Received: 18 April 2022 | Revised: 15 May 2022 | Accepted: 29 May 2022

DOI: 10.1111/jcpt.13713

ORIGINAL ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

# LASSO-derived nomogram predicting new-onset diabetes mellitus in patients with kidney disease receiving immunosuppressive drugs

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**Funding information**
The Construction of Key Projects by Zhejiang Provincial Ministry, Grant/Award Numbers: WKJ-ZJ-1915, WKJ-ZJ-2017; The Medical and Health Technology Program of Zhejiang Province, Grant/Award Numbers: 2019KY312, 2021KY448

## Abstract

**What is known and objective:** Patients with kidney disease receiving immunosuppressive drugs (ISDs) (tacrolimus, cyclosporine and glucocorticoids) have a high risk of developing new-onset diabetes mellitus (NODM). We aimed to establish a precise and convenient model for predicting NODM in patients receiving immunosuppressive drugs.

**Methods:** This retrospective study recruited 1883 patients receiving ISDs between January 2010 and October 2018. The occurrence of NODM was the primary endpoint. The patients were randomly divided into training ($n = 1318$) and validation cohorts ($n = 565$) at a 7:3 ratio. A nomogram was established based on a least absolute shrinkage and selection operator (LASSO)-derived logistic regression model. The nomogram's discrimination and calibration abilities were evaluated in both cohorts using the Hosmer-Lemeshow test and calibration curves. Decision curve analysis (DCA) was used to evaluate the net benefit of the predictive efficacy.

**Results and discussion:** Amongst the 1883 patients with kidney disease receiving immunosuppressive drugs, 375 (28.5%) and 169 (29.9%) developed NODM in the training ($n = 1318$) and validation cohorts ($n = 565$), respectively. Nine clinic predictors were included in this LASSO-derived nomogram, which is easy to be operated clinically. The discriminative ability, determined by the area under the receiver operating characteristic curve (AUC), was 0.816 (95% confidence interval [CI] 0.790–0.841) and 0.831 (95%CI 0.796–0.867) in the training and validation cohorts, respectively. Calibration was confirmed with the Hosmer-Lemeshow test in the training and validation cohorts ($p = 0.238$, $p = 0.751$, respectively).

**What is new and conclusion:** Nearly one-third of patients with kidney disease receiving immunosuppressive drugs developed NODM. The nomogram established in this

Lina Shao and Chuxuan Luo contributed equally to this work and should be considered as co-first authors.

study may aid in predicting the occurrence of NODM in patients with kidney disease receiving immunosuppressive drugs.

KEYWORDS
immunosuppressive drugs, LASSO, new-onset diabetes mellitus, nomogram, risk model

## 1 | WHAT IS KNOWN AND OBJECTIVE

The prevalence of kidney disease and mortality associated with it have gradually increased since 1990, and kidney disease is now recognized as a major and growing public health concern worldwide.[1] First-line immunosuppressive agents, such as tacrolimus, cyclosporine and glucocorticoids, are widely used and have proven successful in the treatment of kidney diseases.[2] However, immunosuppressive drug (ISD) therapy is associated with adverse effects, such as hyperglycemia.[3] In general, the administration of corticosteroids and calcineurin inhibitors (CNIs) is considered the predominant factor associated with the development of post-transplant diabetes mellitus.[4] A growing body of evidence has indicated potential associations between ISD use and increased risk of incident new-onset diabetes mellitus (NODM).[5–8] In addition, studies have documented that the prognosis and survival are poorer amongst patients with NODM than amongst those without NODM.[9–12]

Early evaluation of patients who are likely to develop NODM may aid in guiding adjuvant therapy, thereby improving outcomes. Of note, findings regarding the incidence of and risk factors for the development of NODM in patients treated with ISDs have been heterogeneous. More accurate predictive tools are required, given the controversial conclusions of previous models. These controversial conclusions likely occurred due to the small sample sizes or a focus on specific kidney diseases, such as renal transplantation and idiopathic membranous nephropathy.

The least absolute shrinkage and selection operator (LASSO) regression, which is an advanced variable selection algorithm for multicollinear or high-dimensional data, has proven to be the best algorithm for reducing multicollinearity amongst variables.[13] It is especially suitable for dealing with an enormous number of clinical factors and avoiding over-fitting. Nomograms are simple statistical visual tools that can be used as regression algorithms to predict the probability of a given outcome.[14] They have become increasingly popular given their benefits of easy visualization and understandability. However, nomograms have rarely been used to predict the development of NODM in patients with kidney disease. Accordingly, the present study aimed to establish a LASSO-based nomogram for precisely and conveniently identifying patients receiving ISDs who are likely to develop NODM.

## 2 | METHODS

### 2.1 | Data sources and processing

Demographic data, medical histories, clinical diagnoses, laboratory data, and medical data, which were generally found or tested in those patients, were extracted from the hospital's electronic medical records system.

A total of 2954 patients treated for kidney disease using ISDs (tacrolimus, cyclosporine and glucocorticoids) between January 2010 and October 2018 were enrolled in this retrospective study. Those with a history of diabetes mellitus ($n = 124$) and abnormal baseline fasting blood glucose (FBG) level of >7 mmol/L ($n = 86$), those with missing key parameters such as FBG after ISD therapy or body mass index (BMI) ($n = 486$), and those with a follow-up duration of <4 weeks ($n = 375$) were excluded from the study. Finally, a total of 1883 patients were included in the study. Patients were divided into the training ($n = 1318$) and validation ($n = 565$) cohorts at a ratio of 7:3 using R software.

### 2.2 | Statement of human and animal rights

The study was approved by the Ethics Committee of Zhejiang Provincial People's Hospital (2021QT184). The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).[15]

### 2.3 | Informed consent

The need for informed consent was waived owing to the retrospective study design.

### 2.4 | Definitions

To receive a diagnosis of NODM, patients must have had no history of diabetes or diabetes-related symptoms, as well as normal FBG before ISD treatment. NODM was defined as follows: persistence of abnormally elevated FBG or elevated random blood glucose during the 1 year after beginning ISD treatment, based on the American Diabetes Association guidelines.[16] These guidelines included symptoms of diabetes with a rapid plasma glucose level ≥ 11.1 mmol/L, a fasting plasma glucose level ≥7.0 mmol/L, a 2-h plasma glucose level ≥ 11.1 mmol/L during an oral glucose tolerance test, or plasma haemoglobin (Hb) A1c ≥6.5%.[16]

### 2.5 | Statistical analyses

The baseline characteristics of the two cohorts were described using counts and percentages for categorical variables and medians with

interquartile ranges for continuous variables. Differences between groups were examined using chi-square tests or Fisher's exact tests for categorical variables and t-tests or Wilcoxon tests for continuous variables, depending on the nature of the distribution.

Imputation was conducted if missing values were <20%. We used predictive mean matching to impute numeric features, and logistic regression to impute binary variables. We used LASSO regression to minimize the potential collinearity of over-fitting variables and variables measured from the same patient. The R package "glmnet" (R Foundation) was used to perform the LASSO regression. This is a logistic regression model that penalizes the absolute size of the coefficients of a regression model based on the value of $\lambda$. With larger penalties, the estimates of weaker factors shrink towards zero, such that only the strongest predictors remain in the model. The most predictive covariates were selected based on the $\lambda$ ($\lambda$ = Lambda.1se). Subsequently, variables identified via the LASSO regression analysis were entered into logistic regression models by using forward stepwise (Likelihood Ratio), and those that were consistently statistically significant were used to construct the risk model. The independent variables were checked for collinearity using the variance inflation factor (VIF) and tolerance test.

A nomogram was developed based on the final model. Validations were implemented to evaluate the predictive performance of the derived nomogram in terms of discrimination and calibration. For independent validation, to account for the potential discrepancy between the training and validation datasets, calibration plots were created for the original and recalibrated nomograms. Discrimination was assessed using the receiver operating characteristic (ROC) curve and the area under the curve (AUC). Calibration was assessed by comparing the observed NODM rates with predictions from the final model. Decision curve analysis (DCA) was performed to evaluate the net clinical benefits. All statistical analyses were performed using R software, version 3.6.2 (R Foundation for Statistical Computing), and a two-sided $p$-value of <0.05 was considered statistically significant for all tests.

## 3 | RESULTS AND DISCUSSION

### 3.1 | Baseline characteristics of the training and validation cohorts

We analysed the data from 1318 patients in the training cohort (median age: 56 years), which included 588 (44.6%) men. Thirty-one (2.4%) patients had a family history of diabetes, whilst 246 (18.7%) had hypertension. The median FBG level was 4.88 mmol/L. Amongst the included patients, 14.9% ($n$ = 196) received tacrolimus therapy, 6.3% ($n$ = 83) received cyclosporine therapy, 9.9% ($n$ = 130) received intravenous glucocorticoids at a dosage of 500 mg (GC 500 mg) and 67.6% ($n$ = 891) received intravenous glucocorticoids at a dosage of 40 mg (GC 40 mg). The morbidity rates of NODM were 28.5% (375/1318) and 29.9% (169/565) in the training and validation cohorts, respectively. Table 1 shows the comparison of the demographic and clinical variables between the training and validation cohorts. There were no statistically significant differences between the two cohorts.

### 3.2 | Predictor selection and identification

Fifty variables measured at baseline (i.e., hospital admission) (Table 1) were included in the LASSO regression analysis. After LASSO regression selection (Figure 1), the following 20 variables remained significant predictors of NODM, including clinical features, ISD therapy, and blood test results: sex, age, tacrolimus use, duration of tacrolimus use, cyclosporine use, number of intravenous glucocorticoid treatments at a dosage of 500 mg, intravenous glucocorticoid treatment at a dosage of 40 mg, duration of intravenous glucocorticoid treatment at a dosage of 40 mg, hypertension, FBG, haematocrit, Hb, serum creatine, uric acid, high sensitivity C-reactive protein, white blood cell count, red cell distribution width, diagnosis of lupus nephritis, diagnosis of acute kidney injury (AKI) and diagnosis of other kidney diseases (renal transplant recipients, interstitial nephritis and other glomerular diseases of uncertain pathologic type).

These 20 variables were included in the logistic regression model, and nine variables were found to be significant independent predictors of NODM. These variables included sex (female) (odds ratio [OR], 0.659; 95% confidence interval [CI], 0.494–0.879; $p$ = 0.005), age (OR, 1.029; 95% CI, 1.021–1.037; $p$ < 0.001), tacrolimus use (OR, 2.986; 95% CI, 1.973–4.520; $p$ < 0.001), cyclosporine use (OR, 2.571; 95% CI, 1.488–4.440; $p$ = 0.001), number of intravenous glucocorticoid treatments at a dosage of 500 mg (OR, 1.180; 95% CI, 1.068–1.304; $p$ = 0.001), intravenous glucocorticoid treatment at a dosage of 40 mg (OR, 3.545; 95% CI, 2.364–5.137; $p$ < 0.001), duration of intravenous glucocorticoid treatment at a dosage of 40 mg (OR, 1.019; 95% CI, 1.008–1.030; $p$ < 0.001), FBG (OR, 1.295; 95% CI, 1.091–1.536; $p$ = 0.003) and diagnosis of AKI (OR, 8.216; 95% CI, 5.321–12.678; $p$ < 0.001) (Table 2). Furthermore, the tolerance was >0.1, and VIF was significantly <10 for the training set, indicating no collinearity amongst the independent variables (Table S1).

### 3.3 | Nomogram construction

The risk of NODM was calculated using the following multivariate logistic regression equation: $\ln(p/1-p) = -0.417 \times \text{Sex} + 0.029 \times \text{Age} + 1.094 \times \text{Tacrolimus use} + 0.944 \times \text{Cyclosporine use} + 0.166 \times \text{GC 500 mg} + 1.266 \times \text{GC 40 mg} + 0.019 \times \text{GC 40 mg Time} + 0.258 \times \text{FBG} + 2.106 \times \text{Diagnosis AKI} - 4.930$. In the equation, $p$ represents the probability of NODM.

A prognostic nomogram for patients receiving ISD therapy that would likely progress to NODM was constructed using the multivariate logistic regression results (Figure 2). Points were assigned to the identified factors according to the absolute maximum beta value based on the logistic regression model, given that the units are different for the continuous (age, number of intravenous glucocorticoid

**TABLE 1** Comparison of variable characteristics between training cohort and validation cohort

| Variables | Training cohort | Validation cohort | *p*-Value |
|---|---|---|---|
| No. | 1318 | 565 | |
| Age (years) | 56 (38–69) | 56 (41–70) | 0.370 |
| BMI | 21.8 (19.5–24.5) | 22.0 (19.6–24.3) | 0.841 |
| Gender (male) *n* (%) | 588 (44.6) | 239 (42.3) | 0.354 |
| Smoking habit *n* (%) | 275 (20.9) | 99 (17.5) | 0.178 |
| Drinking habit *n* (%) | 191 (14.5) | 61 (10.8) | 0.083 |
| DM family history *n* (%) | 31 (2.4) | 15 (2.7) | 0.696 |
| Hypertension *n* (%) | 246 (18.7) | 106 (18.8) | 0.961 |
| Cardiovascular disease *n* (%) | 22 (1.7) | 10 (1.8) | 0.877 |
| Cerebrovascular disease *n* (%) | 16 (1.2) | 7 (1.2) | 0.964 |
| Fasting blood-glucose, mmol/L | 4.88 (4.43–5.49) | 4.83 (4.47–5.47) | 0.993 |
| Haematocrit | 0.360 (0.306–0.410) | 0.362 (0.305–0.405) | 0.995 |
| Haemoglobin, g/L | 118 (99–136) | 119 (99.4–135) | 0.901 |
| Albumin, g/L | 33.3 (27.0–39) | 33.8 (27.95–39.3) | 0.117 |
| Creatinine, μmol/L | 82.4 (66.1–127.5) | 80.3 (67.2–125) | 0.954 |
| LDLC, mmol/L | 2.71 (1.99–3.55) | 2.65 (1.94–3.55) | 0.258 |
| Triglyceride, mmol/L | 1.49 (1.04–2.18) | 1.47 (1.09–2.22) | 0.871 |
| Uric acid, μmol/L | 336 (257–437) | 340 (266–437) | 0.512 |
| HDLC | 1.11 (0.84–1.46) | 1.09 (0.82–1.47) | 0.615 |
| hsCRP | 7.8 (1.9–31.95) | 7.2 (1.9–31.95) | 0.818 |
| White blood cell count, $\times 10^9$/L | 6.83 (4.9–9.61) | 6.90 (4.83–10.05) | 0.668 |
| Lymphocyte count, $\times 10^9$/L | 1.40 (0.93–2.01) | 1.41 (0.99–2.06) | 0.382 |
| Lymphocyte % | 22.04 (14.6–30.2) | 22.70 (14.9–29.6) | 0.511 |
| RDW-SD | 45.1 (41.4–48.2) | 45.2 (41.8–48.25) | 0.565 |
| RDW-CV | 13.7 (12.8–15.1) | 13.7 (12.8–14.9) | 0.792 |
| Neutrophil cell count, $\times 10^9$/L | 4.70 (3.14–6.87) | 4.77 (3.12–7.19) | 0.665 |
| Neutrophil cell % | 70.2 (61.4–78.4) | 69.60 (61.2–78.5) | 0.808 |
| FK506, mean (SD) [range] ng/L | 0.58 (2.2) [0–22] | 0.61 (2.3) [0–20.5] | 0.847 |
| Tacrolimus *n* (%) | 196 (14.9) | 88 (15.6) | 0.696 |
| Duration of tacrolimus, mean (SD) [range] | 3 (11) [0–242] | 3 (10) [0–88] | 0.760 |
| Ciclosporin *n* (%) | 83 (6.3) | 26 (4.6) | 0.149 |
| Duration of ciclosporin, mean (SD) [range] | 2 (9) [0–170] | 1 (5) [0–59] | 0.300 |
| GC 500 mg *n* (%) | 130 (9.9) | 47 (8.3) | 0.292 |
| GC 500 mg time mean (SD) [range] | 0 (1) [0–19] | 0 (1) [0–7] | 0.138 |
| GC 40 mg *n* (%) | 891 (67.6) | 390 (69) | 0.544 |
| GC 40 mg time (day) | 4 (0–11) | 4 (0–12) | 0.295 |
| GCoral *n* (%) | 1011 (76.7) | 425 (75.2) | 0.487 |
| GCoral time (day) | 4 (1–13) | 4 (1–13) | 0.909 |
| *Diagnosis* | | | |
| Nephrotic syndrome | 278 (21.1) | 107 (18.9) | 0.288 |
| Idiopathic membranous nephropathy | 109 (8.3) | 48 (8.5) | 0.871 |
| IgA naphropathy | 83 (6.3) | 44 (7.8) | 0.237 |
| Minimal change disease | 8 (0.6) | 1 (0.2) | 0.294 |
| Mesangial proliferative glomerular nephritis | 10 (0.8) | 3 (0.5) | 0.584 |
| Anca associated systemtc vasculitis | 76 (5.8) | 41 (7.3) | 0.220 |
| Lupus nephritis | 271 (20.6) | 100 (17.7) | 0.152 |

**TABLE 1** (Continued)

| Variables | Training cohort | Validation cohort | *p*-Value |
|---|---|---|---|
| Sjogren's syndrome | 106 (8) | 45 (8) | 0.955 |
| Rheumatoid arthritis | 117 (8.9) | 58 (10.3) | 0.342 |
| Henoch-schonlein purpura nephritis | 30 (2.3) | 11 (1.9) | 0.654 |
| Renal transplant recipients | 17 (1.3) | 2 (0.4) | 0.063 |
| Acute kidney injury | 153 (11.6) | 67 (11.9) | 0.877 |
| Other kidney disease | 188 (14.3) | 91 (16.1) | 0.302 |
| Follow up time (day) | 183 (53–513) | 144 (56–409) | 0.187 |
| *NODM* | | | |
| Yes | 375 (28.5) | 169 (29.9) | 0.522 |
| No | 943 (71.5) | 396 (70.1) | |

Abbreviations: BMI, body mass index; DM family History, diabetes mellitus family history; FK506, minimum concentration of tacrolimus; GC 40 mg, intravenous glucocorticoid of 40 mg dosage form use; GC 40 mg time, duration intravenous glucocorticoid of 40 mg dosage form; GC 500 mg, intravenous glucocorticoid of 500 mg dosage form; GC 500 mg time, numbers of intravenous glucocorticoid of 500 mg dosage form; GCoral, oral dosage form of glucocorticoids; GCoral time, duration of oral dosage form of glucocorticoids; HDLC, high density lipoprotein cholesterol; hsCRP, high sensitivity C reactive protein; LDLC, low-density lipoprotein cholesterol; NODM, new onset diabetes mellitus; RDW-CV, red blood cell distribution width—coefficient of variation; RDW-SD, red blood cell distribution width—standard deviation.

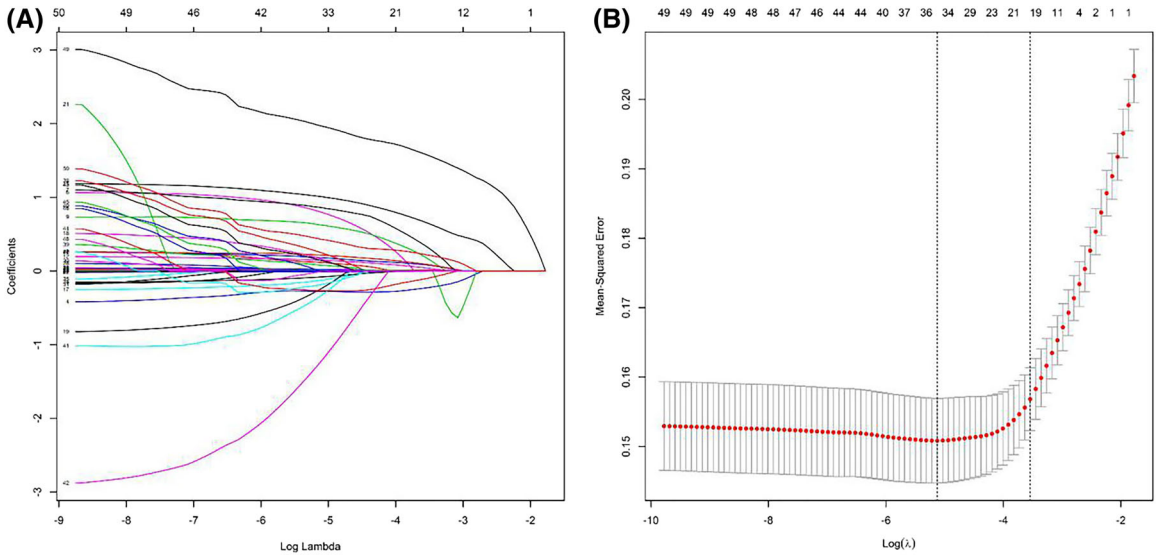


**FIGURE 1** Feature selection using the least absolute shrinkage and selection operator (LASSO) binary logistic regression model. (A) LASSO coefficient profiles of the 50 baseline features. (B) Tuning parameter ($\lambda$) selection in the LASSO model used 10-fold cross-testing via minimum criteria.

treatments at a dosage of 500 mg, intravenous glucocorticoid treatment at a dosage of 40 mg, duration of intravenous glucocorticoid treatment at a dosage of 40 mg and FBG) and categorical (sex, tacrolimus use, cyclosporine use and diagnosis of AKI) predictors. As shown in the nomogram, patients with the following characteristics were more likely to progress to NODM: male sex, older in age, treatment with tacrolimus, treatment with cyclosporine, more frequent intravenous glucocorticoid treatments at a dosage of 500 mg, intravenous glucocorticoid treatment at a dosage of 40 mg, longer duration of intravenous glucocorticoid treatment at a dosage of 40 mg, higher FBG and diagnosis of AKI. The longer the length of the line was, the larger the impact of those factors in developing NODM might have. Summing all points led to a total score. Locating the total score on the nomogram scale, the risk of progressing to NODM could be determined at patient presentation.

A hypothetical case illustrating our nomogram usage is presented in Figure S1. If a 60-year-old male patient with an FBG of 5.5 mmol/L is treated with oral tacrolimus, in combination with intravenous glucocorticoid 40 mg per day for 8 weeks, the total points add up to 190 and the corresponding risk of NODM is approximately 78%, which indicates a high predicted probability of NODM for this patient.

### 3.4 | Nomogram validation

We performed independent validation of our nomogram in the validation cohort (Figure 3B), which yielded an AUC value of 0.831 (95% CI: 0.796–0.867). The calibration curve revealed excellent concordance between the nomogram prediction and actual observation of NODM. The Hosmer–Lemeshow test yielded *p*-values of 0.238 and 0.751 in the training and validation cohorts, respectively (Figure 4). We further plotted the DCA curves of the training and validation cohorts to assess the clinical utility of our risk model. Our nomogram showed a net benefit across a wide scale of threshold probabilities for the prediction of NODM, regardless of the training cohort or the validation cohort (Figure 5).

**TABLE 2** LASSO-derived multivariable logistic regression model for predicting NODM in training cohort ($n = 1318$)

| Variables | OR | Odds ratio (95% CI) | *p* Value |
|---|---|---|---|
| Female | 0.659 | 0.494–0.879 | 0.005 |
| Age (years) | 1.029 | 1.021–1.037 | <0.001 |
| Tacrolimus | 2.986 | 1.973–4.520 | <0.001 |
| Ciclosporine | 2.571 | 1.488–4.440 | 0.001 |
| GC 500 mg time (No.) | 1.18 | 1.068–1.304 | 0.001 |
| GC 40 mg | 3.545 | 2.364–5.137 | <0.001 |
| GC 40 mg time (day) | 1.019 | 1.008–1.030 | <0.001 |
| FBG (mmol/L) | 1.295 | 1.091–1.536 | 0.003 |
| Diagnosis AKI | 8.216 | 5.321–12.678 | <0.001 |

Abbreviations: Diagnosis AKI, be diagnosed as acute kidney injury; FBG, fasting blood-glucose; GC 40 mg, intravenous glucocorticoid of 40 mg dosage form use; GC 40 mg time, duration intravenous glucocorticoid of 40 mg dosage form; GC 500 mg time, numbers of intravenous glucocorticoid of 500 mg dosage form.

### 3.5 | Discussion

In the present study, we developed and validated a nomogram for predicting NODM in patients with kidney disease receiving ISDs based on a combination of variables. This predictive nomogram exhibited satisfactory accuracy based on AUCs (>0.81) in both the training and validation cohorts. In addition, high discriminative and calibration abilities were confirmed in both the training and validation cohorts. To the best of our knowledge, this is the first LASSO-derived risk model for NODM in patients with kidney disease receiving ISD. In practice, our easy-to-use nomogram may aid in clinical decision-making, as the required data are generally easily accessible in a clinical setting. If the patient's estimated risk for NODM is low, the clinicians may choose to perform continuous

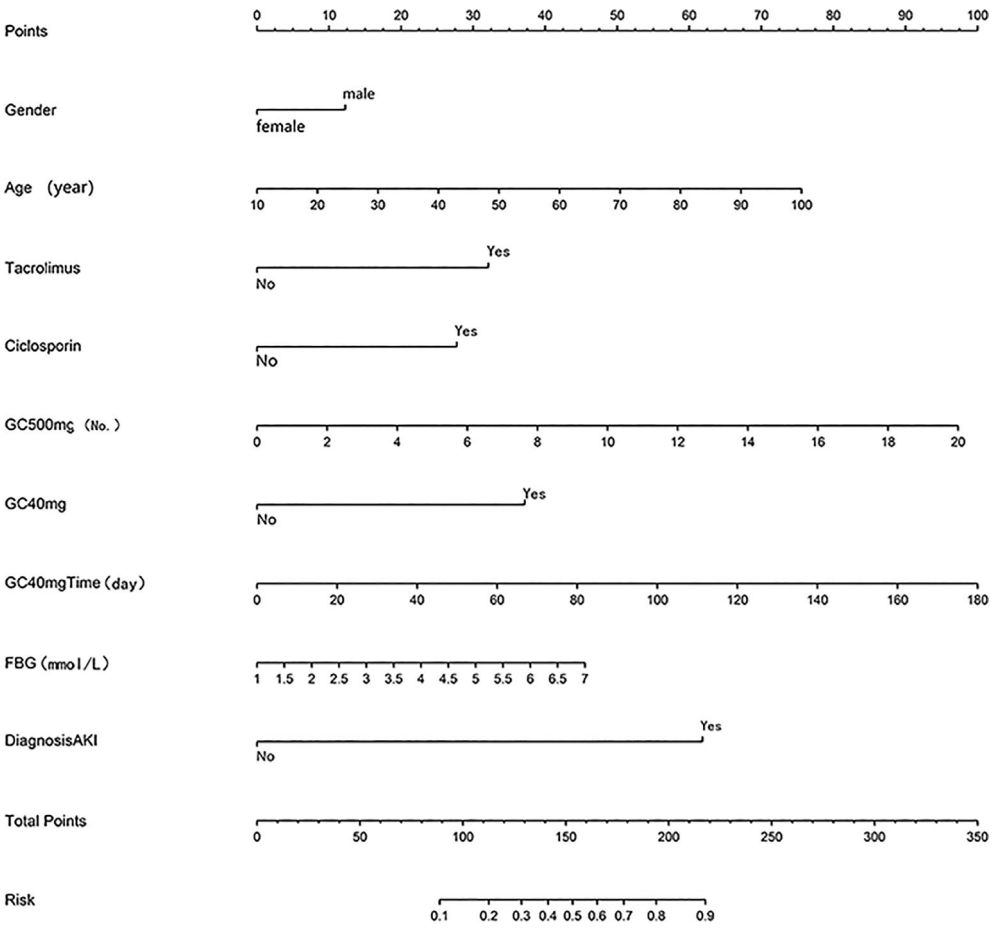


**FIGURE 2** Nomogram of probability to develop NODM. To use the nomogram, draw an upward vertical line from each covariate to the points bar to calculate the number of points. Based on the sum of the covariate points, draw a downward vertical line from the total points line to calculate the probability of developing NODM. GC 500 mg (No.): number of treatments with intravenous glucocorticoid at a dose of 500 mg; GC 40 mg: intravenous glucocorticoid at a dose of 40 mg; GC 40 mg Time (day): treatment duration of intravenous glucocorticoid at a dose of 40 mg; FBG: fasting blood-glucose; Diagnosis AKI: diagnosed with acute kidney injury.

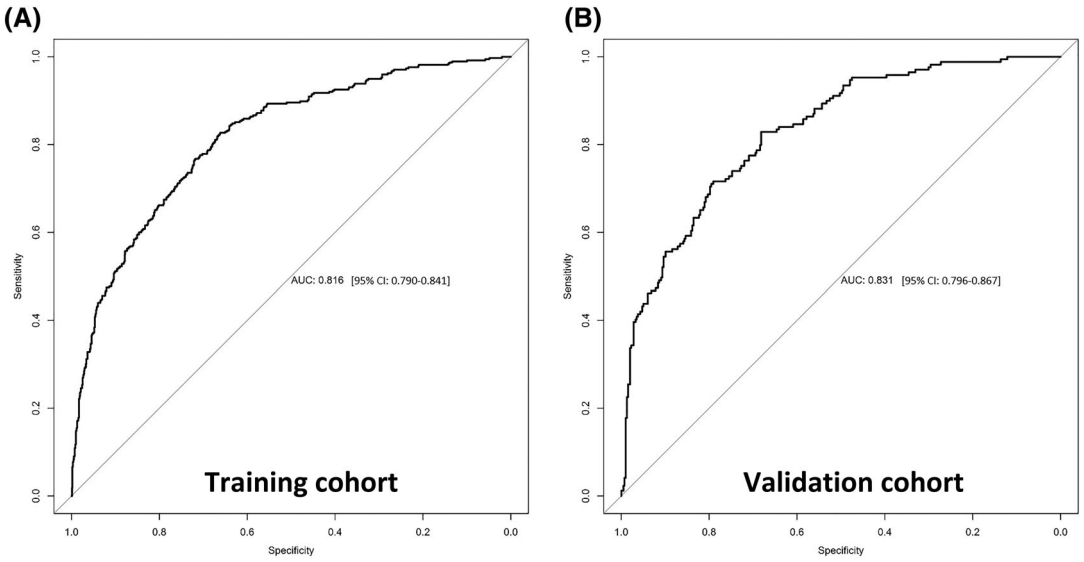


**FIGURE 3** (A) ROC curve for the nomogram based on the training cohort. The bias-corrected AUC is 0.816. (B) ROC curve from the validation cohort and the AUC is 0.831. The estimate of AUC and its 95% confidence interval are shown in the plots. AUC, area under the curve; ROC, receiver operating characteristic.

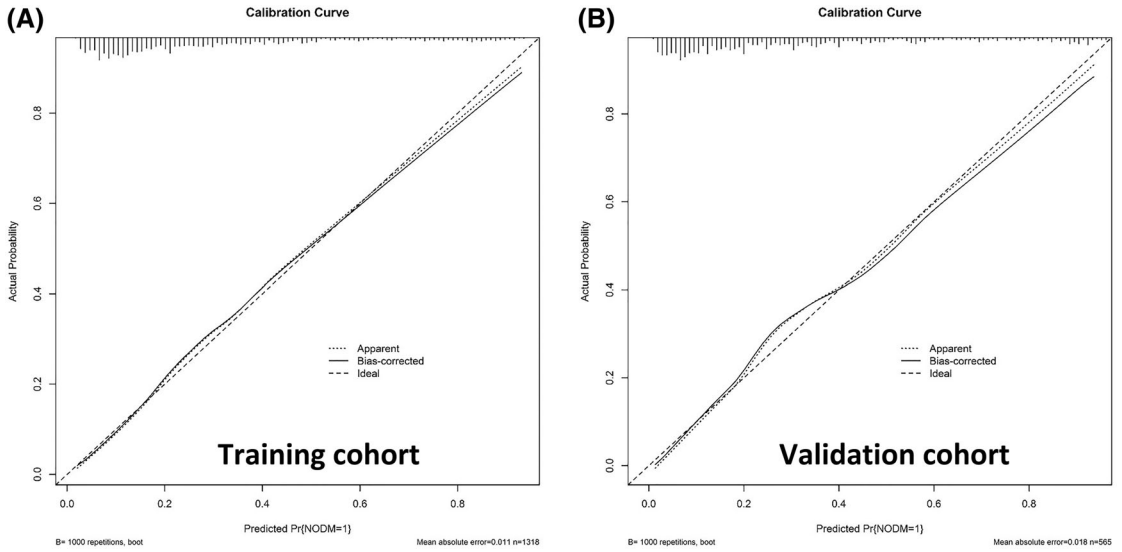


**FIGURE 4** (A) Calibration curves of the nomogram for predicting NODM from the training cohort. The Hosmer–Lemeshow test had a *p*-value of 0.238 in the training cohort. (B) Calibration curves of the nomogram for predicting NODM from the validation cohort. The Hosmer–Lemeshow test had a *p*-value of 0.751 in the validation cohort.

monitoring, whereas high-risk estimates may support a change in the treatment regimen.

Our study demonstrated that the morbidity of NODM in patients with kidney disease receiving ISD was high, with rates of 28.5% in the training cohort and 29.9% in the validation cohort. These rates are lower than those reported in our previous small-scale study involving patients with idiopathic membranous nephropathy undergoing tacrolimus and low-dose corticosteroid therapy.[6] The difference may be explained by the prior diabetogenic effects of tacrolimus, which may reduce insulin secretion due to islet cell necrosis and increase insulin resistance.[17]

In the model derivation, we used the LASSO to select the predictors. LASSO regularization is a statistical approach to address overfitting and to perform a variable selection that has been widely used in many types of predictive models and machine learning algorithms.[18–20] The final nomogram model was developed based on the following nine risk factors identified in the multivariate analysis: sex, age, tacrolimus use, cyclosporine use, number of intravenous glucocorticoid treatments at a dosage of 500 mg, intravenous glucocorticoid treatment at a dosage of 40 mg, duration of intravenous glucocorticoid treatment at a dosage of 40 mg, FBG level and diagnosis of AKI.

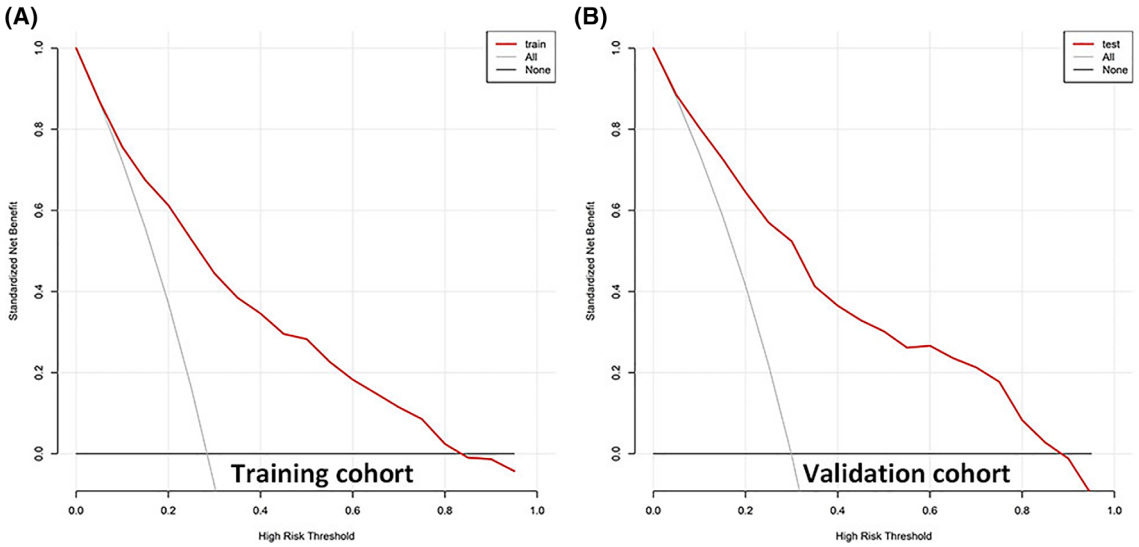


**FIGURE 5** Decision curve analysis (DCA) of the nomogram. (A) The DCA curve of the training cohort; (B) The DCA curve of the validation cohort.

Our analysis revealed that the usage of glucocorticoids, especially high-dosage intravenous glucocorticoids, played an important role in our predictive model, which is consistent with previous research.[5] Tacrolimus and cyclosporine are widely used in patients with kidney disease due to their strong immunosuppressive effects, and previous studies have documented their diabetogenic effects.[3,7] Similar findings were observed in the present study. Multiple studies have indicated that age, current smoking, BMI, family history of diabetes, history of hypertension and tacrolimus use are risk factors for NODM in patients taking ISDs following renal transplantation and for glomerular disease.[5,21–24] Our previous study demonstrated that age is an independent risk factor for NODM in patients with idiopathic membranous nephropathy treated with ISDs.[6] Glucose tolerance progressively declines with age,[25] which may be caused by the shortening of telomeres in β and α cells[26] and by age-related changes in DNA methylation in human islet cells.[27] These two effects may explain the main study finding that older age increased the risk of developing NODM. Surprisingly, FBG within the normal range was a risk factor for NODM. One study recommended that we should pay more attention to patients with baseline glycosylated haemoglobin in the non-diabetic range that reaches >5.65% during chronic kidney disease treatment with CNIs.[7] Although previous studies have not identified AKI as a major risk factor for NODM, AKI was extremely important in our risk model. Of the various kidney diseases included in this study, NODM was most frequently associated with AKI. Patients with renal diseases involving AKI, such as lupus nephropathy, antineutrophil cytoplasmic antibody-associated vasculitis, and nephrotic syndrome, tend to receive higher doses and/or longer durations of glucocorticoid therapy.

There are some limitations to this study. First, this study was conducted using the database of a single centre in China, which may preclude the generalization of this nomogram to patients in the rest of the world. Thus, further studies are required to validate our model using data from multiple centres. Second, some patients with missing data were removed from the analysis, as data were not considered to be missing at random, leading to some selection bias. However, LASSO was used to ensure the accuracy of the model and to prevent over-fitting. Lastly, because this was a retrospective analysis, some cases were lost to follow-up, which may have impacted the accuracy of the model. Prospective studies are required to verify and optimize the model.

## 4 | WHAT IS NEW AND CONCLUSION

In this study, we developed a predictive nomogram to estimate the risk of developing NODM amongst patients with kidney disease receiving ISDs. Estimating the risk of NODM may aid in identifying patients who are and are not likely to develop NODM, thus supporting appropriate treatment and optimizing ISD therapy in patients with kidney disease. The incidence of NODM in these patients was high, which requires the common attention of nephrologists, endocrinologists and community physicians. Over the next years, we look forward to achieve better management of this subset of patients through the multi-disciplinary cooperation of experts in nephrology and endocrinology.

### ACKNOWLEDGEMENTS

We would like to thank our colleagues at Zhejiang Provincial People's Hospital for their valuable contributions to this work and Dr. Zenglei He and Dr. Tian Yang for support with the statistical analysis. We are particularly grateful for the technical support and data platform that Yidu Cloud Technology Company Ltd. provided to make this project a reality. Lastly, we would like to thank Editage (www.editage.cn) for English language editing.

## FUNDING INFORMATION

This work was supported by the Medical and Health Technology Program of Zhejiang Province (No. 2019KY312, No. 2021KY448) and the Construction of Key Projects by Zhejiang Provincial Ministry (No. WKJ-ZJ-1915, No. WKJ-ZJ-2017).

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

## DATA AVAILABILITY STATEMENT

The datasets of this study are available from the corresponding author on reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Shao L, Luo C, Yuan C, et al. LASSO-derived nomogram predicting new-onset diabetes mellitus in patients with kidney disease receiving immunosuppressive drugs. *J Clin Pharm Ther*. 2022;47(10): 1627-1635. doi:10.1111/jcpt.13713