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ORIGINAL RESEARCH

Nomograms Based on Non-High-Density Lipoprotein to Predict Outcomes in Patients with Prior Coronary Artery Bypass Grafting with Acute Coronary Syndrome: A Single-Center Retrospective Study

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Introduction: Non-high-density-lipoprotein cholesterol (non-HDL-C) is a secondary therapeutic target in cardiovascular diseases and is used for residual risk assessment in patients with coronary artery syndrome (ACS). This study was designed to determine the association between non-HDL-C in patients with prior coronary artery bypass graft (CABG) with ACS and clinical outcomes.

Methods: We retrospectively analyzed 468 patients with prior CABG with ACS and categorized them into two groups based on the median non-HDL-C level. The primary endpoints were major adverse cardiovascular events (MACEs), including cardiovascular death and recurrent myocardial infarction. Kaplan–Meier curves, Cox proportional-hazard regressions, and restricted cubic splines were used to determine the association between non-HDL-C and MACEs. The discrimination and reclassification of the nomogram based on non-HDL-C were assessed using time-dependent receiver operating characteristic (ROC) curves and net reclassification improvement (NRI).

Results: During the average follow-up time of 744.5 days, non-HDL-C was independently associated with the occurrence of MACEs (hazard ratio [HR] = 5.01, 95% confidence interval [CI] = 1.65–15.24; $p = 0.005$) after adjusting for other lipid parameters. The spline curves indicated a linear relationship between non-HDL-C and MACEs (p-nonlinear: 0.863). The time-dependent areas under the ROC curves of prior-CABG-ACS nomograms containing non-HDL regarding MACEs in two consecutive years were 91.7 (95% CI: 85.5–97.9) and 91.5 (95% CI: 87.3–95.7), respectively. The NRI analysis indicated that the prior-CABG-ACS model improved the reclassification ability for 1- and 2-year MACEs (22.4% and 7%, $p < 0.05$, respectively).

Discussion: Non-HDL is independently associated with the risk of MACEs in patients with prior CABG with ACS. The prior-CABG-ACS nomogram based on non-HDL-C and five convenient variables generates valid and stable predictions of MACE occurrence.

Keywords: non-HDL cholesterol, major adverse cardiovascular events, prior coronary artery bypass grafting, GRACE score

Introduction

Patients with prior coronary artery bypass graft (CABG) account for 8–10% of individuals admitted for coronary artery syndrome (ACS).[1–3] Generally, patients with a history of CABG had a higher burden of cardiovascular (CV) risk factors, lower ejection fraction, and higher creatinine values on admission. This population is at a high risk of suffering from recurrent CV events in the short and long terms and requires personnel risk assessment to intensify medication therapy or implement intervention strategies to prevent the progression of atherosclerotic CV disease (ASCVD).

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Low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor and the primary and secondary therapeutic target for ASCVD. In the context of mild-to-moderate hypertriglyceridemia and cardiometabolic disorders, such as diabetes mellitus, obesity, and metabolic syndrome, LDL-C levels underestimate the actual risk of ASCVD.[4,5] Non-high-density-lipoprotein cholesterol (non-HDL-C) is highly correlated with the concentrations of LDL-C and includes the atherogenic risk component of remnant lipoprotein particles.[6,7] Several lines of evidence suggest that non-HDL-C is superior to LDL-C for predicting residual ASCVD risk for statin-treated patients and has been identified as the secondary target in some treatment guidelines.[8–10]

Non-HDL-C is more straightforward, convenient, and predictive than LDL-C; however, this test is not widely recognized and is less frequently used in clinical ASCVD assessments.[4] Few studies investigated the predictive value of non-HDL-C for CV outcomes in patients with prior CABG with ACS. Given these considerations, this study was designed to determine the ability of non-HDL-C to predict outcomes in patients with previous CABG with ACS undergoing percutaneous coronary intervention (PCI). Furthermore, we generated a nomogram to stratify this population's risk of CV events.

Methods

Patient Selection

Among the 14,288 patients with ACS undergoing PCI at Beijing Chaoyang Hospital Heart Center between January 2015 and December 2020, 480 consecutive patients with prior CABG were retrospectively enrolled in this study (Supplementary Figure 1). We excluded patients with incomplete statin therapeutic data, a life expectancy < 6 months, and cirrhosis. This study followed the principles of the Declaration of Helsinki and the ethics policies of the institution. Informed consent was waived because of the retrospective nature of the study.

Baseline Data Collection and Non-HDL-C Calculations

Demographic data included age, sex, body mass index (BMI), coronary artery risk factors, and discharge medication, where were obtained from an electronic database. On admission, total serum cholesterol (TC), HDL-C, apolipoprotein A, and triglyceride (TG) levels were assayed with the patients fasting within the first 24 h after admission. LDL-C levels were determined using the Friedewald formula.[11] Non-HDL-C levels on admission were calculated by subtracting HDL from total cholesterol (non-HDL-C= TC- HDL). The creatinine clearance rate (CCr) was calculated based on the Cockroft Gault formula. Two cardiologists retrospectively reviewed coronary angiography. The culprit artery and intervention process were documented.

The Global Registry of Acute Coronary Events (GRACE) score predicts the mortality risk in patients with ACS and is recommended by clinical guidelines.[12,13] The GRACE score was calculated using the following parameters: age, history of myocardial infarction (MI), acute heart failure on admission, discharge systolic blood pressure and heart rate, serum creatinine level at admission, ST-segment depression, elevated myocardial necrosis enzymes, and application of percutaneous coronary revascularization.[14]

Ascertainment of Outcomes

The clinical adverse CV events were recorded through telephone interviews, scheduled outpatient visits, or admission documents. The primary endpoint was the occurrence of MACEs, including CV mortality and recurrent nonfatal MI.

Statistical Analysis

Continuous variables were expressed as means ± standard deviations or medians (interquartile ranges [IQRs]), as appropriate, and categorical variables were expressed as frequencies and percentages. Student's *t*-test was used for continuous variables, and the chi-square test was used for categorical variables. Survival was calculated using Kaplan–Meier curves and compared using the Log rank test to detect intergroup differences. The predictive values of serum lipid parameters and other risk factors for MACEs were identified using Cox proportional-hazard regression analysis. To test the independent association between non-HDL-C and CV events, we further developed a multivariable model, including LDL, TG, and

apolipoprotein A. The restricted cubic splines based on Cox proportional hazards models were used to visualize the relationship of non-HDL-C with CV events in patients with prior CABG in the setting of ACS.[15] Non-HDL-C was brought into the spline models, including the confounding risk factors, other serum lipid variables, and statin dose.

The sample size was derived based on the available data from the Beijing Chaoyang Hospital electronic database, and no power calculation for the sample size was performed upfront because of the retrospective nature of this study. Given the sample size, the model was properly screened using the adaptive least absolute shrinkage and selection operator (LASSO) Cox regression to exploit the best fit model and establish a prior-CABG-ACS nomogram to predict mortality and recurrent MI, and the optimal value of λ was determined via 10-fold cross-valuations. The model was validated in two steps. First, the predictive accuracy of the new model for CV mortality and recurrent MI was evaluated using ROC curves. The internal consistency of the discrimination performance measures was evaluated using the bootstrapping method. Because of the limitations of classical ROC curve analysis, we used the time-dependent ROC curve method.[16] Meanwhile, the NRI for the reclassification ability was also assessed to quantify discrepancies between the new model and GRACE risk score. Second, the calibration slope predicting the probability of MACE occurrence at 12 and 24 months was calculated for the models' calibrations. Statistical analyses were performed using R (version 3.4.0). All statistical tests were two-tailed, and p-values ≤ 0.05 were used to denote statistical significance.

Results

Clinical Information at Baseline and Incidence of MACE

After screening the electronic database based on the keywords and International Classification of Diseases 10th Revision codes of admission diagnosis, we excluded seven cases with incomplete data and five cases without follow-up information. In this study, 468 subjects with ACS with a history of CABG underwent PCI. All eligible patients were categorized into two groups according to the median non-HDL-C (high group: non-HDL-C > 2.6 mmol/L; and low group: non-HDL-C ≤ 2.6 mmol/L). All patients in the high non-HDL-C group had a lower proportion of males and presented with increased BMI, higher platelet counts, lower platelet distribution width and mean platelet volume, and higher creatine kinase–myocardial band, fasting glucose, and erythrocyte sedimentation rate (ESR) (Table 1). Patients in the high group had higher values of total cholesterol and LDL-C than those in the low group, whereas the proportions of β-blocker and statin use were similar

Table 1 Baseline Characteristic

Factor	Total	Low Non-HDL-C (≤2.6 mmol/L)	High Non-HDL-C (>2.6 mmol/L)	p-value
N	468	236 (50.4%)	232 (49.6%)	
Age, (year)	68 (62, 75)	68 (62, 74)	69 (62, 76)	0.56
Male, n (%)	378 (80.8%)	202 (85.6%)	176 (75.9%)	0.01
BMI, (kg/m^2)	26.3 (24.2, 28.3)	25.9 (23.8, 27.8)	26.6 (24.6, 28.7)	<0.01
Diagnosis, n (%)				0.32
STEMI,	56 (12.0%)	24 (10.2%)	32 (13.8%)	
NSTEMI	83 (17.7%)	39 (16.5%)	44 (19.0%)	
UAP	329 (70.3%)	173 (73.3%)	156 (67.2%)	
Killip III or IV, n (%)	19 (4.1%)	10 (4.2%)	9 (3.9%)	0.37
LVEF, %	62 (55, 68)	62 (55, 68)	62.5 (55, 68)	0.64
LVEDD, mm	49 (46, 52)	49 (46, 52)	49 (46, 51)	0.42
LVESD, mm	32(28, 36)	32 (28, 37)	32 (28, 35)	0.63
Discharge HR, (beats/min)	69 (61, 76)	69.5 (61.75, 76)	68 (61.77.25)	0.87
Discharge SBP, (mmHg)	134 (19.1)	133 (18.9)	135 (19.2)	0.41
Discharge DBP, (mmHg)	74 (67, 80)	74 (67, 80)	73 (67, 80)	0.84
Prior MI, n (%)	145 (31.0%)	76 (32.2%)	69 (29.7%)	0.62
History of PCI, n (%)	147 (31.4%)	72 (30.5%)	75 (32.3%)	0.75
History of stroke, n (%)	69 (14.7%)	31 (13.1%)	38 (16.38%)	0.39
Diabetes mellitus, n (%)	213 (45.5%)	107 (45.3%)	106 (45.7%)	-
Hypertension, n (%)	349 (74.6%)	170 (72.0%)	179 (77.2%)	0.24

(*Continued*)

Table 1 (Continued).

Factor	Total	Low Non-HDL-C (≤2.6 mmol/L)	High Non-HDL-C (>2.6 mmol/L)	p-value
Smoker, n (%)	278 (59.4%)	143 (60.6%)	135 (58.2%)	0.66
Statin treatment				0.12
Atorvastatin, n (%)	374 (79.9%)	197 (83.5%)	177 (76.3%)	
Rosuvastatin, n (%)	88(18.8%)	36 (15.3%)	52 (22.4%)	
Other statins	6 (1.3%)	3(1.3%)	3(1.3%)	
Culprit Vessel, n (%)				0.28
LAD, n (%)	79 (16.9%)	36 (15.3%)	43 (18.5%)	
LCX, n (%)	104 (22.2%)	56 (23.7%)	48 (20.7%)	
RCA, n (%)	173 (37.0%)	90 (38.1%)	83(35.8%)	
LM, n (%)	32 (6.8%)	17 (7.2%)	15(6.5%)	
LIMA, n (%)	12 (2.6%)	6 (2.6%)	6 (2.6%)	
AO-SVG-LCX, n (%)	34 (7.3%)	12 (5.1%)	22 (9.5%)	
AO-SVG-RCA, n (%)	34 (7.3%)	19 (8.1%)	15 (6.5%)	
Laboratory test				
White blood cell, (10*9/L)	6.50 (5.40, 7.82)	6.30 (5.23, 7.82)	6.20 (5.74, 7.82)	0.09
Hemoglobin, (g/L)	131 (17.3)	129 (17.4)	132 (17.1)	0.07
Platelet count, (10*9/L)	179 (149, 218.5)	177 (143, 214.5)	185 (156.7, 227)	0.01
MPV, (fl)	10.6 (10.0, 11.3)	10.7 (10.1, 11.4)	10.4 (9.9, 11.1)	0.01
PDW, (fl)	12.3 (11.1, 13.8)	12.5 (11.3, 14.3)	12.1 (11.0, 13.6)	<0.05
TC, (mmol/L)	3.57 (3.09, 4.22)	3.10 (2.80, 3.34)	4.22 (3.83, 4.66)	<0.001
HDL-C, (mmol/L)	0.96 (0.80, 1.10)	0.96 (0.80, 1.12)	0.96 (0.80, 1.10)	0.59
LDL-C, (mmol/L)	1.90 (1.58, 2.47)	1.60 (1.30, 1.80)	2.47 (2.10, 2.90)	<0.001
TG,(mmol/L)	1.37 (0.97, 1.93)	1.07 (0.77, 1.48)	1.68 (1.25, 2.50)	0.61
LP(a), (mg/dl)	19.6 (9.0, 37.5)	20.2 (8.7, 34.65)	19.3 (9.27, 39.3)	0.44
HCY, (umol/L)	18.0 (14.0, 19.0)	17.0 (14.0, 19.0)	18.6 (14.0, 20.0)	0.28
Fasting glucose, (mmol/L)	5.55 (4.62, 7.64)	5.43 (4.52, 7.15)	5.70 (4.81, 7.81)	0.02
HbA1c, (%)	6.65 (6.0, 7.93)	6.5 (5.9, 7.9)	6.7 (6.0, 8.0)	0.19
BNP, (pg/mL)	185 (73, 647)	213 (82, 733)	157 (72, 532)	0.11
CTNI, (ng/mL)	0.03 (0.00, 0.41)	0.02 (0.00, 0.29)	0.03 (0.00, 0.55)	0.12
CK-MB, (ng/mL)	1.1 (0.5, 2.0)	1.0 (0.50, 1.70)	1.2 (0.60, 2.23)	0.03
Creatinine, (umol/L)	78.1 (66.9, 90.8)	78.9 (68.3, 89.8)	76.9 (65.7, 91.6)	0.74
hs-CRP, (mg/dl)	2.74 (0.99, 4.77)	2.38 (0.80, 4.77)	2.92 (1.24, 4.77)	0.08
ESR, (mm/h)	6.0 (2.0, 12.2)	4.0 (2.0, 9.8)	9.0 (3.0, 14.0)	<0.001
GRACE score	95 (79, 112)	93 (80, 107)	95 (79, 113)	0.46
Medication at discharge				
Aspirin, n (%)	464 (99.2%)	234 (99.2%)	230 (99.1%)	1.0
Clopidogrel, n (%)	459 (98.1%)	233 (98.7%)	226 (97.1%)	0.48
β-blocker, n (%)	347 (74.2%)	174 (73.7%)	173 (74.6%)	0.91
ACEI/ARB, n (%)	178 (38.0%)	85 (36.0%)	93 (40.1%)	0.42

Abbreviations: BMI, body mass index; STEMI, ST-segment elevated myocardial infarction; NSTEM, non ST-segment elevated myocardial infarction; UAP, unstable angina; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; PCI, percutaneous coronary intervention; AF, atrial fibrillation; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; LM, left main artery coronary; AO, Arteriae Aorta; SVG, Saphenous Vein Graft; MPV, mean platelet volume; PDW, platelet distribution width; LP(a), Lipoprotein (a); HCY, homocysteine; BNP, brain natriuretic peptide; CTNI, cardiac troponin I; CK-MB, creatine kinase MB; hs-CRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.

between the two groups. The median LDL-C was 1.90 mmol/L in all patients receiving statins. No significant differences in the baseline characteristics were observed between the non-HDL-C groups.

Kaplan–Meier Survival Curves and Cox Regression Analysis for MACEs

During the median follow-up time of 744.5 days (IQR: 367.5–1430 days), 29 (6.2%) patients experienced adverse clinical events, including CV death (3.2%) and recurrent MI (3.4%). During the observational period, the cumulative

survival curves for MACEs were significantly lower in the high non-HDL-C group than in the low non-HDL-C group (Log rank test; $p = 0.0084$) (Figure 1A). Patients in the high TC group presented a higher risk of MACE occurrence than those in the low TC group (Log rank test; $p = 0.093$) (Figure 1C). No significant difference in the incidence of MACEs was observed between the LDL-C and TG groups (Log rank test; $p = 0.28$ and $p = 0.57$, respectively) (Figure 1B and D).

We performed Cox proportional-hazard regression univariate and multivariate analyses (Table 2 and Figure 2). Univariate analysis revealed that TC (HR = 2.04, 95% CI = 1.43–2.89, $p < 0.01$) and non-HDL-C (HR = 2.42, 95% CI = 1.73–3.38, $p < 0.01$) were independently associated with MACEs, whereas TG, LDL-C, and HDL-C were not. After adjusting for potential confounders (left ventricular ejection fraction [LVEF], cardiac troponin I [CTNI], β-blocker use, ESR, and CCr), multivariate analysis indicated that non-HDL-C (HR = 1.83, 95% CI = 1.24–2.71, $p = 0.002$) remained an independent predictor of MACEs. When all other serum lipid levels were brought into the model containing confounding risk factors, only increased levels of non-HDL-C were significantly associated with an increased risk of MACEs (HR = 5.01, 95% CI = 1.65–15.24, $p = 0.005$).

We performed restricted cubic splines to flexibly model and visualize the relationship of non-HDL-C with MACEs (Figure 3). The splines indicated a linear relationship between the risk of MACEs and serum non-HDL-C in patients with ACS with prior CABG (p-nonlinear = 0.863). As the serum non-HDL-C level was above the median value of 2.6 mmol/L, there was a significant linear risk of suffering MACEs.

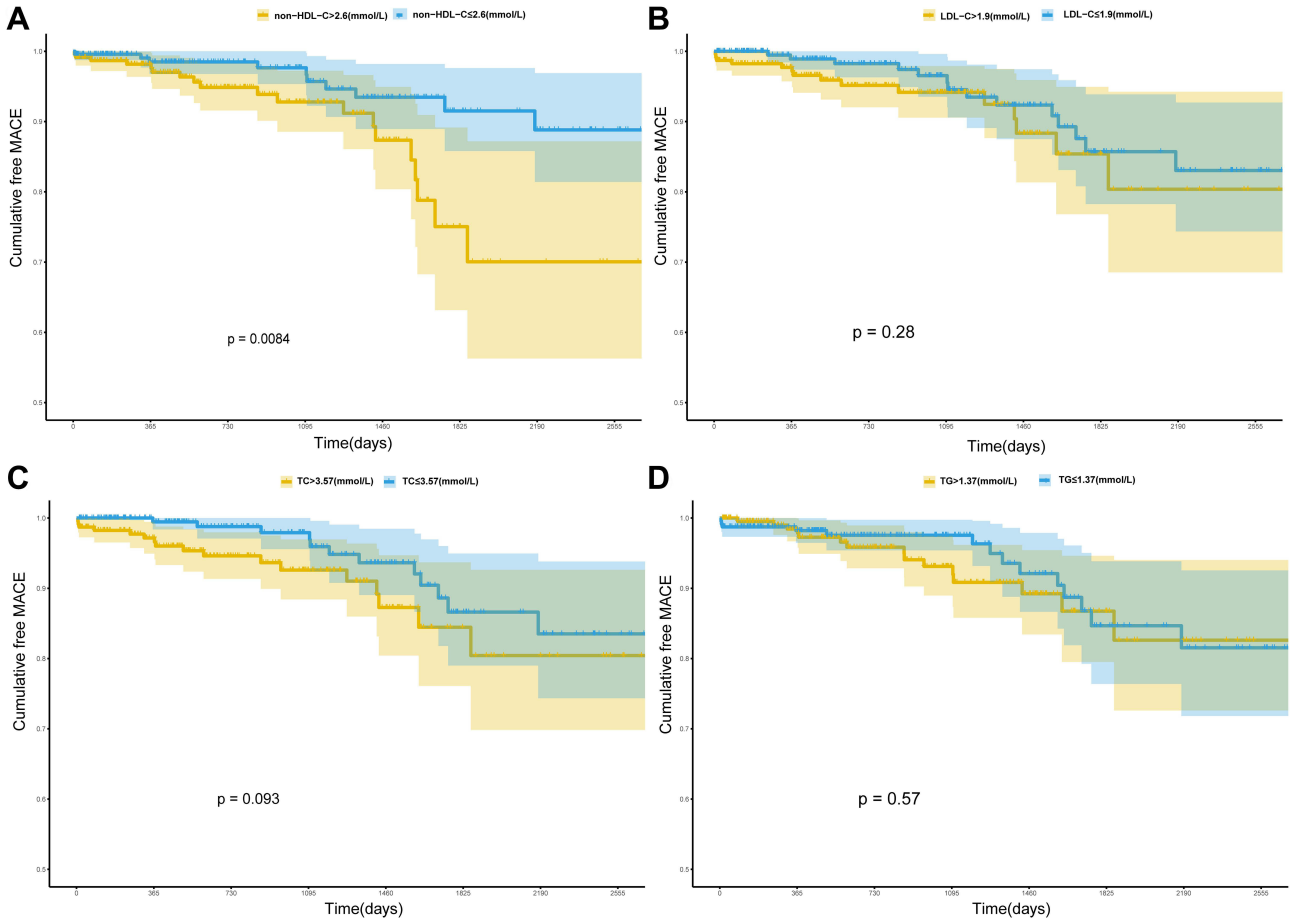

Figure 1 Cumulative survival curves for cardiac death and reinfarction in ACS patients with prior CABG stratified according to the median of different lipid parameters. (**A**) According to the median non-HDL-C level (2.6 mmol/L), significant cumulative survival curves are different for cardiac death and reinfarction in the two groups. (**B**) According to the mean LDL-C level (1.9 mmol/L), no discrepancy regarding cumulative survival curves for cardiac death and reinfarction was observed between the two groups. (**C**) According to the median TC level (3.57 mmol/L), significant cumulative survival curves are different for cardiac death and reinfarction in the two groups. (**D**) According to the median TG level (1.37 mmol/L), no discrepancy regarding cumulative survival curves for cardiac death and reinfarction was observed between the two groups.

Table 2 Cox Proportional Hazard Regression Analysis for Major Adverse Cardiovascular Events

Outcomes	Variables	Univariate Analysis	
		HR (95% CI)	P-value
MACE (29/468)	Age	1.03 (1.00, 1.07)	0.08
	Female	0.77 (0.33, 1.80)	0.54
	BMI	0.97 (0.87, 1.08)	0.55
	Diagnosis		
	UAP	Reference	–
	NSTEMI	1.67 (0.59, 4.76)	0.33
	STEMI	4.67 (2.09, 10.5)	<0.01
	Heart rate at discharge	1.03 (1.00, 1.07)	0.03
	SBP at discharge	1.01 (0.99, 1.03)	0.56
	DBP at discharge	0.96 (0.93, 1.00)	0.03
	White blood cell	1.23 (1.03, 1.46)	0.02
	HGB	0.98 (0.96, 1.00)	0.06
	TC	2.04 (1.43, 2.89)	<0.01
	LDL-C	1.16 (0.98, 1.38)	0.08
	HDL-C	1.14 (0.34, 3.84)	0.84
	TG	1.08 (0.78, 1.50)	0.63
	Lp(a)	1.00 (0.99, 1.01)	0.20
	Non-HDL-C	2.42 (1.73, 3.38)	<0.01
	CTNI	1.02 (1.01, 1.03)	<0.01
	CKMB	1.01 (1.00, 1.01)	<0.01
	Fasting glucose	1.09 (1.01, 1.18)	0.04
	CCr	0.98 (0.97, 1.00)	0.01
	LVEF	0.95 (0.92, 0.98)	<0.01
	LVESD	1.07 (1.03, 1.11)	0.001
	LVEDD	1.07 (1.01, 1.13)	0.02
	ESR	1.06 (1.03, 1.08)	<0.01
	Hs-CRP	1.03 (1.00, 1.06)	0.05
	History of PCI	2.02 (0.96, 4.24)	0.06
	β-blocker treatment	0.39 (0.19, 0.82)	0.01
	GRACE score	1.02 (1.01, 1.04)	<0.001

Abbreviations: SE, standard error; CI, confidence interval; HR, hazard ratio; BMI, body mass index; UAP, unstable angina; STEMI, ST-segment elevated myocardial infarction; NSTEM, non ST-segment elevated myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; HGB, hemoglobin; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; apolipoprotein A, Lp(a); CTNI, cardiac troponin I; CKMB, creatine kinase–myocardial band; Hs-CRP, high sensitivity C-reaction protein; ESR, erythrocyte sedimentation rate; CCr, creatinine clearance rate; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter; PCI, Percutaneous coronary intervention; GRACE, Global Registry of Acute Coronary Event; MACE, major adverse cardiovascular events.

Variable Selection for Constructing a Prediction Model and Prior-CABG-ACS Nomogram

For the LASSO regression models, we chose the most regularized and parsimonious model with a tuning λ (log scale), giving a cross-validated error within the minimum (Supplementary Figure 2). Finally, the six parameters were screened from all 17 variables, which were associated with the risk of MACEs and identified by the Cox proportional-hazard regression univariate analysis. Those six critical factors, including non-HDL, LVEF, peak of CTNI level, CCr, receiving β-blocker treatment, and ESR on admission, were integrated into a predictive prior-CABG-ACS nomogram for predicting the cardiac clinical outcomes of patients with ACS with prior CABG at 12 and 24 months.

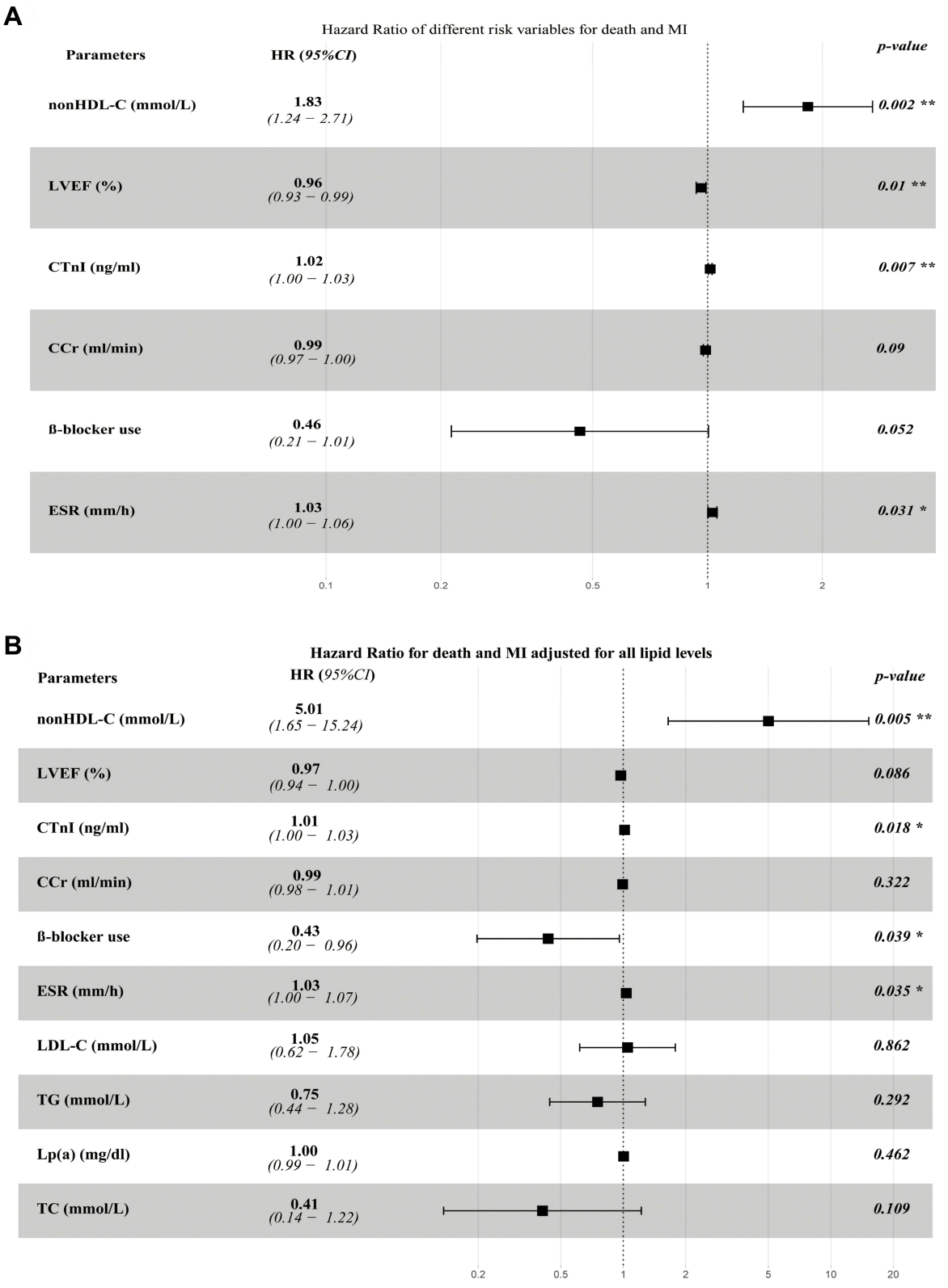

Figure 2 A forest plot of cardiovascular risk factors related to the risk of MACEs using the Cox proportional-hazard regression models. (**A**) Adjusted for conventional coronary risk factors at baseline as continuous variables; (**B**) adjusted for all lipid levels and cardiovascular risk factors at baseline.

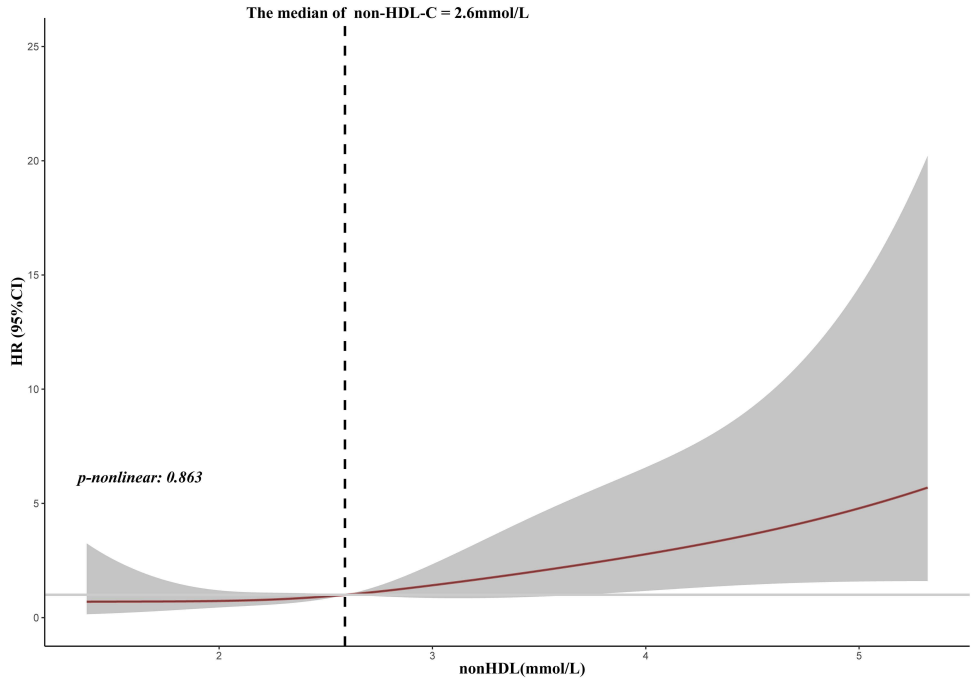

Figure 3 The restricted cubic spline curve between the non-HDL-C level and cardiovascular events presented as a roughly linear relationship.

Performance of Prior-CABG-ACS Nomogram

The 12- and 24-month areas under the curves for the prior-CABG-ACS model, which was established based on non-HDL-C and the five other parameters, were 91.7 (95% CI: 85.5–97.9) and 91.5 (95% CI: 87.3–95.7), respectively (Figure 4A). The model's predicted probabilities were close to the actual probabilities on the calibration plots (Supplementary Figure 3). According to the time-dependent ROC curves (Figure 4B), the prior-CABG-ACS model containing non-HDL-C could durably predict middle- or long-term MACEs in a patient with prior CABG who underwent PCI treatment compared with the classical GRACE risk score. The NRI analysis indicated that the prior-CABG-ACS model improved the reclassification ability for 1- and 2-year MACEs (22.4% and 7%, respectively, $p < 0.05$) compared with the GRACE score. The nomogram based on the prior-CABG-ACS model is shown in Figure 4C. The following is an example: non-HDL of 4.5 mmol/L (12 points), LVEF of 40% (8 points), CTNI of 30 ng/mL (2 points), CCr of 30 mL/min (11 points), receiving β-blocker treatment (0 points), and ESR of 10 mm/h (1.5 points), this patient with ACS with prior CABG scored 34.5 points, had a 90% 1-year MACE-free chance, and an 80% 2-year MACE-free chance.

Discussion

In this study, we found a linear association between serum non-HDL-C and long-term adverse clinical events in patients with ACS with prior CABG. After adjusting for confounding risk factors and lipid variables, serum non-HDL-C remained an independent predictor for the residual risk of MACEs under statin therapy for secondary prevention. Our nomogram combining non-HDL-C and five other noninvasive clinical parameters favorably and stably predicted survival and MI occurrence at 1- and 2-year.

The association between non-HDL-C and CV mortality and other events has been assessed to identify primary and secondary preventive measures for CV diseases.[4,17,18] The residual risk might be partially explained by the elevated small dense LDL particles, hypertriglyceridemia, reduced HDL-C, increased remnant lipoproteins, and postprandial hyperlipidemia.[19] Our findings revealed that elevated non-HDL-C reflects the residual risk of MACEs in patients with ACS with prior CABG. In a study by Fukushima,[20] individuals with higher concentrations of non-HDL-C after CABG presented a more significant risk of CV mortality and other clinical outcomes in a community-based cohort. Similar findings were reported by other series of studies, which have demonstrated that the predicted ability of non-HDL-C for

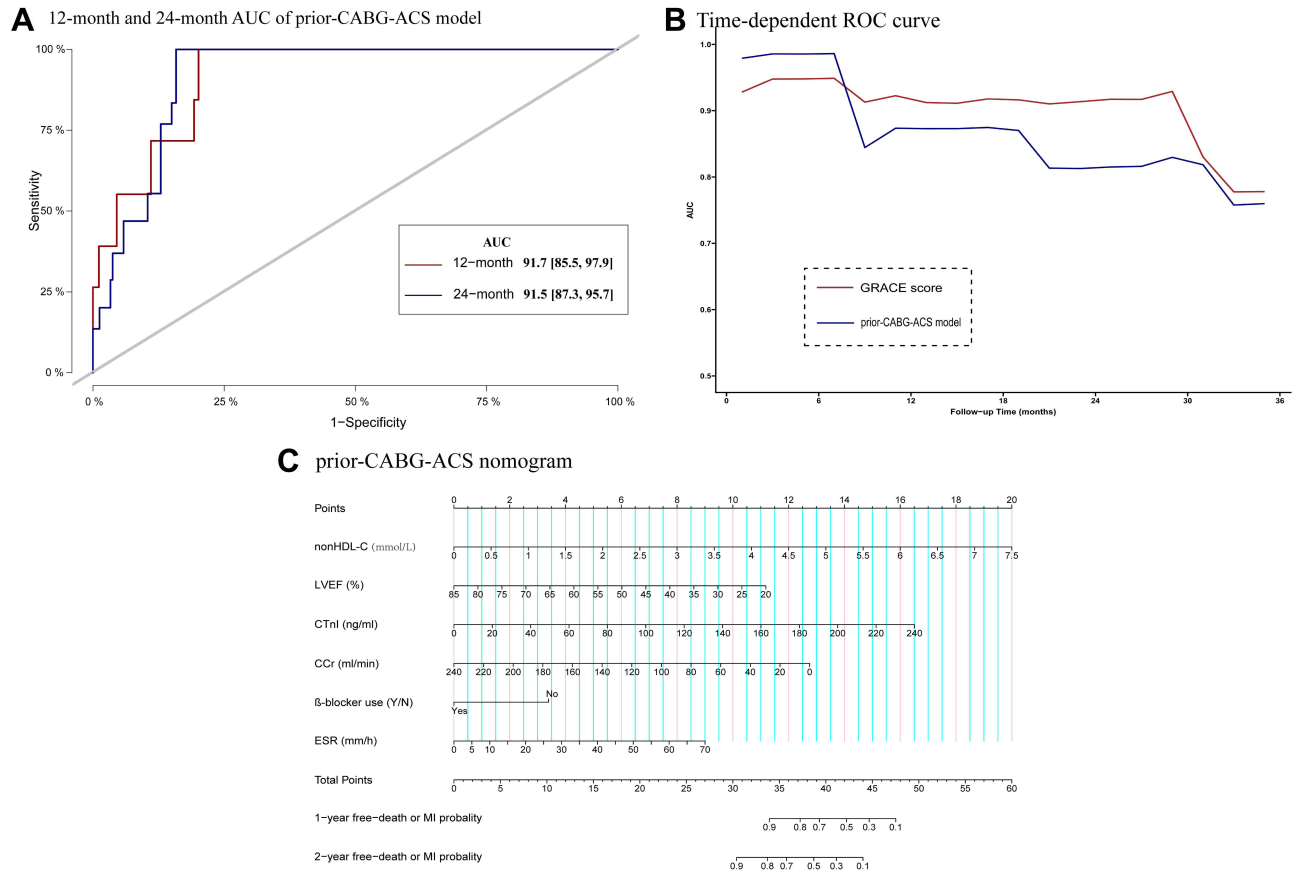

Figure 4 (**A**) The conventional receiver operating characteristic (ROC) curve of the prior-CABG-ACS model predicts 12- and 24-month MACEs. (**B**) The time-dependent receiver operating characteristic (ROC) curve for the prior-CABG-ACS model and GRACE risk score predicts long-term MACEs over 3 years. (**C**) A prior-CABG-ACS nomogram for predicting the probability of overall MACE-free chance at 1 and 2 years.

CV clinical events was more stable and durable than other lipid parameters.[9,10,18] In this study, we observed a linear relationship between long-term CV outcomes and serum concentrations of non-HDL-C in patients with prior CABG undergoing PCI. Non-HDL-C levels more than 2.6 mmol/L are probably robust and efficient risk markers of CV outcomes, consistent with the findings of Brunner et al.[17] Our findings suggest that non-HDL-C could be a secondary treatment target for assessing the residual risk of MACEs and intensifying lipid-lowering therapy for statin-treated patients with previous CABG.

Subjects with prior CABG have greater anatomical complexity and a higher risk of other complications (eg, peripheral vascular disease, chronic obstructive pulmonary disease, and renal insufficiency) and experience more fatal and nonfatal outcomes.[1,2,21] The GRACE risk score is a valid predictor of short-term outcomes following ACS, similar to the estimated 6-month post-discharge risk of death and reinfarction in this study.[22,23] In contrast, the validity of the GRACE score in predicting outcomes becomes unfathomable after ≥1 year, particularly in patients with prior CABG.[24–26] In this study, the time-dependent ROC curve of the prior-CABG-ACS model yielded validated predictions of short- and long-term MACEs in terms of discrimination and reclassification. Hironori et al (in the GLOBAL LEADERS trial)[27] found that the updated logistic clinical SYNTAX score had a reasonable predictive probability for 2-year all-cause death after PCI in patients with prior CABG; the area under the curve was 0.806 (95% CI: 0.714–0.899). However, in the setting of net adverse clinical events, this risk system performed poorly, with an area under the curve of 0.592 (95% CI: 0.500–0.685). Regardless of CV mortality, recurrent CV events are more frequent in patients with prior CABG than in those without prior CABG. In contrast, studies suggested that non-HDL-C improves the risk assessment of future coronary heart disease beyond LDL-C and TG and could be considered in a new model.[4,7,17] Except for the non-HDL-C, the literature suggests that five parameters in the prior-CABG-ACS model (ie, LVEF, CCr, CTNI, ESR, and β-blocker use) were related to CV outcomes and considered in various

prediction models.[28–31] Therefore, all six variables in this prior-CABG-ACS model were combined to facilitate the ASCVD risk assessment in patients with ACS with previous CABG at various timepoints.

Note that β-blocker treatment in patients with ACS with prior CABG reduced CV mortality and re-infarctions. Other secondary preventive medications might affect the protective effect of β-blockers; this phenomenon requires further study. According to previous studies,[32,33] beta-blocker treatment is associated with a reduced risk of MACE and MI occurrence. As reported in other studies, Lindgren et al[32] highlighted that this phenomenon may not apply to all patients undergoing CABG.[34,35] Hence, our findings support the notion that continued beta-blocker therapy improves the outcomes in patients with ACS with CABG following PCI.

Limitations

This study has several limitations. First, the prognostic discrimination of the models (AUC: 91.7 for 1-year MACE-free chance and 91.5 for 2-year MACE-free chance) was made without a validation cohort, and the performance was too idealized. Multicenter studies with larger patient populations might increase the model's generalizability and prognostic discrimination ability. Second, studies indicated that the all-cause mortality rate was 7% at 1 year,[1,28] which is much higher than what we have found in this study (3.2%). This discrepancy might be attributed to high ratios of native-vessel intervention, lower proportions of patients with acute MI, and the higher revascularization frequency, which might improve outcomes. In contrast, a similar prevalence of CV deaths was observed in another large-scale trial in China.[36] Hence, we speculate that the discrepancy is probably derived from the ethnic composition, contributing to selection bias. Third, a selection bias was inevitable because of the retrospective nature of this study. Extensive prospective studies and subgroup analyses are required.

Conclusions

Non-HDL-C is linearly associated with the risk of MACEs in patients with ACS with prior CABG undergoing PCI, independent of other lipid variables. When the level of non-HDL-C is more than 2.6 mmol/L, the risk of MACEs significantly increases. Models containing non-HDL and five other clinical parameters could provide an efficient and valid predictive tool for assessing residual MACE risk in this population.

Abbreviations

ACS, acute coronary syndrome; MACE, major adverse cardiovascular events; CAD, coronary artery disease; PCI, percutaneous coronary intervention; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; CABG, coronary artery bypass grafting; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; CCr, creatinine clearance rate; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; CTNI, cardiac troponin I; CKMB, creatine kinase–myocardial band; BMI, body mass index; LVEF, left ventricular ejection fraction; ROC, receiver operating characteristic; AUC, area under ROC; NRI, net reclassification improvement.

Data Sharing Statement

The datasets generated and analyzed are not publicly available because of the policies of the Beijing Chaoyang Hospital regarding individual confidentiality; however, they are available from the corresponding author upon reasonable request.

Ethics and Consent to Participate

This study was approved by the Ethics Committee of the Beijing Chaoyang Hospital with Capital Medical University. All procedures in this study were performed according to the ethical standards of the Beijing Chaoyang Hospital with Capital Medical University Research Committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Disclosure

All authors declare no conflicts of interest in this work.

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