Original Paper

A Prediction Model of Early Diabetic Nephropathy Based on Conventional Ultrasound Parameters and Hematological Indices and Its Application

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Keywords. Ultrasonic parameters; Hematological index; Early diabetic nephropathy; Prediction model

Introduction. Diabetic nephropathy (DN) is a chronic microvascular complication of diabetes mellitus, leading to end-stage kidney disease and increased mortality. Early detection and treatment are essential to prevent DN. This study aims to develop a diagnostic prediction model for early DN.

Methods. This retrospective analysis study was conducted on 205 patients with type 2 diabetes mellitus (T2DM) treated between September 2019 and September 2022. Patients with stage A1 albumin-to-creatinine ratio (ACR) (< 30 mg/g) were categorized as the simple diabetes mellitus group (n = 134), and those with ACR 30-300 mg/g at stage A2 were classified as the early diabetic nephropathy group (n = 71). Relevant ultrasound parameters and hematological indices were selected through univariate and multivariate screenings. A nomogram model was constructed based on the results of multi-factor screening. Internal validation was performed by using Bootstrap methods with 1000 repetitions, receiver operating characteristic (ROC) curve analysis evaluated model differentiation, calibration curves verified model consistency, and decision curve analysis assessed clinical utility.

Results. Multivariate logistic regression identified renal artery resistance index (RI), renal cortex shear wave velocity (SWV), Cystatin C (CysC), Retinol-binding protein (RBP), and Glycated Hemoglobin (HbA1C) as significant factors for early DN (all $P < .05$). The nomogram model showed good differentiation and consistency and has high clinical value and practicality in predicting DN.

Conclusion. The prediction model for early DN, based on conventional ultrasound parameters and hematological indices, demonstrates good prediction efficiency and clinical practicability.

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INTRODUCTION

Diabetic nephropathy (DN) is among the chronic microvascular complications of diabetes mellitus, as well as a major cause of end-stage kidney disease, the leading cause of death in diabetic patients.[1] Early identification and treatment are essential for addressing DN. Abnormal glomerular filtration rate and urinary albumin excretion are clinical features of renal injury. Epidemiological studies have pointed out that the incidence of kidney disease in patients with type 2 diabetes mellitus (T2DM) with normal urinary albumin excretion but reduced renal function significantly increased.[2] When the glomerular filtration rate and urinary albumin excretion are significantly abnormal, 60%-70% of nephrons are damaged.[3] This index is not sensitive

to early renal injury assessment. In addition, there are many factors affecting urinary albumin excretion results, and some patients with DN have no clear indications at an early stage, which is easy to be missed by clinical diagnosis. When diagnosed, kidney lesions have become irreversible, delaying the best treatment opportunity.[3] At present, renal pathology examination remains the gold standard for diagnosing diabetic nephropathy, but the expensive and invasive means will cause adverse effects on the body and psychology of patients, making the acceptance of pathological examination in diabetic nephropathy patients low.[4] Hence, there is an urgent need to find an exact and noninvasive means to predict early diabetic nephropathy. In recent years, scholars in related fields have established relevant models for the assessment of diabetic nephropathy by taking clinical, laboratory and ultrasound parameters as joint indicators, and discussed their effectiveness in the diagnosis of diabetic nephropathy, achieving corresponding results.[5-7] However, there are few research reports to assess early nephropathy. Therefore, this study established a prediction model for the detection of early diabetic nephropathy based on conventional ultrasound parameters and hematological indices and discussed its clinical diagnostic efficacy and application value.

MATERIALS AND METHODS

Data source

We conducted a retrospective analysis of the clinical information of 205 patients with T2DM who were treated in Changning County Traditional Chinese Medicine Hospital from September 2019 to September 2022. Inclusion criteria were: 1) Meeting the diagnostic criteria for T2DM in "Diabetes Diagnosis and Treatment Standards (2018 Edition)";[8] 2) Age > 18 years old; 3) Routine ultrasound examination and blood tests were performed after admission, and the relevant data were complete; 4) Random urinary albumin-to-creatinine ratio (ACR) ≤ 300 mg/g. Exclusion criteria were: 1) Patients complicated with obstructive kidney disease, thrombosis, urinary calculi, liver disease, malignant tumors, and other diseases; 2) long-term use of glucocorticoids, immunosuppressants, immune enhancers and other drugs; 3) presence of mental disease, cognitive dysfunction; 4) vital organs dysfunction; 5) severe immune deficiency, infectious disease, blood system disease or acute metabolic disorder; 6) pregnant or breastfeeding persons; 7) recent acute infection and acute kidney injury; 8) a history of drug abuse; 9) the onset of kidney disease is earlier than the time of diagnosis of diabetes mellitus or presence of primary glomerular disease and systemic diseases. By "Guidelines for Screening, Diagnosis and Prevention of Chronic Kidney Disease",[9] Patients with stage A1 ACR < 30 mg/g were treated as a simple diabetes mellitus group (n = 134), and patients with stage A2 ACR 30 mg/g - 300 mg/g were treated as early diabetic nephropathy group (n = 71). The present research was approved by the Changning County Traditional Chinese Medicine Hospital Medical Ethics Committee (Ethical Code: No.202209).

Observation index

We collected and recorded the following indicators of the research participants: (1) general information: age, sex, body mass index (BMI), duration of diabetes mellitus; (2) laboratory test data (collected within 24 hours of admission): white Blood Cell count (WBC), serum creatinine (Scr), blood uric acid (UA), blood urea nitrogen (BUN), retinol-binding protein (RBP), glycosylated hemoglobin (HbAlc), Alanine Transaminase (ALT), platelet count (PLT), triglycerides (TG), total cholesterol (TC), cystatin C (CysC) and other hematological indices, and ACR values for random urine measurements; (3) Conventional ultrasound parameters: The peak systolic velocity (PSV), end-diastolic minimum velocity (EDV) and resistance index (RI) at the locations of renal artery, segmental artery and interlobar artery, and shear wave velocity (SWV) in the renal cortex, renal medulla and renal sinus. The above ultrasound parameters were detected by color Doppler ultrasound (Shenzhen Mindray Biomedical Electronics Co., LTD; model: Resona5).

Statistical methods

The data information was analyzed and processed by using SPSS 23.0 software (The company: International Business Machines Corporation, Country: United States of America), and the normally distributed quantitative data were expressed by using ($\bar{x} \pm s$), and between-group comparisons were made using the t-test. Count data were compared between groups using

the chi-square test. The factors that independently influence early diabetic nephropathy were studied by multifactorial logistic regression analysis; a significant difference was defined as $P < .05$. The random function in R 4.0.3 was used to randomly divide the data into the modelling set and the validation set in a ratio of 6:4. The modelling set is used for generating the nomogram prediction model, and the validation set is used for estimating the accuracy of the model. Evaluating the discriminative ability of nomogram models, we used the receiver operating characteristic curve (ROC). Evaluating the consistency of the nomogram model, we used calibration curves, and evaluation of model clinical utility using decision curve analysis (DCA), and internal validation of the model by repeated sampling 1000 times through Bootstrap methods.

RESULTS

Comparison of general clinical data

Comparison of age, Sex, BMI, and course of diabetes mellitus between the simple diabetes mellitus group and the early diabetic nephropathy group showed no statistically significant differences ($P > .05$). See Table 1.

Comparison of conventional ultrasound parameters and hematological indexes

There were significant differences between the simple diabetic mellitus group and the early diabetic

Table 1. Comparison of general clinical data

Clinical data	Simple diabetes mellitus group	Early diabetic nephropathy group	χ^2/t	*P*
age	53.30 ± 10.53	52.72 ± 9.78	0.385	.701
Sex (Male/female)	71/63	39/32	0.071	.791
BMI (kg/m^2)	27.24 ± 3.90	26.82 ± 2.82	0.885	.378
Duration of diabetes mellitus (month)	33.98 ± 4.73	32.76 ± 5.09	1.711	.089

Notes: BMI: body mass index.

Table 2. Comparison of ultrasound parameters and hematologic indexes

Parameters/indicators	Simple diabetes mellitus group	Early diabetic nephropathy group	*t*	*P*
Interlobar artery PSV (cm/s)	33.98 ± 4.73	32.76 ± 5.09	-1.711	.089
Interlobar artery RI	0.51 ± 0.08	0.53 ± 0.11	1.345	.181
Interlobar artery EVD (cm/s)	13.06 ± 2.14	12.76 ± 1.84	-1.003	.317
Segmental artery PSV (cm/s)	50.93 ± 8.22	49.26 ± 8.09	-1.396	.164
Segmental artery RI	0.61 ± 0.09	0.63 ± 0.11	1.370	.172
Segmental artery EVD (cm/s)	18.44 ± 3.12	17.98 ± 2.64	-1.053	.294
Renal artery PSV (cm/s)	74.96 ± 10.23	73.35 ± 9.89	-1.080	.281
Renal artery RI	0.63 ± 0.08	0.71 ± 0.09	6.333	< .001
Renal artery EVD (cm/s)	21.23 ± 3.97	20.28 ± 3.11	-1.749	.082
Renal cortex SWV (m/s)	2.63 ± 0.33	2.41 ± 0.43	-3.682	< .001
Renal medulla SWV (m/s)	1.71 ± 0.31	1.66 ± 0.25	-1.227	.221
Renal sinus SWV (m/s)	1.26 ± 0.21	1.21 ± 0.19	-1.629	.105
WBC (*10^9/L)	6.25 ± 1.53	6.57 ± 1.78	-1.370	.172
Scr (umol/L)	76.40 ± 10.15	78.78 ± 12.47	1.384	.169
BUN (mmol/L)	6.88 ± 1.13	7.11 ± 1.26	1.376	.170
UA (mg/dL)	6.33 ± 0.55	6.36 ± 0.53	0.473	.637
CysC (mg/L)	1.21 ± 0.22	1.41 ± 0.19	6.477	< .001
RBP (mg/L)	36.20 ± 7.01	42.89 ± 8.53	5.669	< .001
HbAlc (%)	8.43 ± 1.56	9.36 ± 1.63	4.005	< .001
ALT (u/L)	31.58 ± 4.06	32.18 ± 4.21	0.989	.324
PLT (*10^9/L)	99.75 ± 11.19	102.43 ± 12.83	1.548	.123
TG (mmol/L)	2.29 ± 0.37	2.23 ± 0.31	-1.226	.222
TC (mg/dL)	240.00 ± 33.63	234.77 ± 32.50	-1.071	.285

Notes: PSV:The peak systolic velocity, RI: resistance index, EVD:end-diastolic minimum velocity, SWV:The shear wave velocity, WBC: White Blood Cell Count, Scr: Serum Creatinine, BUN: blood urea nitrogen, UA: blood uric acid, CysC: cystatin C, RBP: retinol-binding protein, HbAlc: glycosylated hemoglobin, ALT: Alanine Transaminase, PLT: platelets, TG: triglycerides, TC: total cholesterol.

nephropathy group in renal artery RI, renal cortex SWV, CysC, RBP and HbAlc ($P < .05$), but differences between other parameters and indicators were not significant ($P > .05$). For details, see Table 2

Multivariate logistic regression analysis of influencing early diabetic nephropathy

Regression analysis was conducted with the presence or absence of early DN (0 = absence,1 = presence) as the dependent variable and renal artery RI, renal cortex SWV, CysC, RBP and HbAlc as the independent variables (Tables 3). The results showed that RI of the renal artery, SWV of the renal cortex, CysC, RBP, and HbAlc were independent influencing factors of early diabetic nephropathy.

Construction of a nomogram prediction model for early diabetic nephropathy

Factors affecting the development of early diabetic nephropathy from multifactorial logistic regression analysis were included to construct a column-line graphical prediction model, as shown in Figure 1. The total score was obtained by summing the values of each indicator and the corresponding scores of the nomogram model, and the total score was transformed into the predicted probability of early DN based on the nomogram.

Validation of the predictive nomogram model for early diabetic nephropathy

The ROC curve analysis results (Figure 2) revealed that the nomogram model has an AUC

Table 3. logistic regression analysis of multiple factors influencing the occurrence of early diabetic nephropathy

Variable	B value	S.E.value	Wald value	*P*	OR value	95%CI
Renal artery RI	1.372	0.280	24.079	< .001	3.942	2.279-6.817
Renal cortex SWV (m/s)	-1.628	0.581	7.849	.005	0.196	0.063-0.613
CysC (mg/L)	2.556	1.102	5.383	.020	12.884	1.487-111.633
RBP (mg/L)	0.113	0.028	16.023	< .001	1.120	1.059-1.183
HbAlC (%)	0.378	0.133	8.095	.004	1.459	1.125-1.893

Notes: RI: resistance index, SWV:The shear wave velocity, CysC: cystatin C, RBP: retinol-binding protein, HbAlC: glycosylated hemoglobin.

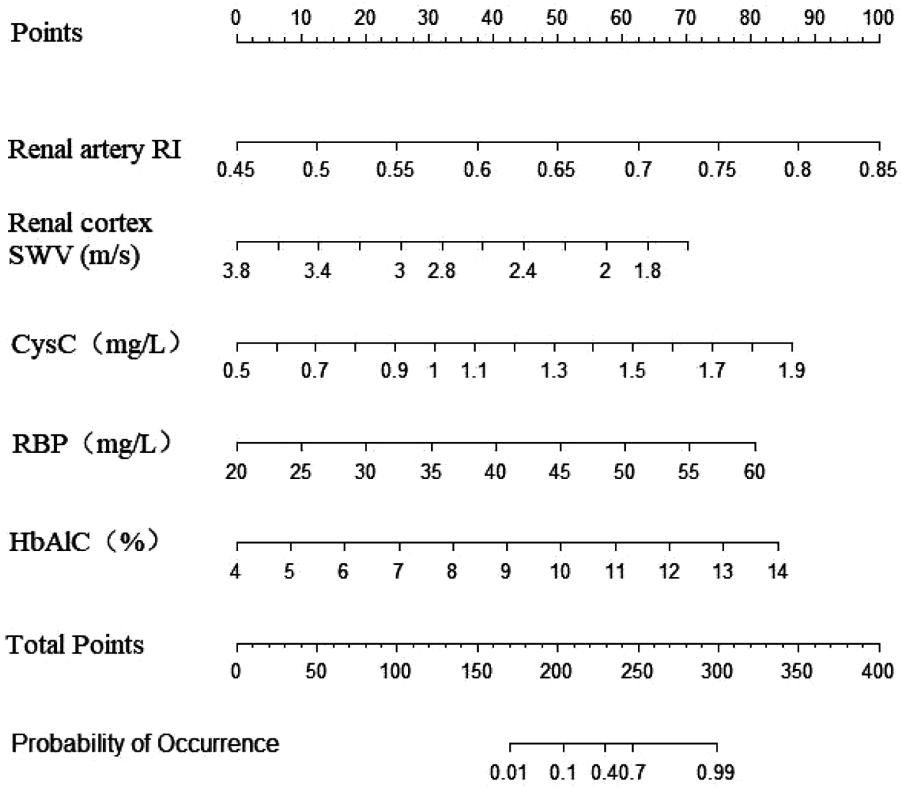

Figure 1. Nomogram prediction model for the development of early diabetic nephropathy. RI: resistance index, SWV: shear wave velocity, CysC: cystatin C, RBP: retinol-binding protein, HbAlC: glycosylated hemoglobin.

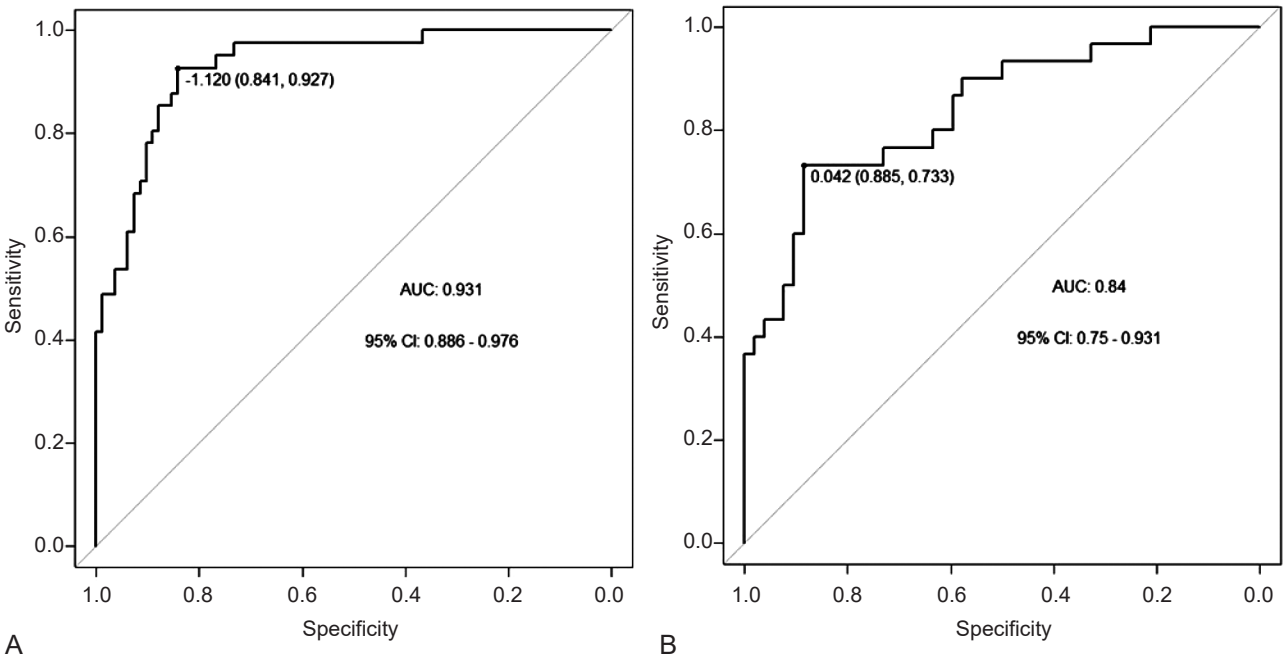

Figure 2. ROC curve of the model for predicting early diabetic nephropathy (A is the modelling set, B is the validation set).AUC: Area under the ROC curve.

of 0.931 (95% CI: 0.886-0.976) in the modelling set, with a sensitivity of 0.927 and a specificity of 0.841; in the validation set, the AUC is 0.840 (95% CI: 0.750-0.931), with a sensitivity of 0.733 and a specificity of 0.885. These results suggest that the nomogram model is well-distinguished. The predicted values of calibration curves in both the modelling set and validation set of the nomogram model were consistent with the actual observed values (Figure 3), and the Hosmer-Lemeshow goodness of fit test $\chi 2 = 2.814$, $P = .945$ showed good consistency.

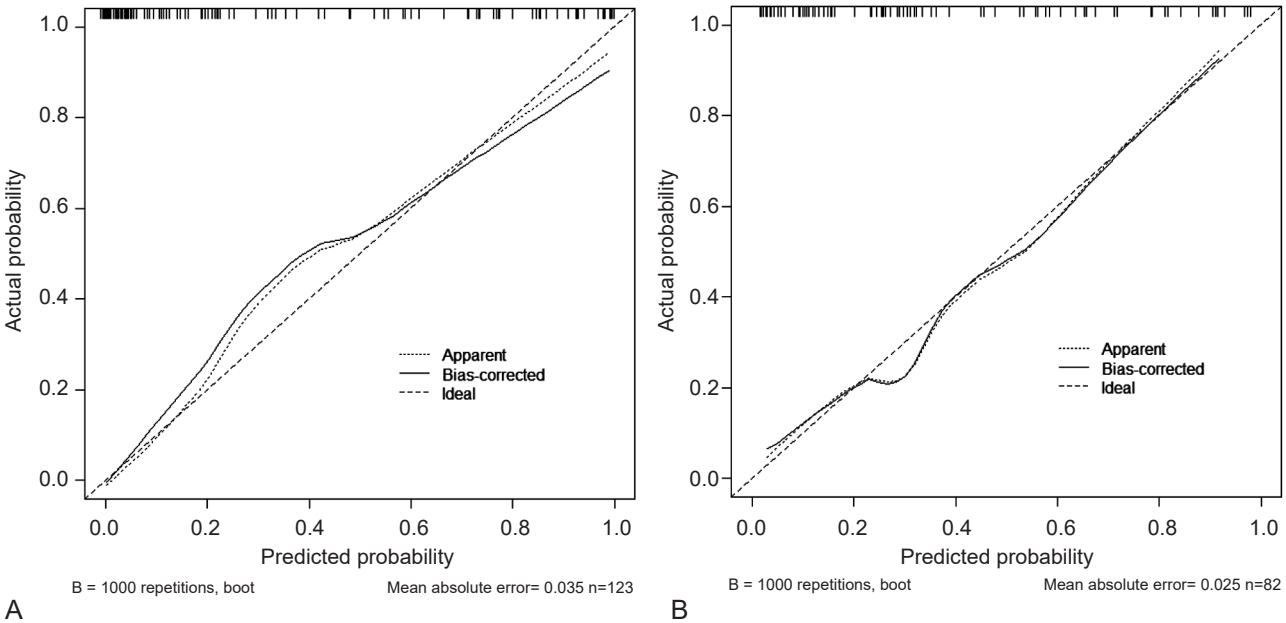

Figure 3. Calibration curve of the model for predicting the occurrence of early diabetic nephropathy (A is the modelling set, B is the validation set).

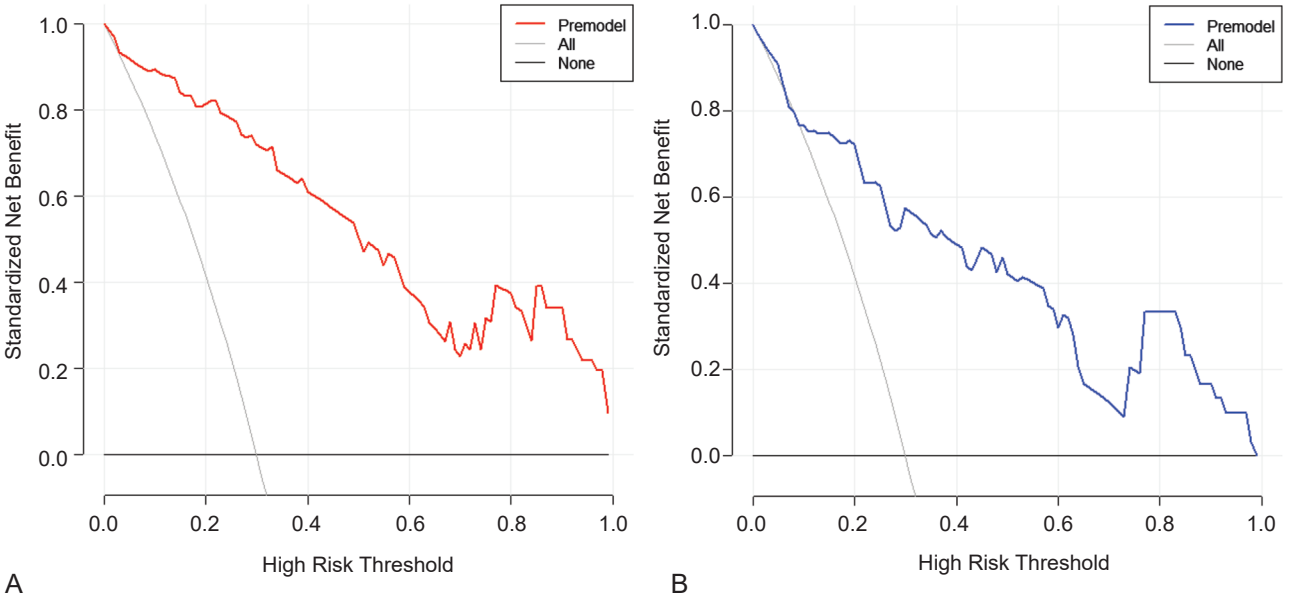

Figure 4. Decision curve of the model for predicting the occurrence of early diabetic nephropathy (A is the modelling set, B is the validation set).

The impact of the nomogram model on clinical treatment decisions was analyzed by using a decision curve. The decision curve (Figure 4) shows that when the risk threshold of the modelling set is greater than 5% or less than 99%, and the risk threshold of the validation set is greater than 10% or less than 99%, the nematographic model predicts a net benefit rate of > 0 for early diabetic nephropathy. It is suggested that the model is clinically valid in this range.

DISCUSSION

In the early stage of DN, the damage to renal function can be alleviated or even reversed. Once entering the stage of clinical macroalbuminuria, the damage to renal function will be progressively aggravated and irreversible under the action of continuous hyperglycemia.[10,11] Thus, it is significant to actively seek an exact method for non-invasive prediction and evaluation of early DN occurrence.[23,24] The results of this study showed that renal artery RI, renal cortex SWV, CysC, RBP and HbAlc were the leading factors in the early development of DN. In patients with early DN, due to glomerular capillaries thickening and blockage of the basement membrane, the forward resistance of blood flow increases, the renal artery RI increases, and a vicious cycle is formed, which further increases the resistance of the renal vascular bed, and eventually leads to the damage and irreversible changes of the kidney.[12] Sugahara *et al.* have pointed out that with the aggravation of renal function injury in diabetic patients, renal artery RI gradually increases.[13] Early diabetic nephropathy mainly involves the glomerulus distributed in the renal cortex. The changes in renal elasticity can be quantitatively analyzed by detecting the velocity changes of renal cortical SWV in the pathological kidney, and the decrease in SWV of the renal cortex implies an increase in the degree of damage to the organs.[14,15] CysC is a low molecular weight alkaline protein, with little impact on individual characteristics in the external circulation.[16,17] When renal function is damaged in the early stage of DN, the compensatory function of the kidney reduces, the only way to clear CysC is limited, and the level of CysC in peripheral blood significantly increases, and its level will gradually increase with the severity of kidney injury.[18] ZHAO *et al.* showed that CysC showed specific changes at the very early stage of renal function injury, with high diagnostic sensitivity and specificity.[19] The increased HbAlc will increase tissue hypoxia, which will lead to ischemic dysgenesis and induce vascular endothelial dysfunction.[20] In addition, HbAlc can also affect the deformability of red blood cells,[21] resulting in increased blood viscosity, microcirculatory perfusion disorder, aggravated renal ischemia

and hypoxia, and renal function impairment.[22] RBP is a small molecular weight protein formed by the combination of thyroid functioning protein and retinol, which is synthesized by the liver and metabolized by the kidney. In patients with early diabetic nephropathy, the glomerular filtration rate decreases, leading to the renal tubule reabsorption disorder and a decrease in the RBP filtration rate, consequently increasing blood RBP level

Nomogram is a combination of multiple indicators to predict or diagnose the occurrence or development of diseases, which has a high value for the individualized prediction of patients' diseases.[25] In this study, a nomogram model was built on the basis of the factors affecting the occurrence of early diabetic nephropathy, and the accuracy of the model was verified by using modelling set and verification set data. The results indicate that the AUC of the modelling set and the validation set were 0.931 (95%CI: 0.886-0.976) and 0.840 (95%CI: 0.750-0.931), respectively, all over 0.8. This indicates that the model was effective in predicting early diabetic nephropathy, and the calibration curve in the results are intimate to the actual curve, suggesting that the model has good calibration degree and prediction consistency. The results of the decision curve analysis indicate that when the risk threshold of the modelling set was greater than 5% or less than 99%, and the risk threshold of the validation set was greater than 10% or less than 99%, the nomogram model was superior to "all treated" or "no treated", and the net benefit rate predicted by the model for early diabetic nephropathy was greater than 0, so the model was clinically valid within this range.

THE STUDY LIMITATIONS

This study has certain limitations. As a retrospective study, the determination of the duration of diabetes mellitus in patients relies on medical records and patient surveys, which may be subject to some information bias. Moreover, this study is a single-center study with a small sample size of early DN patients. The nomogram model for predicting the risk of early DN needs to be further validated by studies with larger sample sizes.

CONCLUSION

In summary, renal artery RI, renal cortex SWV, CysC, RBP, and HbAlc are influential factors in the occurrence of early diabetic nephropathy. The nomogram prediction model constructed based on these factors demonstrates good diagnostic efficacy and application value.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The present research was approved by the Changning County Traditional Chinese Medicine Hospital Medical Ethics Committee (Ethical Code: No.202209).

CONSENT FOR PUBLICATION

Manuscript is approved by all authors for publication.

AVAILABILITY OF DATA AND MATERIALS

The data and materials of this experiment are available upon a reasonable request from the corresponding author.

COMPETING INTERESTS

The authors declare no conflict of interests.

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