Original Article

Development and validation of a prediction model of left ventricular systolic dysfunction in type 2 diabetes mellitus

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Background: Left ventricular longitudinal myocardial systolic dysfunction (LVSD) represents a critical risk factor for diabetes-related cardiovascular events. This study aimed to develop a well-calibrated and convenient risk prediction model to investigate early predictive risk of LVSD in type 2 diabetes mellitus (T2DM) patients with preserved left ventricular ejection fraction (LVEF), and to evaluate its performance.

Methods: A total of 310 patients with T2DM from June 2020 to October 2021 at the Second Affiliated Hospital of Nanchang University were prospectively enrolled and randomly assigned to a training set (n=217) and a validation set (n=93) at a 7:3 ratio. Basic characteristics, laboratory tests, echocardiographic parameters, two-dimensional global longitudinal strain (GLS) parameters, and medication use were collected. LVSD in patients with T2DM with preserved LVEF was defined as an absolute value of GLS <18%. The least absolute shrinkage and selection operator (LASSO) regression was applied to optimize the screening variables, followed by multivariate logistic regression to identify independent risk factors for predicting LVSD, and a nomogram was established. The receiver operating characteristic (ROC) curves, area under the curve (AUC) values, calibration plot, and decision curve analysis (DCA) were used to verify and evaluate the nomogram's discrimination, calibration, and clinical validity.

Results: A total of 8 independent risk predictors of LVSD in T2DM were extracted and incorporated into the nomogram, as evaluated using LASSO regression analysis and multivariate logistic regression analysis, including body mass index (BMI), T2DM duration, blood urea nitrogen (BUN), left ventricular (LV) mass index, E/e', diabetic retinopathy, diabetic peripheral neuropathy, and diabetic nephropathy. The nomogram indicated excellent prediction properties with AUC values of 0.922 and 0.918 for the training set and validation set, respectively. Further, the predictive nomogram demonstrated outstanding consistency between the predicted probability and the actual probability in terms of the calibration plots. DCA showed also that the predicted nomogram was clinically beneficial.

Conclusions: This study identified independent risk factors for LVSD in patients with T2DM and developed a predictive nomogram. It allows for clinical decision-making to timely intervene or delay the occurrence of LVSD.

Keywords: Diabetes mellitus; global longitudinal strain (GLS); nomogram; prediction model; left ventricular (LV)

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Introduction

Type 2 diabetes mellitus (T2DM) is a group of metabolic disorders characterized by insulin resistance and relative insulin deficiency, accounting for 90–95% of all diabetes cases (1). It is associated with both macrovascular and microvascular diseases and often coexists with poor lifestyle factors, obesity, hypertension, and fatty liver, which increase the risk of diabetes-related organ damage, such as peripheral vascular disease, retinopathy, renal dysfunction, and coronary artery disease (CAD). T2DM was thought to be an important contributor in accelerating the progression of heart failure (HF), even independent of CAD or hypertension (2,3). Numerous studies suggest that left ventricular longitudinal myocardial systolic dysfunction (LVSD) is a crucial factor in diabetes-related cardiovascular events (4-7), and is regarded as a preclinical marker of DM-related cardiac dysfunction without overt HF (7,8).

The specific causes leading to impaired systolic longitudinal strain during LV are still unclear, so early assessment and identification of risk factors involved in the progression of LVSD are eagerly awaited. Although studies, such as Mochizuki *et al.*'s (5) research on 144 samples, have attempted to identify predictors of LVSD in T2DM patients, they have been limited by sample size and confounding factors. Moreover, no nomogram-based predictive models have been developed. Hence, we aimed to develop and validate a model for early prediction of risk factors for LVSD in T2DM patients using routinely measured variables. We present this article in accordance with the TRIPOD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-95/rc).

Methods

Study population

Initially, 345 patients with T2DM who were admitted to The Second Affiliated Hospital of Nanchang University between June 2020 to October 2021 were enrolled. The inclusion criteria were as follows: (I) diagnosed with T2DM (American Diabetes Association diagnostic criteria in 2020) (9), (II) age between 18 and 75 years, (III) left ventricular ejection fraction (LVEF) >50%. We excluded those with LVEF <50% (n=5), poorly controlled hypertension (n=8), CAD (n=7), atrial fibrillation (n=5), and poor image quality (n=10). Finally, 310 patients were enrolled for the present study. Subsequently, participants were randomly assigned to the training and validation sets according to a ratio of 7:3. A flow chart outlining the selection of T2DM patients is shown in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Second Affiliated Hospital of Nanchang University (No. 20240805102436398) and informed consent was provided by all the patients.

Data collection

Information was collected on baseline clinical data (age, sex, duration of diabetes, history of medication,), physical measurements [height, weight, body mass index (BMI), systolic/diastolic blood pressure (SBP/DBP), heart rate (HR)], laboratory examination [glycosylated hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), total cholesterol (TC), triglycerides (TG), high-density/low-density lipoprotein cholesterol (HDL-C/LDL-C), urinary albumin to creatinine ratio (ACR)], and diabetic microvascular complications, including diabetic retinopathy (DR), diabetic peripheral neuropathy (DPN), and diabetic nephropathy (DN). Occurrence of DPN was evaluated by experienced diabetologists according to nerve conduction study and current guidelines (9). Moreover, DR was diagnosed by experienced ophthalmologists, either on fundoscopy or retinography (10). DN was defined as albuminuria of not less than 30 mg/day accompanied by GFR >30 mL/min/1.73 m^2) (11).

Echocardiography

All patients underwent standard two-dimensional (2D) transthoracic echocardiographic examination with commercial Vivid E95 ultrasound scanners equipped with a M5SC-D transducer (GE Vingmed Ultrasound, Horten, Norway). 2D gray-scale echocardiography of three consecutive cardiac cycles was obtained from standard parasternal and apical views upon calm breathing. Sector

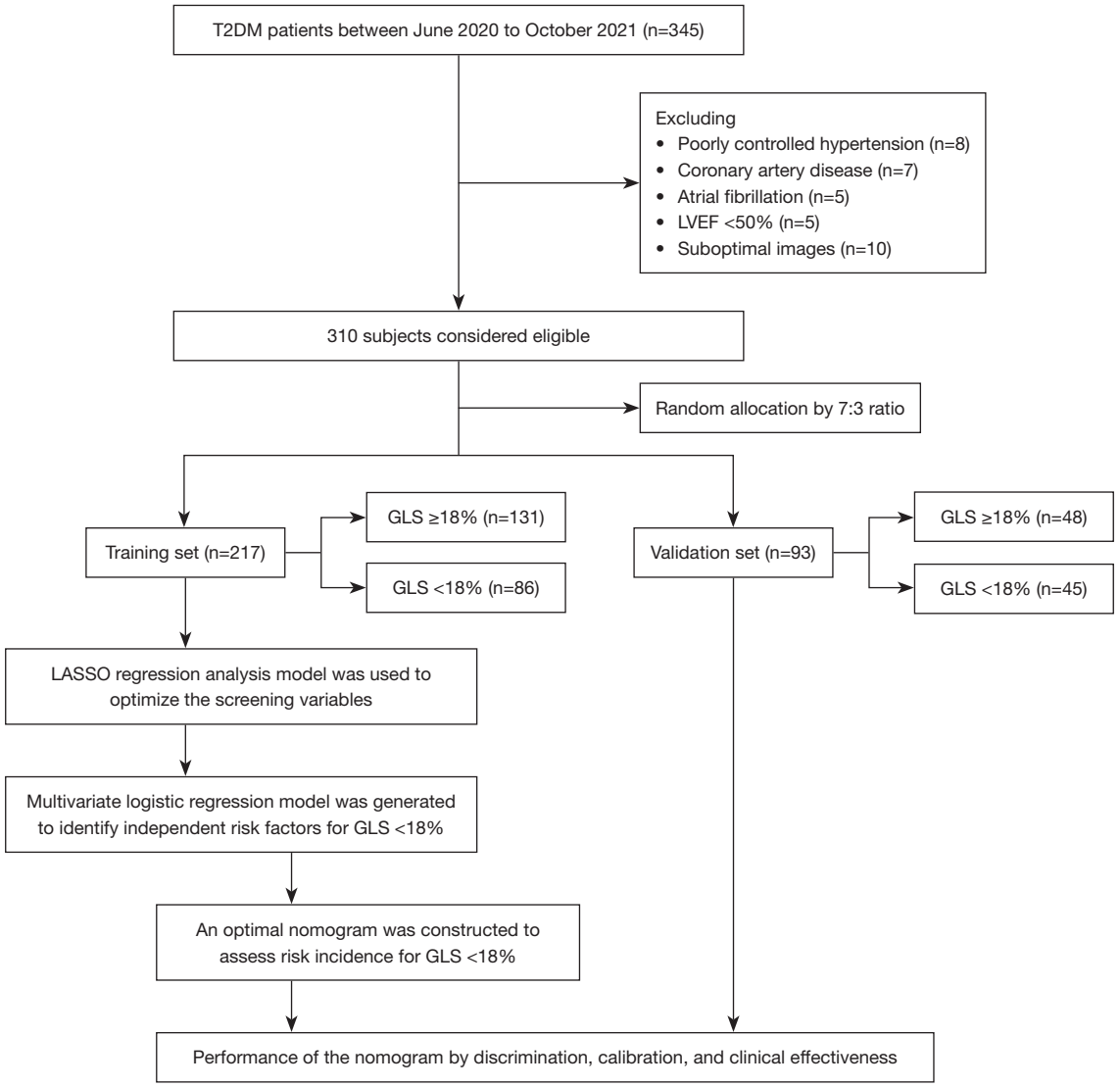

Figure 1 Flow chart of the population in this study. T2DM, type 2 diabetes mellitus; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain.

width was optimized to maximize frame rate and achieve the whole LV myocardial visualization concurrently. All standard acquisitions and measurements were completed relying on the guidelines of the American Society of Echocardiography (12).

Measurement of global longitudinal myocardial strain

To perform the speckle tracking strain analysis, three standard apical views (apical four-chamber, two-chamber, and three-chamber) were acquired using grayscale harmonic imaging at frame rates between 50–80 frames/s and was saved in cine-loop digital format for offline analysis. Quantification of 2D strain was performed with dedicated software (EchoPAC 203, GE). The algorithm automatically traces the endocardial border or width throughout the cardiac cycle and calculates strain values at the three apical views; if necessary, end-diastolic frame was manually contoured for optimal assessment. GLS was then determined as the average value of the peak systolic longitudinal strain of each myocardial segment from the three apical views. For this study, we chose to report global longitudinal strain (GLS) using the absolute value. As previously detailed, LVSD in T2DM patients with preserved LVEF was set at GLS <18% (5,8,13).

Statistical analysis

Continuous variables were expressed as means ± standard deviation (for normally distributed data) or median [interquartile range (IQR)] (for non-normally distributed data), and independent *t*-test or the Wilcoxon test was used for comparisons between groups. Categorical variables were expressed as frequency/percentage (%) and compared using the chi-square test or Fisher's exact test as appropriate. To address potential collinearity and avoid overfitting, least absolute shrinkage and selection operator (LASSO) regression analysis was used to screen risk factors and optimal predictive features from a large set of variables in T2DM patients. Subsequently, multivariable logistic regression analysis is performed. Finally, the risk factors were visualized with a forest plot and a nomogram was constructed based on these factors. Model performance was evaluated through discrimination ability [with area under the curve (AUC) >0.7 indicating satisfactory performance], calibration (using the Hosmer-Lemeshow test and calibration curve), and clinical utility [assessed by decision curve analysis (DCA)]. The P values were two-sided and considered significant if <0.05. The statistical analysis was performed using the software SPSS 22.0 (IBM Corp., Armonk, NY, USA), R software (version 4.1.1; http://www.r-project.org/), and the R package with 'rio', 'rms', 'glmnet', 'InformationValue', 'forestplot', 'ROCR', 'rmda', 'ResourceSelection', and 'regplot'.

Results

Characteristics of patients with T2DM This study included 310 T2DM patients with an average age of 56 years; 217 comprised the training set and 93 comprised the validation set. Of the 310 patients included, 130 patients (41.9%) presented with LVSD, with 86 (39.6%) in the training set and 44 (47.3%) in the validation set, respectively. All baseline characteristics of both sets are summarized in *Table 1*. The variables did not show statistical differences except for eGFR and E/e', which were comparable in both the training and validation sets (P>0.05).

Feature selection

LASSO method was used for the selection of potential predictors from the training set, which allowed for reducing the dimensionality that was associated with decreased predictive ability and improving the accuracy of the nomogram model. Seven variables in the LASSO regression analysis were selected as potential predictors based on the results of 217 patients with nonzero coefficients (min λ of 0.056), which included BMI, T2DM duration, BUN, left ventricular mass index (LVMI), E/e', DR, DN, and DPN, (*Figure 2A*,*2B*).

Independent risk factors and nomogram construction

Multivariate logistic analysis was performed to identify independent risk factors in the training set based on the most significant features selected by LASSO. The results (*Table 2*) revealed that BMI [odds ratio (OR): 1.248; 95% confidence interval (CI): 1.082–1.439; P=0.002]; DM course (OR: 1.149; 95% CI: 1.047–1.261; P=0.003); BUN (OR: 1.312; 95% CI: 1.030–1.671; P=0.028); LVMI (OR: 1.034; 95% CI: 1.008–1.060; P=0.009); E/e' (OR: 1.267; 95% CI: 1.065–1.507; P=0.007); DR (OR: 3.264; 95% CI: 1.091–9.764; P=0.034); DPN (OR: 2.999; 95% CI: 1.047–8.589; P=0.041); and DN (OR: 3.878; 95% CI: 1.455–10.337; P=0.007) were independent risk factors of LVSD, as shown in the forest plot (*Figure 3A*). Underlying the above introduced results, a nomogram was constructed by integrating these independent risk factors (*Figure 3B*). In the nomogram, each predictor corresponds to a specific score by drawing its straight line at the top of the scale and drawing a vertical line from the total points axis down to the LVSD risk axis. Finally, the predicted probability of LVSD was obtained.

Performance assessment of the nomogram

The results showed that the AUC was 0.922 (95% CI: 0.886–0.958) and 0.918 (95% CI: 0.859–0.978) for the training and validation sets, respectively, indicating excellent discrimination (*Figure 4A*,*4B*). The calibration was also good in the training and validation sets (*Figure 4C*,*4D*), with the Hosmer–Lemeshow test showing no significant difference (P>0.05). DCA indicated that the nomogram had higher net benefit compared to assuming all patients have LVSD, within a risk threshold range of 40% to 95% (*Figure 5*).

Clinical application of the nomogram

We randomly selected a patient as an example of practicing the nomogram: BMI (29.6 kg/m^2), T2DM duration (5.0 years), BUN level (5.5 mmol/L), LVMI (73.3 g/m^2), E/e' (11.5) and the presence of DR and DN. By applying

Table 1 Demographic and clinical characteristics of T2DM patients in the training and validation sets

Clinical characteristics	Training set (n=217)	Validation set (n=93)	P value
Age (years)	55.9±11.6	57.7±9.6	0.156
Gender			
Female	80 (36.9)	33 (35.5)	0.817
Male	137 (63.1)	60 (64.5)	
T2DM duration (years)	6 (1–10)	7 (2–10)	0.346
Body surface area (m^2)	1.72±0.18	1.72±0.18	0.966
Body mass index (kg/m^2)	24.4±3.4	24.4±2.9	0.078
Systolic blood pressure (mmHg)	130.6±17.4	132.2±17.3	0.461
Diastolic blood pressure (mmHg)	81.1±10.2	80.9±9.0	0.848
Heart rate (bpm)	76.9±12.0	76.8±10.9	0.950
Laboratory results			
HbA1c (%)	8.6 (6.8–10.2)	7.9 (6.5–10.0)	0.321
Total cholesterol (mmol/L)	5.2±1.5	5.0±1.4	0.208
Triglycerides (mmol/L)	1.53 (1.07–2.55)	1.63 (1.12–2.66)	0.569
Low-density lipoprotein cholesterol (mmol/L)	3.14 (2.49–3.85)	2.86 (2.26–3.80)	0.503
High-density lipoprotein cholesterol (mmol/L)	1.12 (0.92–1.37)	1.07 (0.87–1.35)	0.359
Blood urea nitrogen (mmol/L)	5.73±1.88	5.76±1.63	0.886
eGFR ($mL/min/1.73\ m^2$)	105.4 (82.0–126.4)	87.9 (75.6–105.3)	<0.001
Albumin to creatinine ratio (mg/g)	12 (4.00–52.55)	15.6 (6.26–67.4)	0.321
Diabetic microvascular complications			
Retinopathy	156 (71.9)	72 (77.4)	0.312
Peripheral neuropathy	49 (22.6)	29 (31.2)	0.110
Nephropathy	66 (30.4)	32 (34.4)	0.488
Medications			
Metformin	161 (74.2)	60 (64.5)	0.084
Sulfonylureas	72 (33.2)	32 (34.4)	0.834
Glitazones	46 (21.2)	18 (19.4)	0.713
Insulin	86 (39.6)	31 (33.3)	0.295
ACE inhibitors or ARBs	119 (54.8)	43 (46.2)	0.165
Statins	126 (58.1)	55 (59.1)	0.860
Echocardiography			
LV mass index (g/m^2)	89.3±18.7	90.3±24.0	0.704
LV ejection fraction (%)	65.9±4.1	65.2±4.3	0.151
E/e’	11.5±3.1	13.2±3.3	<0.001
GLS (%)	18.0±2.0	17.9±2.2	0.930
GLS <18% (%)	86 (39.6)	44 (47.3)	0.209

Data are presented as mean ± standard deviation for normally distributed data and median (interquartile range) for non-normally distributed data, or n (%). T2DM, type 2 diabetes mellitus; HbA1c, glycosylated hemoglobin A1c; eGFR, estimated glomerular filtration rate; ACE, angiotensin-convertingenzyme; ARB, angiotensin II receptor blocker; LV, left ventricular; E, peak early diastolic mitral flow velocity; e’, spectral pulsed-wave Doppler-derived early diastolic; GLS, global longitudinal strain.

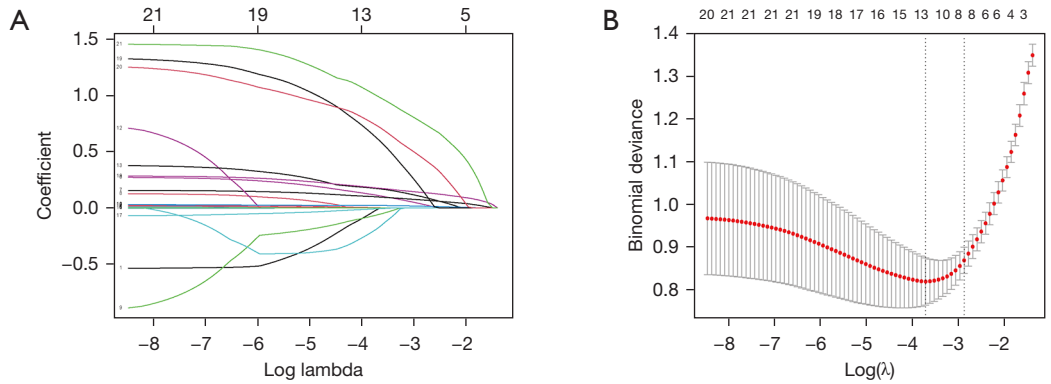

Figure 2 LASSO binary logistic regression analysis to select predictors of LVSD. (A) LASSO coefficient profiles of the 21 features. A coefficient profile plot was produced with the log(λ) sequence and 8 nonzero coefficients (indicated by a vertical line in the plot) were selected. (B) The optimum parameter (λ) selection in the LASSO model performed 10-fold cross-validation via minimum criteria. The partial likelihood deviance was plotted versus log (λ). Dotted vertical lines were drawn based on the minimum criteria and 1 standard error of the minimum criteria (the 1-SE criteria). LVSD, left ventricular longitudinal myocardial systolic dysfunction; LASSO, least absolute shrinkage and selection operator; SE, standard error.

Table 2 Potential risk factors identified by multivariate logistic regression analysis for LVSD in T2DM in the training set

Variable	Multivariate analysis	
	OR (95% CI)	P value
Body mass index (kg/m^2)	1.248 (1.082–1.439)	0.002
T2DM duration (years)	1.149 (1.047–1.261)	0.003
Blood urea nitrogen (mmol/L)	1.312 (1.030–1.671)	0.028
LV mass index (g/m^2)	1.034 (1.008–1.060)	0.009
E/e'	1.267 (1.065–1.507)	0.007
Retinopathy	3.264 (1.091–9.764)	0.034
Peripheral neuropathy	2.999 (1.047–8.589)	0.041
Nephropathy	3.878 (1.455–10.337)	0.007

LVSD, left ventricular longitudinal myocardial systolic dysfunction; T2DM, type 2 diabetes mellitus; OR, odds ratio; CI, confidence interval; LV, left ventricular; E, peak early diastolic mitral flow velocity; e', spectral pulsed-wave Doppler-derived early diastolic.

the above values to the nomogram, the probability of DR was estimated to be 66.2% (*Figure 6*).

Discussion

Currently, nomograms are widely used as prognostic tools in medicine and oncology (14). A nomogram-based predictive model is capable of improving accuracy, and provides more easily understood prognoses to help make better clinical decisions (15). Our study is the first nomogram to predict the risk factors of LVSD in T2DM patients. The major findings indicate that the incidence of LVSD is 41.9%. Patients with LVSD have higher BMI, longer duration of T2DM, elevated BUN, increased LVMI, and E/e', and are more likely to have complications such as DR, DPN, and DN. BMI, T2DM course, BUN, LVMI, E/e', DR, DPN, and DN are independent risk factors for LVSD, with DN being the highest risk factor. Our predictive model demonstrates acceptable accuracy and discrimination. Based on the eight risk factors listed in the nomogram, it is easy to calculate the score and estimate the probability of developing LVSD in T2DM patients.

In this work, we developed a quantifiable and simple nomogram to predict the risk factors for LVSD for T2DM patients. The specific implementation steps were as follows: all patients were randomly divided into groups at a 7:3 ratio for training and validation, respectively. LASSO regression was used to select features, then perform multivariable logistic regression analysis. Finally, the risk factors were visualized with a forest plot and a nomogram was constructed based on these factors. After validation by multiple methods, our nomogram showed excellent performance with respect to discrimination ability, calibration ability, and clinical usefulness.

In our study, overweight/obesity (indicated by a high BMI) was found to be an independent risk factor for LVSD, consistent with previous research (16-18). Obesity-related inflammation, metabolic disturbances, and insulin resistance

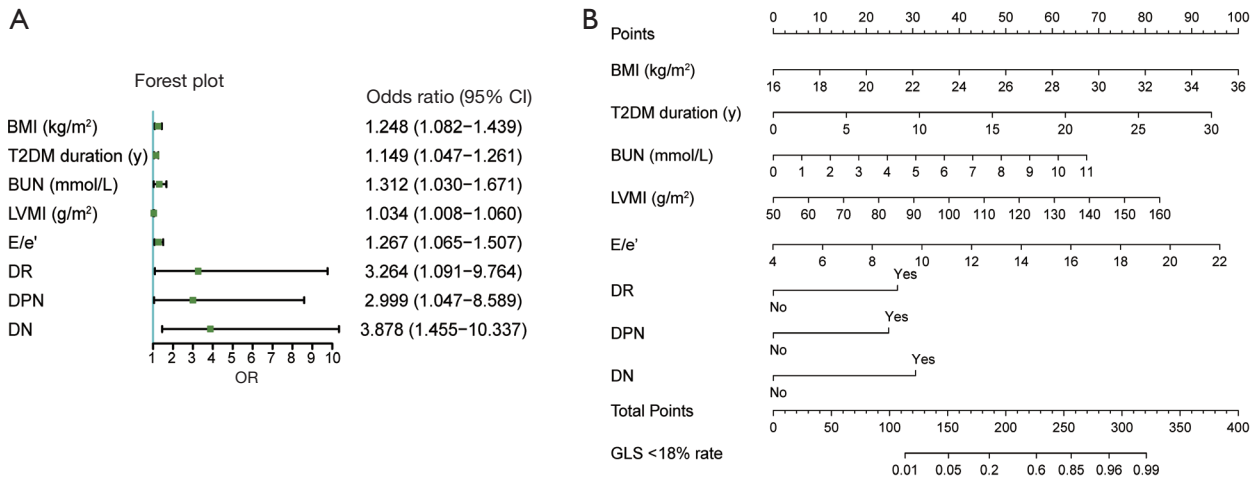

Figure 3 Forest plot and nomogram. (A) Forest plot of independent predictors of LVSD with OR. (B) Nomogram scaled by the proportional regression coefficient of each predictor to estimate LVSD presence in T2MD. BMI, body mass index; T2DM, type 2 diabetes mellitus; BUN, blood urea nitrogen; LVMI, left ventricular mass index; E, peak early diastolic mitral flow velocity; e', spectral pulsed-wave Doppler-derived early diastolic; DR, diabetic retinopathy; DPN, diabetic peripheral neuropathy; DN, diabetic nephropathy; OR, odds ratio; CI, confidence interval; GLS, global longitudinal strain; LVSD, left ventricular longitudinal myocardial systolic dysfunction.

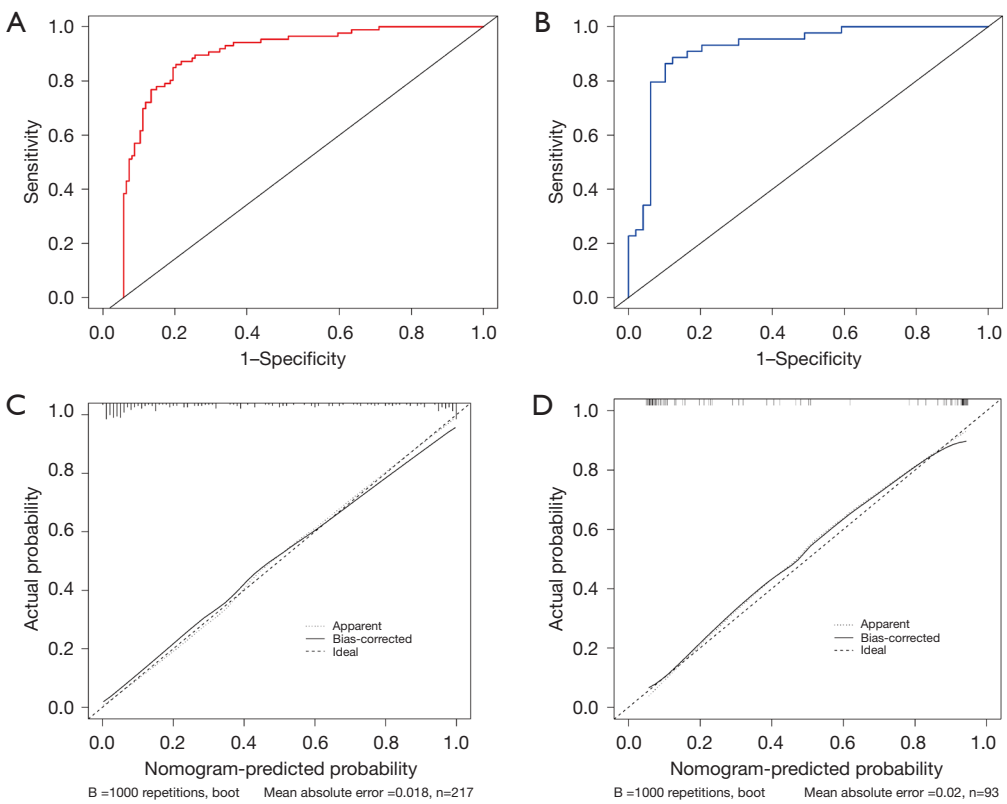

Figure 4 Performance of nomogram to predict LVSD rate in T2DM. (A) ROC curve in training set. (B) ROC curve in validation set. (C) Calibration curve in training set. (D) Calibration curve in validation set. LVSD, left ventricular longitudinal myocardial systolic dysfunction; T2DM, type 2 diabetes mellitus; ROC, receiver operating characteristic.

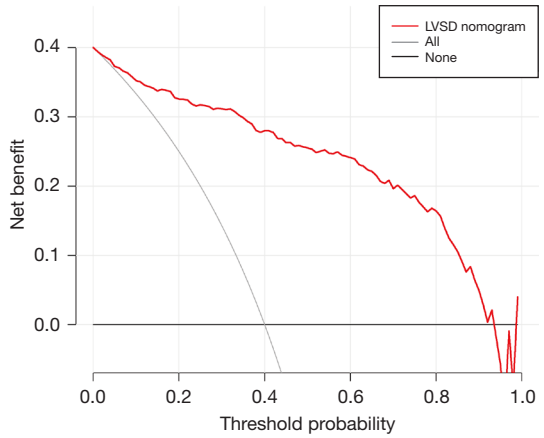

Figure 5 Decision curve analysis for the nomogram for predicting LVSD in whole set. The y-axis measures the net benefit. The gray or black line hypothesizes that all patients were LVSD positive or negative, respectively. The red line represents the net benefit of the nomogram at different threshold probabilities. LVSD, left ventricular longitudinal myocardial systolic dysfunction.

may worsen LV function (19). LVSD was also associated with the duration of diabetes. Advanced glycation end-products (AGEs) and their receptors (RAGEs) negatively impact the heart and promote atherosclerosis (20). Long-term hyperglycemia and poorly controlled diabetes can alter hemoglobin structure, increasing erythrocyte viscosity and contributing to microangiopathy and diabetic complications (21). Among ultrasonic features, LVMI and E/e' were identified as independent risk factors for LVSD. E/e' is closely related to LV filling pressures (22), and long-term dysglycemia may directly or indirectly contribute to elevated filling pressures and increased risk of HF symptoms and mortality (23). Larger LVMI indicates more severe cardiac hypertrophy, which can lead to apoptosis, autophagy, and extracellular matrix (ECM) synthesis abnormalities, potentially altering gene expression related to LVSD over time (24). Furthermore, our results align with those of Pararajasingam *et al.* (25) and Mochizuki *et al.* (5), showing that microvascular

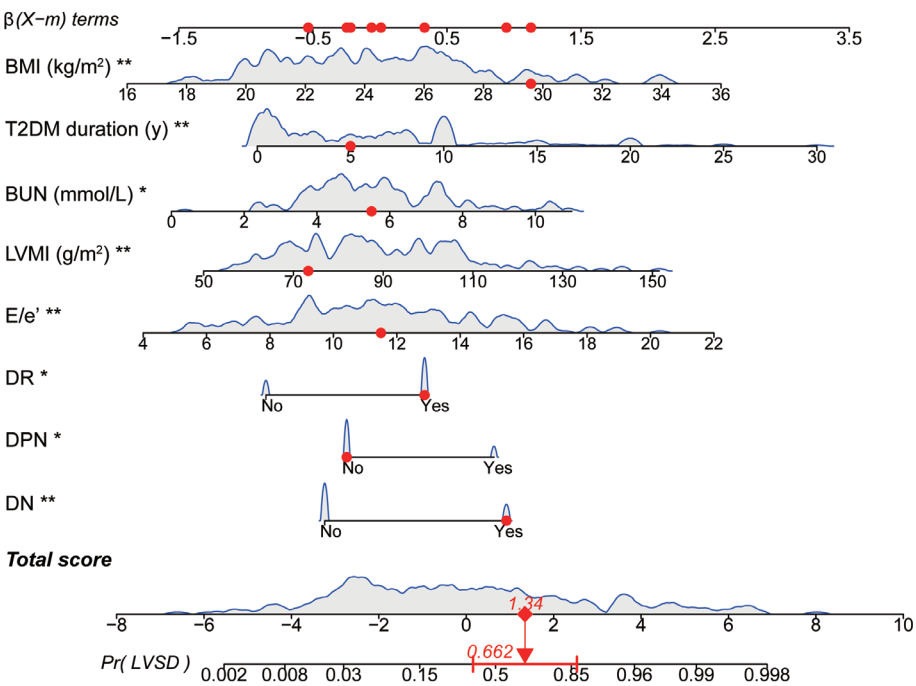

Figure 6 Dynamic nomogram. A T2DM patient was randomly selected from the population, and the LVSD incidence of the patient was predicted based on the 8 characteristic indicators of the nomogram. BMI, body mass index; T2DM, type 2 diabetes mellitus; BUN, blood urea nitrogen; LVMI, left ventricular mass index; E, peak early diastolic mitral flow velocity; e', spectral pulsed-wave Doppler-derived early diastolic; DR, diabetic retinopathy; DPN, diabetic peripheral neuropathy; DN, diabetic nephropathy; LVSD, left ventricular longitudinal myocardial systolic dysfunction.

complications (including DR, DPN, and DN) are associated with impaired GLS in T2DM patients, independent of CAD. Microvascular complications in diabetes often arise early and are interlinked through complex pathological mechanisms. Evidence suggests that patients with one or more complications are more susceptible to microvascular dysfunction, such as reduced myocardial perfusion (26,27). We hypothesize that the deterioration of cardiac function in patients with microvascular complications may be due to severe pathological abnormalities in the myocardium, including neurohormonal and metabolic disturbances (e.g., apoptosis, inflammation, oxidative stress, and fibrosis), as well as microvascular and cardiac remodeling abnormalities (28-30).

Limitations

Despite our efforts to enhance the study's validity by making the data from the training and validation sets completely independent, several unavoidable limitations remain. First, this study was conducted at a single center with a small sample size. Although model validation was carried out in a validation cohort, external validation was lacking; future multicenter prospective studies are needed to further validate the model and improve individualized risk assessment. Second, the study focused on specific clinical data and echocardiographic parameters, which may limit the generalizability of the findings to other factors. Finally, as a cross-sectional study without long-term follow-up, the relationship between LVSD and prognosis in T2DM patients requires further investigation.

Conclusions

This study developed a nomogram-based predictive model with good accuracy and clinical applicability for predicting the risk of LVSD among people with T2DM. This has the potential to be a convenient and accurate tool to predict LVSD in T2DM patients with preserved LVEF.

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None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-95/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-95/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Second Affiliated Hospital of Nanchang University (No. 20240805102436398) and informed consent was provided by all the patients.

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