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Development and validation of a novel metabolic health-related nomogram to improve predictive performance of cardiovascular disease risk in patients with prediabetes

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Abstract

Objective The prevalence of prediabetes among adults in the U.S. is three times higher than that of diabetes, highlighting a greater disease burden. Both diabetes and prediabetes have been demonstrated to be associated with an increased risk of cardiovascular disease (CVD). However, research has primarily focused on diabetes, with limited attention to CVD risk prediction in prediabetes. Emerging 13 metabolic health-related indicators have been proposed to optimize the predictive effect on CVD risk in patients with prediabetes. This study aimed to compare the predictive efficacy of these biomarkers and further develop a nomogram to improve predictive performance of the CVD risk in patients with prediabetes.

Methods All eligible participants in the National Health and Nutrition Examination Survey (NHANES) 1999–2020 were enrolled in this study and randomly assigned to the development and validation cohorts in a ratio of 7:3. In the development cohort, the efficacy of 13 indicators used to predict the CVD risk was assessed by receiver operative characteristic (ROC) curves. Independent risk predictors identified by multivariate logistic regression were used to construct a nomogram, and internal and external validation were further implemented.

Results The ROC curve demonstrated that the triglyceride-glucose (TyG) index was an effective predictor of CVD risk [area under the curve (AUC) = 0.694] and exhibited the best predictive performance among the 13 metabolic

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health-related indices. Based on independent risk factors identified by multivariate logistic regression, the CVD risk nomogram [including age, gender, hypertension, TyG, stress hyperglycemia ratio (SHR), and neutrophil-to-lymphocyte ratio (NLR)] was successfully constructed and validated with good performance (AUCs/C-indexes > 0.70 for all).

Conclusion This study developed a reliable nomogram for predicting CVD risk in patients with prediabetes. The model demonstrated robust performance and offered a simple yet individualized approach for predicting the CVD risk in patients with prediabetes.

Keywords Cardiovascular disease, Prediabetes, Metabolic health-related biomarkers, Risk prediction

Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide, accounting for approximately one-third of global deaths [1]. Similarly, diabetes mellitus is one of the most prevalent metabolic disorders globally, affecting over 34.1 million adults in the U.S. alone [2]. Prediabetes—a condition characterized by elevated blood glucose levels below the diagnostic threshold for diabetes , is recognized as a precursor to diabetes or a condition indicating a high risk of developing diabetes, with studies estimating that up to 70% of individuals with prediabetes will progress to diabetes in their lifetime [3]. Numerous studies have demonstrated that compared to the general population, individuals with diabetes or prediabetes face a higher risk of developing CVD and are associated with adverse outcomes and high mortality rates [4, 5]. It is worth noting that based on The National Diabetes Statistics Report for 2020, among adults in the U.S., the number of individuals with prediabetes is approximately three times higher than the number of those with diabetes [6]. This indicated the presence of a large population with prolonged hyperglycemia and a significantly elevated risk of CVD. However, current research predominantly focuses on individuals diagnosed with diabetes, with limited attention given to the prediction of CVD risk in individuals with prediabetes. Therefore, developing predictive models for CVD risk in individuals with prediabetes holds significant clinical importance [7].

In recent years, increasing attention has been given to novel metabolic health-related biomarkers for their potential to predict CVD risk in individuals with prediabetes. These emerging metabolic health-related biomarkers were listed as follows: triglyceride-glucose (TyG) index, triglyceride glucose-body mass index (TyG-BMI), triglyceride glucose-waist circumference (TyG-WC), triglyceride glucose-waist height ratio (TyG-WHtR), triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C), atherogenic index of plasma (AIP), urinary albumin-to-creatinine ratio (uACR), stress hyperglycemia ratio (SHR), a body shape index (ABSI), homeostatic model assessment for insulin resistance (HOMA-IR), metabolic score for insulin resistance (METS-IR), neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII). Although the above biomarkers have shown promise in predicting CVD risk in individuals with prediabetes, there are at least two key issues that need to be addressed before they can be implemented in actual clinical practice. (1) While the predictive value of each emerging biomarker has been reported, the best option for clinical application remains unclear, emphasizing the need for a systematic comparison of the risk-predictive efficacy of these 13 biomarkers alongside ongoing development of new ones [8–12]. (2) Previous studies indicated that single metabolic health-related markers often demonstrate limited predictive capacity via the receiver operating characteristic (ROC) curves, with area under the curve (AUC) values generally below 0.7 [11, 13–18]. This highlights the need to integrate multiple predictors into a comprehensive nomogram, providing a more optimized risk assessment tool for improving predictive performance.

This study aimed to systematically compare the predictive efficacy of these metabolic health-related biomarkers in prediabetic patients with CVD risk and develop a nomogram integrating key predictors to improve predictive performance. We believed that these efforts would provide a more optimized tool for early identification and prevention of high-risk CVD in individuals with prediabetes.

Methods

Study design and participants

The National Health and Nutrition Examination Survey (NHANES) is a continuous, cross-sectional research initiative conducted biennially by the National Center for Health Statistics. This survey aims to evaluate the health and nutritional status of U.S. residents through comprehensive data collection methods, including interviews, physical examinations, clinical and laboratory tests, and other measurement procedures. The data gathered are publicly available and can be accessed through the NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm). In this study, cross-sectional data of 116,876 participants from the NHANES (1999–2020) were initially included. The exclusion criteria were set as follows: (1) aged ≤ 18 years or probably have type 1 diabetes (defined as participants < 20 years of age receiving insulin therapy only) ($n = 50308$); (2) with incomplete data,

abnormal values [mean ± 3 times standard deviation (SD)], as well as known cases of malignancy, renal failure, or any liver-related diseases, including potential liver disease (aspartate/alanine aminotransferase ≥ 120 U/L) or renal insufficiency [serum creatinine (SCr) ≥ 133μmol/L] ($n = 49348$); (3) diagnosed with normal blood glucose levels/diabetes or lack of self-reported history of CVD/prediabetes ($n = 9743$). After manual data filtration, we ultimately selected a total of 7477 participants, and randomly divided them into development ($n = 5233$) and validation ($n = 2244$) cohorts in a ratio of 7:3. The flowchart of participant selection is shown in Fig. 1.

Diagnostic criteria for diabetes/prediabetes and CVD

According to the American Diabetes Association's diabetes diagnostic criteria [19], diabetes was defined as having any of the following conditions: (a) hemoglobin A1c (HbA1c) concentration ≥ 6.5% or fasting plasma glucose (FPG) level ≥ 126 mg/dL; (b) physician-diagnosed diabetes or use of insulin/antidiabetic medications to control blood glucose. Prediabetes status was defined as having any of the following: (a) HbA1c concentration between 5.7% and 6.4% or FPG level between 100 mg/dl and 125 mg/dL; (b) physician-diagnosed prediabetes, impaired fasting glucose, impaired glucose tolerance, borderline diabetes, or elevated blood glucose levels not reaching the diabetes threshold.

The presence of CVD was defined as a self-reported diagnosis of one or more of the following: stroke, congestive heart failure, angina pectoris, coronary heart disease, or myocardial infarction. The diagnostic process for CVD involved gathering self-reported information through standardized medical questionnaires during personal interviews. Physicians utilized this information for diagnostic confirmation. During the interview, participants were queried by medical professionals about prior diagnoses of specific CVD. These questions were recorded in the family questionnaire as MCQ160B-F. Affirmative responses to these inquiries were used to thoroughly evaluate an individual's CVD history.

Variables

Demographic, physical examination, questionnaire data, and laboratory blood tests of participants were collected in this study. (1) Demographic data included age, gender, education level, race, and marital status. Education levels were classified as less than high school, high school or equivalent, and college or above. Race was divided into four sections: non-Hispanic White, non-Hispanic Black, Mexican American, and Other. (2) Physical examination included BMI, height, WC, systolic blood pressure (SBP), and diastolic blood pressure (DBP). BMI was calculated as weight in kilograms divided by height in meters squared. SBP and DBP are calculated as the average of four measurements. (3) Questionnaire data included smoking status, alcohol consumption, physical activity, hypertension, and CVD. Smoking status was defined as never smoker, former smoker, and current

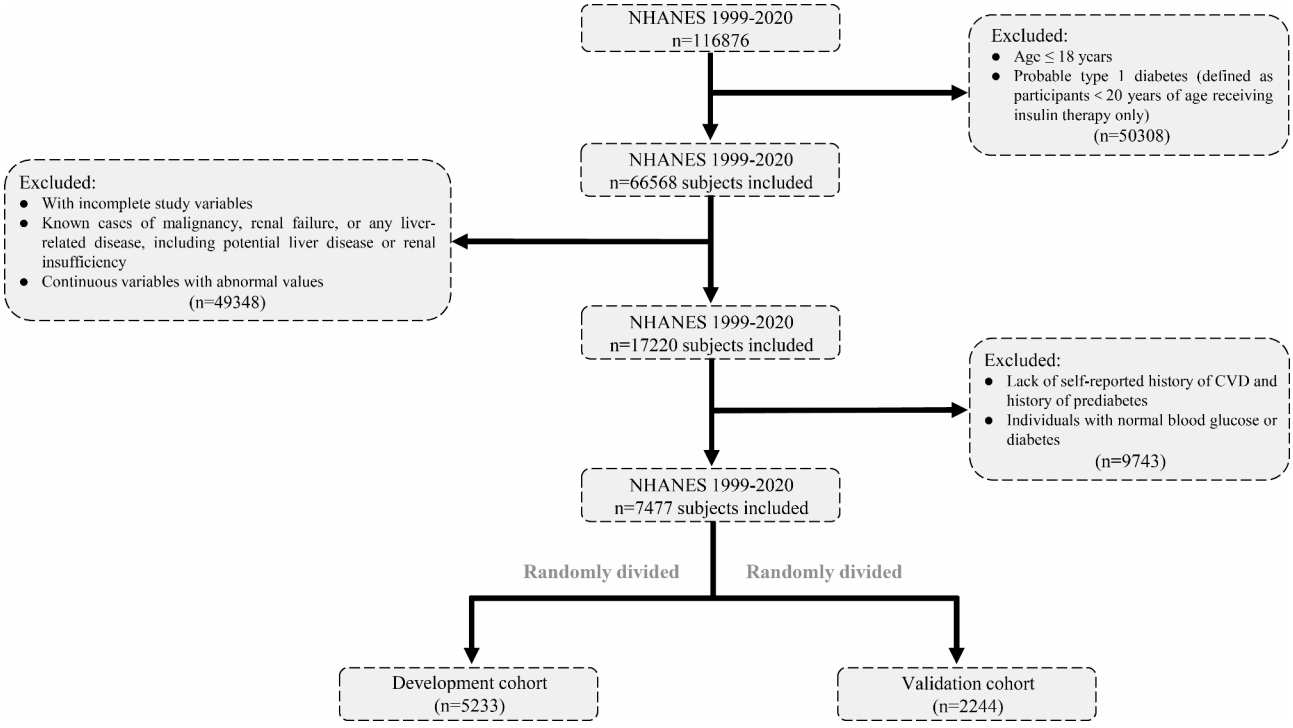

Fig. 1 Flow chart for participants recruitment from NHANES 1999–2020 in this study

smoker. Alcohol consumption was defined as having at least 12 alcoholic drinks in the past year [20]. The definition of hypertension was either a self-reported diagnosis or determined based on multiple measurements, with an average SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. (4) Laboratory results included triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), HbA1c, fasting insulin (FINS), serum uric acid (Serum UA), SCr, blood urea nitrogen (BUN), neutrophil, lymphocyte, and platelet were collected. Based on the aforementioned single indicators, we further calculated a series of new metabolic health-related indicators using the formulas provided in Table S1.

Statistical analysis

Through obtaining NHANES-generated data representative of the U.S. noninstitutionalized civilian population, 116,876 participants were randomly divided into development and validation sets in a ratio of 7:3. The Kolmogorov-Smirnov test, t-test, Kruskal-Wallis H test, and chi-square test were used to analyze the comparability between the two datasets. The quantitative data were expressed as median value and interquartile range (IQR), and categorical variables were expressed as counts and percentages. Subsequently, the AUCs of the 13 metabolic health-related indicators were determined from the development cohort using ROC curves. The highest Youden index was used to obtain the best cut-off value for clinical application. Next, the optimal predictors were identified from the development cohort via least absolute shrinkage and selection operator (LASSO) regression. After considering the results of LASSO and univariate logistic regression comprehensively, we included statistically significant variables in multivariate logistic regression for analysis. Finally, the independent risk factors identified by multivariate logistic regression were selected to further construct nomograms. In the model validation phase, this study implemented internal and external validation of the nomograms established based on the development cohort. Internal validation was performed using the bootstrap resampling technique, in which regression models were fitted in 500 repeated samplings, drawn with replacement from the development sample. External validation evaluated the nomograms through using a separate validation cohort. We used three methods to assess the proposed nomogram. First, ROC curve was used to evaluate the discrimination of the nomogram. Second, a calibration curve was used to validate how well the nomogram was calibrated. Third, decision curve analysis (DCA) was used to assess the clinical validity and net benefit of the nomogram. We performed restricted cubic spline (RCS) analysis to identify potential nonlinear relationships between the metabolic health-related biomarkers used in the nomogram and CVD risk. All statistical analyses were done in R software (Version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria), and $P < 0.05$ was regarded as significant.

Results

Descriptive statistics of study participants

This study enrolled 7477 individuals with prediabetes who participated in the NHANES 1999–2020, with an average age of 58.0 (IQR 46.0, 68.0) years. Among them, 4234 (56.6%) participants were male, and 3243 (43.4%) participants were female, as well as the prevalence of CVD was 18.9%. The baseline characteristics of these patients were shown in Table 1. Subsequently, all patients with prediabetes were randomly assigned to the development cohort ($n = 5233$) and validation cohort ($n = 2244$) in a ratio of 7:3. Of note, the clinical variables involved in this study did not show any statistically significant differences between the development and validation cohorts, indicating that our grouping was successful ($P > 0.05$ for all).

Comparison of predictive efficacy by ROC curves

This study compared the predictive efficacy of 13 metabolic health-related indices on the CVD risk in patients with prediabetes by plotting ROC curves in the development cohort (Fig. 2). The results of ROC curves showed that the AUCs for uACR, TyG-WHtR, ABSI, AIP, TG/HDL-C, TyG, TyG-WC, TyG-BMI, SHR, HOMA-IR, METS-IR, SII, and NLR were 0.577, 0.672, 0.582, 0.657, 0.657, 0.694, 0.678, 0.612, 0.553, 0.615, 0.611, 0.526, and 0.574, respectively. After thoroughly assessing the AUC, sensitivity, specificity, predictive values (both positive and negative), and overall accuracy of 13 composite indicators, TyG emerged as the most effective predictor of CVD risk, with an AUC of 0.694 (95 CI%: 0.674–0.715, $P < 0.001$). It is important to note that this study found the 13 widely reported metabolic health-related indicators to have low predictive value for CVD risk. Even TyG, which performed relatively well, failed to achieve an AUC above 0.70. Detailed results of ROC curves for 13 widely reported metabolic health-related indicators were provided in Table S2.

Screening results of variables of the Prediction models

We incorporated 39 indicators from the development cohort into a LASSO regression model to identify potential predictors of CVD risk in patients with prediabetes (Fig. 3). In this study, based on the non-zero coefficients of the LASSO regression (λ-1se = 0.023), the following 11 variables were identified as potential predictors of CVD risk in patients with prediabetes: age, hypertension, TyG,

Table 1 Baseline characteristics of patients with prediabetes in the development cohort and validation cohort

Variables	All cohort ($n=7477$)	Development cohort ($n=5233$)	Validation Cohort ($n=2244$)	*P*
Demographics data				
Age (years)	58.0 (46.0, 68.0)	58.0 (46.0, 68.0)	59.0 (46.0, 68.0)	0.227
Male, n (%)	4234 (56.6)	2964 (56.6)	1270 (56.6)	0.971
Education level, n (%)				0.155
Less than high school	2342 (31.3)	1667 (31.9)	675 (30.1)	
High school or equivalent	1814 (24.3)	1241 (23.7)	573 (25.5)	
College or above	3321 (44.4)	2325 (44.4)	996 (44.4)	
Race, n (%)				0.210
Non-Hispanic White	2966 (39.7)	2045 (39.1)	921 (41.1)	
Non-Hispanic Black	1604 (21.5)	1124 (21.5)	480 (21.4)	
Mexican-American	1519 (20.3)	1094 (20.9)	425 (18.9)	
Other Race	1388 (18.5)	970 (18.5)	418 (18.6)	
Current married, n (%)	4435 (59.3)	3091 (59.1)	1344 (59.9)	0.505
Examination data				
BMI (kg/m^2)	28.7 (25.6, 32.7)	28.7 (25.6, 32.7)	28.7 (25.6, 32.7)	0.572
Height (cm)	167.4 (160.0, 174.9)	167.4 (159.9, 174.9)	167.3 (160.2, 175.1)	0.564
WC (cm)	100.4 (92.4, 110.0)	100.3 (92.3, 110.0)	100.6 (92.6, 109.7)	0.499
SBP (mmHg)	127.8 (117.0, 140.0)	127.2 (117.0, 140.0)	128.0 (117.0, 140.0)	0.565
DBP (mmHg)	72.6 (66.0, 80.0)	73.0 (66.0, 80.0)	72.0 (66.0, 79.3)	0.356
Laboratory data				
TG (mmol/L)	1.54 (1.16, 1.98)	1.54 (1.16, 1.98)	1.54 (1.16, 1.99)	0.927
HDL-C (mmol/L)	1.27 (1.06, 1.54)	1.27 (1.06, 1.55)	1.27 (1.06, 1.53)	0.545
LDL-C (mmol/L)	3.03 (2.43, 3.65)	3.04 (2.43, 3.65)	3.01 (2.41, 3.60)	0.264
FBG (mmol/L)	6.00 (5.67, 6.72)	6.00 (5.68, 6.72)	6.00 (5.66, 6.72)	0.797
HbA1c (%)	5.8 (5.5, 6.2)	5.8 (5.5, 6.2)	5.8 (5.5, 6.2)	0.402
FINS (μU/mL)	11.51 (7.46, 18.27)	11.49 (7.41, 18.34)	11.55 (7.55, 18.06)	0.918
Serum UA (μmol/L)	333.1 (279.6-392.6)	333.1 (285.5-392.6)	333.1 (279.6-392.6)	0.935
SCr (μmol/L)	76.91 (63.65, 88.40)	76.91 (62.76, 88.40)	76.91 (63.65, 88.40)	0.945
BUN (mmol/L)	5.00 (3.93, 6.07)	5.00 (3.93, 6.07)	5.00 (3.93, 6.07)	0.558
Neutrophil ($\times10^9$/L)	3.80 (3.00, 4.80)	3.80 (3.00, 4.80)	3.80 (2.98, 4.80)	0.597
Lymphocyte ($\times10^9$/L)	2.00 (1.60, 2.40)	2.00 (1.60, 2.40)	1.90 (1.60, 2.40)	0.322
Platelet ($\times10^9$/L)	241.0 (203.0, 287.0)	241.0 (203.0, 287.0)	241.0 (203.0, 286.3)	0.954
Questionnaire data				
Smoking status, n (%)				0.550
Never	3836 (51.3)	2698 (51.6)	1138 (50.7)	
Former	2167 (29.0)	1497 (28.6)	670 (29.9)	
Current	1474 (19.7)	1038 (19.8)	436 (19.4)	
Alcohol consumption, n (%)	4743 (63.4)	3317 (63.4)	1426 (63.6)	0.895
Physical activity, n (%)	2355 (31.5)	1645 (31.4)	710 (31.6)	0.861
Hypertension, n (%)	3287 (44.0)	2311 (44.2)	976 (43.5)	0.594
CVD, n (%)	1415 (18.9)	1008 (19.3)	407 (18.1)	0.255
Composite indicators				
TyG	7.35 (7.04, 7.69)	7.35 (7.04, 7.69)	7.35 (7.04, 7.69)	0.786
TyG-BMI	213.66 (186.09, 246.26)	213.34 (185.69, 246.26)	214.38 (187.02, 246.27)	0.644
TyG-WC	744.82 (669.16, 833.24)	743.51 (668.56, 833.92)	747.71 (669.95, 832.68)	0.637
TyG-WHtR	4.46 (4.00, 4.99)	4.46 (3.99, 4.98)	4.46 (4.01, 5.00)	0.796
TG/HDL-C	1.16 (0.82, 1.78)	1.16 (0.82, 1.79)	1.16 (0.82, 1.77)	0.892
AIP	0.07 (-0.09, 0.25)	0.07 (-0.09, 0.25)	0.06 (-0.09, 0.25)	0.892
uACR (mg/g)	7.04 (4.43, 13.33)	7.09 (4.41, 13.73)	6.96 (4.47, 12.52)	0.385
SHR	0.94 (0.85, 1.03)	0.94 (0.85, 1.03)	0.94 (0.84, 1.03)	0.220
ABSI	0.08 (0.08, 0.09)	0.08 (0.08, 0.09)	0.08 (0.08, 0.09)	0.697
HOMA-IR	3.25 (2.02, 5.43)	3.26 (2.01, 5.46)	3.22 (2.03, 5.30)	0.917

Table 1 (continued)

Variables	All cohort (*n* = 7477)	Development cohort (*n* = 5233)	Validation Cohort (*n* = 2244)	*P*
METS-IR	51.78 (44.09, 60.79)	51.73 (44.10, 60.68)	51.82 (44.09, 61.10)	0.954
NLR	1.92 (1.46, 2.58)	1.91 (1.45, 2.57)	1.94 (1.46, 2.60)	0.216
SII	461.68 (332.82, 648.58)	459.19 (333.00, 647.06)	467.60 (332.25, 654.79)	0.356

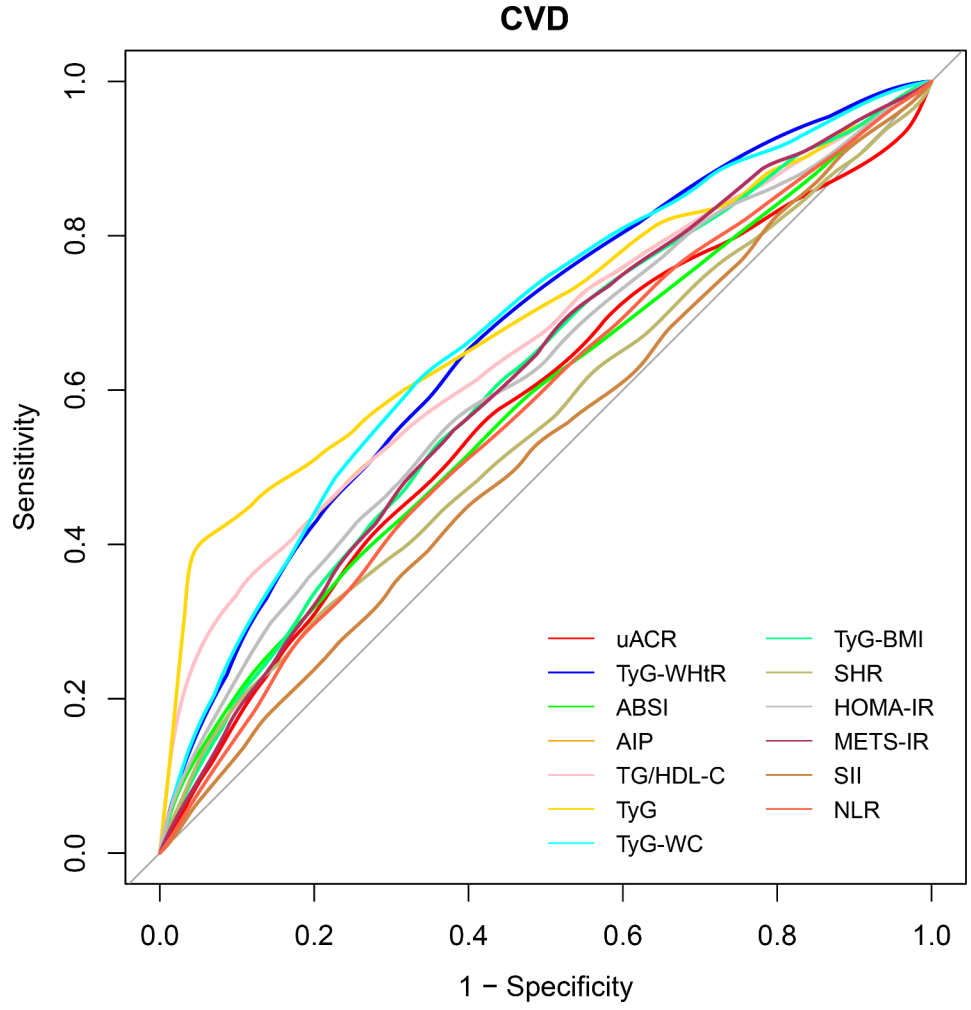

Fig. 2 ROC curves were used to compare the ability of 13 metabolic health-related indicators to predict CVD risk in patients with prediabetes

METS-IR, TyG-WC, TG/HDL-C, uACR, AIP, SHR, gender and NLR.

A total of 11 indicators were selected through LASSO regression recommended for inclusion in the multifactorial regression, followed by the execution of univariate logistic regression analysis to screen the 39 indicators again. After considering the results of LASSO and univariate logistic regression comprehensively, 15 predictors were selected to be included in the multivariate regression, and the results were shown in Table 2. Finally, 9 predictors were screened as independent risk factors for comorbid CVD in patients with prediabetes, including gender ($P = 0.001$), hypertension ($P < 0.001$), age ($P < 0.001$), TyG ($P < 0.001$), TyG-BMI ($P = 0.025$), SHR ($P < 0.001$), METS-IR ($P = 0.013$), SII ($P = 0.029$), and NLR ($P < 0.001$).

Construction, validation, and performance evaluation of nomograms

To avoid overcomplicating the model and compromising the interpretability of the nomogram, this study focused on selecting the most meaningful and explanatory variables for constructing a nomogram. To obtain a streamlined prediction model prediction model, age, gender, hypertension, and the three most significant predictors (TyG, SHR, NLR) were selected to

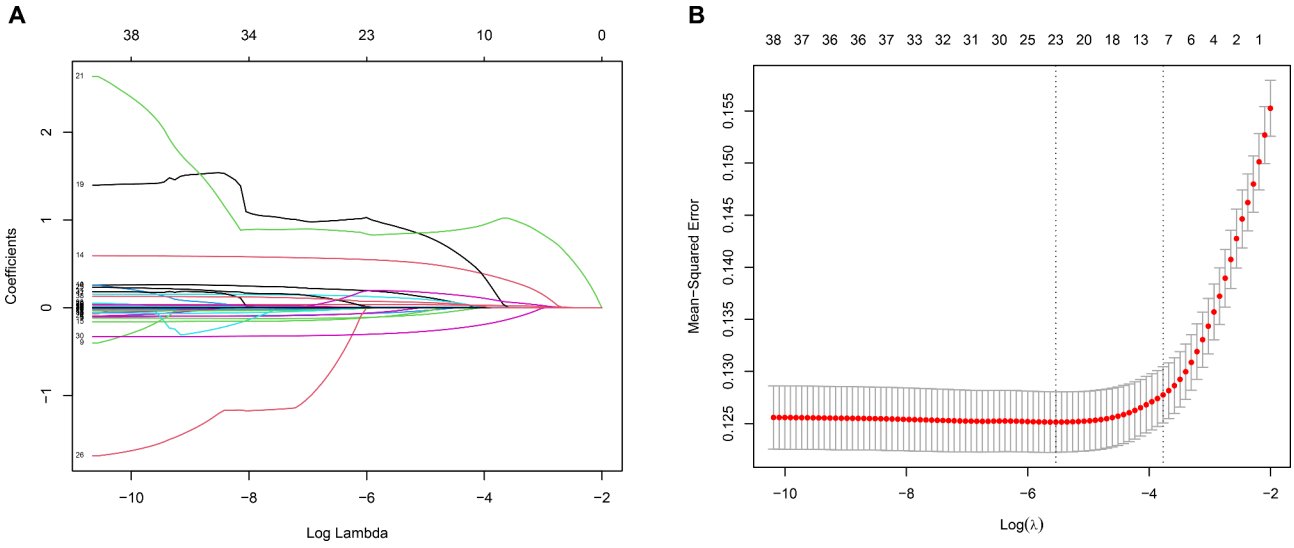

Fig. 3 (A-B) Texture feature selection via the LASSO regression model for predicting CVD

Table 2 Variables that showed statistical significance by multiple regression analysis in the development cohort

Variables	OR	95% CI	*P*
Age	1.040	1.032–1.047	**<0.001**
Gener			**0.001**
Female	1.000	Reference	
Male	1.448	1.156–1.816	
Hypertension			**<0.001**
No	1.000	Reference	
Yes	1.955	1.659–2.306	
TyG	5.160	3.778–7.061	**<0.001**
TyG-BMI	0.994	0.988–0.999	**0.025**
TyG-WC	1.001	0.999–1.004	0.307
TyG-WHtR	1.108	0.732–1.677	0.627
TG/HDL-C	0.990	0.944–1.051	0.712
AIP	0.721	0.378–1.363	0.317
uACR	1.002	0.998–1.007	0.330
SHR	0.349	0.198–0.613	**<0.001**
HOMA-IR	1.003	0.994–1.013	0.510
METS-IR	1.017	1.003–1.030	**0.013**
NLR	1.259	1.112–1.427	**<0.001**
SII	1.000	0.999-1.000	**0.029**

develop the nomogram (Fig. 4A). Additionally, this model can be accessed online at https://evo3.shinyapps.io/99cvdapp/, where other researchers can replicate the analysis and validate the performance of this model (Fig. 4B). The prediction formula for the model is Logit (p) = -16.255 + 0.455 * Gender + 0.042 * Age + 1.619 * TyG + 0.116 * NLR + 0.706 * Hypertension − 0.827 * SHR. As an example, given a female aged 76 years, with no history of hypertension, TyG of 7.37, NLR of 2.5, and SHR of 1.08, the result showed that this female had a 21.77% probability for CVD (Fig. 4B). We further determined the optimal cut-off value of the nomogram. At the maximum Youden index, the optimal cut-off value in the training set was 14.8%. This means that patients with a predicted value ≥ 14.8% were classified as high-risk, while patients with a predicted value < 14.8% were classified as low-risk. Furthermore, the coefficients of the variables included in the logistic regression, as well as the regression fitted value and residual plot were shown in Fig. 4C and D.

We then validated the constructed nomograms both internally using the bootstrap resampling technique and externally with a separate validation cohort. The results of ROC curves, calibration curves, and DCA plots confirmed that the risk nomograms constructed in this study performed well. ROC curves showed that the AUCs of the CVD risk nomogram were 0.803 (Fig. 5A), 0.834 (Fig. 5B), and 0.818 (Fig. 5C) for the development cohort, internal validation, and external validation. As shown in Fig. 5D-F, the C-index of the CVD risk nomogram was 0.803 (95% CI: 0.789–0.817, Fig. 5D) in the development cohort, and it demonstrated similar performance in internal validation at 0.834 (95% CI: 0.833–0.836; Fig. 5E) and in external validation at 0.818 (95% CI: 0.796–0.839; Fig. 5F). In the development cohort and both internal and external validation, the calibration curves closely aligned with the 45° ideal line, indicating strong agreement between predicted and observed values and demonstrating good calibration of the nomogram. Moreover, DCA conducted in the development cohort, as well as in internal and external validation, confirmed that the nomogram demonstrates a superior net benefit across various clinically relevant threshold probabilities, thus supporting its generalizability and applicability.

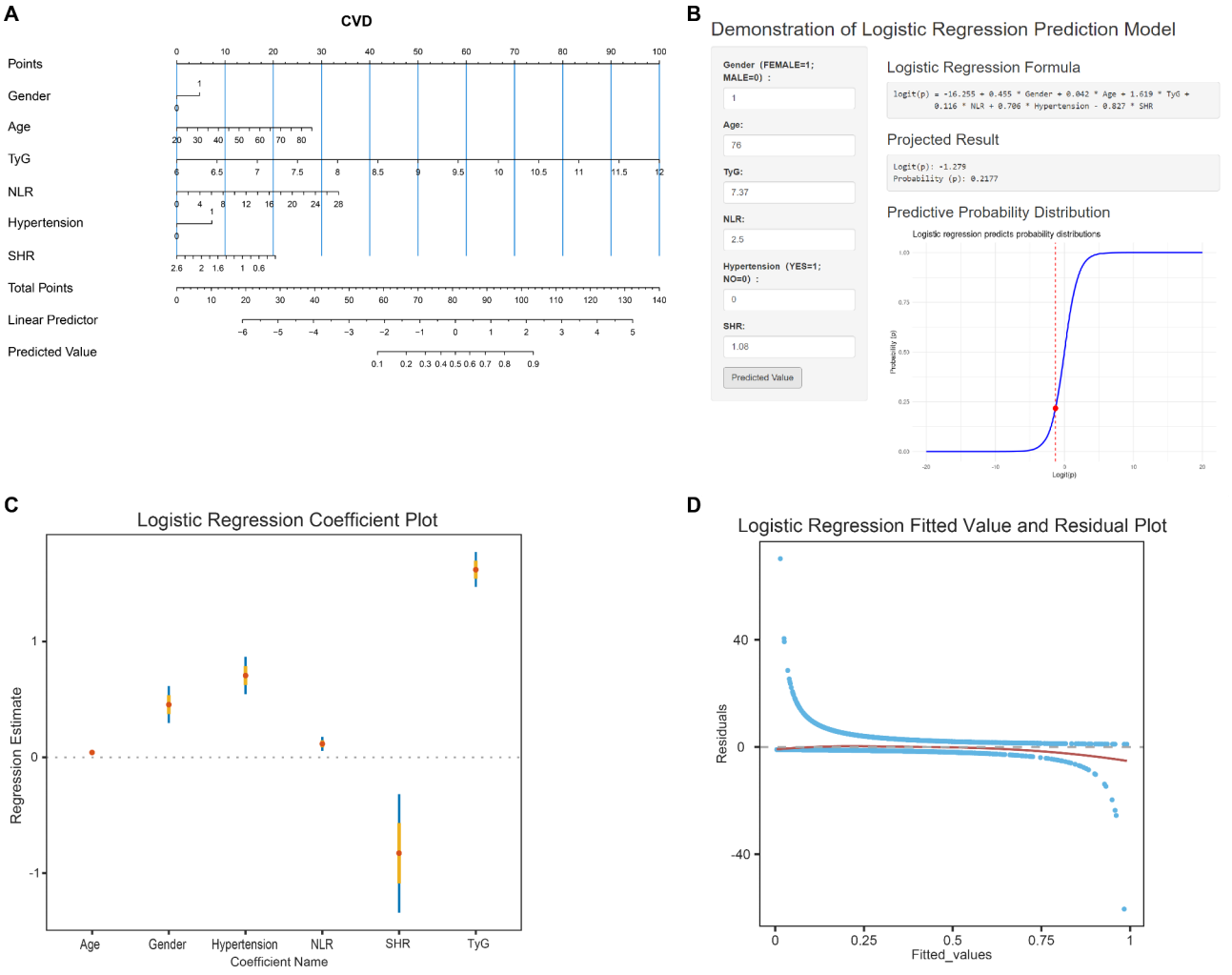

Fig. 4 (**A**) A nomogram was constructed in the development cohort to predict the risk of CVD in patients with prediabetes. (**B**) An online dynamic nomogram was accessible at https://evo3.shinyapps.io/99cvdapp/. (**C-D**) The coefficients of the variables included in the logistic regression, as well as the regression fitted value and residual plot

Detection of nonlinear relationships by restricted cubic spline curves

We performed RCS analysis to identify potential nonlinear relationships between the metabolic health-related biomarkers used in the nomogram and CVD risk (after adjusting for covariates). The results of the RCS analysis showed that there was a nonlinear relationship between the risk of concurrent CVD in patients with prediabetes and TyG (*P* for nonlinearity<0.001, Fig. 6B) and SHR (*P* for nonlinearity = 0.001, Fig. 6C), respectively. Furthermore, RCS analysis showed that the age (*P* for nonlinearity = 0.563, Fig. 6A) and NLR (*P* for nonlinearity = 0.232, Fig. 6D) were positively linearly correlated with the CVD risk in patients with prediabetes.

Discussion

In this study, we systematically evaluated 13 metabolic health-related biomarkers to identify the most effective predictors of CVD risk in individuals with prediabetes. The TyG emerged as the most effective metabolic health-related biomarker for predicting CVD risk, demonstrating higher predictive accuracy compared to other indices. Using independent risk predictors further identified through multivariate logistic regression, the CVD risk nomogram (including gender, hypertension, age, TyG, NLR, and SHR) was developed and validated. The predictive performance of the nomogram was evaluated using the AUC values, calibration curves, and DCA, confirming its validity. Compared to individual metabolic health-related biomarkers, the constructed nomogram demonstrated superior performance and clinical utility.

Our overall findings in the present study were in line with the previous literature. The TyG, which incorporates

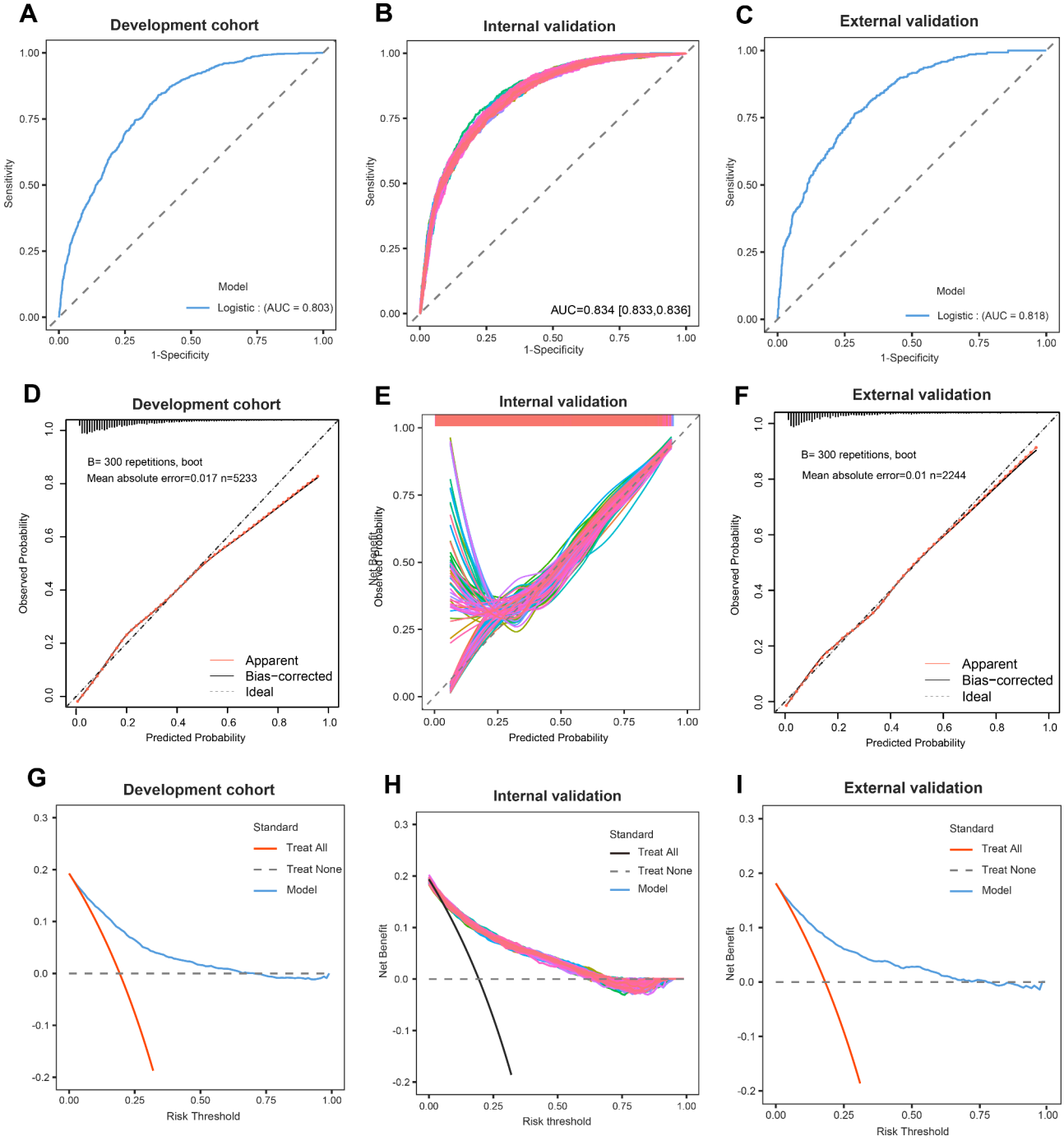

Fig. 5 Visualize the performance of the CVD risk nomogram through ROC curves, calibration curves, and DCA plots. The ROC curves and AUCs of the CVD risk nomogram in the development cohort (**A**), internal validation (**B**), and external validation (**C**). The calibration curves of the CVD risk nomogram in the development cohort (**D**), internal validation (**E**), and external validation (**F**). The DCA plots of the CVD risk nomogram in the development cohort (**G**), internal validation (**H**), and external validation (**I**)

two major metabolism biomarker subtypes, was considered to be a representative index of IR [21]. Several studies demonstrated that TyG exhibited the strongest diagnostic performance for predicting CVD risk in patients with prediabetes. For example, Dang et al. [22] demonstrated that the TyG strongly predicted coronary heart disease, with participants in the highest TyG quartile facing a two-fold increase in risk compared to those in the lowest quartile. Furthermore, the SHR and NLR also showed consistent associations with CVD risk. Cui et al. [11] found that SHR captured acute metabolic stress, serving as an early marker for cardiovascular

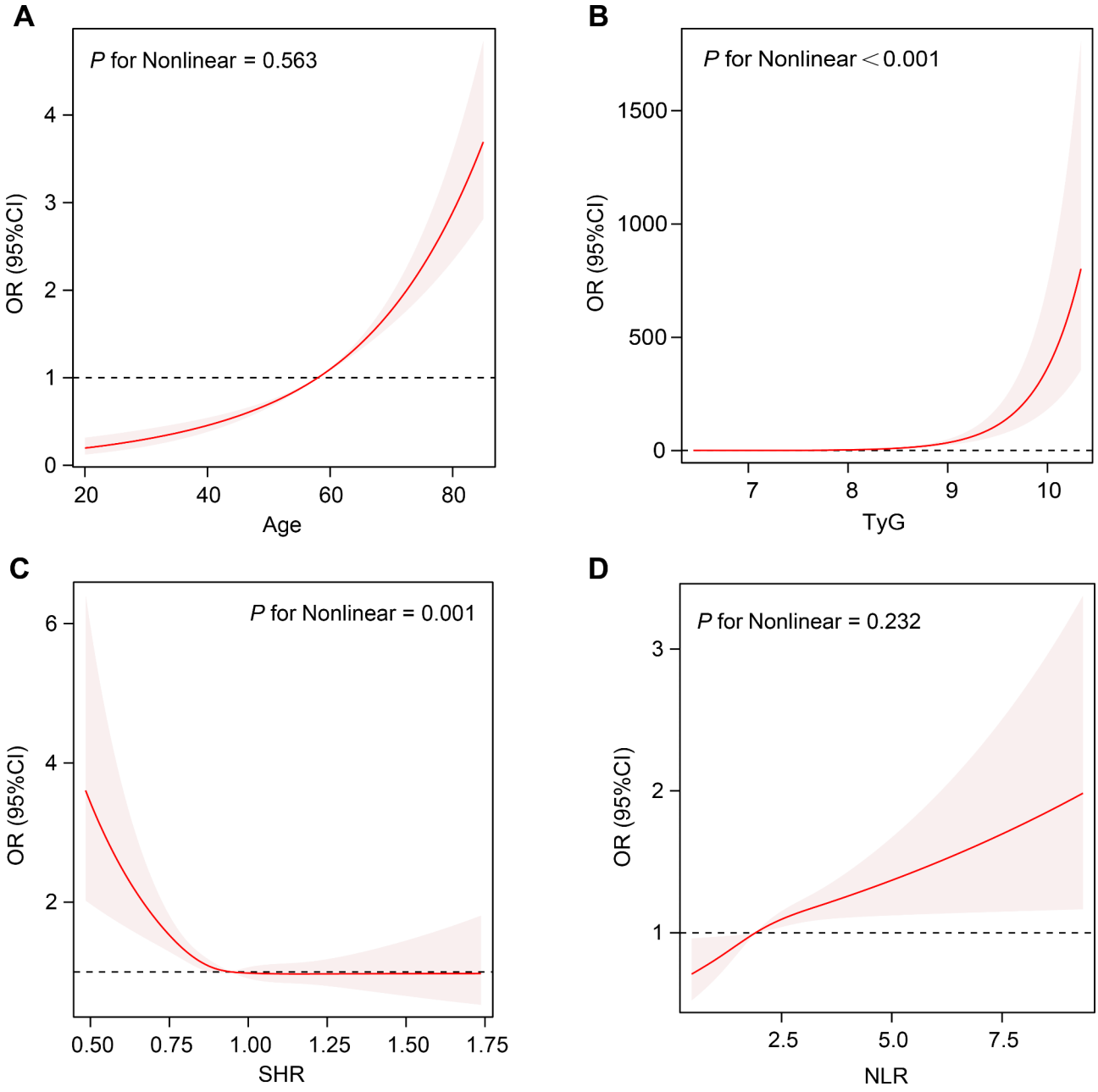

Fig. 6 Detection of nonlinear relationships by RCS analysis. (**A**-**D**). RCS analysis between the risk of concurrent CVD in patients with prediabetes and age (**A**), TyG (**B**), SHR (**C**), NLR (**D**). Odds ratios were subjected to covariate adjustment

complications. This aligned with Ding et al. [23], who demonstrated SHR's predictive value in patients with acute coronary syndromes. Similarly, NLR, a marker of systemic inflammation, is well-documented in its ability to predict cardiovascular mortality and adverse events in diverse patient cohorts [17, 24]. In summary, the integration of TyG, SHR, and NLR into our predictive nomogram reflected their established roles as key indicators of metabolic and inflammatory pathways contributing to CVD.

Compared with other approaches in previous research, our nomogram provided several key strengths. First, our model integrates traditional risk factors (age, sex, hypertension) with novel biomarkers (TyG, SHR, NLR), enhancing its capacity to capture the multifactorial nature of CVD risk in populations with prediabetes. This comprehensive integration addresses the limitations of single-predictor models, which often fail to account for the synergistic interactions between metabolic, inflammatory, and hemodynamic factors [25]. For instance, while TyG effectively predicts insulin resistance and

associated cardiovascular risks, combining it with inflammatory markers like NLR and acute stress indicators like SHR adds depth to the predictive model [26, 27]. Second, our nomogram's design facilitates its practical application in clinical settings. The incorporated predictive factors are easily measurable through routine laboratory tests, ensuring accessibility without the need for invasive procedures. We also established clinical cut-off value for the nomogram, enabling clinicians to identify high-risk patients in a more effective and timely manner in practical applications. Meanwhile, we developed an online platform to simplify the utilization of the nomogram, facilitating healthcare professionals in rapidly performing risk stratification and designing personalized intervention plans. In contrast, some earlier models relied on markers that were either expensive or not universally available, limiting their clinical utility [28, 29]. Third, the robustness of our nomogram has been demonstrated through comprehensive validation. Internal validation and external validation using metrics like ROC values, calibration curves, and DCA confirmed its superior performance compared to standalone predictors. Finally, our study specifically targets individuals with prediabetes, a population often overlooked in CVD risk research. Our study fills a gap in this field by developing a tailored nomogram for this specific population, providing a valuable tool for early risk identification and targeted preventive healthcare.

To the best of our knowledge, several equations have already been developed and applied for predicting CVD risk, and we aim to compare our model with these existing equations. The Framingham Risk Score (FRS) and Pooled Cohort Equations (PCE) have been widely used and advocated in guidelines for predicting the 10-year risk of CVD in the general population [30]. However, increasing evidence is emerging regarding the limitations of these equations. The FRS was derived from the Framingham Heart Study between the 1950s and 1970s, which led to a significant discrepancy between those data and the characteristics of contemporary populations. Furthermore, the FRS primarily relies on traditional cardiovascular risk factors and does not incorporate emerging metabolic risk factors, such as insulin resistance and other aspects of metabolic health [31, 32]. These limitations restrict its applicability to contemporary populations, particularly those with diabetes or related conditions [33]. Similarly, although PCE is an important tool for predicting the risk of atherosclerotic cardiovascular disease (ASCVD), it also has notable shortcomings. First, the limitations in racial classification of the PCE reduce its adaptability across different racial groups. Currently, to address the lack of specific categorization for Asian and Latino populations, the PCE tentatively groups these populations with White individuals. This generalization leads to less accurate predictions of CVD risk for these groups [34, 35]. Second, the PCE may overestimate or underestimate CVD risk in specific populations, as it was originally developed using data from the general population [31, 36]. Liang et al. [37] and Lim et al. [38] observed that the PCE underestimated CVD risk in diabetic populations, thereby hindering early identification of patients and the timely initiation of primary prevention strategies. Furthermore, prediabetes, as a high-risk stage of diabetes, is not adequately addressed by the PCE. Instead, individuals with prediabetes are grouped with those with normal blood glucose levels, which is detrimental to CVD prevention in this population. Third, the PCE focuses exclusively on ASCVD, overlooking other forms of CVD such as arrhythmias and peripheral arterial disease, thereby limiting its comprehensiveness in predicting the risk and prognosis of non-ASCVD conditions [39].

With the increasing multidimensional research on CVD, more scholars have recognized that traditional risk assessment models may not accurately capture the cardiovascular health status of all populations. To address biases and sensitivity issues in risk assessment, many new CVD prediction models targeting specific populations or diseases have been developed. For instance, SCORE2-Diabetes has been developed to enhance the identification of 10-year CVD risk in European patients with type 2 diabetes [40]. Similarly, Dong et al. [41] have developed and validated a 10-year CVD risk prediction model specifically for Chinese patients with diabetes. Additionally, Gragnano et al. developed the PRECISE-HBR score to address bleeding complications following percutaneous coronary intervention [42]. This score resolves inconsistencies in previous predictive models for identifying high-bleeding-risk PCI patients, aiding clinicians in predicting and preventing post-PCI bleeding. These models have enhanced the tools available for predicting CVD risk and prognosis, offering new perspectives for the development of CVD risk prediction models. Based on these findings, we are further convinced of the necessity to develop and validate new models to complement and enhance the predictive performance of existing tools like FRS and PCE, particularly for specific patient groups. To this end, we developed a novel model tailored for patients with prediabetes. This model does not have explicit racial stratification limitations, making it promising for risk assessment across diverse racial groups. Furthermore, unlike the PCE, which primarily focuses on ASCVD risk, our model predicts total CVD risk for patients with prediabetes, serving as a complementary tool to existing methods. However, it is important to emphasize that our intention was not to create a model to directly replace the widely validated models used in the general population. Instead, our goal was to develop a complementary tool to

enhance the performance of CVD risk prediction in prediabetic individuals. We recommend that clinicians use this new model in conjunction with existing models, as this approach can assist in designing more personalized and precise prevention strategies.

TyG, SHR, and NLR were well-established and have strong associations with CVD risk in patients with prediabetes through distinct but interconnected mechanisms. The TyG is a robust surrogate marker for IR, IR promotes endothelial dysfunction, dyslipidemia, and chronic inflammation, all of which accelerate plaque formation and vascular remodeling [43, 44]. Besides, the TyG integrates fasting glucose and triglyceride levels, capturing the metabolic stress that underpins hyperglycemia and hypertriglyceridemia [13]. This stress contributes to oxidative damage and inflammatory activation, directly linking TyG to heightened cardiovascular risk [45]. SHR quantifies the relationship between fasting plasma glucose and HbA1c, reflecting acute glycemic excursions relative to chronic glucose control [46]. Stress-induced hyperglycemia exacerbates oxidative stress, activates the renin-angiotensin-aldosterone system, promotes endothelial apoptosis, and impairs coronary flow reserve, increasing myocardial oxygen demand and contributing to vascular damage and myocardial injury [43, 47]. NLR serves as an indicator of systemic inflammation and immune dysregulation [48]. Neutrophils, the first responders in inflammation, release proteolytic enzymes and reactive oxygen species that exacerbate endothelial damage and plaque instability [49]. Conversely, lymphopenia reflects suppressed adaptive immunity, limiting the resolution of inflammation and enabling chronic low-grade inflammatory states [50]. This marker integrates inflammatory and immune responses, offering insights into the inflammatory burden of atherosclerosis [51]. Together, TyG, SHR, and NLR capture the multifactorial nature of CVD risk in individuals with prediabetes. TyG reflects chronic metabolic dysfunction and insulin resistance, SHR highlights acute metabolic disturbances during stress states, and NLR addresses the role of systemic inflammation in atherosclerosis progression. These mechanisms are not isolated but interlinked [24]. For instance, insulin resistance (indicated by TyG) exacerbates systemic inflammation (reflected by NLR) and enhances vulnerability to stress-induced hyperglycemia (captured by SHR), creating a vicious cycle that accelerates cardiovascular damage [52, 53].

Despite its strengths, this study has some limitations. Firstly, the cross-sectional dataset from NHANES did not allow a causal relationship to be determined. Prospective studies are required to establish temporal relationships. Secondly, this result is only applicable to the U.S. population, because our nomogram used the nationwide health and nutrition survey in America. It is widely accepted that there exist some differences in the pathophysiology of diabetes between Asians and Caucasians. Thus, necessitating broader population studies for comprehensive applicability. An appropriate CVD risk model in patients with prediabetes that reflects regional characteristics will be needed in each country, which will help to effectively prevent CVD in areas where there is an outbreak of diabetes. Thirdly, the lack of external validation using cohorts from different countries and ethnic groups limits the generalizability of the findings. Future studies should test the nomogram in diverse populations to confirm its applicability. Fourthly, the presence of CVD in this study was determined based on patient-reported medical history, without validation through objective diagnostic tests or physician-confirmed diagnoses, which may introduce recall bias or misclassification. For cases where the reported CVD history dates back many years, there may be limited relevance between the laboratory data collected during the survey and past CVD events. Future research should incorporate physician-confirmed diagnoses or objective diagnostic data to enhance the validity of the findings. Finally, the absence of gender-specific and age-specific stratified analyses may overlook subgroup-specific differences in CVD risk. In the future, expanding the sample size, incorporating additional risk factors, as well as conducting multicenter and larger prospective studies can enhance the reliability of this nomogram.

Conclusion

In conclusion, TyG was identified as the most effective metabolic health-related biomarker for predicting CVD risk in patients with prediabetes. A nomogram integrating age, gender, hypertension, TyG, NLR, and SHR significantly improved predictive performance, as confirmed in the development cohort and both internal and external validation. This nomogram provided a practical and accurate tool for CVD risk assessment in populations with prediabetes.

Abbreviations

ABSI	A body shape index
AIP	Atherogenic index of plasma
ASCVD	Atherosclerotic cardiovascular disease
AUC	Area under the curve
BUN	Blood urea nitrogen
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DCA	Decision curve analysis
FBG	Fasting blood glucose
FINS	Fasting insulin
FPG	Fasting plasma glucose
FRS	Framingham Risk Score
HbA1c	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic model assessment for insulin resistance
IQR	Interquartile range
LASSO	Least absolute shrinkage and selection operator
LDL-C	Low-density lipoprotein cholesterol
METS-IR	Metabolic score for insulin resistance

NHANES	National Health and Nutrition Examination Survey
NLR	Neutrophil-to-lymphocyte ratio
PCE	Pooled Cohort Equations
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
SBP	Systolic blood pressure
SCr	Serum creatinine
SD	Standard deviation
Serum UA	Serum uric acid
SHR	Stress hyperglycemia ratio
SII	Systemic immune-inflammation index
TG/HDL-C	Triglyceride to high-density lipoprotein cholesterol ratio
TG	Triglyceride
TyG-BMI	Triglyceride glucose-body mass index
TyG-WC	Triglyceride glucose-waist circumference
TyG-WHtR	Triglyceride glucose-waist height ratio
TyG	Triglyceride-glucose
uACR	Urinary albumin-to-creatinine ratio
WC	Waist circumference

Supplementary Information

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Supplementary Material 1

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Author contributions
Xiaodong Wang and Guanghao Su contributed equally to this work as co-corresponding authors. Erya Xiao and Ronghui Yu contributed equally to this work as co-first authors. Erya Xiao was responsible for the conception, preparation, and writing of the paper. Ronghui Yu and Erya Xiao tested the entire index for all samples and were responsible for the statistical analysis. Xiaodong Wang and Guanghao Su supervised the drafting of the manuscript and provided funding support. Erya Xiao, Ronghui Yu, Xinyuan Cai, and Cong Ma made critical revisions to the manuscript. Erya Xiao, Ronghui Yu, and Lang Jiang created all the charts and proofread the manuscript. Junhong Li, Cong Ma, Yuankang Liu, and Le Liu collected and checked all the references, and provided suggestions for important intellectual content. All authors read and approved the final version of the manuscript.

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Data availability
All data analyzed during this study are publicly available on the NHANES website at https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
The study was performed according to the guidelines of the *Helsinki Declaration*. The original protocol of the NHANES survey adhered to the STROBE statement and was approved by the Ethics Review Committee of the National Center for Health Statistics. All participants signed informed consent forms. The data is publicly available, therefore, the ethical approval statement and the requirement for informed consent were waived for this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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