• Investigation •

Development and validation of a visual impairment prediction nomogram in chronic kidney diseases: the National Health and Nutrition Examination Survey, 1999-2008

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Abstract

● **AIM:** To develop a nomogram to predict the risk of visual impairment (VI) in patients with chronic kidney disease (CKD).

● **METHODS:** Totally 897 patients with CKD were selected from the National Health and Nutrition Examination Survey (NHANES). The training and validation sets were divided in a 7:3 ratio. Multivariate logistic regression and bidirectional stepwise regression was used to select the factor of developing nomogram. The performance of the nomogram was evaluated by receiver operator characteristic curve, calibration curve and decision curve analysis (DCA).

● **RESULTS:** Age, diastolic blood pressure, glucose, serum creatinine, income at or above poverty, and history of smoking were included in the nomogram. And the area under the receiver operating characteristic curve of the training and validation sets were 0.684 and 0.640, respectively. The fit of the model was demonstrated the calibration curve, and DCA showed the value of clinical application.

● **CONCLUSION:** The nomogram may help to screening the probability of VI in patients with CKD. Larger samples are needed to validate and improve the model to increase its efficacy.

● **KEYWORDS:** Visual impairment; chronic kidney disease; clinical prediction model; nomogram; National Health and Nutrition Examination Survey

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INTRODUCTION

Visual impairment (VI) places a huge burden on global health care. The main causes of VI include refractive error, cataract, macular degeneration, glaucoma, and diabetic retinopathy[1]. In 2020, 160.7 million people of working age suffer from moderate and severe VI or blindness, which costs the world about $410.7 billion in economic losses[2]. As life expectancy increases and population aging progresses, the number of VI is likely to show a gradual increase[3]. VI seriously affects the work and life of patients, causing unemployment, depression, and an increased risk of death[2,4-5].

Chronic kidney disease (CKD) is a global public health concern for its impact on individuals and society. The prevalence of CKD is increasing and affecting hundreds of millions of people[6]. The relationship between the eye and the kidney is considered to be very close-as they share many similarities in development, structure, regulatory factors, and etiology[7]. Many previous studies have shown a strong association between CKD and VI and major eye diseases, such as cataract, glaucoma, diabetic retinopathy, and age-related macular degeneration[8-9]. Additionally, substances produced by CKD can lead to retinal damage. Some studies have shown that elevated angiotensin II in CKD can cause injury to retinal vascular endothelial cells[10], and uremic toxins can cause damage to retinal ganglion cells[11]. However, to our knowledge, few studies have been conducted to predict the risk of VI in patients with CKD.

In medical research, the nomogram is a commonly used clinical prediction tool[12]. In this study, we used the National Health and Nutrition Examination Survey (NHANES) database to develop and validate a nomogram for predicting the risk of risk of VI in patients with CKD.

PARTICIPANTS AND METHODS

Ethical Approval This study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki[13]. This study was reported in compliance with the TRIPOD guidelines[14]. Informed consent was obtained from all participants. The NHANES dataset is freely available to the public, and the participants involved in the database have obtained ethical approval. Users can download relevant data for free for research and publish relevant articles.

Study Design and Participants The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey examines a nationally representative sample of about 5000 persons each year. The NHANES includes demographic, socioeconomic, dietary, health-related questions, and medical examinations. We selected the NHANES dataset for analysis from 1999 to 2008. CKD patients aged 18y and older from the dataset were included in this study. Exclusion criteria were: 1) individuals under 18 years of age, 2) those without CKD, 3) those with missing variables in this study. Out of 51 632 participants, 897 persons were selected for the study, and the flowchart was shown in Figure 1.

Data Selection and Measurements The presence of CKD was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) organization by a decreased estimated glomerular filtration rate (eGFR) of lower than 60 mL/min·1.73 m^2 or albumin-creatinine ratio ≥30 mg/g[15]. The eGFR was estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.

Visual acuity of participants was measured by the visual acuity chart. In brief, participants were asked to wear their habitual correction such as glasses and correctly identifying at least 4 of the 5 optotypes on each line allowed the participant to proceed to the next visual acuity line. Visual acuity of worse than 20/40 in the better-seeing eye was defined as VI.

Besides, the basic characteristics were obtained from the NHANES dataset, including age, sex (male and female), race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other race), education (high school or over and not), marital status (married and unmarried), IPR (income at or above poverty and not), history of diabetes, smoking and alcohol drinking, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), albuminuria, urine creatinine (UC), albumin in urine (AU), urine albumin-creatinine ratio (UACR), hemoglobin (Hb), C-reactive protein (CRP), glycosylated hemoglobin (HbA1c), blood albumin, blood urea nitrogen (BUN), serum total cholesterol (TC), glucose, lactate dehydrogenase (LDH), uric acid, serum creatinine (SCr).

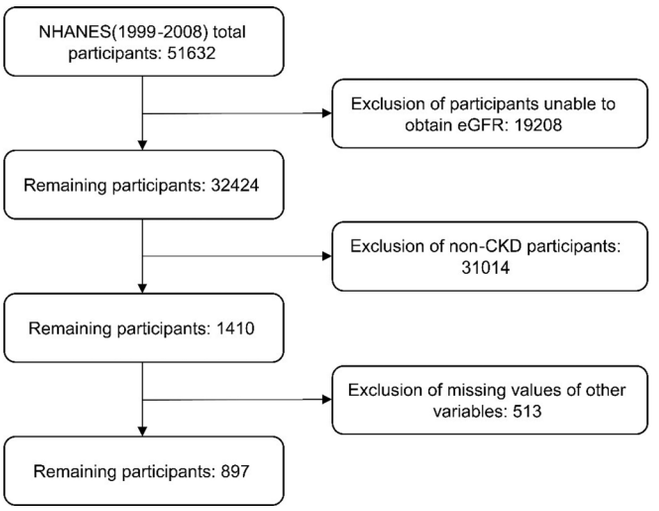

Figure 1 The flowchart of participants selection eGFR: Estimated glomerular filtration rate; CKD: Chronic kidney disease.

Statistical Analysis For continuous variables, those that conformed to normal distribution were showed using the mean and standard error, and those that did not conform to normal distribution were expressed using the median, first and third quartiles (Q1 and Q3). For categorical variables, the number and percentage of each category were used to express them. Chi-square tests or Fisher's exact test were used to We determine group differences. Univariate and multivariate logistic regression were used to explore risk factors for VI in CKD patients. And, we used multivariate logistic regression and bidirectional stepwise regression to screen the factors used to construct the nomogram. The odds ratio (OR) and 95% confidence interval (CI) were used for effect assessment. The training and validation sets were randomly divided in the ratio of 7:3.

The area under the receiver operating characteristic curve (AUC) was used to assess model performance, calibration curve was used to assess the agreement between predicted and actual results, and decision curve analysis (DCA) was used to determine the clinical benefits of the model. $P<0.05$ was considered statistically significant. Data processing and analysis were performed using R version 4.3.0.

RESULTS

Basic Characteristics The basic characteristics were shown in Table 1. Of the 897 CKD patients selected in the study, 163 were identified as VI and 734 as non-VI. The male ratio in the population exceeds that of females.

Univariate and Multivariate Logistic Regression Analysis The results of univariate and multivariate logistic regressions were shown in Table 2. Age, SBP, DBP, BMI, UC, AU, UACR, Hb, CRP, HbA1c, albumin, BUN, TC, glucose, LDH, uric acid (UA), SCr, eGFR, sex, race, education,

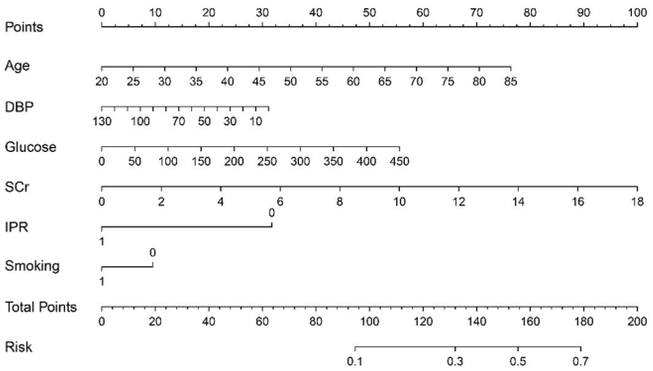

Figure 2 Nomogram for the prediction of the risk of VI in CKD patients DBP: Diastolic blood pressure; SCr: Serum creatinine; IPR: Income at or above poverty; VI: Visual impairment; CKD: Chronic kidney disease.

Table 1 Basic characteristics of the dataset *n* (%)

Characteristics	Total (*n*=897)	Non-VI (*n*=734)	VI (*n*=163)
Sex			
Male	663 (74)	550 (75)	113 (69)
Female	234 (26)	184 (25)	50 (31)
Age, median (Q1, Q3)	76 (69, 80)	75 (68, 80)	79 (72, 84)
Race			
Mexican American	70 (8)	58 (8)	12 (7)
Other Hispanic	24 (3)	18 (2)	6 (4)
Non-Hispanic White	631 (70)	518 (71)	113 (69)
Non-Hispanic Black	152 (17)	123 (17)	29 (18)
Other race	20 (2)	17 (2)	3 (2)
High school or over	589 (66)	497 (68)	92 (56)
Married	562 (63)	477 (65)	85 (52)
IPR	779 (87)	654 (89)	125 (77)
Diabetes	308 (34)	249 (34)	59 (36)
Smoking	506 (56)	422 (57)	84 (52)
Alcohol	755 (84)	626 (85)	129 (79)

VI: Visual impairment; Q1, Q3: First and third quartiles; IPR: Income at or above poverty.

marriage, income at or above poverty (IPR), and history of diabetes, smoking and alcohol consumption were included in univariate and multivariate logistic regression analysis. In the univariate analysis, age, SBP, DBP, Hb, BUN, education, marriage, IPR, and history of alcohol consumption were statistically significant (P<0.05). Further, in the multivariate logistic regression analysis, age and IPR were statistically significant (P<0.05). In order to screen the risk factors used to construct the nomogram, multivariate logistic regression and bidirectional stepwise regression was used in the dataset. Age, DBP, glucose, SCr, IPR and history of smoking were selected. The results were shown in Table 3.

Performance of the Nomogram Model According to the results of multivariate logistic regression and bidirectional stepwise regression analysis, the nomogram (Figure 2) was developed to predict the risk of VI in CKD patients.

ROC curves (Figure 3) were used to evaluate the performance of the nomogram. The AUC of the training set was 0.684,

Table 2 Univariate and multivariate logistic regression analysis of the dataset

Variables	Univariate		Multivariate	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Age	1.03 (1.01-1.06)	0.005	1.05 (1.02-1.08)	0.004
SBP	1.01 (1.01-1.02)	0.029	1.01 (1.00-1.02)	0.286
DBP	0.99 (0.98-0.99)	0.007	0.99 (0.98-1.00)	0.119
BMI	1.00 (0.96-1.03)	0.826	1.02 (0.98-1.07)	0.328
UC	1.00 (1.00-1.00)	0.382	1.00 (0.99-1.00)	0.502
AU	1.00 (1.00-1.00)	0.807	1.00 (1.00-1.00)	0.153
UACR	1.00 (0.99-1.02)	0.944	0.98 (0.95-1.02)	0.313
Hb	0.87 (0.78-0.98)	0.019	0.95 (0.81-1.10)	0.486
CRP	1.07 (0.90-1.28)	0.434	0.98 (0.80-1.21)	0.866
HbA1c	1.14 (0.98-1.33)	0.095	1.01 (0.75-1.35)	0.967
Albumin	0.81 (0.46-1.42)	0.457	0.94 (0.46-1.95)	0.876
BUN	1.02 (1.01-1.04)	0.029	1.01 (0.98-1.04)	0.499
TC	1.00 (1.00-1.01)	0.214	1.01 (1.00-1.01)	0.128
Glucose	1.00 (1.00-1.01)	0.053	1.00 (1.00-1.01)	0.182
LDH	1.00 (1.00-1.01)	0.787	1.00 (0.99-1.01)	0.737
UA	1.04 (0.92-1.16)	0.541	1.03 (0.90-1.19)	0.637
SCr	1.14 (0.98-1.33)	0.084	1.21 (0.95-1.55)	0.129
eGFR	0.99 (0.97-1.00)	0.052	1.00 (0.98-1.03)	0.931
Sex		0.245		0.188
Male	1.00 (reference)		1.00 (reference)	
Female	1.30 (0.84-2.02)		0.67 (0.37-1.22)	
Race				
Non-Hispanic White	1.00 (reference)		1.00 (reference)	
Mexican American	1.05 (0.49-2.25)	0.898	0.80 (0.32-1.98)	0.629
Other Hispanic	2.05 (0.76-5.51)	0.154	2.55 (0.80-8.11)	0.113
Non-Hispanic Black	1.17 (0.68-2.02)	0.578	1.03 (0.51-2.09)	0.934
Other race	0.74 (0.16-3.33)	0.692	0.84 (0.17-4.25)	0.833
High school or over				0.128
Yes	1.00 (reference)		1.00 (reference)	
No	1.79 (1.18-2.70)	0.006	1.45 (0.90-2.33)	
Marriage				0.261
Yes	1.00 (reference)		1.00 (reference)	
No	1.58 (1.04-2.39)	0.031	1.32 (0.81-2.13)	
IPR				0.003
Yes	1.00 (reference)		1.00 (reference)	
No	2.71 (1.64-4.49)	<0.001	2.47 (1.35-4.52)	
Hyperlipoidemia				0.417
Yes	1.00 (reference)		1.00 (reference)	
No	0.87 (0.58-1.31)	0.506	1.30 (0.69-2.47)	
Alcohol				0.317
Yes	1.00 (reference)		1.00 (reference)	
No	1.72 (1.03-2.85)	0.037	1.37 (0.74-2.54)	
Smoking				0.22
Yes	1.00 (reference)		1.00 (reference)	
No	1.50 (1.00-2.26)	0.051	1.35 (0.83-2.19)	
Diabetes				0.441
No	1.00 (reference)		1.00 (reference)	
Yes	1.18 (0.77-1.80)	0.442	0.78 (0.42-1.47)	

OR: Odds ratio; CI: Confidence interval; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; UC: Urine creatinine; AU: Albumin in urine; UACR: Urine albumin-creatinine ratio; Hb: Hemoglobin; CRP: C-reactive protein; BUN: Blood urea nitrogen; TC: Serum total cholesterol; LDH: Lactate dehydrogenase; UA: Uric acid; SCr: Serum creatinine; eGFR: Estimated glomerular filtration rate; IPR: Income at or above poverty; P<0.05 was considered statistically significant.

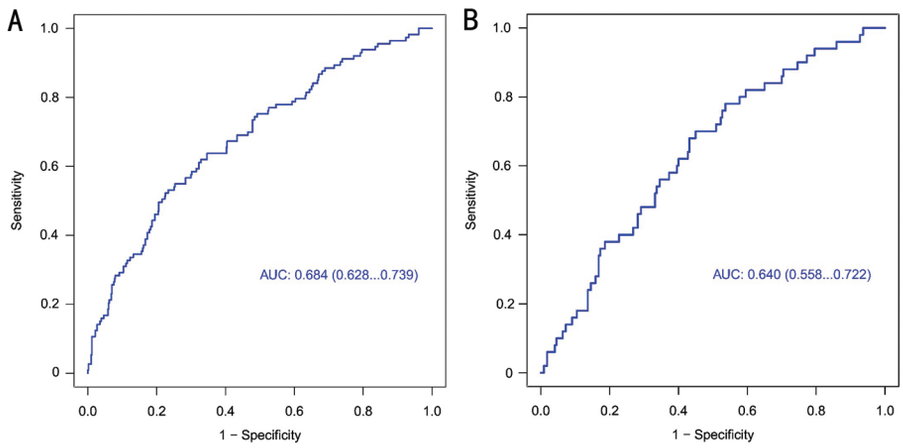

Figure 3 ROC curves for training (A) and validation (B) set AUC: Area under the curve; ROC: Receiver operating characteristic curve.

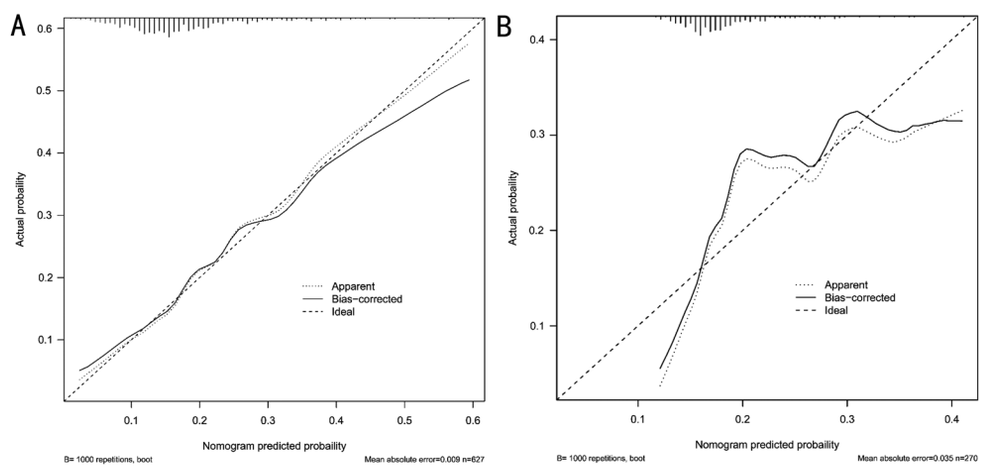

Figure 4 Calibration curve for training (A) and validation (B) set.

Table 3 Multivariate logistic regression and bidirectional stepwise regression of the dataset

Variables	OR (95%CI)	*P*
Age	1.04 (1.02-1.07)	0.002
DBP	0.99 (0.98-1.00)	0.117
Glucose	1.01 (1.01-1.01)	0.042
SCr	1.22 (1.04-1.44)	0.015
IPR		
Yes	1.00 (reference)	
No	3.15 (1.85-5.36)	<0.001
Smoking		
Yes	1.00 (reference)	
No	1.41 (0.92-2.16)	0.114

OR: Odds ratio; CI: Confidence interval; DBP: Diastolic blood pressure; SCr: Serum creatinine; IPR: Income at or above poverty. *P*<0.05 was considered statistically significant.

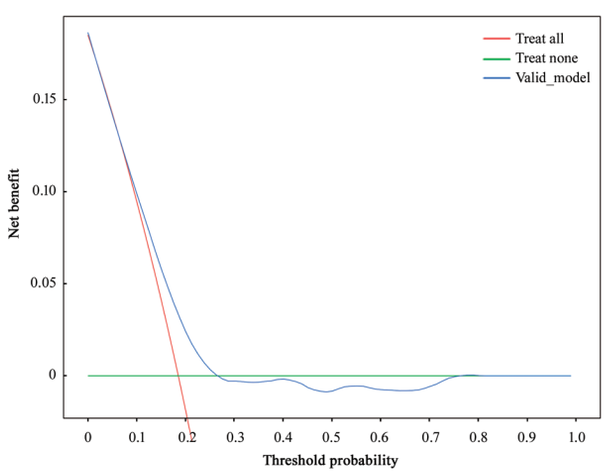

Figure 5 DCA curve for nomogram DCA: Decision curve analysis.

and the AUC of the validation set was 0.640. The results of calibration curve and DCA were showed in Figures 4 and 5.

DISCUSSION

In this study, we developed a nomogram to predict VI in CKD patients, which showed a good performance in the validation dataset. For the first time, the study provided a simple prediction model for VI in CKD patients and it may serve as a quick tool for population screening in the future.

Age, DBP, glucose, SCr, IPR and history of smoking were selected to develop the nomogram by multivariate logistic regression and bidirectional stepwise regression. Actually, due to the close relationship between the eye and the kidney, there are many risk factors that are common to both VI and CKD[9]. It is corroborated by the factors we chose for the

nomogram again. The median age of CKD patients with VI was 79 years old, higher than 76y for non-VI. Previous studies have shown that the prevalence of both CKD and VI gradually increases with age[16-17]. In addition, CKD patients had a higher prevalence of VI and eye diseases compared to non-CKD patients[18-19]. Some researchers have even suggested that CKD is an independent risk factor for VI and eye diseases[8]. Blood pressure, eye and kidney are intricately linked. The blood vessels of the eye and kidney are viewed as part of the microvascular system, and changes in blood pressure can affect both eye and kidney[20-21]. On the other hand, kidney is one of the key organs in blood pressure regulation, and CKD can cause hypertension and eye diseases[19,22-23]. Similar to hypertension, hyperglycemia plays an important role in VI and CKD, which leads to diabetic retinopathy and diabetic nephropathy[24]. In addition, it is worthy mentioned that income plays an important role in the prevalence of VI. Patients in low- and middle-income countries account for 90% of the total number of VI patients[25]. Poverty makes it difficult for these patients to afford normal eye care service, even for reversible VI such as refractive error and cataract. Also, many studies have shown that smoking is a very important risk factor that can cause damage throughout the body, including the eye and kidney[26].

The strength of this study lies in its focus on the probability of VI in patients with CKD and the provision of a clinical tool for predicting risk through the nomogram. There have also been studies that have explored the relationship between VI and CKD, for example, Zhu *et al*[8] analyzed the influence on VI by CKD, and the prevalence of VI is higher in patients with more severe CKD. While previous studies have extensively explored the correlation between CKD and VI and eye diseases[8-9], these studies have primarily served to provide physicians with indirect indicators when managing patients with CKD, and have limited practical application in clinical settings. Our study allows physicians to initially assess the visual status of CKD patients to determine whether to seek help from ophthalmologists.

The study also had some limitations. First, this study lacks an external validation dataset, thereby the generalizability of the nomogram needs to be further validated. Second, the NHANES dataset constitutes a U.S. population-based dataset and does not include data from other countries and regions, which may be a confounding factor. Third, due to the current paucity of relevant studies, there may be some factors related to VI that have not been taken into account. It is hoped that more studies in the future can focus on the ocular status of patients with CKD.

In conclusion, we developed a predictive model to predict the risk of VI in CKD patients using data from the NHANES. The nomogram helps doctors assess the visual status of patients crudely. We hope that more similar tools will be developed for clinical use to enhance the collaboration between ophthalmology and nephrology.

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Conflicts of Interest: Tan YH, None; **Li JQ,** None; **Sun XF,** None.

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