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ORIGINAL RESEARCH

Association of Neutrophil/High-Density Lipoprotein Cholesterol Ratio with Metabolic Dysfunction-Associated Steatotic Liver Disease in Type 2 Diabetes Mellitus Patients: A Cross-Sectional Study and Predictive Model Construction

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Objective: The neutrophil/high-density lipoprotein cholesterol ratio (NHR) has been identified as a combined indicator of inflammatory cells and lipid metabolism. The objective of this study was to investigate the relationship between the NHR and metabolic dysfunction-associated steatotic liver disease (MASLD) in patients with type 2 diabetes mellitus (T2DM).

Methods: This cross-sectional study selected patients with T2DM who were admitted to the Department of Endocrinology at the First Hospital of Zhangjiakou City. Liver ultrasound was performed on all patients to determine the presence or absence of MASLD, and NHR values were calculated. The patients were grouped according to the median NHR, and a difference analysis was performed to compare the differences in clinical information between groups.Logistic regression was used to assess independent influences of MASLD, and subgroup analyses were performed. The final stage of this project involved construction of a novel predictive model for MASLD, derived from the screened influential factors, alongside an evaluation of its predictive value using the receiver operating characteristic.

Results: A total of 621 patients with T2DM were included in this study according to the inclusion and exclusion criteria. Logistic regression analyses showed a significant negative correlation between NHR and MASLD, and this correlation was particularly significant in men and in patients not using GLP-1A. In addition, restricted cubic spline curve (RCS) plots showed a nonlinear correlation between NHR and MASLD. The area under the curve (AUC) of the novel prediction model constructed on the basis of NHR reached 0.78 (95% CI 0.75–0.82), which can be used to predict the onset of MASLD, and is effective in clinical applications.

Conclusion: NHR is significantly correlated with MASLD, and NHR has the potential to be an early detection and intervention indicator for screening T2DM patients for MASLD.

Keywords: neutrophil/high-density lipoprotein cholesterol ratio, type 2 diabetes mellitus, metabolic dysfunction-associated steatotic liver disease

Introduction

The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) has increased dramatically over the past 30 years.[1] MASLD has grown almost in parallel with the prevalence of obesity and type 2 diabetes mellitus (T2DM), and is considered to be one of the most common causes of chronic liver disease in adults, with a current estimated global prevalence of 30%.[2–4] This rising prevalence has prompted recent studies suggesting that MASLD may soon become the most common indication for liver transplantation and one of the most prevalent causes of hepatocellular

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carcinoma.[5] Nonetheless, awareness of MASLD remains extremely limited, and the World Health Organization has formally acknowledged MASLD as an important non-communicable disease.

The liver is one of the main organs involved in the regulation of metabolic balance within the body. Evidence suggests obesity, T2DM, and insulin resistance may be manifestations of a metabolic disorder. Recent research indicates that T2DM may be an independent risk factor for MASLD, and that the resolution of hepatic steatosis may impede the development of T2DM.[6,7] Inflammation and disorders of lipid metabolism have been identified as significant risk factors for the progression to MASLD. The accumulation of lipids in the liver results in early liver injury, followed by the recruitment of neutrophils by pro-inflammatory factors secreted by hepatic macrophages. This process further exacerbates liver injury and contributes to the development of MASLD. The ability of high-density lipoprotein cholesterol (HDL-C) to reverse cholesterol transport and its potential anti-inflammatory effects are noteworthy. In recent years, a number of novel hypoglycaemic agents have demonstrated effective therapeutic effects on MASLD. A large number of studies have demonstrated the effective effects of glucagon-like peptide-1 agonists (GLP-1A) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) on MASLD in clinical and animal models, in which the improvement of lipid metabolism is an important mechanism for their action.[8–11]

The neutrophil/high-density lipoprotein cholesterol ratio (NHR) has been identified as a combined indicator of inflammatory cells and lipid metabolism. Previous studies have demonstrated an association between NHR and various health outcomes, including cardiovascular disease, fractures, and metabolic diseases.[12–14] Moreover, NHR has been shown to have a strong correlation with MASLD, and NHR has been demonstrated to be a valid predictor of MASLD in a healthy physical examination population.[15,16] However, the correlation between NHR and MASLD in patients with T2DM remains unclear.

In this study, we explored the association between NHR and MASLD by collecting data from T2DM patients based on cross-sectional analyses, and constructing a new model for predicting MASLD through NHR. This provides new ideas for clinical diagnosis and treatment.

Methods

Study Participants

This was a cross-sectional study of patients with T2DM admitted to the Department of Endocrinology of the First Hospital of Zhangjiakou City from January 2023 to December 2024, which was a cross-sectional study. The study had the approval of the Ethics Committee of the First Hospital of Zhangjiakou to be conducted, and all patients signed an informed consent form (no. 2024100). The inclusion criteria comprised patients with T2DM who were at least 18 years of age and had complete basic information. The exclusion criteria encompassed 1) patients younger than 18 years of age; 2) non-T2DM patients; 3) patients with incomplete basic collateral clinical information; 4) patients who had not undergone liver ultrasonography or whose diagnosis of MASLD was unclear; 5) patients with other definite causes of liver injury; and 6) patients with pronounced dyslipidemia and /or a family history of dyslipidemia. The final total of T2DM patients analysed was 621, following the application of the inclusion and exclusion criteria (Figure 1).

Information Collection

All patients admitted to the hospital were provided with basic information and a preliminary physical examination by a specialist nurse. The basic information comprised details such as age, sex, smoking and drinking history, and medical histories including hypertension and coronary heart disease. The physical examination included the measurement of height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP) (yuwell sphygmomanometer, YE670AR), and the assessment of drug usage, specifically metformin, glucagon-like peptide-1 agonists (GLP-1A), sodium-glucose cotransporter 2 inhibitors (SGLT2i), dipeptidyl peptidase-4 inhibitors (DPP4i), and insulin. Venous blood was collected from all patients on the second day of admission for analysis. The following parameters were measured: haemoglobin A1c (HbA1c), fasting blood glucose (FBG), aspartate transaminase (AST), alanine transaminase (ALT), white blood cells (WBC), red blood cells (RBC), platelets (PLT), blood urea nitrogen (BUN), Serum creatinine (Scr), uric acid (UA), total cholesterol (TC), triglycerides (TG), HDL-C and low-density lipoprotein cholesterol (LDL-C) (BeckmanCoulter AU5800 Automated Biochemistry Analyzer).

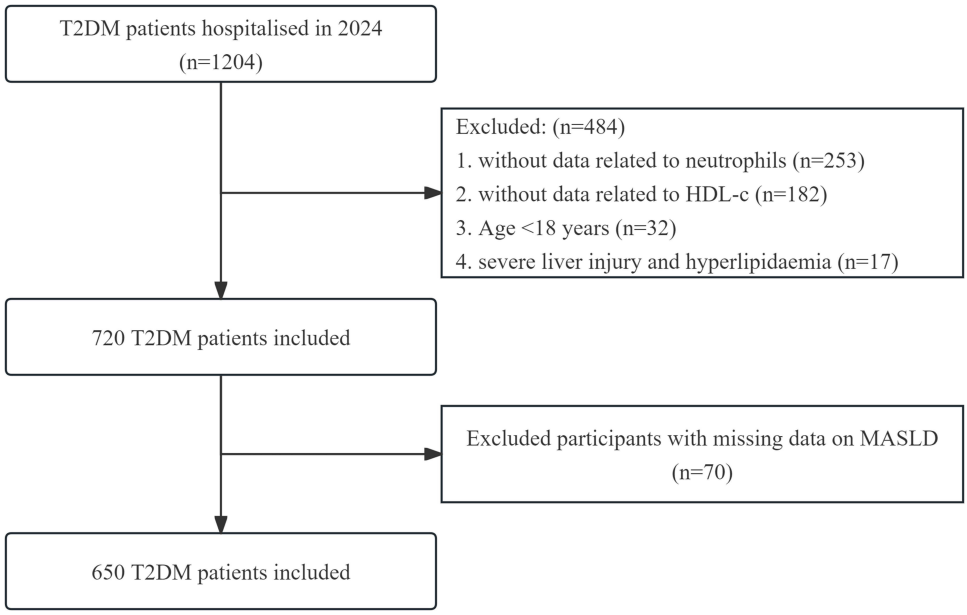

Figure 1 Flowchart of participants enrollment.

Indicators Calculation

The body mass index (BMI) is calculated using the following formula: BMI=weight (kg)/height (m^2). NHR = Neutrophils ($\times 10^9$)/HDL-C (mmol/L). Homeostatic model assessment of insulin resistance (HOMA-IR) = FBG (mmol/L)× fasting insulin (μU/mL)/22.5.

Definition of MASLD

The specific diagnostic criteria for a positive diagnosis of MASLD based on histological (biopsy), imaging or blood biomarker evidence of fat accumulation in the liver were based on previous literature.[17]

Statistical Analysis

All data analysis and data visualisation in this study was conducted utilising the R language R 4.2 software. For missing data mean interpolation was used in the statistics. The Shapiro–Wilk test indicated that the continuous variables were normally distributed. In the context of normally distributed continuous variables, characterised by mean and standard deviation, the *t*-test was employed for the analysis of differences. Conversely, for non-normally distributed variables, characterised by median (interquartile spacing), the *U*-test was utilised for the purpose of analysis. Categorical variables are presented as proportions, and analysis of variance uses the chi-square test. For correlations between variables, univariate and multivariate logistic regression were used, taking into account various confounding factors.Subgroup analyses were also performed and finally presented as forest plots. To further explore the non-linear correlation between variables, restricted cubic spline (RCS) plots were used. Constructive predictive models based on variables screened by logistic regression were presented as column line plots. The diagnostic values between multiple variables were compared by receiver operating characteristic (ROC) curves, and finally, decision and calibration curves were used to assess the value and reliability of the new model for clinical application. Statistically significant differences were considered to be those with a P-value less than 0.05.

Results

Comparison of Clinical Characteristics of High and Low NHR in T2DM Patients

The present study comprised a total of 621 patients diagnosed with T2DM. The mean age of the subjects was 57.49 years (± 12.32), of whom 414 (66.67%) were male.The prevalence of MASLD was 49.44%. The baseline characteristics of the study population, grouped according to NHR quartiles, are displayed in Table 1. The study revealed statistically

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Table 1 Baseline Characteristics of Study Participants (Grouped According to NHR Quartile)

Variables	Total (n = 621)	NHR (Q1, n = 155)	NHR (Q2, n = 155)	NHR (Q3, n = 155)	NHR (Q4, n = 156)	P
Age (y)	57.49 ± 12.32	58.52 ± 9.43	59.69 ± 12.20	57.26 ± 12.61	54.53 ± 14.08	0.002
BMI (kg/m^2)	25.07 ± 3.51	24.56 ± 3.02	24.49 ± 3.42	25.28 ± 3.55	25.98 ± 3.82	<0.001
SBP (mmHg)	129.15 ± 18.14	128.50 ± 18.20	130.64 ± 18.20	128.37 ± 17.30	129.10 ± 18.91	0.676
DBP (mmHg)	78.10 ± 11.21	76.94 ± 10.96	78.12 ± 11.80	77.85 ± 11.11	79.51 ± 10.89	0.240
HbA1c (%)	9.09 ± 2.29	9.30 ± 2.17	9.07 ± 2.35	8.93 ± 2.40	9.05 ± 2.25	0.556
WBC (×10^9/L)	6.40 ± 1.76	4.96 ± 0.92	5.85 ± 1.03	6.70 ± 1.07	8.07 ± 2.02	<0.001
RBC (×10^{12}/L)	4.99 ± 7.50	4.50 ± 0.47	6.25 ± 14.94	4.55 ± 0.64	4.68 ± 0.69	0.118
PLT (×10^9/L)	192.03 ± 59.21	182.28 ± 47.87	185.21 ± 54.57	192.92 ± 54.76	207.60 ± 73.65	<0.001
ALT (U/L)	25.50 ± 17.51	24.35 ± 15.89	23.72 ± 17.33	25.92 ± 17.51	28.01 ± 19.03	0.135
AST (U/L)	22.34 ± 10.59	23.40 ± 11.43	21.32 ± 8.57	22.12 ± 11.67	22.54 ± 10.39	0.374
BUN (mmol/L)	6.74 ± 2.34	6.50 ± 1.73	6.51 ± 1.84	6.81 ± 2.40	7.15 ± 3.10	0.045
Scr (mmol/L)	67.79 ± 43.49	56.41 ± 17.06	60.32 ± 19.11	72.48 ± 41.40	81.94 ± 69.45	<0.001
UA (mmol/L)	334.14 ± 97.21	312.94 ± 92.43	321.23 ± 85.27	338.90 ± 97.15	363.48 ± 105.92	<0.001
TC (mmol/L)	4.65 ± 1.16	5.06 ± 1.21	4.78 ± 1.06	4.55 ± 1.15	4.20 ± 1.04	<0.001
TG (mmol/L)	2.13 ± 1.69	1.72 ± 1.36	2.00 ± 1.46	2.14 ± 1.62	2.65 ± 2.12	<0.001
HDL-C (mmol/L)	1.09 ± 0.27	1.32 ± 0.26	1.14 ± 0.22	1.03 ± 0.19	0.88 ± 0.18	<0.001
LDL-C (mmol/L)	2.83 ± 0.91	3.11 ± 1.04	2.91 ± 0.81	2.78 ± 0.89	2.51 ± 0.80	<0.001
FBG (mmol/L)	8.58 ± 3.90	8.68 ± 3.14	8.58 ± 3.57	8.21 ± 3.72	8.86 ± 4.93	0.508
HOMA-IR	6.75 ± 6.08	5.92 ± 5.55	5.90 ± 5.32	6.55 ± 5.88	8.62 ± 7.06	<0.001
Sex (Male), n(%)	414 (66.67)	87 (56.13)	89 (57.42)	116 (74.84)	122 (78.21)	<0.001
Smoking, n(%)	231 (37.20)	31 (20.00)	53 (34.19)	70 (45.16)	77 (49.36)	<0.001
Drinking, n(%)	247 (39.77)	63 (40.65)	61 (39.35)	65 (41.94)	58 (37.18)	0.849
Hypertension, n(%)	336 (54.11)	75 (48.39)	92 (59.35)	76 (49.03)	93 (59.62)	0.064
CAD, n(%)	69 (11.11)	15 (9.68)	15 (9.68)	18 (11.61)	21 (13.46)	0.669
MASLD, n(%)	307 (49.44)	63 (40.65)	69 (44.52)	85 (54.84)	90 (57.69)	0.006
Metformin, n(%)	316 (50.97)	79 (51.30)	84 (54.19)	78 (50.32)	75 (48.08)	0.753
GLP-1A, n(%)	40 (6.44)	8 (5.16)	13 (8.39)	9 (5.81)	10 (6.41)	0.682
SGLT2i, n(%)	211 (33.98)	52 (33.55)	55 (35.48)	56 (36.13)	48 (30.77)	0.752
DPP4i, n(%)	124 (20.00)	25 (16.13)	36 (23.23)	38 (24.52)	25 (16.13)	0.117
Insulin, n(%)	228 (36.71)	66 (42.58)	48 (30.97)	51 (32.90)	63 (40.38)	0.095

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; ALT, alanine aminotransferase; AST, aspartate transaminase; WBC, white blood cell count; RBC, red blood cell count; PLT, blood platelet count; BUN, blood urea nitrogen; Scr, scrum creatinine; UA, uric acid; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; CAD, coronary artery disease; GLP-1A, glucagon-Like peptide-1 agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; MASLD, metabolic dysfunction-associated steatotic liver disease.

significant differences (P<0.05) between the groups with respect to age, BMI, WBC, PLT, BUN, Scr, UA, TC, TG, HDL-C, LDL-C, HOMA-IR, sex, smoking, and MASLD. However, statistical analysis did not reveal any significant differences between the study groups with regard to SBP, DBP, HbA1c, RBC, ALT, AST, FBG, Drinking, Hypertension, CAD, GLP1, SGLT2, DPP4 and insulin use (P>0.05).

Association Between NHR and MASLD

To further explore the relationship between NHR and MASLD, regression analyses were performed, which showed that BMI, DBP, AST, ALT, UA, TG, and GLP-1 use were risk factors for MASLD. In contrast, age, BUN, and HDL-C were protective factors for MASLD (Table 2). A notable positive correlation was observed between NHR and MASLD (OR=1.74, 95% CI (1.26 ~ 2.38), p<0.001).

Multivariate logistic regression analyses indicated that significant correlations between NHR and MASLD remained in Model 1 (unadjusted), Model 2 (adjusted for age, BMI, sex, SBP, DBP, Smoking, Hyptension, CAD, GLP-1A, SGLT2i, DPP4i, Insulin), Model 3 (adjusted for age, BMI, sex, SBP, DBP, Smoking, Hyptension, CAD, GLP-1A, SGLT2i, DPP4i, Insulin, HbA1c, ALT, AST, BUN, Scr, UA, FBG, HOMA-IR) and Model 4 (adjusted for age, BMI, sex, SBP, DBP, Smoking, Hypertension, CAD, GLP-1A, SGLT2i, DPP4i, Insulin, HbA1c, ALT, AST, BUN, Scr, UA, FBG, HOMA-IR,TC, TG, LDL-C) (Table 3, all P<0.001).

Table 2 Univariate Logistic Regression Analysis of Risk Factors for MASLD

Variables	β	S.E	z	*P*	OR (95% CI)
Age (y)	−0.04	0.01	−6.09	<0.001	0.96 (0.94 ~ 0.97)
BMI (kg/m^2)	0.24	0.03	8.06	<0.001	1.28 (1.20 ~ 1.36)
SBP (mmHg)	0.01	0.00	1.67	0.094	1.01 (1.00 ~ 1.02)
DBP (mmHg)	0.05	0.01	6.31	<0.001	1.05 (1.04 ~ 1.07)
HbA1c (%)	−0.02	0.04	−0.67	0.505	0.98 (0.91 ~ 1.05)
WBC (×10^9/L)	0.16	0.05	3.17	0.002	1.17 (1.06 ~ 1.29)
RBC (×10^{12}/L)	−0.01	0.02	−0.91	0.365	0.99 (0.95 ~ 1.02)
PLT (×10^9/L)	0.00	0.00	1.23	0.217	1.00 (1.00 ~ 1.00)
ALT (U/L)	0.04	0.01	6.25	<0.001	1.04 (1.03 ~ 1.05)
AST (U/L)	0.04	0.01	4.26	<0.001	1.04 (1.02 ~ 1.06)
BUN (mmol/L)	−0.19	0.04	−4.59	<0.001	0.83 (0.76 ~ 0.90)
Scr (mmol/L)	−0.00	0.00	−1.02	0.310	1.00 (0.99 ~ 1.00)
UA (mmol/L)	0.01	0.00	3.94	<0.001	1.01 (1.01 ~ 1.01)
TC (mmol/L)	0.16	0.07	2.30	0.021	1.18 (1.02 ~ 1.35)
HDL-C (mmol/L)	−1.63	0.33	−4.99	<0.001	0.20 (0.10 ~ 0.37)
LDL-C (mmol/L)	0.21	0.09	2.33	0.020	1.23 (1.03 ~ 1.47)
TG (mmol/L)	0.33	0.06	5.58	<0.001	1.39 (1.24 ~ 1.56)
FBG (mmol/L)	−0.01	0.02	−0.58	0.563	0.99 (0.95 ~ 1.03)
HOMA-IR	−0.00	0.01	−0.04	0.966	1.00 (0.97 ~ 1.03)
Sex (Female)	−0.27	0.17	−1.59	0.112	0.76 (0.55 ~ 1.07)
Smoking	0.22	0.17	1.29	0.195	1.24 (0.90 ~ 1.72)
Drinking	0.51	0.17	3.09	0.002	1.67 (1.21 ~ 2.30)
Hypertension	0.26	0.16	1.59	0.111	1.29 (0.94 ~ 1.77)
CAD	0.29	0.26	1.13	0.258	1.34 (0.81 ~ 2.22)
Metformin	0.14	0.16	0.89	0.374	1.15 (0.84 ~ 1.58)
GLP-1A	1.19	0.37	3.18	0.001	3.29 (1.58 ~ 6.86)
SGLT2i	−0.15	0.17	−0.90	0.368	0.86 (0.62 ~ 1.20)
DPP4i	−0.50	0.20	−2.44	0.015	0.61 (0.41 ~ 0.91)
Insulin	−0.49	0.17	−2.94	0.003	0.61 (0.44 ~ 0.85)
NHR	0.55	0.16	3.40	<0.001	1.74 (1.26 ~ 2.38)

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; WBC, white blood cell count; RBC, red blood cell count; PLT, blood platelet count; BUN, blood urea nitrogen; Scr, scrum creatinine; UA, uric acid; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; ALT, alanine aminotransferase; AST, aspartate transaminase; CAD, coronary artery disease; GLP-1A, glucagon-Like peptide-1 agonists; SGLT2i, sodium-glucose cotransporter2 inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; MASLD, metabolic dysfunction-associated steatotic liver disease.

NHR and MASLD Relationship Subgroup Analysis

A subgroup study was conducted to ascertain whether the correlation between NHR and MASLD remained consistent across diverse populations (Figure 2). The analysis revealed that, based on gender and GLP-1A subgroups, there appeared to be independent correlational associations between NHR and MASLD in men and GLP-1A users (p for interaction 0.015, 0.017, respectively). However, the positive association between NHR and MASLD remained significant when stratified according to smoking, hypertension, CAD, metformin, SGLT2i, DPP4i and insulin status (p for interaction >0.05).

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Table 3 Multivariate Logistic Regression Analysis of the Relationship Between NHR and MASLD

Variables	Model1		Model2		Model3		Model4	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
No-MASLD	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
MASLD	1.74 (1.26–2.38)	<0.001	1.85 (1.30–2.64)	<0.001	1.94 (1.33–2.85)	<0.001	2.01 (1.35–3.00)	<0.001

Notes: Model 1: Unadjusted. Model 2: Adjusted for Age, BMI, Sex, SBP, DBP, Smoking, Hypertension, CAD, GLP-1A, SGLT2i, DPP4i, Insulin. Model 3: Model 2 +adjustment for HbA1c, ALT, AST, BUN, Scr, UA, FBG, HOMA-IR. Model 4: Model 3+adjustment for TC, TG, LDL-C.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell count; BUN, blood urea nitrogen; UA, uric acid; TC, total cholesterol; FBG, fasting blood glucose; ALT, alanine aminotransferase; AST, aspartate transaminase; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; GLP-1A, glucagon-Like peptide-1 agonists; SGLT2i, sodium-glucose cotransporter2 inhibitors; DPP4i, dipeptidyl peptidase-4 inhibitors; CAD, coronary artery disease; MASLD, metabolic dysfunction-associated steatotic liver disease.

Non-Linear Relationship Between NHR and MASLD

To determine a possible correlation between NHR and MASLD, we used the RCS to determine the nonlinear association between these two variables (Figure 3). The results of a univariate analysis showed a nonlinear correlation between NHR and NAFLD (P for nonlinear = 0. 002) and were adjusted for age, BMI, gender, SBP, DBP, smoking, hypertension, CAD, GLP-1A, SGLT2i, DPP4i, insulin, HbA1c, ALT, AST, BUN, Scr, UA, FBG, HOMA-IR, TC, TG, and LDL-C, the nonlinear correlation remained significant (P for nonlinear = 0.001).

Construction of a New Model for Predicting MASLD

In order to enhance the accuracy of predictions regarding the occurrence of MASLD and to determine the practical clinical value of the prediction model, a regression analysis was performed. All patients were randomly divided into a training set (70%) and a validation set (30%). The results of the regression analysis and clinical practice were used to screen the key influencing factors. The key influencing factors that were identified are NHR, CAD, GLP-1A, insulin use, BMI, DBP, ALT, HOMA-IR, TG and FBG. The prediction model was constructed using these factors (Figure 4). The ROC results showed that the predictive model had good diagnostic value with an AUC of 0.83 (95% CI 0.79–0.87) in the training set and 0.72 (95% CI 0.65–0.80) in the validation set (Figure 5). The calibration curve and decision curve analyses demonstrated the reliability of the model (Figures 6 and 7).

Discussion

The objective of the present study was to investigate the association between NHR values and MASLD. The investigation entailed the quantification of NHR values in patients diagnosed with T2DM, followed by regression analyses to identify the key factors contributing to the development of MASLD. The findings of this analytical study led to the formulation of a prediction model for the identification of MASLD, which is predicated on the key influencing factors of NHR and MASLD. The results of the study demonstrated that NHR functions as an independent risk factor for the development of MASLD and that there exists a nonlinear relationship between the two. Furthermore, the AUC value of the MASLD prediction model, which was constructed based on NHR, CAD, GLP-1A, insulin use, BMI, DBP, ALT, HOMA-IR, TG and FBG, was 0.78. This model exhibited both stability and reliability.

The hallmark features of MASLD encompass hepatic lipid accumulation and an inflammatory response, culminating in hepatocellular injury and liver fibrosis. Excessive lipid accumulation serves as a pivotal catalyst for the progression of MASLD's pathological cascade.[18] Moreover, both local and systemic inflammatory states within the liver play a pivotal role in the progression of MASLD. Neutrophils, a subpopulation of leukocytes, represent a pivotal component of the immune system's defence mechanism. As the predominant inflammatory cells within the body, they play a critical role in the progression of numerous diseases.The accumulation of lipids in the liver serves as a trigger for an inflammatory response, which in turn activates neutrophils, leading to the release of neutrophil extracellular traps (NETs). These NETs have the potential to exacerbate the progression of MASLD.[19] In addition, NET has the potential to exacerbate the development of MASLD by triggering a further inflammatory response and attracting more immune cells, including macrophages and T-regulatory cells, to the liver, inducing neutrophil death.[20] Previous studies have identified the

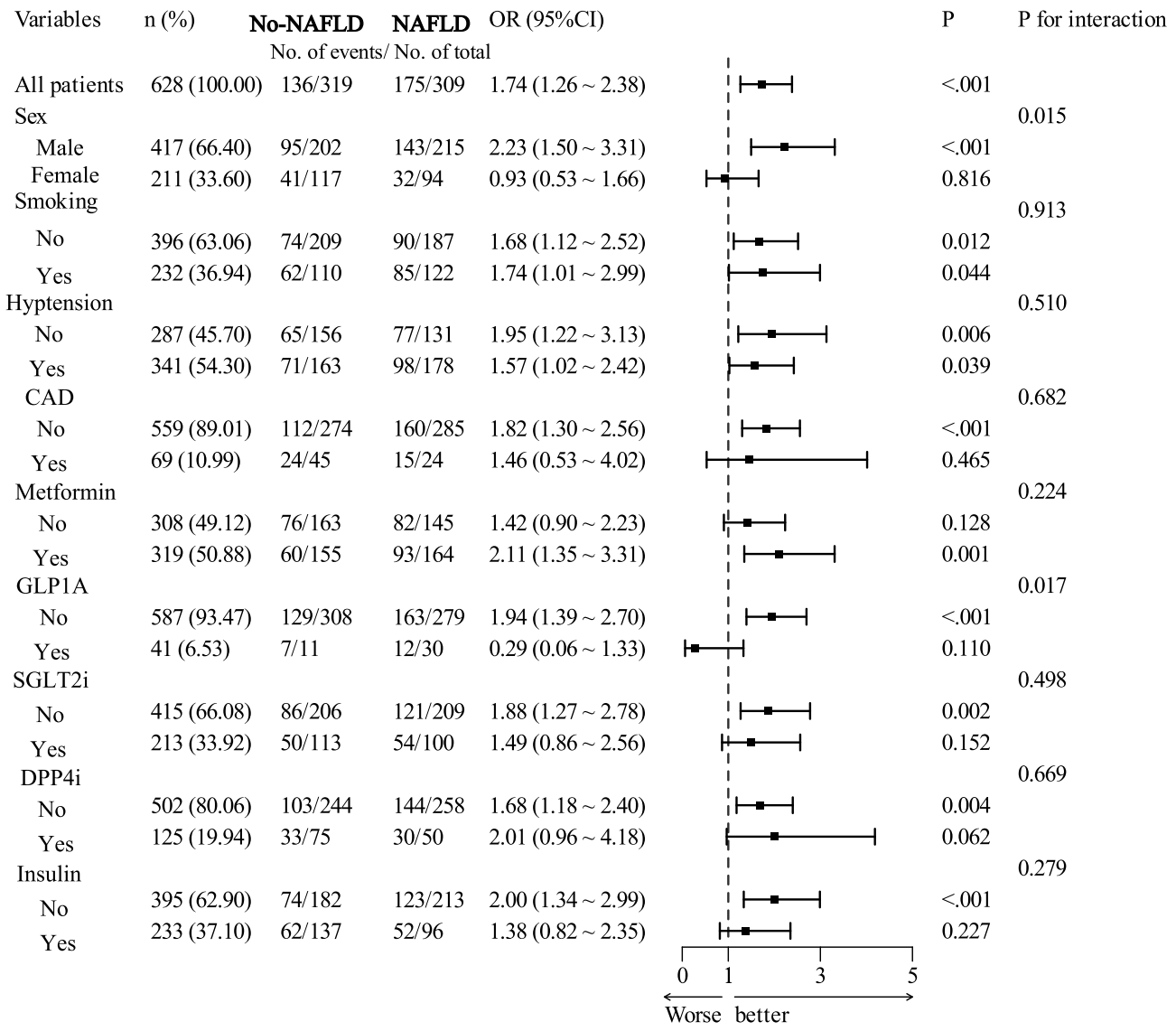

Figure 2 Subgroup analyses of the association between NHR and MASLD in patients with T2DM.

removal of dietary cholesterol via the reverse cholesterol transport pathway and the presence of anti-inflammatory and antioxidant properties as key functions of HDL-C.[21] Reduced HDL-C levels have been identified as a risk factor for various diseases and also affect the development of MASLD due to decreased anti-inflammatory and antioxidant properties. NHR, a novel metric, has been previously demonstrated to be associated with the development of MASLD in analogous studies.[22] However, no study has yet reported the relationship between NHR and MASLD in patients with T2DM.

The findings of this study indicated that NHR exhibited a positive correlation with MASLD in patients with T2DM and functioned as an independent risk factor for MASLD. These outcomes were consistent with those reported in earlier population-based studies.[15,22] Subgroup analyses revealed a higher prevalence of MASLD in the male population, and GLP-1A use was found to significantly reduce this prevalence. With regard to the gender disparity observed in the study, the analysis of preceding research suggests that this may be attributable to the elevated levels of oestrogen in women. These levels have been demonstrated to exert anti-inflammatory and antioxidant effects, which have been shown to mitigate liver damage resulting from inflammatory reactions and lipid metabolism disorders, at least to a certain extent.[23–25] A plethora of earlier studies have demonstrated the clinical efficacy of GLP-1A in the treatment of

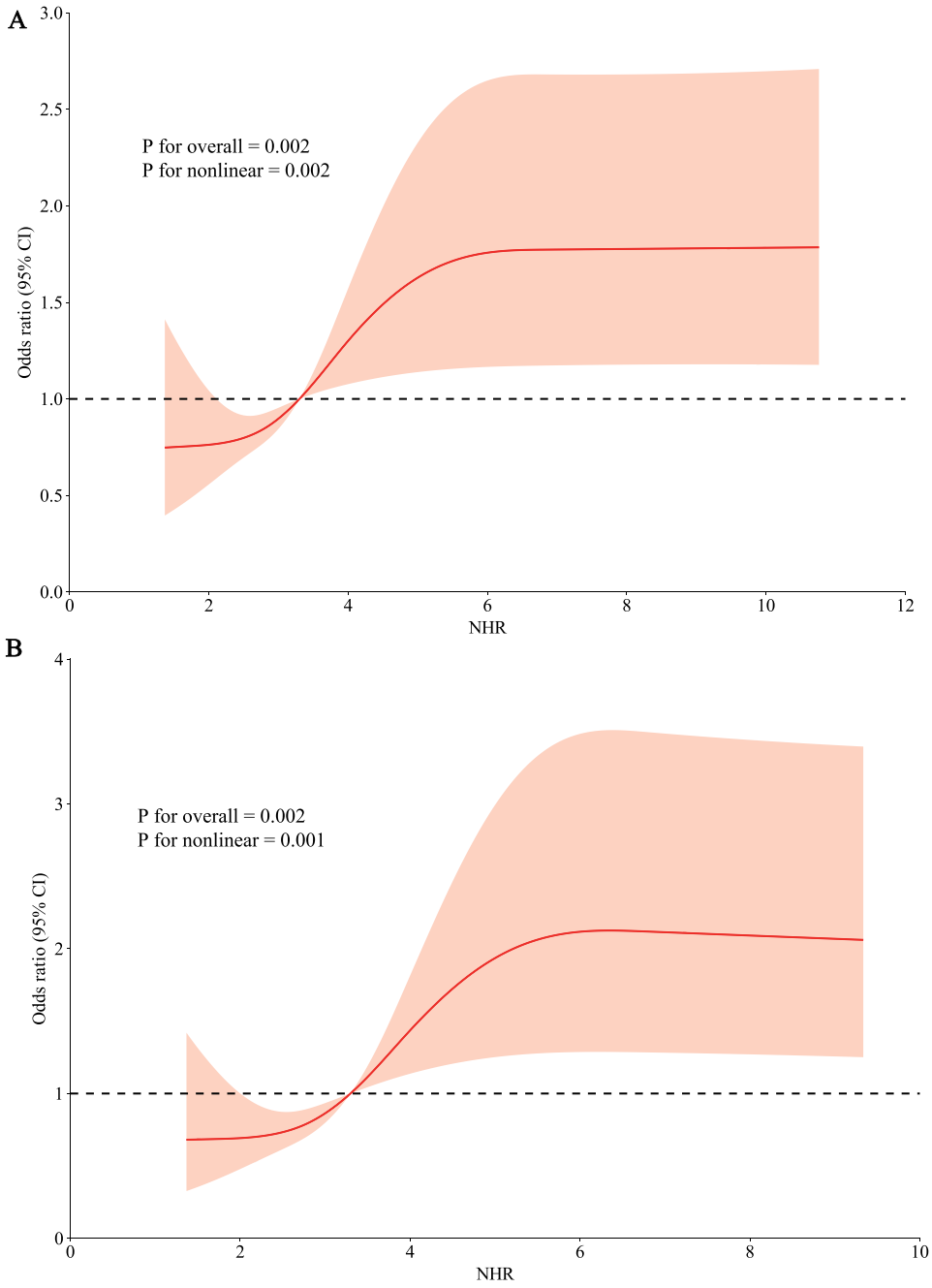

Figure 3 Restricted cubic spline (RCS) plot of the non-linear relationship between NHR and risk of MASLD in patients with T2DM. (**A**) Univariate non-linear correlation analysis. (**B**) A nonlinear relationship was detected after age, BMI, gender, SBP, DBP, smoking, hypertension, CAD, GLP-1A, SGLT2i, DPP4i, insulin, HbA1c, ALT, AST, BUN, Scr, UA, FBG, HOMA-IR, TC, TG, and LDL-C.

MASLD in combination with diabetes mellitus. The therapeutic benefits of GLP-1A for patients with MASLD may be attributable to its influence on gut microbiota, its capacity to induce weight loss, and its anti-inflammatory effects.[26–29] Nonlinear correlation analysis showed that there was also a nonlinear correlation between NHR and MASLD this is consistent with previous studies.[22] The risk of MASLD was shown as being increased significantly when the NHR exceeded the value of 3.3.

In this study, regression analysis was employed to screen key factors affecting MASLD. The identified key influencing factors included NHR, CAD, GLP-1A, insulin use, BMI, DBP, ALT, BUN, TG, FBG, and HOMA-IR. The new predictive model based on NHR demonstrated good diagnostic value with an AUC of 0.78 (95% CI 0.75–0.82). The reliability of the

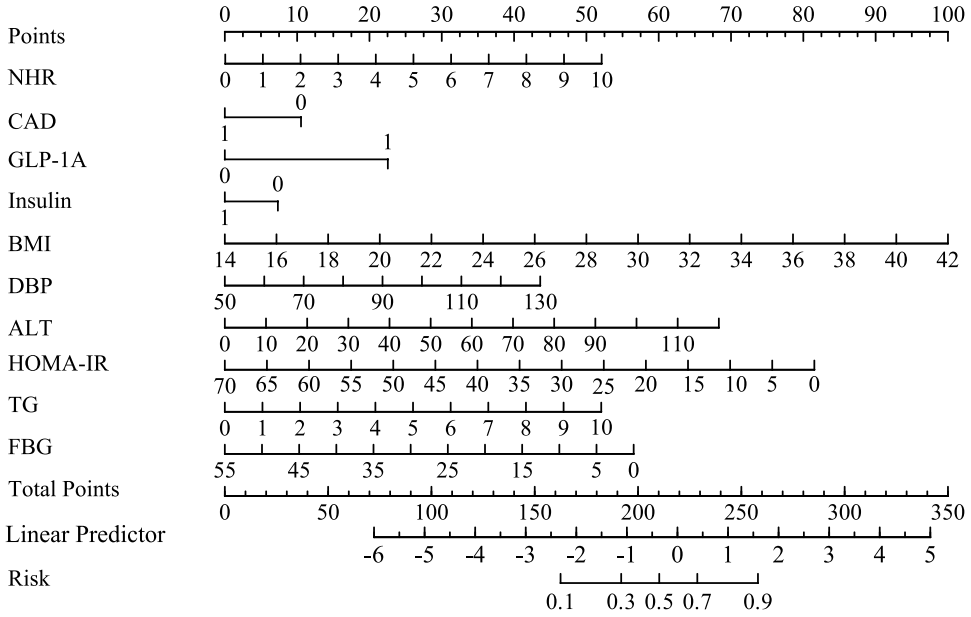

Figure 4 New nomogram for predicting MASLD in patients with T2DM.

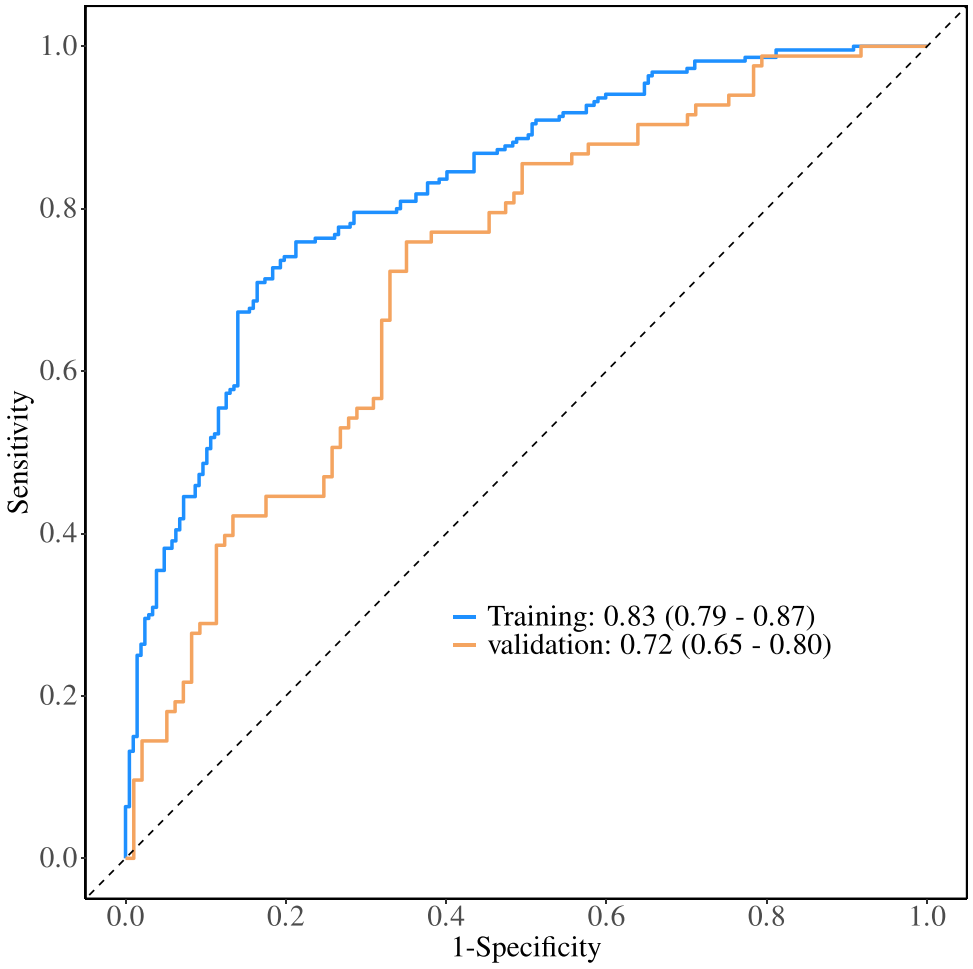

Figure 5 The new model predicts the ROC curve for MASLD.

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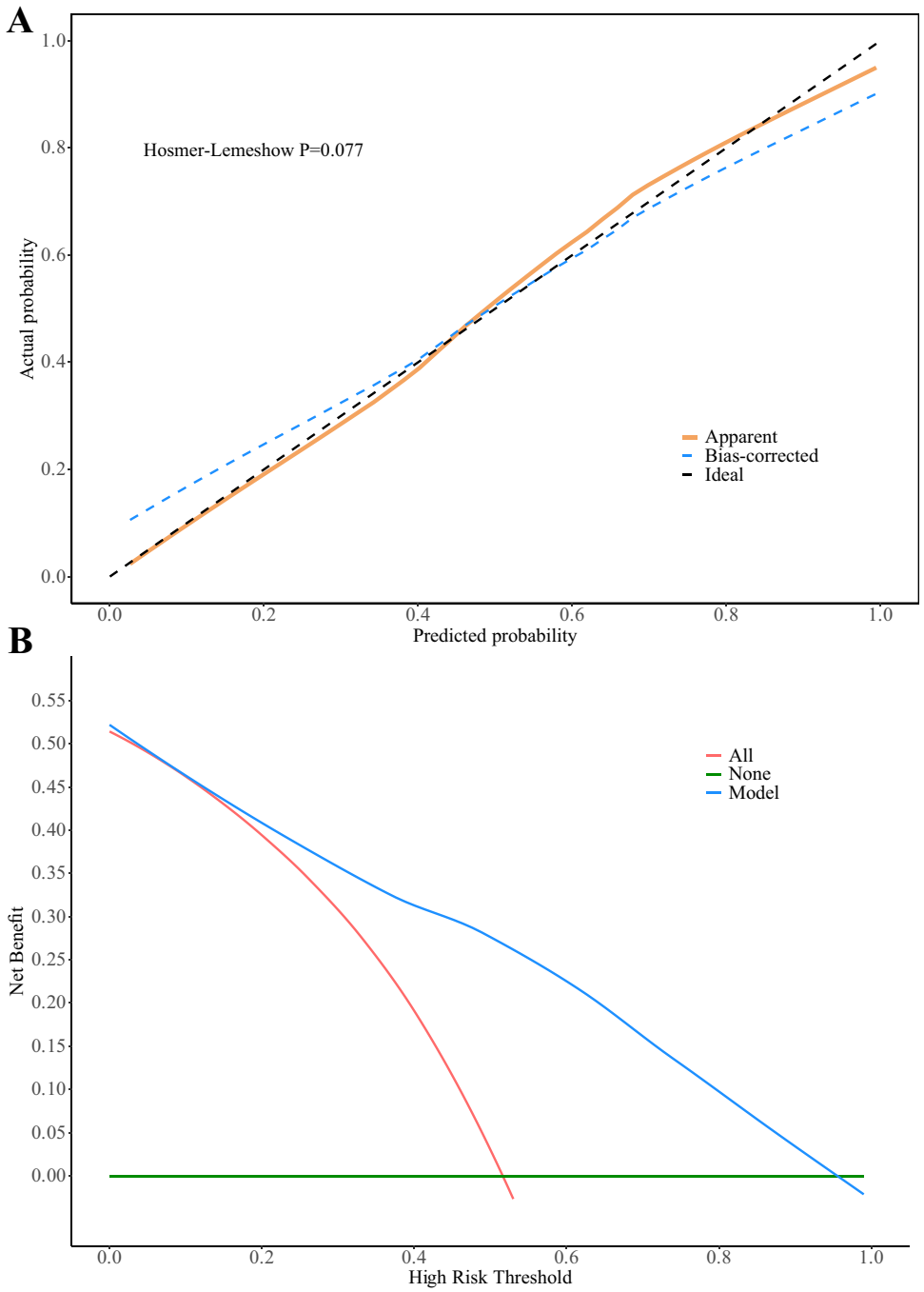

Figure 6 Calibration curves and decision curve analysis of nomogram in training set. (**A**) Calibration curves. (**B**) Decision curve analysis.

model was further substantiated by calibration curve and decision curve analysis. It is important to note that BMI has been identified as a risk factor for MASLD, and this is further compounded by higher blood pressure.[30–32] The present study hypothesises that insulin use is a risk factor for MASLD, which may be associated with a longer duration of diabetes in patients and heavier metabolic disturbances in the body. In addition, the study suggests that patients with coronary artery disease have a lower prevalence of MASLD, which may be associated with the use of more medications in patients with coronary artery disease. This was not considered in the present study and is a worthy direction for future research. As demonstrated by preceding studies, elevated blood glucose levels, abnormal lipids, and impaired liver function are all

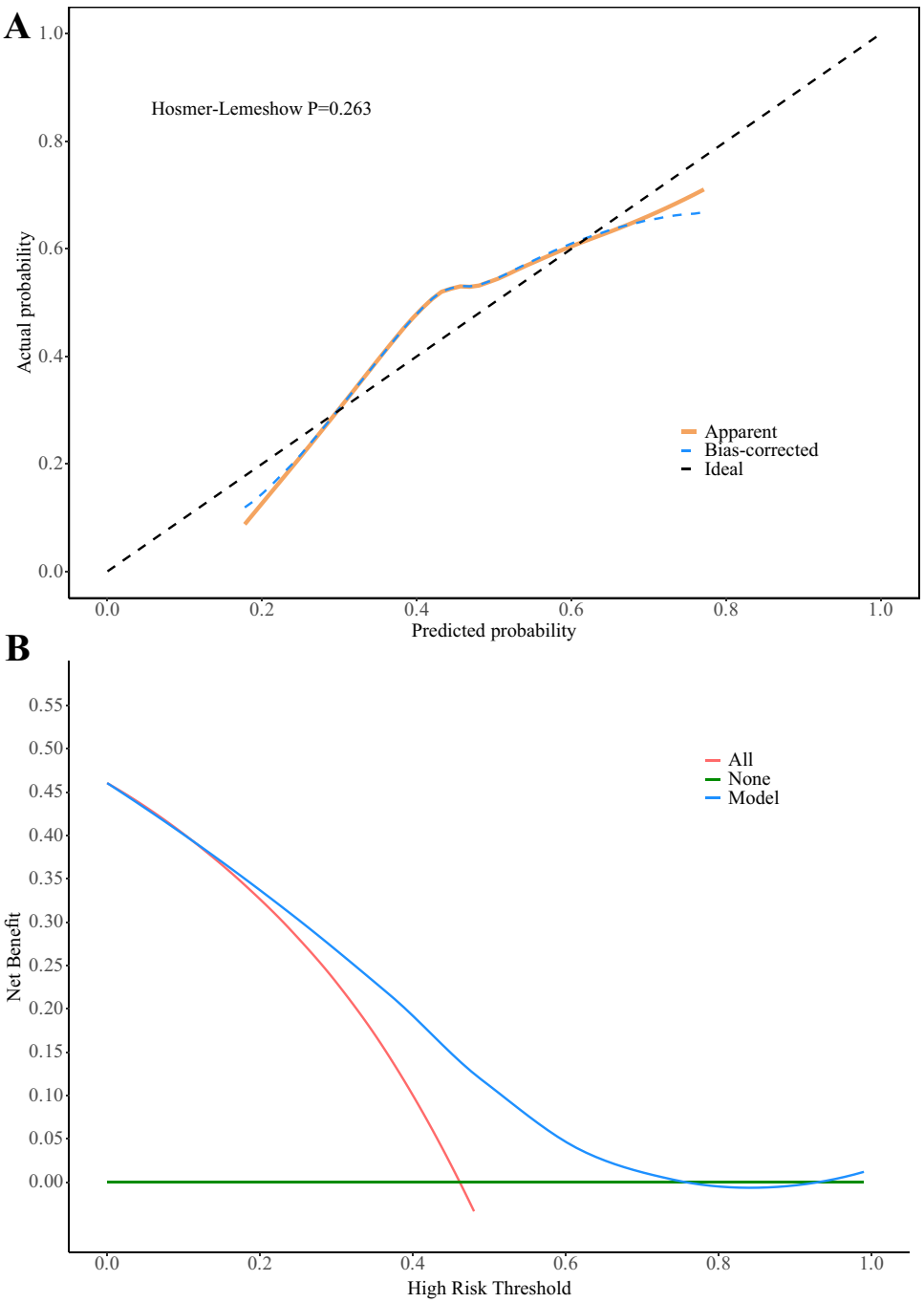

Figure 7 Calibration curves and decision curve analysis of nomogram in validation set. (**A**) Calibration curves. (**B**) Decision curve analysis.

established risk factors for MASLD. Consequently, this novel model was developed by integrating the factors identified by the regression model with the well-established risk factors. This approach has proven to be valuable.

The present study demonstrated that NHR is an independent risk factor for MASLD. The utilisation of NHR as an extensive indicator is pivotal in elucidating the discordance between systemic inflammation and lipid metabolism, and its interrelation with MASLD is characterised by a multifaceted and intricate process. In the context of chronic inflammation, there is an increase in neutrophilia, and inflammatory factors interfere with the synthesis and metabolism of HDL-C. This, in turn, leads to an increase in NHR, which reflects inflammation and lipid metabolism. Consequently, this contributes to the development of MASLD through multiple pathways. Inflammation has been demonstrated to trigger

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insulin resistance, leading to lipid metabolism disorders and fat accumulation in hepatocytes. Reduced HDL-C levels have been shown to impair reverse cholesterol transport, further exacerbating hepatic lipid deposition. Oxidative stress has been demonstrated to exacerbate hepatocellular injury and dysfunction on the basis of inflammation and lipid metabolism disorders, contributing to the progression of the disease.

However, the study is not without its limitations. Firstly, due to the cross-sectional nature of the study, further research is required to ascertain whether there is a causal relationship between NHR and MASLD. Secondly, while several factors influencing MASLD were considered in this study, there may be additional potential confounders influencing MASLD that were not included in the study, which need to be further confirmed in future studies. Thirdly, as this study was performed in a single centre, the findings may require confirmation from further research. Finally, more precise liver biopsies may be required in order to verify the diagnosis of MASLD.

Conclusion

This study demonstrated a significant correlation between NHR and MASLD, and NHR has the potential to be a potential marker for the development of MASLD in T2DM patients.

Ethics Approval and Informed Consent

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of The First Hospital of Zhangjiakou (no. 2024100).

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Disclosure

The authors declare no competing conflicts of interest in this work.

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