the value of P through chi-square test; P_2 denotes the value of P by trend test.
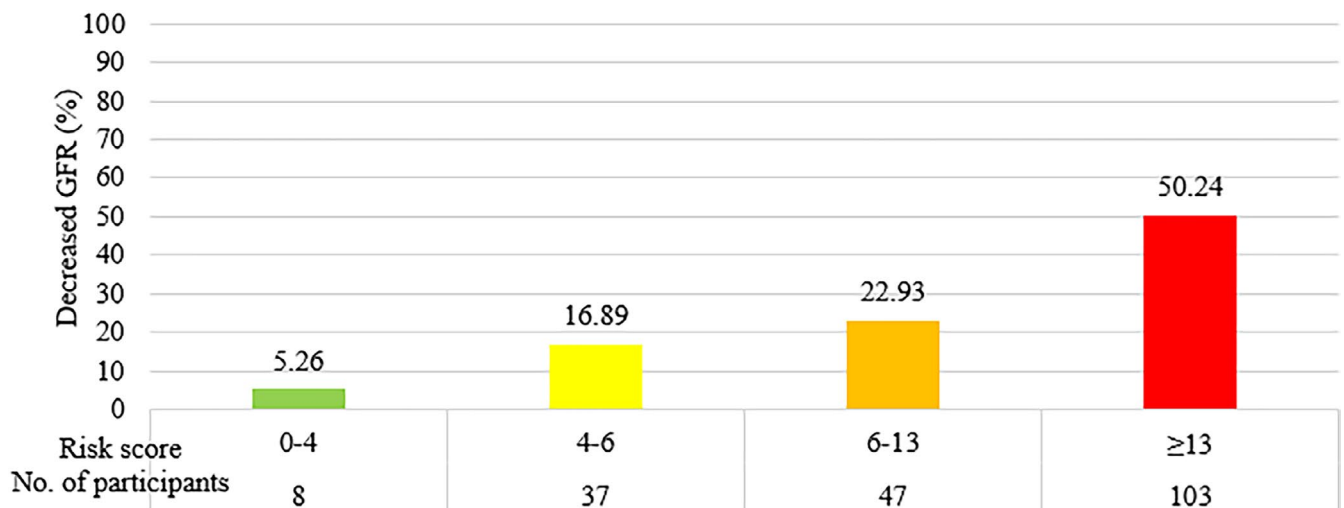

FIGURE 3 Prevalence of the decreased GFR based on four risk categories

studies suggested that the increase of plasma Hcy level was ascribed to a decline of GFR in patients with kidney damage, and the GFR gradually went down with the increased Hcy level.[33,34] In the general population, the increased Hcy level was also reported to have a significant correlation with a reduction of renal function, indicating a key risk factor for the development of CKD in the general population.[35,36]

Gender difference is fundamentally crucial in a lot of diseases, including CKD.[37] Males are prone to develop CKD than females, which may be resulted from sex hormones per se.[38] Various cellular processes are under the influence of sex hormones which modulate the synthesis of multiple cytokines, vasoactive agents, and growth factors. In particular, estrogen participates in the regulation of genes involved in extracellular matrix metabolism via a receptor-dependent mechanism and has significant impacts on the renin-angiotensin system and transforming growth factor-β signal transduction. The kidney hemodynamics can be altered by these impacts, thereby affecting the progression of kidney diseases.[38] In this study, the gender was shown to be a predictive factor for the decreased GFR in Chinese general population, supported by the results of Saranburut et al.[21]

It is well known that GFR declines with age, which may be associated with the kidney structural changes.[39] At the macrostructural level, the volume of renal cortex reduces, surface coarseness augments, and the size and number of simple renal cysts raise with age; at the microstructural level, the histological characteristics of nephrosclerosis, such as tubular atrophy, interstitial fibrosis and glomerulosclerosis, are gradually evident with age. The development of kidney reaches the summit at the age of 40 years, and then its weight and volume start to shrink.[40] GFR decreased annually at about 0.75 mL/min in a relatively healthy population,[41] and this reduction remains apparent in living kidney donors.[42] It was estimated that approximately 17% of people aged over 60 year had a moderately or severely decreased GFR.[43] In this study, the people aged over 40 years were enrolled and assigned into groups based on the quartile. The results showed that when compared with the people aged <46 years, those at the age of 46-52 years, 52-59 years and ≥59 years were all subjected to GFR reduction.

Risk scores, a kind of clinical prediction tools, are frequently used to stratify the individuals at an increased risk of developing diseases.[44] In this study, a risk scoring system for the decreased GFR which had been demonstrated a better predictive value was developed in Chinese general population, with several potential implications. First, the data required from this scoring system were easy to be achieved in clinic, which may contribute to the clinicians to rapidly assess the people's kidney function. Secondly, the information on the risk stratification for GFR reduction may be favorable for the personalized management, such as evaluation on the necessity for reexamination and treatment. Finally, it was of great importance to improve the cognition of high-risk people using this scoring system because GFR declined with age. However, the limitations were also present in this study. Chronic kidney disease-epidemiology

collaboration equation used for calculating eGFR was favored in European, Australian, and North American populations,[45] but was presented to be less accurate in Asian population.[46,47] This risk scoring system may exert a better predictive effect on the decreased GFR if the Asian coefficient for CKD-EPI equation is adopted in eGFR.[21] Moreover, the eGFR was measured only once, which may result in an overestimation of incident CKD. It is thus necessary to conduct more studies with repeated Scr measurements to confirm whether the decreased GFR occurs.

5 | CONCLUSION

A risk scoring system for the decreased GFR is developed in Chinese general population through analysis on the relevant risk factors, which provides a clear risk stratification for GFR reduction in Chinese general population.

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