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Influencing factors of post-transplantation diabetes mellitus in kidney transplant recipients and establishment of a risk prediction model.

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Keywords: kidney transplant; diabetes mellitus; influencing factor; prediction model.

Abstract. The aim was to explore the influencing factors of post-transplantation diabetes mellitus (PTDM) in kidney transplant recipients and to establish a risk prediction model. A retrospective analysis was performed on the clinical data of 408 patients subjected to kidney transplantation from May 2015 to March 2022. With the simple random sampling method, they were divided into a training set (n=306) and a test set (n=102) at a ratio of 3:1. According to the occurrence of PTDM, the training set was further classified into PTDM and non-PTDM groups. The influencing factors of PTDM were identified by least absolute shrinkage and selection operator and multivariate logistic regression analysis. A nomogram prediction model was constructed and validated. Non-PTDM and PTDM groups had significantly different preoperative body mass index (BMI), family history of diabetes mellitus, 2-h preoperative and postprandial blood glucose, 2-h preoperative and postprandial peptide index, postoperative hypomagnesemia, whole blood concentration of tacrolimus, triacylglycerol, glycated albumin and fasting blood glucose ($P<0.05$). BMI, family history of diabetes mellitus, 2-h preoperative and postprandial blood glucose, and postoperative whole blood tacrolimus concentration were independent risk factors for PTDM. In contrast, the 2-h preoperative and postprandial peptide index was an independent protective factor ($P<0.05$). The incidence of PTDM in patients receiving kidney transplantation correlates with the family history of diabetes mellitus, preoperative BMI, 2-h postprandial blood glucose, 2-h postprandial peptide index, and postoperative whole blood tacrolimus concentration.

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Factores que influyen en la diabetes mellitus post-trasplante en receptores de trasplante renal y el establecimiento de un modelo de predicción de riesgo.

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Palabras clave: trasplante renal; diabetes mellitus; factores de influencia; modelo de predicción.

Resumen. El propósito del trabajo fue explorar los factores que influyen en la diabetes mellitus post-trasplante (PTDM) en receptores de trasplante renal y establecer un modelo de predicción. Se realizó un análisis retrospectivo de los datos clínicos de 408 pacientes sometidos A trasplante renal de mayo de 2015 a marzo de 2022. La muestra se obtuvo con el método de generar números aleatorios en una computadora, y fueron divididos en un conjunto de entrenamiento (n=306) y un conjunto de prueba (n=102) en una proporción de 3:1. De acuerdo con la ocurrencia de PTDM, el conjunto de entrenamiento fue clasificado en grupos PTDM y no PTDM. Los factores de influencia de PTDM se identificaron mediante el operador de menor contracción y selección absoluta y el análisis de regresión logística multivari. Se construyó y validó un modelo de predicción de nomograma. Los grupos no PTDM y PTDM presentaron diferencias significativas en el índice de masa corporal (IMC) preoperatorio, antecedentes familiares de diabetes mellitus, glucosa sanguínea preoperatoria y postprandial 2-h, índice de péptido preoperatorio y postprandial 2-h, hipomagnesemia posoperatoria, concentración sanguínea total de tacrolimus, triacilglicerol, albúmina glicosilada sanguínea en ayunos ($p<0,05$). Entre ellos, el IMC, los antecedentes familiares de diabetes mellitus, la glucemia preoperatoria y postprandial de 2-h y la concentración de tacrolimus en sangre total postoperatoria fueron factores de riesgo independientes para PTDM, mientras que el índice de péptido preoperatorio y postprandial de 2-h fue un factor de protección independiente ($p<0,05$). La incidencia de PTDM en pacientes que reciben trasplante renal tiene correlaciones con los antecedentes familiares de diabetes mellitus, IMC preoperatorio, glucosa sanguínea postprandial 2-h, índice de péptido postprandial 2-h y concentración de tacrolimus en sangre total posoperatoria.

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INTRODUCTION

Kidney transplantation is currently considered effective in treating end-stage renal disease. The five-year survival rate reaches over 80% among kidney transplant recipients [1], but some still experience different postoperative complications. A common metabolic complication after kidney transplantation is post-transplantation diabetes mellitus (PTDM), increasing the risk of cardiovascular and cerebrovascular diseases and resulting in deaths and seriously affecting the prognosis of patients [2,3]. PTDM, with an incidence of about 4-25%, usually occurs within one year after surgery [4]. It may be triggered

by such factors as the patient's age, family history of diabetes mellitus, high-fat diet, and donor type [5,6]. Thus, exploring the risk factors of PTDM in kidney transplant recipients and constructing a risk prediction model is of great significance in reducing the incidence rate of PTDM and improving the prognosis of patients. This study conducted a retrospective analysis of the clinical data of 312 patients experiencing living-donor kidney transplantation in our hospital from May 2015 to August 2021. On this basis, the influencing factors in the development of PTDM in patients were identified, and a nomogram prediction model was built to provide a clinical reference.

PATIENTS AND METHODS

General data

A retrospective analysis was performed on the clinical data of 408 patients who received kidney transplantation in our hospital (the Second People's Hospital of Shanxi) from May 2015 to March 2022. These patients were assigned to a training set (n=306) and a test set (n=102) at a ratio of 3:1 by generating random numbers on a computer. These two sets were used to construct a risk prediction model and validate the model's prediction performance, respectively. The training set [160 males and 146 females, (34.02 ± 7.71 years old)] and the test set [53 males and 49 females, (34.15±7.32 years old)] did not have significant differences in the general data (P>0.05). The inclusion criteria were: (1) Patients who received allogeneic kidney transplantation for the first time, (2) had a follow-up time ≥ one year, and (3) whose age ≥ 18 years old. Exclusion criteria were patients who (1) had no family history of diabetes before surgery, (2) experienced more than one kidney transplantation, (3) experienced the preoperative use of glucocorticoids for > three months, (4) had incomplete clinical data, or (5) died within one year after transplantation. This study was reviewed and approved by the ethics committee of our hospital, and all enrolled patients were informed and signed the informed consent.

Postoperative immunosuppressive regimen

The postoperative immunosuppressive regimen for patients was orally taking cyclosporine A (3-5 mg·kg^{-1}·d^{-1}) or tacrolimus (0.05-0.10 mg·kg·1·d^{-1}) + mycophenolate mofetil (1.0-1.5 g/d) or sodium mycophenolate (720-1080 mg/d) or mizoribine (3-4 mg·kg^{-1}·d^{-1}). The dose was adjusted based on the plasma concentration of cyclosporine A or tacrolimus. Then methylprednisolone (30 mg/d) was taken orally from the fourth day after surgery, and the dose was reduced to 5 mg on the seventh day after surgery and continually taken.

Clinical data collection

The clinical data of patients collected included (1) preoperative clinical data: age, gender, family history of diabetes mellitus, body mass index (BMI), causes of end-stage renal disease, type of dialysis, dialysis time, type of donor's kidney, warm ischemia time, cold ischemia time, glycated albumin, 2-h postprandial blood glucose, and 2-h postprandial peptide index, and (2) postoperative data: delayed functional recovery of the transplanted kidney, rejection, cytomegalovirus, hypomagnesemia, postoperative immune induction drugs, whole blood concentration of tacrolimus, whole blood concentration of cyclosporine, triglyceride, glycated albumin, total cholesterol, creatinine, urea nitrogen, uric acid and estimated glomerular filtration rate.

Diagnostic criteria

Patients were diagnosed six weeks after kidney transplantation according to the diagnostic criteria issued by the American Diabetes Association (ADA) in 2019 [7] if they had stable immunosuppression, stable renal function, and no acute infection. Those satisfying the diagnostic criteria were included in the PTDM group, while the rest of the patients were included in the non-PTDM group.

Statistical analysis

The statistical analysis of data was performed with the IBM SPSS® 23.0 software. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and the *t*-test was applied to compare the two groups. Count data were expressed as a percentage (%), and the χ^2 test was used to compare groups. The independent risk factors of PTDM were analyzed with the least absolute shrinkage and selection operator (LASSO) and multivariate logistic regression. The nomogram prediction model was built by R software, and its predictive value, accuracy, and clinical practicability were evaluated using the receiver operating characteristic (ROC) curve, calibration curve, and decision curve, respectively. A significance level of $\alpha=0.05$ was utilized.

RESULTS

Univariate analysis results of PTDM in patients

Among the 306 patients, the incidence rate of PTDM within one year after surgery was 24.84% (76/306). The non-PTDM group and the PTDM group had statistically significant differences in preoperative BMI, family history of diabetes mellitus, 2-h preoperative and postprandial blood glucose, 2-h preoperative and postprandial peptide, postoperative hypomagnesemia, whole blood concentration of tacrolimus, triglyceride, glycated albumin and fasting blood glucose ($P<0.05$) and no statistically significant differences in other clinical data ($P>0.05$) (Table 1).

Multivariate analysis results of PTDM in patients

The occurrence of PTDM was taken as the dependent variable, and a total of 29 independent variables were included. LASSO reduced the dimensionality of independent variables to avoid model overfitting. The optimal penalty coefficient λ of the model was identified by the 10-fold cross-validation method. When λ kept increasing to one standard error, it was the optimal value of the model. Nine predictors were screened out, including BMI, family history of diabetes mellitus, 2-h preoperative and postprandial blood glucose, 2-h preoperative and postprandial peptide index, postoperative hypomagnesemia, whole blood concentration of tacrolimus, triacylglycerol, glycated albumin and fasting blood glucose (Fig. 1).

With the occurrence of PTDM as the dependent variable (yes =1, no =0), the above nine predictors were included in the multivariate logistic regression model. It was found that BMI, family history of diabetes mellitus, 2-h preoperative and postprandial blood glucose, and postoperative whole blood concentration of tacrolimus were independent risk factors for PTDM. In contrast, the 2-h preoperative and postprandial peptide index was an independent protective factor for PTDM ($P<0.05$) (Table 2).

Model establishment

By means of the "rms" program package, the nomogram prediction model was built based on the five independent influencing factors for predicting the occurrence of PTDM in patients. The results showed that the five independent influencing factors obtained 263 points (56.75 points for the family history of diabetes mellitus, 82.5 points for 2-h preoperative and postprandial blood glucose PG >6.65 mmol/L, 66.25 points for 2-h preoperative and postprandial CPI<5.26, 26 points for BMI >23.85 kg/m^2, and 31.50 points for whole blood concentration of tacrolimus >8.62 C0) in total and the corresponding risk value of PTDM was 0.875, meaning that the probability of PTDM predicted by the model was 87.50% (Fig. 2).

Discrimination evaluation of the nomogram model

Here, the discrimination of the model was evaluated by the ROC curve. The training set obtained the area under the curve (AUC) of 0.758 (95%CI: 0.682-0.834, $p<0.001$) and the C-index of 0.882. The test

Table 1
Clinical data of the two groups of patients.

Preoperative data Item	Non-PTDM group (n=230)	PTDM group (n=76)	t/χ^2 value	*p*
Age (years old)**	34.02±7.71	34.15±7.32	0.892	0.215
Male*	160 (69.57)	53 (69.74)	0.112	0.902
BMI (kg/m²)**	**22.45±1.32**	**24.61±1.45**	**5.943**	**<0.001**
Family history of diabetes mellitus*	**23 (10.00)**	**26 (34.21)**	**6.934**	**<0.001**
Smoking*	57 (24.78)	24 (31.58)	1.082	0.345
Type of dialysis before transplantation			1.023	0.093
Hemodialysis*	187 (81.30)	57 (75.00)		
Peritoneal dialysis*	43 (18.70)	19 (25.00)		
Dialysis time (month)**	25.92±8.12	24.81±7.96	1.009	0.116
Causes of end-stage renal disease			0.863	0.345
Glomerulus nephritis*	171 (74.35)	57 (75.00)		
IgA nephropathy*	29 (12.61)	8 (10.53)		
Polycystic kidney*	18 (7.83)	6 (7.89)		
Others*	12 (5.21)	5 (3.13)		
Type of donor kidney			0.834	0.226
Living body*	34 (14.78)	17 (22.37)		
Corpse*	196 (85.22)	59 (77.63)		
Warm ischemia time (min)**	7.56±5.43	7.67±4.76	0.782	0.324
Cold ischemia time (h)**	5.71±1.24	5.85±1.13	0.343	0.872
Glycated albumin (%)**	13.52±1.12	14.15±1.34	0.345	0.668
2-h postprandial blood glucose (mmol/L)**	**5.33±1.32**	**7.29±1.45**	**4.012**	**0.012**
2-h postprandial peptide index**	**5.42±1.31**	**4.61±1.10**	**3.024**	**0.015**
Delayed functional recovery of transplanted kidney*	22 (9.57)	7 (10.34)	0.283	0.692
Rejection*	6 (2.84)	4 (5.17)	0.091	0.804
Cytomegalovirus*	16 (7.95)	4 (5.17)	0.224	0.782
Hypomagnesemia*	**41 (21.59)**	**27 (41.38)**	**5.9723**	**<0.001**
Postoperative immune induction drugs				
Basiliximab*	46 (20.00)	20 (26.32)	0.852	0.203
Rabbit anti-human thymocyte immunoglobulin*	128 (55.65)	35 (46.05)	0.773	0.334
Antithymocyte immunoglobulin*	132 (57.39)	38 (50.00)	0.765	0.204
Whole blood trough concentration of tacrolimus (C0)**	**7.19±2.21**	**9.34±3.12**	**6.245**	**<0.001**
Whole blood trough concentration of cyclosporine (C0)**	158.23±21.32	161.14±20.34	2.034	0.098
Triacylglycerol (mmol/L)**	**1.96±0.21**	**2.38±0.32**	**7.304**	**<0.001**

Table 1
CONTINUATION

Preoperative data Item	Non-PTDM group (n=230)	PTDM group (n=76)	t/χ^2 value	*p*
Glycated albumin (%)**	**12.78±1.23**	**15.11±1.23**	**5.492**	**<0.001**
Fasting blood glucose (mmol/L)**	**4.32±0.34**	**5.18±0.34**	**7.472**	**<0.001**
Albumin (g/L)**	42.45±1.34	42.45±1.26	0.603	0.402
Total cholesterol (mmol/L)**	3.09±0.34	3.17±0.32	0.282	0.828
Urea nitrogen (mmol/L)**	13.83±1.23	10.45±1.25	0.447	0.548
Creatinine (μmol/L)**	151.31±24.34	151.72±20.23	0.682	0.392
Uric acid (μmol/L)**	309.124±24.23	295.19±20.83	0.332	0.672
Estimated glomerular filtration rate [mL (min·1.73 m^2)]**	60.45±5.72	72.98±5.15	1.114	0.092

Measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± s) and the *t*-test was applied to the comparison between the two groups. Count data were expressed as a percentage (%), and the χ^2 test was applied to the comparison between groups. C0: Whole blood trough concentration. *: n (%); **: ($\bar{x}$ ± s).

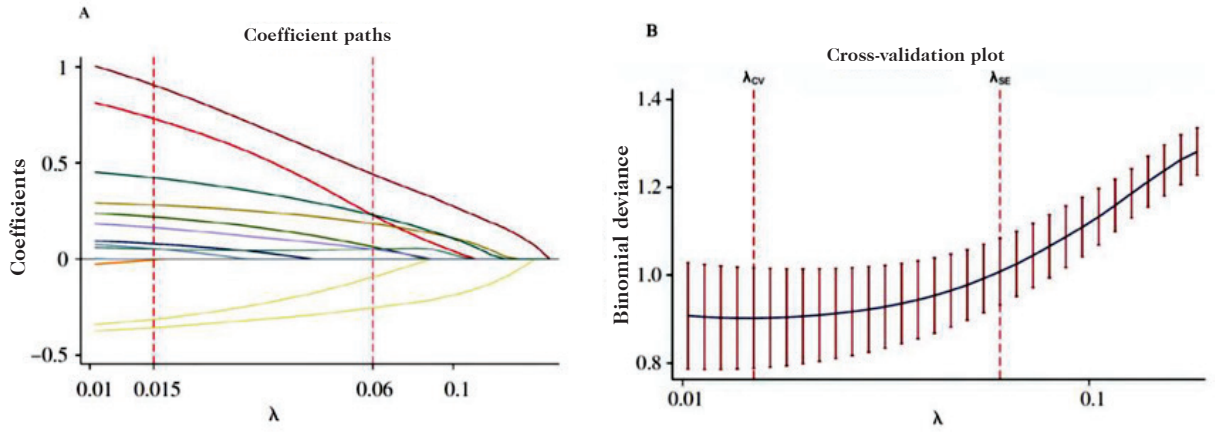

Fig. 1. LASSO regression analysis results for 27 predictors. A: Coefficient curve of 27 variables, B: Optimal clinical features selected by 10-fold cross-validation.

set had an AUC of 0.732 (95% CI: 0.682-0.782, P<0.001) and a C-index of 0.878. The prediction model had a C-index >0.75 in both sets, showing high discrimination (Fig. 3).

Calibration evaluation of the nomogram model

According to the calibration curve of the prediction model plotted, the prediction probability curve of the model well fit the reference probability, and no significant difference was revealed by the Hosmer-Lemeshow test results (P>0.05), indicating high accuracy of the model (Fig. 4).

Efficiency evaluation of the nomogram model

According to the plotted clinical decision curve, the model was far away from the extreme curve in both the training and test sets and obtained high a net benefit, indicating high reliability and practicability of the constructed nomogram model (Fig. 5).

Table 2
Multivariate logistic regression analysis results of related factors affecting PTDM in patients.

Factor	β	SE	Wald	p	OR	95%CI
BMI	1.825	1.538	2.417	0.009	3.474	2.045~4.856
Family history of diabetes mellitus	2.672	2.358	3.983	0.006	4.728	3.049~5.861
2-h preoperative and postprandial blood glucose	0.501	0.146	11.775	0.012	1.156	1.024~1.572
2-h preoperative and postprandial peptide index	-0.342	0.172	0.835	0.003	0.710	0.518~0.849
Postoperative hypomagnesemia	0.794	0.519	7.68	0.066	2.213	0.986~4.733
Whole blood concentration of tacrolimus	2.583	2.067	4.075	0.004	4.369	2.358~5.592
Postoperative triglycerides	0.507	0.179	0.750	0.038	1.661	0.731~2.439
Postoperative glycated albumin	0.502	0.492	0.757	0.024	1.652	0.915~2.903
Postoperative fasting blood glucose	1.578	1.326	2.805	0.091	2.152	0.937~3.498

BMI, family history of diabetes mellitus, 2-h preoperative and postprandial blood glucose, and postoperative whole blood concentration of tacrolimus were independent risk factors for PTDM, while 2-h preoperative and postprandial peptide index was an independent protective factor for PTDM. BMI: Body mass index; CI: confidence interval; OR: odds ratio; PTDM: post-transplantation diabetes mellitus; SE: standard error.

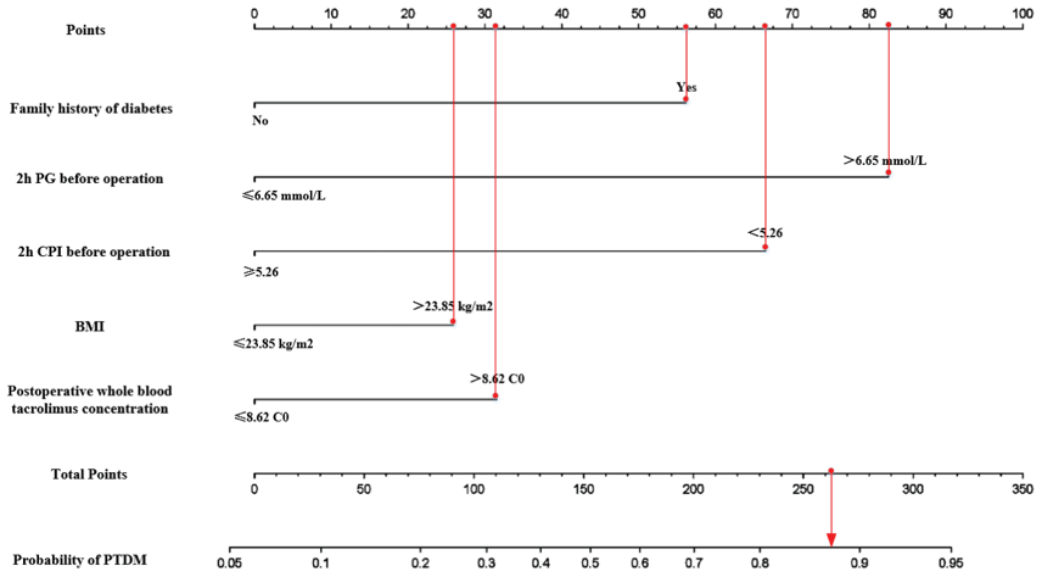

Fig. 2. Nomogram prediction model for predicting PTDM in patients.

DISCUSSION

PTDM is a common complication after kidney transplantation, the pathogenesis of which remains unclear. Its correlation with insulin resistance and insufficient insulin secretion is accepted in most literature [8,9], while hyperglycemia is closely associated with insulin production and target tissue demand. In addition, PTDM is also a high-risk factor inducing cardiovascular and cerebrovascular diseases in kidney transplantation, possibly resulting in the reduction or loss of transplanted kidney function and increased risk of postoperative death in patients [10]. For this reason, exploring the influencing factors of PTDM in kidney transplant recipients is significant in improving patients' prognosis and postoperative survival rate.

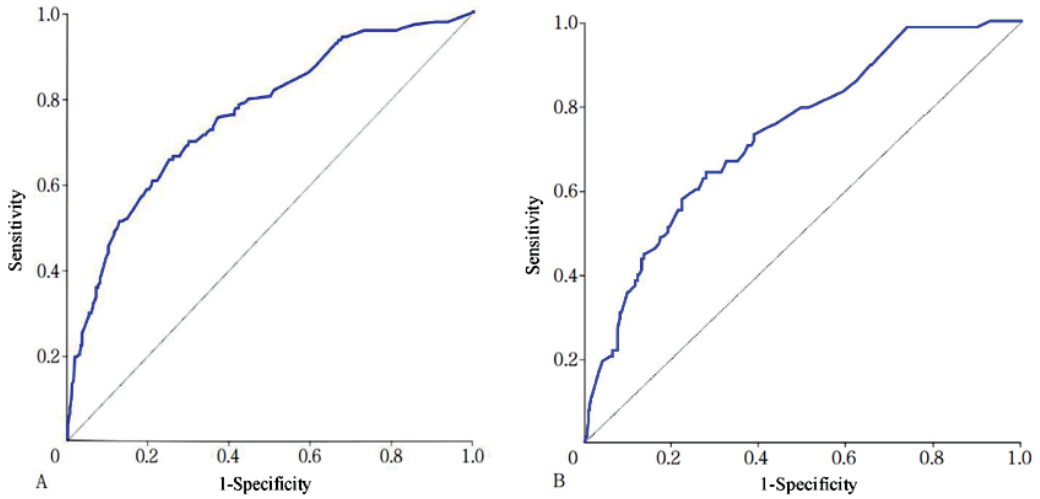

Fig. 3. ROC curves of prediction model in training and test sets. A: Training set, B: test set.

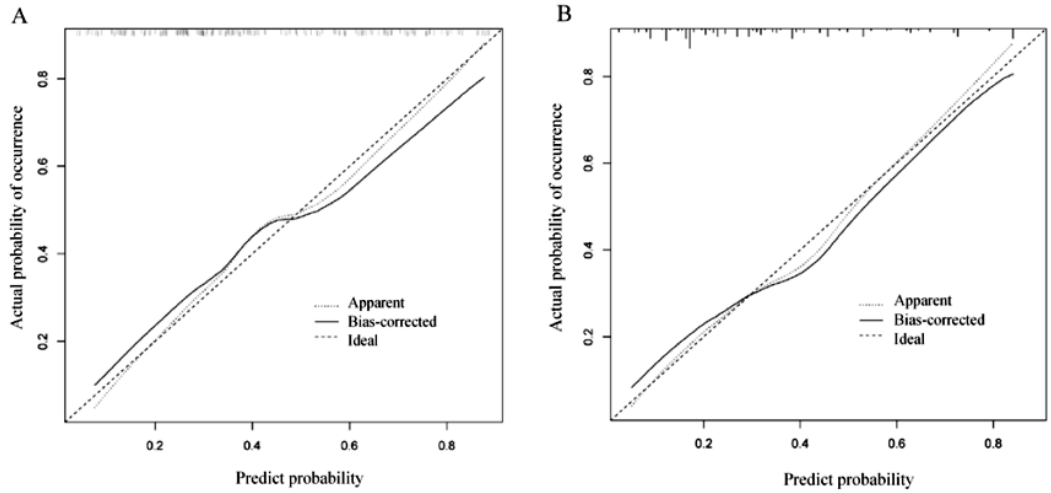

Fig. 4. Calibration curves of nomogram prediction model. A: Training set, B: test set.

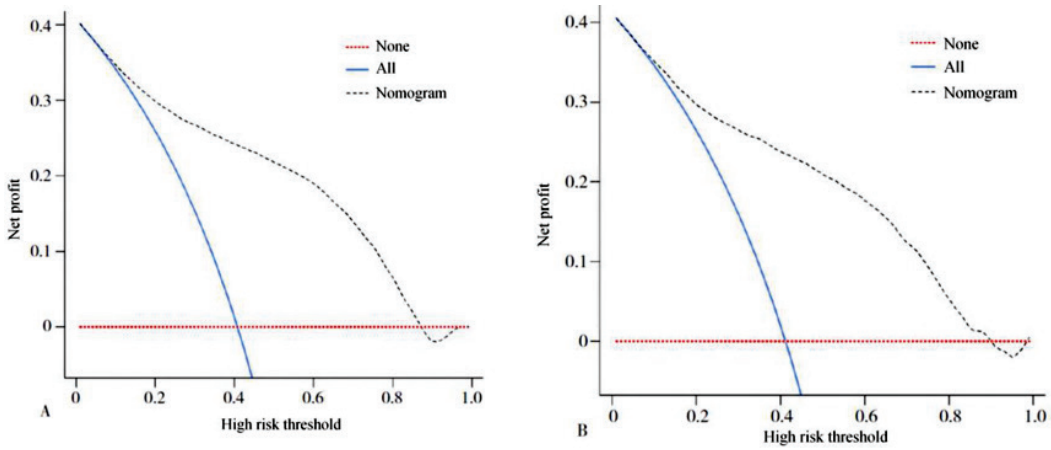

Fig. 5. Clinical decision curve analysis results of prediction model in training and validation sets. A: Training set, B: test set.

A total of 58 patients (24.78%) in this study's test set (n=234) had PTDM within one year after surgery. PTDM is a major cause of postoperative serious infection and even death in patients. Herein, preoperative BMI, family history of diabetes mellitus, 2-h preoperative and postprandial blood glucose, 2-h preoperative and postprandial peptide index, postoperative hypomagnesemia, the whole blood concentration of tacrolimus, triacylglycerol, glycated albumin, and fasting blood glucose were all determined in the univariate analysis to be influencing factors of PTDM in patients. BMI, family history of diabetes mellitus, 2-h preoperative and postprandial blood glucose, and postoperative whole blood concentration of tacrolimus were independent risk factors for PTDM. In contrast, the 2-h preoperative and postprandial peptide index was an independent protective factor for PTDM, as revealed by the multivariate logistic regression analysis result. The close correlation of BMI with the occurrence of PTDM in kidney transplant recipients has been reported in previous literature [11].

According to a study on the Korean population [12], kidney transplant recipients with BMI ≥25 kg/m^2 suffered a 3.64 times higher risk of PTDM than those with BMI< 25 kg/m^2. A possible mechanism is that obesity triggers chronic inflammation and stimulates pancreatic beta cells, thus causing insulin resistance and reduced glucose clearance rate, eventually increasing the risk of PTDM. It was found in a study [13] that a family history of diabetes presented a significant correlation with the risk of PTDM. People with a family history of diabetes may be subjected to abnormal glucose metabolism, which in turn influences the function of pancreatic β-cells and thus causes abnormal changes in postoperative blood glucose levels and even the occurrence of PTDM. Hence, for patients with a family history of diabetes mellitus, measures should be taken to closely monitor their blood glucose and carry out timely interventions to reduce the incidence rate of PTDM. A related study [14] published by the ADA showed that the majority of patients experience an abnormal glucose tolerance stage before diabetes development, and those showing abnormal glucose tolerance possibly become potential diabetic patients. The study of Sato *et al.* [15] unveiled that preoperative glucose tolerance was a risk factor for postoperative diabetes in transplant recipients. The 2-h postprandial peptide index, which reflects the function of pancreatic islet B cells and reduces with the increasing duration of type 2 diabetes mellitus, is related to insulin sensitivity and is considered a protective factor against PTDM in transplant recipients [16]. Moreover, tacrolimus is a typical drug for treating antirejection reactions. Its significantly positive correlation with the occurrence of PTDM and stronger sugar-causing effect than cyclosporine A [17] has been revealed. Additionally, for patients receiving kidney transplantation, the administration of tacrolimus can reduce the synthesis and secretion of insulin in the body, increasing the body's blood glucose level and thus resulting in diabetes [18]. Further, some believe that other important influencing factors on the occurrence of PTDM in transplant recipients include hypomagnesemia and rejection [19]. However, no statistically significant difference in rejection was found between the two groups of patients in this study. In addition, postoperative hypomagnesemia was found in the multivariate analysis not to be an independent influence factor of PTDM, possibly related to the small sample size of this study, which failed to present statistical differences.

Based on the influencing factors on the occurrence of PTDM in kidney transplant recipients, the nomogram model was built in this study, whose predictive performance was evaluated with the ROC curve, calibration curve, and clinical decision curve. The results showed that the predicted value approximated the actual observed value, signifying high discrimination and clinical validity of the model. Compared with a single

influencing factor, the prediction model can better identify patients subjected to high-risk liver metastasis, which boosts the clinical application of the research results.

This study still has some limitations. First, the subjects were collected from a single center, and the types of potential predictive variables collected were limited by clinical practice. Second, the prediction model was built through retrospective analysis, while limited clinical data were collected, and further validation in a prospective cohort was not carried out. Hence, the results may have bias. The research should be further improved by prolonging the follow-up time and increasing the collected data on influencing factors.

In conclusion, the model established in this study showed that BMI, family history of diabetes mellitus, 2-h postprandial blood glucose, postoperative whole blood tacrolimus concentration, and 2-h postprandial peptide index were independent influencing factors for predicting the occurrence of PTDM. Based on this model, attention can be paid to these factors, and early intervention can be taken to reduce the incidence rate of PTDM. Thus, this model is potentially applicable to clinical practice.

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Conflicts of interest

The author reported no potential conflict of interest.

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