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# Association between serum Reg Iα and the risk of chronic kidney disease in patients with diabetes mellitus

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**Abstract: Objective** To investigate the correlation between serum pancreatic regenerating (Reg) protein Ⅰα and chronic kidney disease (CKD) in diabetic patients, to develop a risk prediction model for diabetes combined with CKD. **Methods** The clinical data of 500 diabetic patients admitted to the Zhongda Hospital Southeast University from September 2021 to September 2023 were selected for a retrospective study, including general data, medical history, and laboratory indexes [blood routine tests, fasting plasma glucose (FPG), blood urea nitrogen (BUN), serum creatinine (Scr), serum uric acid (UA), and urinary albumin/creatinine ratio (UACR)]. Additionally, estimated glomerular filtration rate (eGFR) was calculated. Serum Reg Ⅰα level was measured by enzyme-linked immunosorbent assay, and patients were classified into groups R1 (Reg Iα≤38.60 ng/mL, *n*=98), R2 (38.60<Reg Iα≤82.17ng/mL, *n*=97) R3 (82.17<Reg Iα≤196.15 ng/mL, *n*=97) and R4 (Reg Iα>196.15 ng/mL, *n*=97) according to quartile levels. Patients were randomly divided into a training set (234 cases) and a validation set (155 cases) using a random number table method in a ratio of 6:4. Multiple logistic stepwise regression was utilized to identify model variables and create a nomogram model for predicting the risk of diabetes combined with CKD. The predictive value, calibration, and clinical utility of the model were comprehensively assessed using receiver operating characteristic curves (ROC), calibration curves, and clinical decision curves. **Results** (1) A total of 389 diabetic patients with complete data were included, including 240 males (61.7%), 149 females (38.3%), aged 64.00 (53.50, 70.00) years, and 210 (53.98%) patients with CKD. Patients in the R4 group exhibited significantly higher levels of FPG, BUN, Scr, UA, increased rates of hypertension, coronary heart disease, and CKD, as well as lower levels of red blood cell count, hemoglobin (HGB), and eGFR compared to those in the R1 group (*P*<0.05). (2) The indicators in the training and validation sets were found to be well-balanced (*P*>0.05). In the training set, the CKD group showed higher levels of white blood cell count, Reg Iα, BUN, Scr, and UA, a higher prevalence of hypertension and coronary artery disease, and lower levels of erythrocyte count, HGB, and eGFR compared to the NCKD group (*P*<0.05). Binary logistic regression analysis was performed on the basis of collinearity diagnosis, and the results showed that history of hypertension (*OR*=2.901), Reg Iα>82.17 ng/mL, decreased HGB (*OR*=0.965) and increased UA (*OR*=1.005) were the risk factors of diabetes complicated with CKD (*P*<0.05). (3) The areas under the ROC of the training set and validation set were 0.846(95%*CI*:0.796-0.896) and 0.920(95%*CI*: 0.875-0.965), respectively. The calibration curves and the Hosmer-Lemeshow test indicated good agreement of the observed and predicted outcomes (*P*>0.05). Clinical decision curves demonstrated that the nomogram provided a substantial net benefit and had practical clinical utility. **Conclusion** Hypertension, elevated Reg Iα levels, decreased HGB and elevated UA are risk factors for CKD in diabetic patients, and the nomogram model constructed in this study has good predictive power and clinical value.

**Keywords:** Diabetes mellitus; chronic kidney disease; Pancreatic regenerating protein Iα; Hypertension; Hemoglobin; Kidney function; Risk prediction

According to the International Diabetes Federation, the global diabetic population reached 537 million in 2021 and is projected to increase to 784 million by 2045 [1]. Chronic kidney disease (CKD), characterized by structural and functional abnormalities of the kidneys for ≥3 months due to multiple causes, is significantly accelerated by diabetes, with over a quarter of diabetic patients developing CKD [2]. CKD onset is insidious, often asymptomatic in early stages (G1-G2), and many newly diagnosed CKD patients are already in the intermediate stage, contributing to its high prevalence, disability rates, and low awareness. Kidney damage progression is often underestimated. The ADA/KDIGO consensus recommends annual CKD screening for type 1 and type 2 diabetes patients with a disease duration of more than 5 years [3]. However, China currently lacks a standardized system for CKD screening among diabetic patients [4]. Many community medical institutions utilize urine tests as initial CKD screening tools [5], but proteinuria results are highly variable, unstable, less sensitive, and lead to underdiagnosis in many CKD patients.

Regenerating protein (Reg), a low molecular weight secretory protein and a subtype such as Reg Iα from the calcium-dependent lectin gene superfamily, is predominantly found in pancreatic acinar cells. It promotes pancreatic islet β-cell regeneration and tissue

reconstruction post pancreatic injury [6-7], and its expression increases in damaged kidney tissues [8]. We have found elevated serum Reg Iα levels in type 2 diabetic patients, significantly negatively correlated with eGFR [9-10], indicating a close association between Reg Iα and impaired renal function in diabetic patients. Clinical application of predictive models quantifies this risk, playing a crucial role in identifying high-risk CKD populations for early screening and diagnosis.

Currently, most research focuses on analyzing CKD risk factors, but has not translated them into clinical models to apply [11]. Some studies have constructed CKD prediction models based on clinical indicators, primarily in the general population, with varying predictive efficacies ranging from 0.6 to 0.9 [12]. Due to regional and racial factors, CKD prediction models established from Western populations cannot be directly applied to Chinese patients [13]. There is an urgent need to develop a simple, inexpensive predictive model suitable for large-scale CKD screening among diabetic patients in China. Reg Iα, as an effective serum biomarker, serves as an alert for renal damage in diabetic patients, is easy to detect, and is suitable for clinical application. Therefore, this study aims to explore the relationship between serum Reg Iα levels in diabetic patients and the risk of CKD occurrence, as well as to establish a predictive model to identify high-risk populations early and improve screening rates.

## 1 Materials and methods

### *1.1 Study subjects*

From September 2021 to September 2023, diabetic patients treated at the Affiliated Zhongda Hospital Southeast University were retrospectively selected. **Inclusion criteria:** (1) meeting diabetes diagnostic criteria [14]; (2) aged 18-80 years; (3) capable of understanding the research procedures. **Exclusion criteria:** (1) patients in stressful states or acute infections; (2) those with severe liver function impairment, connective tissue diseases, malignant hematologic diseases, or tumors; (3) patients with mental illness; (4) pregnant or lactating women; (5) patients currently participating in another clinical study; (6) those with acute or chronic gastrointestinal inflammation or gastrointestinal tumors; (7) those with significant data missing.

A total of 389 patients meeting the inclusion and exclusion criteria were included. This study was approved by the Ethics Committee of Zhongda Hospital Southeast University (2022ZDSYLL204-P01), with registration in the Chinese Clinical Trial Registry (ChiCTR2300072247).

### *1.2 Study methods*

**(1) Data collection:** General information (age and gender), medical history (history of hypertension, history of coronary heart disease), and laboratory tests [complete blood count, fasting plasma glucose (FPG), blood urea nitrogen (BUN), serum creatinine (Scr), serum uric acid (UA), urine albumin-to-creatinine ratio (UACR)] were collected. Estimated glomerular filtration rate (eGFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) recommended by the Improving Global Outcomes (KDIGO) guidelines. (2) According to the " Guidelines for early screening, diagnosis, prevention and treatment of chronic kidney disease (2022 Edition)" [4], CKD was defined as UACR > 30 mg/g and/or eGFR < 60 mL/(ml • 1.73 $m^2$ ), persisting for more than 3 months. (3) Serum Reg Iα detection: we developed a method for Reg Iα detection. Frozen plasma (200 μL) was used, and serum Reg Iα levels were determined using enzyme-linked immunosorbent assay (ELISA). Patients were categorized into R1 (Reg Iα ≤ 38.60 ng/mL), R2 (38.60 < Reg Iα ≤ 82.17 ng/mL), R3 (82.17 < Reg Iα ≤ 196.15 ng/mL), and R4 (Reg Iα > 196.15 ng/mL) groups based on quartile levels.

### *1.3 Statistical methods*

Statistical analyses were performed using SPSS 26.0 and R 3.4.2 software. Normally distributed continuous data were expressed as $\bar{x} \pm s$, while non-normally distributed continuous data were presented as $M$ ($P_{25}$, $P_{75}$). Categorical data were presented as case (%). The Kruskal-Wallis $H$ test was used for multiple group comparisons of continuous variables among groups R1 to R4, followed by post hoc pairwise comparisons. $\chi^2$ test was employed for comparisons involving rates or proportions. Model variable selection was conducted using single-factor regression and binary logistic regression methods.

Model construction followed the Type 2a principles outlined in the TRIPOD statement for predictive modeling [15]. Data were randomly divided into training set and validation set at a ratio of 6:4. Mann-Whitney $U$ test was used for comparing continuous variables between groups in both training set and validation set. A nomogram predicting the risk of diabetes combined with CKD was constructed based on the training set. The validation set was used for internal validation, and model performance was assessed using measures such as the concordance index, calibration curves, and clinical decision curves. $P$<0.05 indicated statistical significance.

## 2 Results

### *2.1 Comparison of general characteristics in diabetes patients with different Reg Ia levels*

In this study, 61.7% (240/389) were male and 38.3% (149/389) were female, with a median age of 64.00 (53.50, 70.00) years. Compared with group R1, patients in group R4 showed elevated levels of FPG, BUN, Scr and UA, along with increased proportions of hypertension,

coronary heart disease, and CKD, and decreased levels of red blood cell count, hemoglobin (HGB), and eGFR ($P$<0.05). **See Table 1.**

**Tab. 1** General clinical data of patients with different Reg Iα levels [$M(P_{25}, P_{75})$]

| Indicator | Overall ($n$ = 389) | Group ($n$ = 98) | Group R2 ($n$ = 97) | Group R3 ($n$ = 97) | Group R4 ($n$ = 97) | $\chi^2/Z$ | $P$ |
|---|---|---|---|---|---|---|---|
| Age(years) | 64.00 (54.00, 70.00) | 60.50 (51.00,67.75) | 63.00 (58.00,71.00) | 66.00 (57.00,72.00) | 64.00 (53.00,70.00) | 9.052[a] | 0.029 |
| Gender[case(%)] | | | | | | 0.165[b] | 0.983 |
| Female | 149 (38.30) | 36 (36.73) | 38 (39.18) | 38 (39.18) | 37 (38.14) | | |
| Male | 240 (61.70) | 62 (63.27) | 59 (60.82) | 59 (60.82) | 60 (61.86) | | |
| Hypertension [case(%)] | | | | | | 20.853[b] | <0.001 |
| No | 98 (25.19) | 37 (37.76) | 30 (30.93) | 20 (20.62) | 11 (11.34) | | |
| Yes | 291 (74.81) | 61 (62.24) | 67 (69.07) | 77 (79.38) | 86 (88.66)[c] | | |
| CHD [case(%)] | | | | | | 10.515[b] | 0.015 |
| No | 291 (74.81) | 81 (82.65) | 77 (79.38) | 71 (73.20) | 62 (63.92) | | |
| Yes | 98 (25.19) | 17 (17.35) | 20 (20.62) | 26 (26.80) | 35 (36.08)[c] | | |
| FPG(mmol/L) | 6.90 (5.69, 9.16) | 7.55(6.49,10.33) | 6.90 (5.90,8.80) | 7.10 (5.51,9.83) | 6.12 (4.84,8.20)[c] | 22.124[a] | <0.001 |
| BUN(mmol/L) | 8.10 (6.20, 13.50) | 6.30 (5.20,7.50) | 7.10 (5.90,8.80) | 9.70 (7.30,14.00) | 18.70 (11.50,27.80)[c] | 159.618[a] | <0.001 |
| Scr(μmol/L) | 98.00 (70.00, 204.00) | 68.00 (57.00,83.75) | 80.00 (66.00,101.00) | 113.00 (87.00,167.00) | 379.00 (198.00,659.00)[c] | 187.324[a] | <0.001 |
| UA(mmol/L) | 336.00 (275.00, 423.00) | 293.50 (256.50,347.75) | 319.00 (256.00,377.00) | 370.00 (317.00,452.00) | 374.00 (314.00,466.00)[c] | 44.163[a] | <0.001 |
| eGFR | 67.12 (27.30, 93.67) | 95.06 (83.94,104.29) | 84.77 (62.06,94.94) | 54.64 (33.67,80.20) | 11.88 (6.55,28.94)[c] | 198.577[a] | <0.001 |
| WBC(x10$^9$/L) | 6.59 (5.34, 7.90) | 6.50 (5.20,7.67) | 6.37 (5.24,7.80) | 6.46 (5.34,8.57) | 7.19 (5.74,8.12) | 6.838[a] | 0.077 |
| RBC(x10$^{12}$/L) | 4.32 (3.66, 4.76) | 4.55 (4.24,4.92) | 4.51 (4.15,4.91) | 4.09 (3.65,4.56) | 3.56 (2.94,4.10)[c] | 93.225[a] | <0.001 |
| HGB(g/L) | 128.00 (108.00, 144.00) | 138.00 (128.00,149.00) | 138.00 (124.00,154.00) | 126.00 (109.00,140.00) | 103.00 (85.00,123.00)[c] | 94.446[a] | <0.001 |
| PLT(x10$^9$/L) | 197.00 (158.00, 237.00) | 209.00 (163.50,244.75) | 199.00 (169.00,229.00) | 192.00 (153.00,249.00) | 197.00 (140.00,231.00) | 2.573[a] | 0.462 |
| CKD[case(%)] | | | | | | 117.797* | <0.001 |
| No | 179 (46.02) | 72 (73.47) | 68 (70.10) | 32 (32.99) | 7 (7.22) | | |
| Yes | 210 (53.98) | 26 (26.53) | 29 (29.90) | 65 (67.01) | 90 (92.78)[c] | | |

Note: CHD, coronary heart disease; [a] represented Kruskal-Wailis test; [b] represented $\chi^2$ test; Compared with group R1，[c]$P$<0.05; [d]eGFR[mL/min•1.73m$^2$)].

### *2.2 Comparison of Clinical data between training set and validation set*

Among the 389 diabetes patients, there were 234 cases in the training set and 155 cases in the validation set. Of the 210 CKD patients, 132 cases (62.86%) were in the training set and 78 cases (37.14%) were in the validation set. All indicators between the training set and validation set were balanced and comparable, with no significant difference ($P$>0.05). **See Table 2.**

**Tab. 2** Comparison of general data between the training set and the validation set [$M(P_{25}, P_{75})$]

| Indicator | Overall ($n$ = 389) | training set ($n$ = 234) | validation set ($n$ = 155) | $\chi^2/Z$ | $P$ |
|---|---|---|---|---|---|
| Age(years) | 64.00 (54.00, 70.00) | 63.00 (55.00, 70.00) | 64.00 (53.00, 70.50) | -0.476[a] | 0.634 |
| Gender[case(%)] | | | | 0.515[b] | 0.473 |
| Female | 149 (38.30) | 93 (39.74) | 56 (36.13) | | |
| Male | 240 (61.70) | 141 (60.26) | 99 (63.87) | | |
| Hypertension [case(%)] | | | | 0.529[b] | 0.467 |
| No | 98 (25.19) | 62 (26.50) | 36 (23.23) | | |
| Yes | 291 (74.81) | 172 (73.50) | 119 (76.77) | | |
| CHD [case(%)] | | | | 0.000[b] | 0.991 |
| No | 291 (74.81) | 175 (74.79) | 116 (74.84) | | |
| Yes | 98 (25.19) | 59 (25.21) | 39 (25.16) | | |
| FPG(mmol/L) | 6.90 (5.69, 9.16) | 6.85 (5.83, 9.35) | 6.97 (5.47, 8.79) | -0.460[a] | 0.646 |
| BUN(mmol/L) | 8.10 (6.20, 13.50) | 8.30 (6.30, 13.38) | 7.90 (6.10, 14.10) | -0.226[a] | 0.821 |
| Scr(μmol/L) | 98.00 (70.00, 204.00) | 100.00 (69.00, 199.50) | 93.00 (70.50, 212.00) | -0.167[a] | 0.868 |
| UA(mmol/L) | 336.00 (275.00, 423.00) | 328.50 (265.25, 423.00) | 347.00 (300.50, 426.50) | -1.534[a] | 0.125 |
| eGFR | 67.00 (27.00, 94.00) | 64.00 (27.25, 93.75) | 71.00 (27.00, 93.50) | -0.143[a] | 0.886 |
| WBC(x10$^9$/L) | 6.59 (5.34, 7.90) | 6.59 (5.25, 8.05) | 6.53 (5.55, 7.81) | -0.321[a] | 0.749 |
| RBC(x10$^{12}$/L) | 4.32 (3.66, 4.76) | 4.30 (3.63, 4.71) | 4.37 (3.67, 4.80) | -1.162[a] | 0.245 |
| HGB(g/L) | 128.00 (108.00, 144.00) | 128.00 (107.25, 141.00) | 128.00 (109.50, 145.50) | -1.275[a] | 0.202 |
| PLT(x10$^9$/L) | 197.00 (158.00, 237.00) | 197.00 (163.00, 232.00) | 200.00 (157.00, 246.00) | -0.894[a] | 0.371 |
| CKD[case(%)] | | | | 1.391[b] | 0.238 |
| No | 179 (46.02) | 102 (43.59) | 77 (49.68) | | |

| Indicator | Overall (*n* = 389) | training set (*n* = 234) | validation set (*n* = 155) | $\chi^2/Z$ | *P* |
|---|---|---|---|---|---|
| Yes | 210 (53.98) | 132 (56.41) | 78 (50.32) | | |
| Reg Iα[case(%)] | | | | 1.299[b] | 0.729 |
| ≤38.60 ng/mL | 98 (25.18) | 56 (23.93) | 42 (27.10) | | |
| >38.60~82.17 ng/mL | 97 (24.94) | 62 (26.50) | 35 (22.58) | | |
| >82.17~196.15 ng/mL | 97 (24.94) | 56 (23.93) | 41 (26.45) | | |
| >196.15 ng/mL | 97 (24.94) | 60 (25.64) | 37 (23.87) | | |

Note：CHD, coronary heart disease; [a] represented Mann-Whitney test; [b] represented $\chi^2$ test; [c] eGFR[mL/min•1.73m$^2$)].

## *2.3 Selection of predictive factors*

In the training set, logistic regression analysis showed that compared with the non-CKD group, patients in the CKD group had higher levels of white blood cell count, Reg Iα, BUN, Scr, and UA, along with increased proportions of hypertension and decreased levels of red blood cell count, HGB, and eGFR ($P$<0.01). **[Table 3]** After considering collinearity and including age as a common clinical factor, binary logistic regression analysis identified Reg Iα > 82.17 ng/mL (including 82.17 < Reg Iα ≤ 196.15 ng/mL and Reg Iα > 196.15 ng/mL), history of hypertension, decreased HGB, and elevated UA as risk factors for diabetes combined with CKD ($P$<0.01). **[Table 4]**

**Tab. 3** Univariate logistic regression analysis of the factors affecting diabetes mellitus complicated with CKD

| Indicator | *β* | *S.E* | *Z* | *P* value | *OR* (95%*CI*) |
|---|---|---|---|---|---|
| Age | 0.00 | 0.01 | 0.37 | 0.709 | 1.004 (0.982 ~ 1.027) |
| FPG | -0.05 | 0.04 | -1.16 | 0.248 | 0.956 (0.885 ~ 1.032) |
| BUN | 0.39 | 0.06 | 6.17 | <0.001 | 1.476 (1.304 ~ 1.670) |
| Scr | 0.05 | 0.01 | 6.40 | <0.001 | 1.048 (1.033 ~ 1.063) |
| UA | 0.01 | 0.00 | 4.50 | <0.001 | 1.006 (1.003 ~ 1.008) |
| eGFR | -0.08 | 0.01 | -8.07 | <0.001 | 0.925 (0.907 ~ 0.942) |
| WBC | 0.25 | 0.07 | 3.64 | <0.001 | 1.289 (1.124 ~ 1.477) |
| RBC | -1.34 | 0.22 | -6.01 | <0.001 | 0.263 (0.170 ~ 0.407) |
| HGB | -0.04 | 0.01 | -6.13 | <0.001 | 0.958 (0.945 ~ 0.971) |
| PLT | 0.00 | 0.00 | 0.55 | 0.586 | 1.001 (0.997 ~ 1.005) |
| Male | -0.11 | 0.27 | -0.41 | 0.679 | 0.894 (0.527 ~ 1.518) |
| Hypertension | 1.37 | 0.32 | 4.33 | <0.001 | 3.920 (2.113 ~ 7.272) |
| CHD | 0.44 | 0.31 | 1.43 | 0.154 | 1.559 (0.847 ~ 2.870) |
| Reg Iα(ng/mL) | | | | | |
| ≤38.60 | | | | | 1.000 (Reference) |
| >38.60~82.17 | -0.01 | 0.39 | -0.03 | 0.979 | 0.990 (0.465 ~ 2.106) |
| >82.17~196.15 | 1.18 | 0.39 | 2.98 | 0.003 | 3.240 (1.496 ~ 7.019) |
| >196.15 | 2.79 | 0.51 | 5.43 | <0.001 | 16.200 (5.930 ~ 44.257) |

## *2.4 Construction of predictive model and nomogram*

Based on the four independent predictive factors identified by binary logistic regression, a nomogram was constructed. The nomogram included predictors (history of hypertension, Reg Iα, UA, and HGB), single-item scores, total scores, and graphical lines representing the risk of CKD occurrence. Each segment on the lines represented the range of values corresponding to each risk factor, with the length indicating its contribution to CKD risk. The topmost single-item scores in the model represented the respective scores for each predictive factor at different values, which were summed to calculate the total score corresponding to the predicted probability of CKD risk at the bottom of the model. **See Figure1**.

**Tab.4** Multivariate logistic regression analysis of the factors affecting diabetes mellitus complicated with CKD

| Indicator | *β* | *S.E* | *Z* | *P* value | *OR* (95%*CI*) |
|---|---|---|---|---|---|
| Age | -0.012 | 0.013 | 0.835 | 0.361 | 0.988(0.963 ~ 1.014) |
| Hypertension | 1.065 | 0.326 | 10.687 | <0.001 | 2.901(1.532 ~ 5.493) |
| CHD | -0.209 | 0.339 | 0.38 | 0.538 | 0.811(0.417 ~ 1.577) |
| UA | 0.005 | 0.001 | 12.302 | <0.001 | 1.005(1.002 ~ 1.007) |
| HGB | -0.036 | 0.007 | 28.975 | <0.001 | 0.965(0.952 ~ 0.977) |
| Reg Iα(ng/mL) | | | | | |
| ≤38.60 | | | 35.472 | <0.001 | |
| >38.60~82.17 | 0.043 | 0.358 | 0.015 | 0.904 | 1.044(0.517 ~ 2.108) |
| >82.17~196.15 | 1.129 | 0.363 | 9.661 | 0.002 | 3.094(1.518 ~ 6.306) |
| >196.15 | 2.557 | 0.499 | 26.217 | <0.001 | 12.902(4.847 ~ 34.34) |

Note:[a] WBC, white blood cell count; [b] RBC, Red Blood Cell Count

## *2.5 Model validation and evaluation*

The area under the ROC curve was 0.846 (95% CI: 0.796-0.896) for the training set and 0.920 (95% CI: 0.875-0.965) for the validation set, indicating good stability and fit of the model. Goodness-of-fit curves and Hosmer-Lemeshow tests showed no statistically significant differences between predicted and observed probabilities in both the training set and validation set ($P$>0.05), suggesting that the predictions closely matched actual outcomes and had good fit. Clinical decision curves indicated potential clinical utility. [**Figures 2-4**].

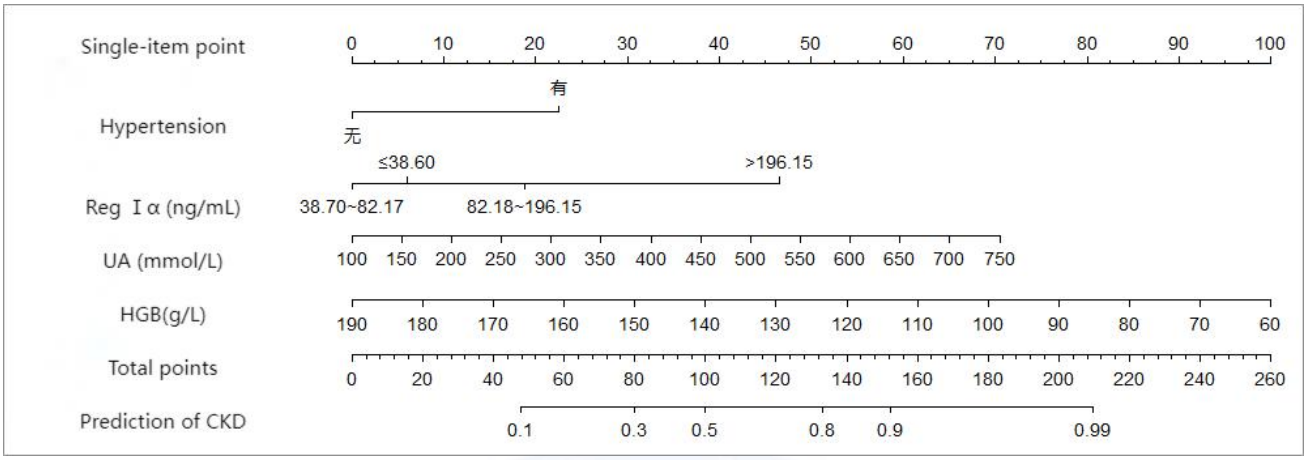


**Fig. 1** Nomogram model for risk prediction of diabetes mellitus complicated with CKD

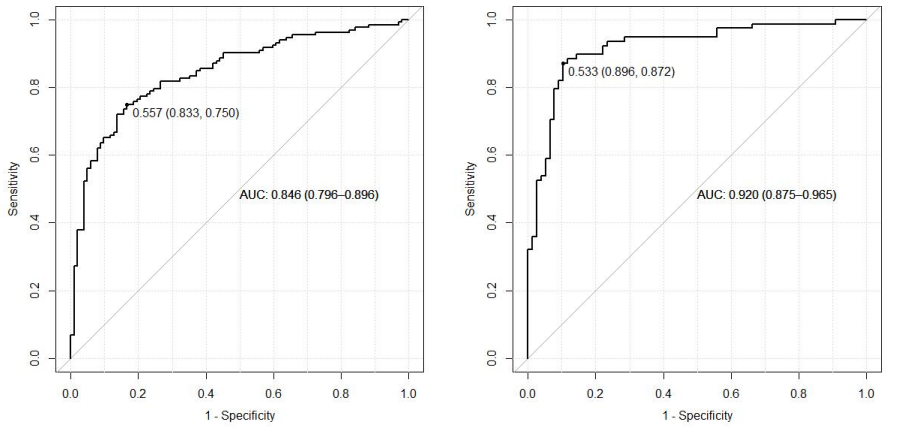


**Fig 2** ROC curves of the prediction model in the training set (left) and the validation set (right)

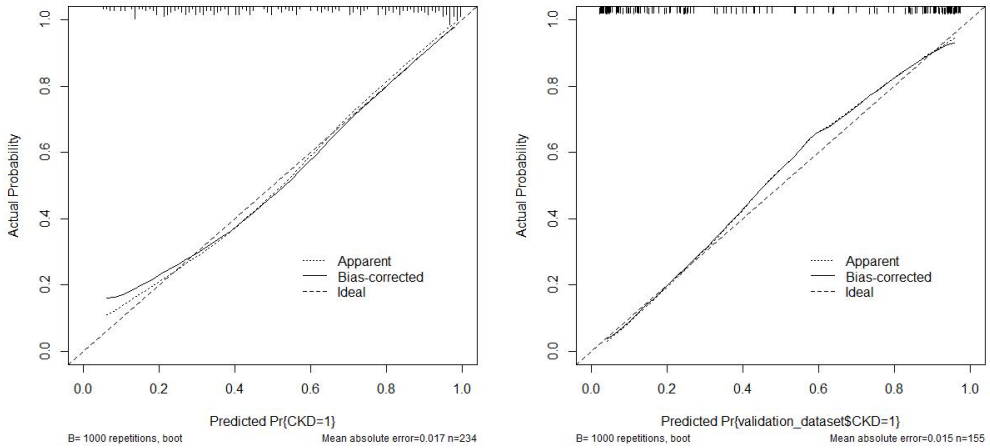


**Fig 3** Calibration curves of the prediction model in the training set (left) and the validation set (right)

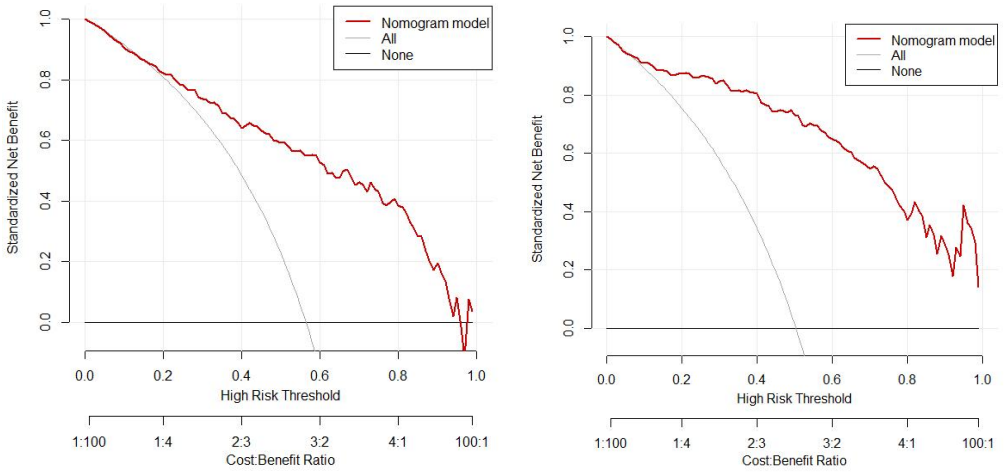


**Fig.4** Clinical decision curve of the prediction model in the training set (left) and the validation set (right)

## 3 \Discussion

The results of this study indicated that elevated levels of Reg Iα, a history of hypertension, decreased HGB, and elevated UA were risk factors for diabetic patients with concurrent CKD. Furthermore, a predictive nomogram model for assessing the risk of CKD in diabetic patients was developed. The areas under the ROC curves for the training set and validation set were 0.846 and 0.920, respectively, demonstrating good stability and fit.

Reg protein was first discovered in 1988 and is a member of the stress protein family secreted by pancreatic acinar cells. It has been shown both *in vivo* and *in vitro* to contribute to pancreatic β-cell regeneration [6,16]. Previous studies by our research group have found that Reg Iα can reflect the extent of renal damage in type 2 diabetic patients [17]. As a small molecular protein, Reg Iα can be directly reabsorbed in the proximal renal tubules and may indirectly participate in the development of CKD through inflammatory reactions, although the specific mechanisms remain unclear. Therefore, exploring the relationship between pancreatic secretory stress protein Reg Iα and renal damage is clinically significant.

Bjornstad *et al.* [18], using the hyperglycemic clamp gold standard technique, assessed insulin secretion levels in type 2 diabetic patients and found that β-cell dysfunction and insulin resistance (IR) increased the risk of renal damage in diabetic patients. IR is a key factor in the development of CKD [19]. In addition, toxins in diabetic patients with CKD can increase oxidative stress and reactive oxygen levels, further exacerbating IR [20], suggesting a mutual influence between IR and CKD in diabetic patients, accelerating disease progression. Inflammatory mediators in diabetic patients can act on glomeruli and renal tubulointerstitium, exacerbating peri-renal inflammation. Hu *et al.* [21] observed significant increases in neutrophil infiltration and inflammatory factor expression in the kidneys of mouse models injected with Reg. Reding *et al.* [22] found that the pancreas can detect damage to distant organs, respond to early inflammatory damage, and promote pancreatic acinar cell secretion of Reg Iα. Thus, elevated serum levels of Reg Iα to some extent indicate early renal inflammatory status, and peri-renal inflammatory reactions may promote pancreatic secretion of Reg Iα, but the specific mechanisms require further elucidation. Consistent with the direction of the aforementioned research, this study found that Reg Iα > 82.17 ng/mL is a risk factor for diabetes complicated by CKD. However, this study did not collect inflammatory markers; future research will further analyze the correlation between Reg Iα and inflammatory factors and their potential connections.

Tangri *et al.* [23] developed a model in the Canadian population, recalibrated through multi-national cohorts, which still requires further validation. Ramspeck *et al.* [24] established a model in the European population, but showed significant performance differences in different validation cohorts, suggesting the need for retraining or redesigning CKD prediction models for different racial populations. Studies based on modeling of the Chinese population have also been reported successively; Cao *et al.* [25] used age, gender, BMI, duration of diabetes, FPG variation, history of stroke, and hypertension history to establish a risk model for predicting CKD in Chinese type 2 diabetic patients. However, FPG variation is influenced by many factors, possibly increasing bias probability. Lin *et al.* [26] conducted a retrospective study using age, duration of diabetes, insulin use, eGFR, UACR, HDL cholesterol, triglycerides, diabetic retinopathy (DR), HbA1c variation, FPG variation, and antihypertensive medication use as 11 indicators to establish a model for predicting the risk of CKD in Chinese type 2 diabetic patients. However, this model includes too many indicators and requires discrimination of whether patients

have concomitant DR, which has a low screening rate and may reduce the practicality of the model. This study established a nomogram model for predicting CKD in diabetic patients using hypertension history, Reg Iα, UA, and HGB, which showed good predictive performance in internal validation and is convenient for clinical application.

This study found that elevated serum Reg Iα levels in diabetic patients were significantly associated with CKD. The predictive model based on Reg Iα allows quantitative analysis of the risk of CKD in diabetic patients. However, this study is cross-sectional and cannot determine causality, necessitating prospective cohort studies for causal inference and development of models that can predict future CKD risk. Additionally, the model lacks external validation; future studies are needed to further explore other data to improve the credibility and generalizability of the model.

**The authors report no conflict of interest**

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·论　著·

# 糖尿病患者血清胰腺再生蛋白Ⅰα水平与慢性肾脏病发生风险的相关性

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**摘要：目的**　探讨糖尿病患者血清胰腺再生(Reg)蛋白Ⅰα与慢性肾脏病(CKD)的关系，建立糖尿病合并 CKD 的风险预测模型。**方法**　回顾性选取 2021 年 9 月至 2023 年 9 月就诊于东南大学附属中大医院的 500 例糖尿病患者。收集一般资料、既往病史、实验室检查[血常规、空腹血糖(FPG)、血尿素氮(BUN)、血肌酐(Scr)、血尿酸(UA)、尿白蛋白/肌酐比值(UACR)]，并计算估算的肾小球滤过率(eGFR)。酶联免疫法测定血清 RegⅠα水平，按照四分位数水平将患者分为 R1（RegⅠα≤38.60 ng/mL，$n$=98）、R2（38.60<RegⅠα≤82.17ng/mL，$n$=97）、R3（82.17<RegⅠα≤196.15 ng/mL，$n$=97）和 R4（RegⅠα>196.15 ng/mL，$n$=97）组。采用随机数字表法按 6∶4 比例将患者随机分为训练集($n$=234)和验证集($n$=155)。多元 logistic 逐步回归法筛选模型变量，构建糖尿病合并 CKD 风险的列线图模型并评估其性能。**结果**　(1) 共纳入资料完整的糖尿病患者 389 例，210 例(53.98%)合并 CKD。与 R1 组相比，R4 组患者 FPG、BUN、Scr、UA 水平升高，高血压病、冠心病和 CKD 比例增加，红细胞计数、血红蛋白(HGB)、eGFR 水平下降（$P$<0.05）。(2) 训练集和验证集所有指标均衡($P$>0.05)。在训练集中，与无 CKD 组相比，CKD 组患者 RegⅠα、白细胞计数、BUN、Scr 及 UA 水平升高，高血压病、冠心病比例增加，红细胞计数、HGB 和 eGFR 水平下降（$P$<0.05）。在共线性诊断基础上二元 logistic 回归分析结果显示，高血压病史（$OR$=2.901）、RegⅠα>82.17 ng/mL、HGB 降低($OR$=0.965)和 UA 升高（$OR$=1.005）是糖尿病合并 CKD 的危险因素($P$<0.05)。(3) 训练集和验证集的 ROC 曲线下面积分别为 0.846(95%$CI$：0.796～0.896)和 0.920(95%$CI$：0.875～0.965)，校正曲线及 Hosmer-Lemeshow 检验结果显示预测结果与实际结果一致性较好($P$>0.05)。**结论**　高血压病史、RegⅠα升高、HGB 降低和 UA 升高是糖尿病患者合并 CKD 的危险因素，本研究构建的列线图模型对糖尿病合并 CKD 的风险具有良好的预测效能和临床使用价值。

**关键词：**糖尿病；慢性肾脏病；胰腺再生蛋白Ⅰα；高血压；血红蛋白；肾功能；风险预测

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# Association between serum pancreatic regenerating protien Ⅰα and the risk of chronic kidney disease in patients with diabetes mellitus

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**Abstract: Objective**　To investigate the correlation between serum pancreatic regenerating (Reg) protein Ⅰα and chronic kidney disease (CKD) in diabetic patients, to develop a risk prediction model for diabetes combined with CKD. **Methods**　The clinical data of 500 diabetic patients admitted to the Zhongda Hospital Southeast University from September 2021 to September 2023 were collected for a retrospective study, including general data, medical history, and laboratory indexes[blood routine tests, fasting plasma glucose (FPG), blood urea nitrogen (BUN), serum creatinine (Scr), serum uric acid (UA), and urinary albumin/creatinine ratio (UACR)]. Additionally, the estimated glomerular

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filtration rate (eGFR) was calculated. Serum RegⅠα level was measured by enzyme-linked immunosorbent assay, and patients were classified into groups R1 (Reg Ⅰα≤38.60 ng/mL, $n$=98), R2 (38.60<Reg Ⅰα≤82.17 ng/mL, $n$=97), R3 (82.17<Reg Ⅰα≤196.15 ng/mL, $n$=97) and R4 (Reg Ⅰα>196.15 ng/mL, $n$=97), according to quartile levels. Patients were randomly divided into a training set (234 cases) and a validation set (155 cases) using a random number table method in a ratio of 6∶4. Multivariate logistic stepwise regression was utilized to identify model variables and create a nomogram model for predicting the risk of diabetes combined with CKD, and evaluate its efficiency. **Results** (1) A total of 389 diabetic patients with complete data were included, and 210 (53.98%) patients with CKD. Patients in the R4 group exhibited significantly higher levels of FPG, BUN, Scr, and UA, increased rates of hypertension, coronary heart disease, and CKD, as well as lower levels of red blood cell count, hemoglobin (HGB), and eGFR compared to those in the R1 group ($P$<0.05). (2) The indicators in the training and validation sets were found to be well-balanced ($P$>0.05). In the training set, the CKD group showed higher levels of Reg Ⅰα, white blood cell count, BUN, Scr, and UA, higher prevalences of hypertension and coronary artery disease, and lower levels of erythrocyte count, HGB, and eGFR compared to the NCKD group ($P$<0.05). Binary logistic regression analysis was performed on the basis of collinearity diagnosis,and the results showed that history of hypertension ($OR$=2.901), Reg Ⅰα>82.17 ng/mL, decreased HGB ($OR$=0.965) and increased UA ($OR$=1.005) were the risk factors of diabetes complicated with CKD ($P$<0.05). (3) The areas under the ROC of the training set and validation set were 0.846(95%$CI$: 0.796-0.896) and 0.920(95%$CI$: 0.875-0.965), respectively. The calibration curves and the Hosmer-Lemeshow test indicated good agreement of the predicted and observed outcomes ($P$>0.05). **Conclusion** Hypertension, elevated Reg Ⅰα levels, decreased HGB and elevated UA are risk factors for CKD in diabetic patients, and the nomogram model constructed in this study has good predictive power and clinical value.

**Keywords**: Diabetes mellitus; Chronic kidney disease; Pancreatic regenerating protein Ⅰα; Hypertension; Hemoglobin; Kidney function; Risk prediction

据国际糖尿病联盟报道,2021 年全球糖尿病患者达 5.37 亿,预计到 2045 年将增加至 7.84 亿[1]。慢性肾脏病(chronic kidney disease, CKD)是由多病因导致的肾脏结构和功能异常(≥3 个月),糖尿病是 CKD 的关键危险因素,超过四分之一的糖尿病患者合并 CKD[2],糖尿病加速 CKD 发展至终末期肾病。CKD 起病隐匿,早期(G1~G2 期)通常无明显症状,多数初诊 CKD 患者已处于中期阶段,因而,CKD 具有高患病率、高致残率和低知晓率,肾脏损伤病程易被低估等特点。ADA/KDIGO 共识主张病程 5 年以上的 1 型糖尿病和 2 型糖尿病患者应每年筛查 CKD[3],但我国目前尚未建立适合于糖尿病患者筛查 CKD 的标准化体系[4],多地基层医疗卫生机构使用尿常规作为 CKD 初筛手段[5],而蛋白尿结果波动大,稳定性差,敏感性不高,易漏诊较多 CKD 患者。

胰腺再生(regenerating, Reg)蛋白是钙依赖性凝集素基因超家族的一种小分子量分泌型蛋白,Reg Ⅰα作为其中的亚型之一,主要存在于胰腺腺泡细胞,能够促进胰岛 β 细胞再生和胰腺损伤后组织重构[6-7],同时在损伤的肾脏组织中表达增加[8]。本课题组前期发现血清 Reg Ⅰα水平在 2 型糖尿病患者中升高,并与估算的肾小球滤过率(eGFR)呈显著负相关[9-10],提示 Reg Ⅰα与糖尿病患者肾功能受损密切相关。临床中应用预测模型能够对此风险进行定量计算,对识别 CKD 高危人群和早筛早诊具有重要价值。目前,多数研究致力于分析 CKD 危险因素,未将其转化为模型应用于临床[11]。部分研究基于临床指标构建 CKD 预测模型,但更多聚焦于一般人群,且存在较大变异性,预测效能介于 0.6~0.9 不等[12],考虑到地域、种族等因素影响,基于西方人群建立的 CKD 预测模型尚不能直接应用于我国患者[13],亟需寻求一种简便、廉价、适合我国糖尿病患者大规模筛查 CKD 的预测模型。Reg Ⅰα作为一种有效的血清标志物,对糖尿病患者肾脏损伤具有警示作用,加之检测简便,易于在临床中应用开展。因此,本研究旨在探讨糖尿病患者血清 Reg Ⅰα水平与 CKD 发生风险的关系,并建立预测模型,以期尽早识别高危人群,提高筛查率。

## 1　对象与方法

1.1　研究对象　回顾性选择 2021 年 9 月至 2023 年 9 月就诊于东南大学附属中大医院的糖尿病患者。纳入标准:(1) 符合糖尿病诊断标准[14];(2) 年龄 18~80 岁;(3) 具有基本理解研究流程能力的受试者。排除标准:(1) 存在应激状态或急性感染;(2) 合并严重肝功能损伤、结缔组织病、恶性血液病以及肿瘤;(3) 有精神疾病;(4) 孕产妇;(5) 正在

参与另一项临床研究;(6) 患有胃肠道急慢性炎症或胃肠道肿瘤;(7) 重要数据缺失者。纳入符合纳排标准的患者 389 例。本研究经东南大学附属中大医院伦理委员会批准 (2022ZDSYLL204-P01),中国临床试验中心注册(ChiCTR2300072247)。

1.2 *研究方法* (1) 资料收集:收集一般信息(年龄和性别)、既往病史(高血压病史、冠心病病史)、实验室检查[血常规、空腹血糖(FPG)、血尿素氮(BUN)、血肌酐(Scr)、血尿酸(UA)、尿白蛋白/肌酐比值(UACR)],并根据改善全球肾脏病预后组织指南推荐的慢性肾脏病流行病学合作研究(CKD-EPI)计算 eGFR。(2) 根据《慢性肾脏病早期筛查、诊断及防治指南(2022 年版)》[4],将 UACR>30 mg/g 和(或) eGFR<60 mL/(min·1.73 $m^2$)且持续 3 个月以上者定义为 CKD。(3) 血清 Reg Ⅰα 检测:本项目组自主研发 Reg Ⅰα 检测方法,取冻存血浆 200 μL,采用酶联免疫法(ELISA)测定血清 Reg Ⅰα 水平。按照四分位数水平将患者分为 R1(Reg Ⅰα≤38.60 ng/mL)、R2(38.60<Reg Ⅰα≤82.17 ng/mL)、R3(82.17<Reg Ⅰα≤196.15 ng/mL)和 R4(Reg Ⅰα>196.15 ng/mL)组。

1.3 *统计学方法* 应用 SPSS 26.0 软件和 R3.4.2 软件进行统计分析。计量资料正态分布的用 $\bar{x}\pm s$ 表示,非正态分布用 $M(P_{25},P_{75})$ 表示,计数资料用例(%)表示;R1~R4 组中计量资料多组间比较及其多重比较采用 Kruskal-Waills $H$ 检验;率或构成比的比较采用 $\chi^2$ 检验。采用单因素和二元 logistic 回归法筛选模型变量,建模方案依据预测模型国际规范 TRIPOD 声明中 Type2a 原则[15],按 6∶4 比例随机分为训练集和验证集,两集中计量资料组间比较采用 Mann-Whitney $U$ 检验,根据训练集构建预测糖尿病合并 CKD 风险的列线图,验证集用于内部验证,利用一致性指数、校正曲线和临床决策曲线综合评估模型性能。$P$<0.05为差异有统计学意义。

## 2 结　果

2.1 *不同 Reg Ⅰα 水平糖尿病患者的一般资料比较* 本研究中,男性 61.7%(240/389),女性 38.3%(149/389),中位年龄 64.00(53.50, 70.00)岁。与 R1 组相比,R4 组患者 FPG、BUN、Scr 和 UA 升高,高血压病、冠心病、CKD 比例增加,红细胞计数、血红蛋白(HGB)、eGFR 下降($P$<0.05)。见表 1。

2.2 *训练集与验证集的临床资料比较* 389 例糖尿病患者中,训练集 234 例,验证集 155 例。CKD 患者共 210 例,其中训练集 132 例,验证集 78 例。训练集和验证集的所有指标均衡可比($P$>0.05)。见表 2。

2.3 *预测因子的筛选* 在训练集中,单因素 logistic 回归分析显示,与无 CKD 组相比,CKD 组白细胞计数、BUN、Scr 及 UA 水平升高,高血压病及 Reg Ⅰα>82.17 ng/mL 比例增加,红细胞计数、HGB 和 eGFR 水平下降($P$<0.01)。见表 3。在共线性诊断的基础上,加之考虑年龄作为临床常见影响因素,因此,将年龄、Reg Ⅰα、高血压病史、冠心病史、HGB 和 UA 纳入二元 logistic 回归分析,分析结果显示,Reg Ⅰα>82.17 ng/mL、高血压病史、HGB 降低和 UA 升高是糖尿病合并 CKD 的危险因素($P$<0.01)。见表 4。

2.4 *预测模型构建及列线图绘制* 根据二元 logistic 回归筛选出的 4 个独立预测因子构建模型,列线图由预测因子(高血压病史、Reg Ⅰα、UA 和 HGB)、单项评分、总分和 CKD 发生风险的图形线组成。每个线段的刻度代表该风险因素对应的可取值范围,线段的长度反映该因素对 CKD 发生风险的贡献大小。模型中最上方的单项评分表示每个预测因子在不同取值下的相应得分,将所有预测因子的单项分数相加后计算总评分,对应模型最下方 CKD 风险的预测概率。见图 1。

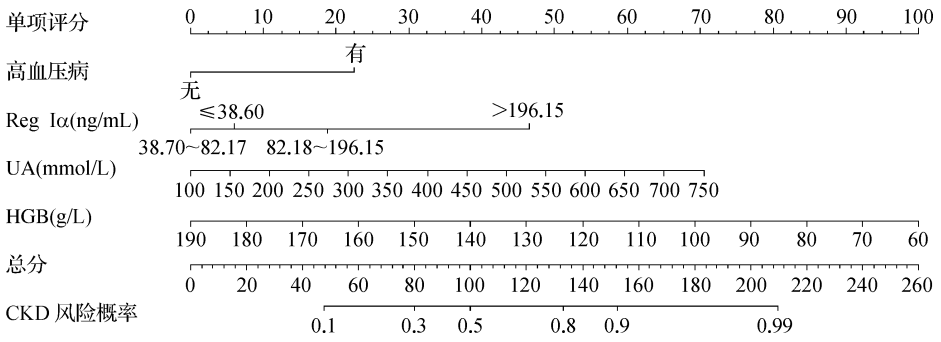


**图 1** 糖尿病合并 CKD 风险预测的列线图模型

**Fig. 1** Nomogram model for risk prediction of diabetes mellitus complicated with CKD

**表 1**　不同 Reg Ⅰα 水平患者一般资料对比　［$M(P_{25},P_{75})$］

**Tab. 1**　Comparison of general clinical data of patients with different Reg Ⅰα levels　［$M(P_{25},P_{75})$］

| 变量 | 总体（$n$=389） | R1 组（$n$=98） | R2 组（$n$=97） | R3 组（$n$=97） | R4 组（$n$ =97） | $Z/\chi^2$ 值 | $P$ 值 |
|---|---|---|---|---|---|---|---|
| 年龄（岁） | 64.00（54.00, 70.00） | 60.50（51.00, 67.75） | 63.00（58.00, 71.00） | 66.00（57.00, 72.00） | 64.00（53.00, 70.00） | 9.052[a] | 0.029 |
| 性别［例（%）］ | | | | | | | |
| 女性 | 149（38.30） | 36（36.73） | 38（39.18） | 38（39.18） | 37（38.14） | 0.165[b] | 0.983 |
| 男性 | 240（61.70） | 62（63.27） | 59（60.82） | 59（60.82） | 60（61.86） | | |
| 高血压病［例（%）］ | | | | | | | |
| 否 | 98（25.19） | 37（37.76） | 30（30.93） | 20（20.62） | 11（11.34） | 20.853[b] | <0.001 |
| 是 | 291（74.81） | 61（62.24） | 67（69.07） | 77（79.38） | 86（88.66）[c] | | |
| 冠心病［例（%）］ | | | | | | | |
| 否 | 291（74.81） | 81（82.65） | 77（79.38） | 71（73.20） | 62（63.92） | 10.515[b] | 0.015 |
| 是 | 98（25.19） | 17（17.35） | 20（20.62） | 26（26.80） | 35（36.08）[c] | | |
| FPG（mmol/L） | 6.90（5.69, 9.16） | 7.55（6.49, 10.33） | 6.90（5.90, 8.80） | 7.10（5.51, 9.83） | 6.12（4.84, 8.20）[c] | 22.124[a] | <0.001 |
| BUN（mmol/L） | 8.10（6.20, 13.50） | 6.30（5.20, 7.50） | 7.10（5.90, 8.80） | 9.70（7.30, 14.00） | 18.70（11.50, 27.80）[c] | 159.618[a] | <0.001 |
| Scr（μmol/L） | 98.00（70.00, 204.00） | 68.00（57.00, 83.75） | 80.00（66.00, 101.00） | 113.00（87.00, 167.00） | 379.00（198.00, 659.00）[c] | 187.324[a] | <0.001 |
| UA（mmol/L） | 336.00（275.00, 423.00） | 293.50（256.50, 347.75） | 319.00（256.00, 377.00） | 370.00（317.00, 452.00） | 374.00（314.00, 466.00）[c] | 44.163[a] | <0.001 |
| eGFR[d] | 67.12（27.30, 93.67） | 95.06（83.94, 104.29） | 84.77（62.06, 94.94） | 54.64（33.67, 80.20） | 11.88（6.55, 28.94）[c] | 198.577[a] | <0.001 |
| WBC（$\times10^9$/L） | 6.59（5.34, 7.90） | 6.50（5.20, 7.67） | 6.37（5.24, 7.80） | 6.46（5.34, 8.57） | 7.19（5.74, 8.12） | 6.838[a] | 0.077 |
| RBC（$\times10^{12}$/L） | 4.32（3.66, 4.76） | 4.55（4.24, 4.92） | 4.51（4.15, 4.91） | 4.09（3.65, 4.56） | 3.56（2.94, 4.10）[c] | 93.225[a] | <0.001 |
| HGB（g/L） | 128.00（108.00, 144.00） | 138.00（128.00, 149.00） | 138.00（124.00, 154.00） | 126.00（109.00, 140.00） | 103.00（85.00, 123.00）[c] | 94.446[a] | <0.001 |
| PLT（$\times10^9$/L） | 197.00（158.00, 237.00） | 209.00（163.50, 244.75） | 199.00（169.00, 229.00） | 192.00（153.00, 249.00） | 197.00（140.00, 231.00） | 2.573[a] | 0.462 |
| CKD［例（%）］ | | | | | | | |
| 否 | 179（46.02） | 72（73.47） | 68（70.10） | 32（32.99） | 7（7.22） | 117.797 * | <0.001 |
| 是 | 210（53.98） | 26（26.53） | 29（29.90） | 65（67.01） | 90（92.78）[c] | | |

注：[a] 代表 Kruskal-Wailis 检验；[b] 代表 $\chi^2$ 检验；与 R1 组相比，[c] $P$<0.05；[d] 表示 eGFR 的单位为 mL/（min · 1.73 $m^2$）。

**表 2**　训练集与验证集一般资料比较　［$M(P_{25},P_{75})$］

**Tab. 2**　Comparison of general data between the training set and the validation set　［$M(P_{25},P_{75})$］

| 变量 | 总体（$n$=389） | 训练集（$n$=234） | 验证集（$n$=155） | $Z/\chi^2$ 值 | $P$ 值 |
|---|---|---|---|---|---|
| 年龄（岁） | 64.00（54.00, 70.00） | 63.00（55.00, 70.00） | 64.00（53.00, 70.50） | 0.476[a] | 0.634 |
| 性别［例（%）］ | | | | | |
| 女性 | 149（38.30） | 93（39.74） | 56（36.13） | 0.515[b] | 0.473 |
| 男性 | 240（61.70） | 141（60.26） | 99（63.87） | | |
| 高血压病［例（%）］ | | | | | |
| 否 | 98（25.19） | 62（26.50） | 36（23.23） | 0.529[b] | 0.467 |
| 是 | 291（74.81） | 172（73.50） | 119（76.77） | | |
| 冠心病［例（%）］ | | | | | |
| 否 | 291（74.81） | 175（74.79） | 116（74.84） | 0.000[b] | 0.991 |
| 是 | 98（25.19） | 59（25.21） | 39（25.16） | | |
| FPG（mmol/L） | 6.90（5.69, 9.16） | 6.85（5.83, 9.35） | 6.97（5.47, 8.79） | 0.460[a] | 0.646 |
| BUN（mmol/L） | 8.10（6.20, 13.50） | 8.30（6.30, 13.38） | 7.90（6.10, 14.10） | 0.226[a] | 0.821 |
| Scr（μmol/L） | 98.00（70.00, 204.00） | 100.00（69.00, 199.50） | 93.00（70.50, 212.00） | 0.167[a] | 0.868 |
| UA（mmol/L） | 336.00（275.00, 423.00） | 328.50（265.25, 423.00） | 347.00（300.50, 426.50） | 1.534[a] | 0.125 |
| eGFR[c] | 67.00（27.00, 94.00） | 64.00（27.25, 93.75） | 71.00（27.00, 93.50） | 0.143[a] | 0.886 |
| WBC（$\times10^9$/L） | 6.59（5.34, 7.90） | 6.59（5.25, 8.05） | 6.53（5.55, 7.81） | 0.321[a] | 0.749 |
| RBC（$\times10^{12}$/L） | 4.32（3.66, 4.76） | 4.30（3.63, 4.71） | 4.37（3.67, 4.80） | 1.162[a] | 0.245 |
| HGB（g/L） | 128.00（108.00, 144.00） | 128.00（107.25, 141.00） | 128.00（109.50, 145.50） | 1.275[a] | 0.202 |
| PLT（$\times10^9$/L） | 197.00（158.00, 237.00） | 197.00（163.00, 232.00） | 200.00（157.00, 246.00） | 0.894[a] | 0.371 |
| CKD［例（%）］ | | | | | |
| 否 | 179（46.02） | 102（43.59） | 77（49.68） | 1.391[b] | 0.238 |
| 是 | 210（53.98） | 132（56.41） | 78（50.32） | | |
| Reg Ⅰα［例（%）］ | | | | | |
| ≤38.60 ng/mL | 98（25.18） | 56（23.93） | 42（27.10） | | |
| >38.60~82.17 ng/mL | 97（24.94） | 62（26.50） | 35（22.58） | 1.299[b] | 0.729 |
| >82.17~196.15 ng/mL | 97（24.94） | 56（23.93） | 41（26.45） | | |
| >196.15 ng/mL | 97（24.94） | 60（25.64） | 37（23.87） | | |

注：[a] 代表 Mann-Whitney 检验；[b] 代表 $\chi^2$ 检验；[c] 表示 eGFR 的单位为 mL/（min · 1.73 $m^2$）。

2.5　模型验证与评估　训练集和验证集的 ROC 曲线下面积分别为 0.846(95%*CI*：0.796～0.896)和 0.920(95%*CI*：0.875～0.965)，最佳截断值(特异度、敏感度)分别为 0.557(0.833,0.750)和 0.533(0.896,0.872)。拟合优度曲线和 Hosmer-Lemeshow 检验显示，训练集和验证集的预测概率与实际概率的差异无统计学意义($P$>0.05)，说明该模型预测结果接近于实际，拟合度较好。临床决策曲线提示，该模型具有临床获益。见图 2～图 4。

**表 3**　糖尿病合并 CKD 影响因素的单因素 logistic 回归分析
**Tab. 3**　Univariate logistic regression analysis of the factors affecting diabetes mellitus complicated with CKD

| 变量 | $\beta$ | *S.E* | *Z* 值 | *P* 值 | *OR*(95%*CI*) |
|---|---|---|---|---|---|
| 年龄 | 0.00 | 0.01 | 0.37 | 0.709 | 1.004(0.982～1.027) |
| FPG | −0.05 | 0.04 | −1.16 | 0.248 | 0.956(0.885～1.032) |
| BUN | 0.39 | 0.06 | 6.17 | <0.001 | 1.476(1.304～1.670) |
| Scr | 0.05 | 0.01 | 6.40 | <0.001 | 1.048(1.033～1.063) |
| UA | 0.01 | 0.00 | 4.50 | <0.001 | 1.006(1.003～1.008) |
| eGFR | −0.08 | 0.01 | −8.07 | <0.001 | 0.925(0.907～0.942) |
| WBC[a] | 0.25 | 0.07 | 3.64 | <0.001 | 1.289(1.124～1.477) |
| RBC[b] | −1.34 | 0.22 | −6.01 | <0.001 | 0.263(0.170～0.407) |
| HGB | −0.04 | 0.01 | −6.13 | <0.001 | 0.958(0.945～0.971) |
| PLT | 0.00 | 0.00 | 0.55 | 0.586 | 1.001(0.997～1.005) |
| 男性 | −0.11 | 0.27 | −0.41 | 0.679 | 0.894(0.527～1.518) |
| 高血压病 | 1.37 | 0.32 | 4.33 | <0.001 | 3.920(2.113～7.272) |
| 冠心病 | 0.44 | 0.31 | 1.43 | 0.154 | 1.559(0.847～2.870) |
| Reg Ⅰα(ng/mL) | | | | | |
| ≤38.60 | | | | | 1.000(Reference) |
| >38.60～82.17 | −0.01 | 0.39 | −0.03 | 0.979 | 0.990(0.465～2.106) |
| >82.17～196.15 | 1.18 | 0.39 | 2.98 | 0.003 | 3.240(1.496～7.019) |
| >196.15 | 2.79 | 0.51 | 5.43 | <0.001 | 16.200(5.930～44.257) |

注：[a]WBC(白细胞计数)；[b]RBC(红细胞计数)。

**表 4**　糖尿病合并 CKD 影响因素的多因素 logistic 回归分析
**Tab. 4**　Multivariate logistic regression analysis of the factors affecting diabetes mellitus complicated with CKD

| 变量 | $\beta$ | *S.E* | *Z* 值 | *P* 值 | *OR*(95%*CI*) |
|---|---|---|---|---|---|
| 年龄 | −0.012 | 0.013 | 0.835 | 0.361 | 0.988(0.963～1.014) |
| 高血压病 | 1.065 | 0.326 | 10.687 | <0.001 | 2.901(1.532～5.493) |
| 冠心病 | −0.209 | 0.339 | 0.38 | 0.538 | 0.811(0.417～1.577) |
| UA | 0.005 | 0.001 | 12.302 | <0.001 | 1.005(1.002～1.007) |
| HGB | −0.036 | 0.007 | 28.975 | <0.001 | 0.965(0.952～0.977) |
| Reg Ⅰα(ng/mL) | | | | | |
| ≤38.60 | | | 35.472 | <0.001 | |
| >38.60～82.17 | 0.043 | 0.358 | 0.015 | 0.904 | 1.044(0.517～2.108) |
| >82.17～196.15 | 1.129 | 0.363 | 9.661 | 0.002 | 3.094(1.518～6.306) |
| >196.15 | 2.557 | 0.499 | 26.217 | <0.001 | 12.902(4.847～34.34) |

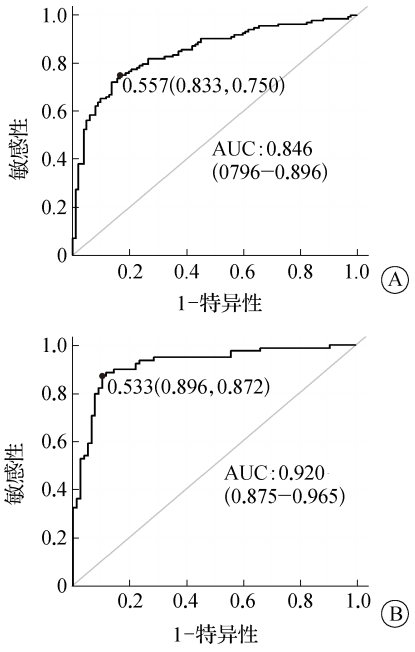


**图 2**　预测模型在训练集(A)和验证集(B)中的 ROC 曲线
**Fig. 2**　ROC curves of the prediction model in the training set (A) and the validation set (B)

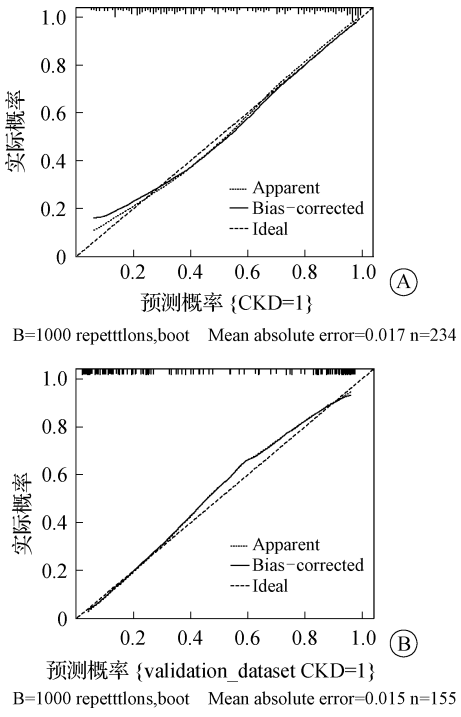


**图 3**　预测模型在训练集(A)和验证集(B)中的拟合优度曲线
**Fig. 3**　Calibration curves of the prediction model in the training set (A) and the validation set (B)

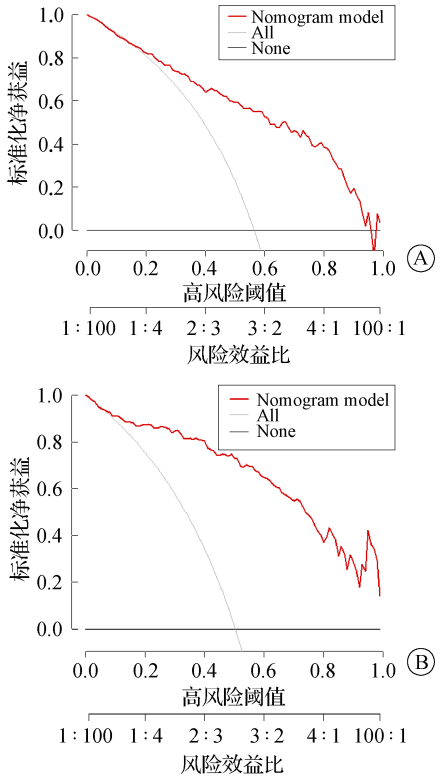


**图 4**　预测模型在训练集(A)和验证集(B)中的临床决策曲线

**Fig. 4**　Clinical decision curve of the prediction model in the training set (A) and the validation set (B)

## 3　讨　论

本研究结果显示,Reg Ⅰα 升高、高血压病史、HGB 降低和 UA 升高是糖尿病患者合并 CKD 的危险因素,进一步建立预测糖尿病患者合并 CKD 风险的列线图模型,训练集和验证集的 ROC 曲线下面积分别为 0.846 和 0.920,具有良好的稳定性和拟合程度。

Reg 蛋白是由胰腺腺泡细胞分泌的应激蛋白家族成员之一,体内外均已证明其有助于胰腺 β 细胞再生[6,16]。本课题组前期发现,Reg Ⅰα 可反映 2 型糖尿病患者肾脏损伤程度[17]。作为小分子蛋白,其可直接在近端肾小管被重吸收,也可通过炎症反应间接参与 CKD 发生发展,但具体机制尚不清楚,因此,探索胰腺分泌的 Reg Ⅰα 与肾脏损伤的关系具有重要临床意义。

Bjornstad 等[18]利用高血糖钳夹金标准技术评估 2 型糖尿病患者胰岛素分泌水平,发现 β 细胞功能障碍和胰岛素抵抗(IR)均增加糖尿病患者肾脏损伤的风险。IR 是 CKD 疾病发生发展的关键因素[19]。另外,糖尿病合并 CKD 患者的体内毒素可增加氧化应激反应和活性氧水平,从而加重 IR[20],提示糖尿病患者 IR 与 CKD 相互影响,共同加速疾病进展。Hu 等[21]在小鼠模型中观察到注射重组 Reg 蛋白后肾脏中性粒细胞浸润和炎症因子表达显著增加。Reding 等[22]发现胰腺能够感知远端器官损伤,对早期炎症损伤做出应激反应,促进胰腺腺泡细胞分泌 Reg Ⅰα。由此可见,血清 Reg Ⅰα 水平升高在一定程度上能够提示肾脏早期炎症状态,肾周炎症反应可能促进胰腺分泌 Reg Ⅰα,但具体机制仍有待进一步阐明。与上述研究结果方向一致,本研究发现 Reg Ⅰα>82.17 ng/mL 为糖尿病合并 CKD 的危险因素,但本研究尚未采集炎症指标,后续将进一步分析 Reg Ⅰα 与炎症因子的相关性及其潜在联系。

Tangri 等[23]在加拿大人群中开发 CKD 进展风险模型,经过多国队列重新校准,仍有待进一步验证;Ramspeck 等[24]在欧洲人群中建立模型,但在不同验证队列中的表现差异较大,表明 CKD 预测模型应用于不同种族人群中,有必要重新训练或设计。基于我国人群建模的研究也相继报道,Cao 等[25]采用年龄、性别、身体质量指数、糖尿病病程、FPG 变异、既往脑卒中史和高血压病史建立预测我国 2 型糖尿病合并 CKD 的风险模型,但 FPG 变异受影响因素较多,可能增加偏倚概率。Lin 等[26]采用年龄、糖尿病病程、是否接受胰岛素治疗、eGFR、UACR、高密度脂蛋白胆固醇、三酰甘油、糖尿病视网膜病变(DR)、糖化血红蛋白变异、FPG 变异以及降压药物使用情况 11 项指标建立了预测我国 2 型糖尿病患者合并 CKD 风险的模型,但该模型纳入指标多且需甄别患者是否并发 DR,而 DR 具有发病隐匿和低筛查率的特点,可能降低模型的实用性。本研究采用高血压病史、Reg Ⅰα、UA 和 HGB 4 项常见临床参数建立预测糖尿病患者合并 CKD 的列线图模型,经过内部验证,模型预测性能较好,同时具有简便易行的特点,便于在临床实践中应用。

本研究结果发现,糖尿病患者血清 Reg Ⅰα 水平升高与 CKD 显著相关,基于 Reg Ⅰα 建立的预测模型可定量分析糖尿病患者合并 CKD 的风险。但本研究为横断面研究,不能确定因果关系,需要后续前瞻性队列研究进行因果推断并建立能够预测未来 CKD 发病风险的模型。其次,模型缺乏外部验证,期待未来其他数据进一步探索,提高模型的可信度以及推广度。

**利益冲突**　无

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