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ORIGINAL RESEARCH

Apolipoprotein B/A1 Ratio for Predicting Major Adverse Cardiovascular Events in Coronary Artery Disease: Development and Validation of a Nomogram

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Background: The apolipoprotein B to apolipoprotein A1 (ApoB/A1) ratio has emerged as a superior lipid marker for cardiovascular risk assessment. This study aimed to develop and validate a nomogram incorporating the ApoB/A1 ratio for predicting major adverse cardiovascular events (MACE) in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI).

Methods: This retrospective cohort study included 2459 patients undergoing PCI, randomly allocated to training (n=1721) and validation (n=738) cohorts. LASSO regression and multivariable Cox regression were used for variable selection and model development. Model performance was evaluated using C-index, calibration curves, and decision curve analysis.

Results: During a median follow-up of 33.8 months, MACE occurred in 187 patients (7.6%). The ApoB/A1 ratio was independently associated with MACE (HR 1.12 per 0.1 increase, 95% CI 1.06–1.19, $P<0.001$). The nomogram incorporating 10 predictors demonstrated good discrimination (C-index: 0.67 in training, 0.72 in validation) and calibration. Decision curve analysis confirmed superior clinical utility across threshold probabilities of 5%–35%. Risk stratification showed distinct separation among low-, intermediate-, and high-risk groups, with 5-year MACE-free survival rates of 93.0%, 89.9%, and 83.1%, respectively (log-rank $P<0.001$).

Conclusion: The ApoB/A1 ratio may be an independent predictor of MACE in CAD patients after PCI. The developed nomogram showed promising performance for risk prediction and stratification in this retrospective cohort. External validation in prospective studies is warranted before clinical implementation.

Keywords: apolipoproteins B, apolipoprotein A-I, coronary artery disease, percutaneous coronary intervention, nomograms, prognosis

Introduction

Cardiovascular diseases (CVD) remain the leading cause of death globally, with approximately 19.8 million deaths reported in 2022.[1] Ischemic heart disease alone accounts for over half of these cardiovascular deaths, with an age-standardized mortality rate of 108.8 per 100,000 population.[2] Although percutaneous coronary intervention (PCI) has revolutionized the management of coronary artery disease (CAD), patients undergoing this procedure continue to face substantial risk of major adverse cardiovascular events (MACE) during follow-up, necessitating accurate risk stratification to guide secondary prevention strategies.[3]

The Global Registry of Acute Coronary Events (GRACE) score and Thrombolysis in Myocardial Infarction (TIMI) risk score are recommended by European and American guidelines for prognostic assessment in acute coronary syndrome (ACS).[4] Meta-analyses have demonstrated that the GRACE score achieves pooled C-statistics of 0.82 for short-term and 0.84 for long-term outcomes, while the TIMI score shows more variable performance depending on

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patient population.[5] However, these risk scores were primarily designed for short-term mortality prediction and inadequately incorporate lipid metabolism markers beyond routine cholesterol measurements.[6] Recent studies have highlighted the limitations of existing prediction models for long-term outcomes after PCI, with most nomograms achieving C-indices between 0.65 and 0.80.[7]

The apolipoprotein B (ApoB) to apolipoprotein A1 (ApoA1) ratio has gained increasing recognition as a superior lipid marker for cardiovascular risk assessment. ApoB represents the total burden of atherogenic lipoprotein particles including low-density lipoprotein (LDL), very-low-density lipoprotein, and lipoprotein(a), while ApoA1 reflects the atheroprotective capacity of high-density lipoprotein (HDL).[8] A cohort study demonstrated that elevated ApoB/A1 ratio was associated with increased risk of MACE across all age groups and both sexes, with hazard ratios (HR) reaching 2.7 for myocardial infarction (MI) in the highest decile compared with the lowest.[9] Recent study confirmed that the ApoB/A1 ratio independently predicted both macrovascular events and microvascular events, whereas traditional lipid markers predicted only macrovascular outcomes.[10] Furthermore, optical coherence tomography studies have demonstrated that elevated ApoB/A1 ratio is associated with vulnerable plaque characteristics including plaque rupture, erosion, and thrombus formation in patients with atherosclerotic cardiovascular disease.[11] These findings support that this ratio captures the balance between proatherogenic and antiatherogenic forces more effectively than individual lipid parameters.

Nomograms provide a practical tool for individualized risk prediction by integrating multiple prognostic factors into a visual scoring system. Several nomograms have been developed for predicting adverse outcomes after PCI, incorporating clinical, laboratory, and angiographic variables.[12,13] However, the integration of the ApoB/A1 ratio into a validated, multivariable prediction nomogram for post-PCI populations remains limited. A recent study reported that the ApoB/ApoA-I ratio was associated with one-year MACE in post-PCI patients,[14] yet this work was confined to short-term follow-up and did not yield a clinically applicable nomogram tool with formal internal validation. Moreover, few prior models have simultaneously incorporated the ApoB/A1 ratio alongside angiographic complexity, revascularization completeness, and statin intensity within a single validated prediction framework. Existing nomograms have largely been developed in unselected or single-syndrome populations, without stratified analyses examining whether the predictive value of the ApoB/A1 ratio is modified by clinical presentation (ACS versus stable CAD) or lipid-lowering treatment status. Therefore, this study aimed to develop and internally validate a nomogram incorporating the ApoB/A1 ratio for predicting MACE in patients with CAD undergoing PCI, using a large single-center cohort with extended follow-up. This approach aimed to produce a readily implementable risk stratification tool to guide individualized secondary prevention in clinical practice.

Materials and Methods

Study Design

This retrospective cohort study was conducted at Haidian Hospital, a tertiary cardiac center in China. Consecutive patients who underwent PCI between January 2018 and December 2022 were screened for eligibility. The study protocol was approved by the Institutional Ethics Committee of Haidian Hospital (approval number: M202619) and was conducted in accordance with the Declaration of Helsinki. Given the retrospective nature of this study, the requirement for written informed consent was waived. All patient data were anonymized/de-identified before analysis, and confidentiality of personal information was strictly protected throughout the study. This study was reported following the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.

Patient Selection

Patients were eligible for inclusion if they were aged ≥18 years, confirmed CAD diagnosis, underwent PCI for the first time during the index hospitalization, and had complete ApoB and ApoA1 measurement at admission. Patients were excluded if they had severe hepatic dysfunction, severe renal insufficiency, active malignancy or life expectancy less than one-year, cardiogenic shock or requirement for mechanical circulatory support during hospitalization, missing data for more than 20% of key variables, or were lost to follow-up.

The eligible patients were randomly allocated to a training cohort and a validation cohort at a ratio of 7:3 using computer-generated random numbers. Randomization was stratified by clinical presentation to ensure balanced distribution of patients with acute coronary syndrome and stable coronary artery disease between the two cohorts. The training cohort was used for variable selection and nomogram development, while the validation cohort was reserved for internal validation of model performance.

Data Collection

Baseline data were extracted from the electronic medical record system by trained investigators using a standardized case report form. The following categories of variables were collected:

(1) Demographic and clinical characteristics: age, sex, body mass index (BMI), smoking status (current, former, or never), comorbidities. Cardiac function was assessed by left ventricular ejection fraction (LVEF).
(2) Laboratory measurements: results of lipid profile tests performed at admission were extracted, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), ApoB, and ApoA1. Additional laboratory parameters retrieved included serum creatinine, estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, fasting plasma glucose, glycated hemoglobin (HbA1c), high-sensitivity C-reactive protein (hs-CRP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP).
(3) Angiographic and procedural data: coronary angiography reports were reviewed to determine the number of diseased vessels. The SYNTAX score was extracted from the procedural records. Procedural variables retrieved included complete versus incomplete revascularization, type of stent implanted (drug-eluting stent [DES] or bare-metal stent [BMS]), total number of stents, and total stent length.
(4) Medication data: statin therapy was documented at two time points, including statin use prior to admission and statin prescription at discharge. Statin intensity was categorized as high-intensity (atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily), moderate-intensity (atorvastatin 10–20 mg, rosuvastatin 5–10 mg, or simvastatin 20–40 mg daily), or low-intensity (simvastatin 10 mg, pravastatin 10–20 mg, or fluvastatin 20–40 mg daily). Other cardiovascular medications at discharge were also recorded, including antiplatelet agents, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), and calcium channel blockers (CCB).

Outcomes and Follow-Up

The primary endpoint was MACE, defined as a composite of all-cause death, non-fatal MI, and stroke. All-cause death was ascertained from hospital records and regional death registry databases. Non-fatal MI was defined as evidence of myocardial necrosis with elevated cardiac troponin values and clinical evidence of acute myocardial ischemia. Stroke was defined as an acute neurological deficit lasting more than 24 hours with confirmation by computed tomography or magnetic resonance imaging.

Outcome ascertainment was performed retrospectively through review of electronic medical records, including hospital readmission records, outpatient clinic documentation, and telephone encounter notes from routine clinical care. Vital status for patients without documented clinical contact was verified through the regional mortality registry database. The follow-up period was calculated from the date of index PCI to the first MACE occurrence, death, last documented contact, or endpoint of this study, whichever occurred first.

Statistical Analysis

Normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) accordingly, and compared using Student's *t*-test or Mann–Whitney *U*-test. Categorical variables were presented as frequencies (percentages) and compared using chi-square or Fisher's exact test. Missing data were handled by median imputation (<5% missingness) or multiple imputation (5–20% missingness, m=5).

Variable selection was performed using least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation in the training cohort. The optimal λ was determined at one standard error above the minimum. The ApoB/A1 ratio and statin intensity were retained in all models given their a priori clinical importance. Variables with non-zero coefficients in LASSO regression were entered into multivariable Cox proportional hazards regression. Multicollinearity was assessed using variance inflation factor (VIF >5 indicating collinearity). The proportional hazards assumption was tested using Schoenfeld residuals. A nomogram was constructed using the "rms" package.

Model discrimination was assessed using Harrell's C-index and time-dependent area under the curve at 1, 2, and 3 years. Calibration was evaluated by calibration curves. Internal validation was performed using bootstrap resampling (B=1000). Clinical utility was assessed by decision curve analysis.

Subgroup analyses were conducted across statin intensity, age, sex, diabetes status, and clinical presentation, with interaction tested (P<0.10 indicating significant interaction). Sensitivity analysis was performed excluding patients without statin therapy. Optimal cutoff values were determined using X-tile software, and survival curves were compared using Log rank test. Analyses were performed using R version 4.3.0, with two-sided P<0.05 considered significant.

Results

Patient Characteristics

A total of 2459 patients were included in the final analysis after applying inclusion and exclusion criteria (Figure 1). Patients were randomly assigned to the training cohort (n = 1721) and validation cohort (n = 738) at a ratio of 7:3.

The baseline characteristics of both cohorts are presented in Table 1. The mean age was 62.93 ± 10.72 years, and 1846 patients (75.07%) were male. Hypertension was present in 1587 patients (64.54%), diabetes mellitus in 770 (31.31%), and current smoking in 1040 (42.29%). A total of 1680 patients (68.32%) presented with acute coronary syndrome. The median ApoB/A1 ratio was 0.78 (interquartile range, 0.62–0.96). Drug-eluting stents were implanted in 2374 patients (96.54%), and 2380 patients (96.79%) were prescribed statin therapy at discharge, with 847 (34.44%) receiving high-intensity regimens. The training and validation cohorts were well balanced for most variables, although differences were observed in BMI, LVEF, hs-CRP, and NT-proBNP levels (all P < 0.05).

The median follow-up duration was 33.8 months (interquartile range, 22.4–45.9 months). During follow-up, MACE occurred in 187 patients (7.6%), including 130 events (7.6%) in the training cohort and 57 events (7.7%) in the validation cohort. The components of MACE included all-cause death in 63 patients (2.6%), non-fatal myocardial infarction in 68 patients (2.8%), and stroke in 56 patients (2.3%).

Variable Selection and Independent Predictors

A total of 20 candidate variables were considered for model development. LASSO regression with 10-fold cross-validation shrunk the coefficients of 9 variables to zero, including sex, BMI, hypertension, current smoking, triglycerides, HbA1c, total stent length, beta-blocker use, and ACEI/ARB use. Together with the prespecified variables (ApoB/A1 ratio and statin intensity), the remaining 10 variables with non-zero coefficients were entered into multivariable Cox regression. No multicollinearity was detected among the predictors (all VIF < 5). The proportional hazards assumption was satisfied for all variables (all $P > 0.05$ by Schoenfeld residuals test).

In multivariable Cox regression analysis (Table 2), the ApoB/A1 ratio was independently associated with increased MACE risk (HR 1.12 per 0.1 increase, 95% CI 1.06–1.19, P < 0.001). Other independent predictors included age (HR 1.28 per 10 years, 95% CI 1.09–1.51, P = 0.003), diabetes mellitus (HR 1.42, 95% CI 1.05–1.92, P = 0.024), decreased LVEF (HR 1.16 per 5% decrease, 95% CI 1.04–1.29, P = 0.008), decreased eGFR (HR 1.09 per 10 mL/min/1.73m^2 decrease, 95% CI 1.01–1.18, P = 0.032), elevated hs-CRP (HR 1.05 per 1 mg/L, 95% CI 1.02–1.09, P = 0.042), elevated NT-proBNP (HR 1.03 per 100 pg/mL, 95% CI 1.01–1.05, P = 0.006), and higher SYNTAX score (HR 1.14 per 5 points, 95% CI 1.03–1.26, P = 0.012). Complete revascularization was associated with reduced MACE risk (HR 0.71, 95% CI 0.52–0.96, P = 0.028). Compared with high-intensity statin therapy, moderate-intensity (HR 1.35, 95% CI 1.01–1.82, P = 0.046) and low-intensity or no statin therapy (HR 1.68, 95% CI 1.12–2.52, P = 0.012) were associated with increased MACE risk.

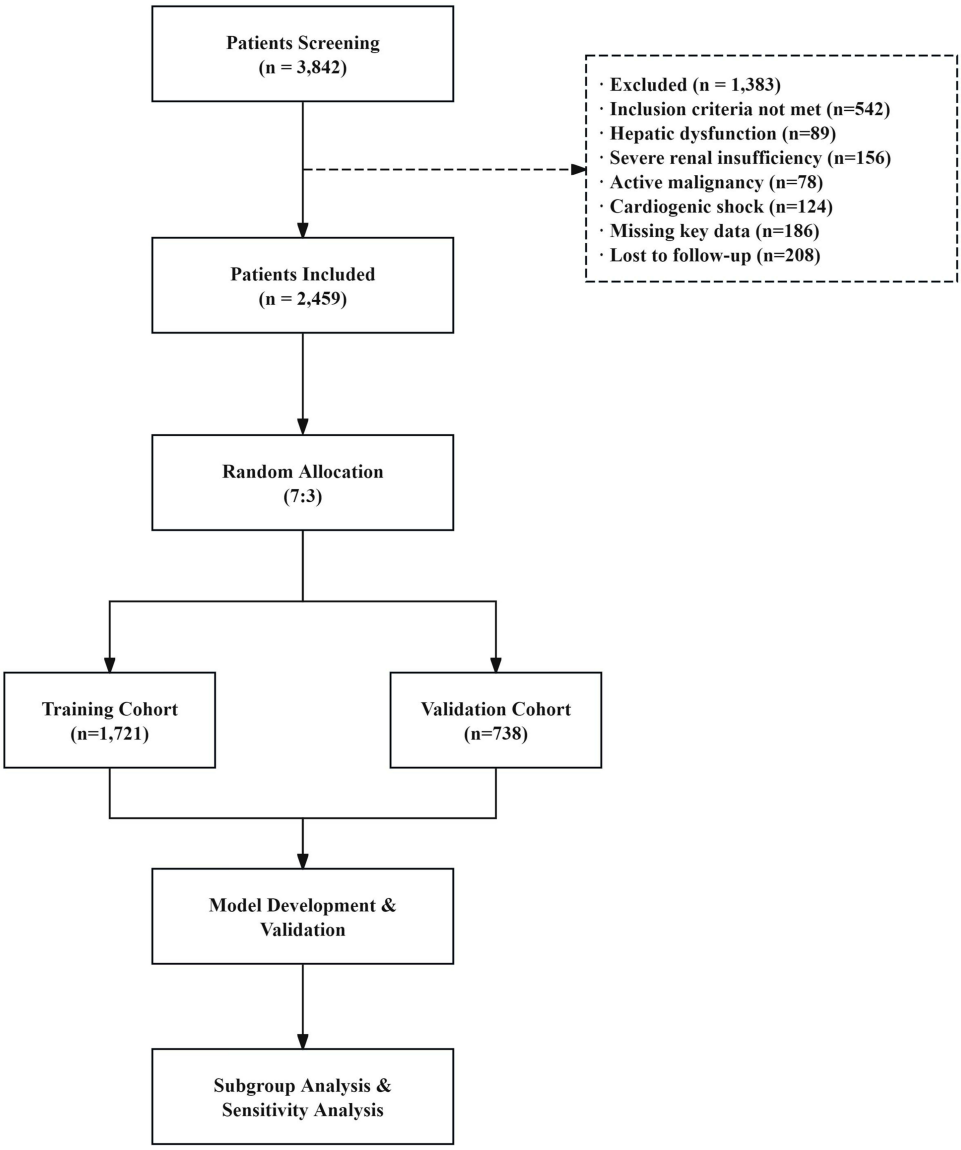

Figure 1 Study Flow Diagram.

Nomogram Development and Performance

Based on the multivariable Cox regression analysis, a nomogram was constructed incorporating ten independent predictors for estimating the probability of MACE at 1, 2, and 3 years (Figure 2A). The predictors included age, diabetes mellitus, LVEF, ApoB/A1 ratio, eGFR, hs-CRP, NT-proBNP, SYNTAX score, complete revascularization, and statin intensity. Each predictor was assigned a point value according to its regression coefficient, and the total points corresponded to the predicted probability of MACE-free survival.

The discriminative ability of the nomogram was evaluated using time-dependent ROC analysis (Figure 2B). In the training cohort, the AUC was 0.699 at 1 year, 0.683 at 2 years, and 0.694 at 3 years. In the validation cohort, the corresponding AUC values were 0.660, 0.691, and 0.715, respectively. The model demonstrated stable discrimination across different time points, with slightly improved performance for longer-term prediction in the validation cohort. The nomogram demonstrated good discrimination in both cohorts. The Harrell's C-index was 0.67 (95% CI: 0.63–0.73) in the training cohort and 0.72 (95% CI: 0.64–0.78) in the validation cohort. Bootstrap internal validation with 1000 resamples yielded an optimism-corrected C-index of 0.67, confirming the robustness of the model performance. Calibration curves

Table 1 Baseline Characteristics of Patients in the Training and Validation Sets

Variable	Total (n=2459)	Training (n=1721)	Validation (n=738)	*P* value
Age, years	62.93 ± 10.72	62.85 ± 10.50	63.10 ± 11.21	0.599[a]
Male, n (%)	1846 (75.07)	1289 (74.90)	557 (75.47)	0.801[b]
BMI, kg/m^2	24.84 ± 3.17	24.75 ± 3.11	25.05 ± 3.29	0.030[a]
Hypertension, n (%)	1587 (64.54)	1109 (64.44)	478 (64.77)	0.912[b]
Diabetes mellitus, n (%)	770 (31.31)	524 (30.45)	246 (33.33)	0.172[b]
Current smoker, n (%)	1040 (42.29)	737 (42.82)	303 (41.06)	0.442[b]
Acute coronary syndrome, n (%)	1680 (68.32)	1180 (68.56)	500 (67.75)	0.726[b]
LVEF, %	56.11 ± 8.79	56.39 ± 8.62	55.47 ± 9.13	0.017[a]
ApoB, g/L	0.91 ± 0.24	0.92 ± 0.24	0.91 ± 0.23	0.823[a]
ApoA1, g/L	1.18 ± 0.22	1.18 ± 0.22	1.18 ± 0.22	0.353[a]
ApoB/A1 ratio	0.78 (0.62–0.96)	0.78 (0.62–0.97)	0.77 (0.62–0.96)	0.354[c]
Total cholesterol, mmol/L	4.31 ± 1.03	4.32 ± 1.03	4.29 ± 1.03	0.585[a]
Triglycerides, mmol/L	1.51 (1.08–2.14)	1.49 (1.07–2.15)	1.56 (1.08–2.12)	0.348[c]
LDL-C, mmol/L	2.61 ± 0.85	2.62 ± 0.85	2.60 ± 0.85	0.622[a]
HDL-C, mmol/L	1.09 ± 0.28	1.09 ± 0.28	1.09 ± 0.27	0.847[a]
eGFR, mL/min/1.73m^2	83.40 (70.80–99.50)	83.20 (71.30–98.90)	83.70 (69.95–100.65)	0.738[c]
HbA1c, %	6.25 (5.48–7.20)	6.26 (5.48–7.18)	6.22 (5.48–7.27)	0.825[c]
hs-CRP, mg/L	3.33 (1.68–6.37)	3.17 (1.55–6.07)	3.89 (2.00–7.30)	<0.001[c]
NT-proBNP, pg/mL	284.30 (145.55–544.20)	273.90 (142.30–526.80)	314.80 (155.62–590.35)	0.022[c]
Number of diseased vessels, n (%)				0.189[b]
1 vessel	700 (28.47)	508 (29.52)	192 (26.02)	
2 vessels	839 (34.12)	574 (33.35)	265 (35.91)	
3 vessels	920 (37.41)	639 (37.13)	281 (38.08)	
SYNTAX score	17.80 (13.40–23.40)	17.80 (13.40–23.20)	17.85 (13.53–23.58)	0.947[c]
Complete revascularization, n (%)	1607 (65.35)	1123 (65.25)	484 (65.58)	0.911[b]
Drug-eluting stent, n (%)	2374 (96.54)	1653 (96.05)	721 (97.70)	0.054[b]
Number of stents	2.00 (1.00–3.00)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	0.871[c]
Total stent length, mm	48.00 (33.00–65.00)	48.00 (34.00–65.00)	47.00 (33.00–65.00)	0.962[c]
Statin use, n (%)	2380 (96.79)	1663 (96.63)	717 (97.15)	0.581[b]
Statin intensity, n (%)				0.493[b]
High-intensity	847 (34.44)	585 (33.99)	262 (35.50)	
Moderate-intensity	1224 (49.78)	870 (50.55)	354 (47.97)	
Low-intensity or none	388 (15.78)	266 (15.46)	122 (16.53)	
Dual antiplatelet therapy, n (%)	2424 (98.58)	1696 (98.55)	728 (98.64)	0.999[b]
Beta-blocker, n (%)	1957 (79.59)	1366 (79.37)	591 (80.08)	0.730[b]
ACEI/ARB, n (%)	1585 (64.46)	1110 (64.50)	475 (64.36)	0.986[b]

Notes: Data are presented as mean ± SD, median (interquartile range), or n (%). [a]Student's *t*-test; [b]Chi-square test; [c]Mann–Whitney *U*-test.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

demonstrated good concordance between the nomogram-predicted probabilities and the observed MACE rates in both cohorts (Figure 2C).

Clinical Utility and Risk Stratification

Decision curve analysis was performed to evaluate the clinical utility of the nomogram (Figure 3A). Across a wide range of threshold probabilities (approximately 5% to 35%), the nomogram demonstrated greater net benefit compared with both the "treat all" and "treat none" strategies, particularly in the training cohort. In the validation cohort, the nomogram showed similar trends, although net benefit approached zero at certain threshold probabilities around 20%.

Table 2 Multivariable Cox Regression Analysis for Major Adverse Cardiovascular Events

Variable	HR	95% CI	P value	VIF
Age (per 10 years)	1.28	1.09–1.51	0.003	1.24
Diabetes mellitus	1.42	1.05–1.92	0.024	1.18
Acute coronary syndrome	1.38	0.98–1.94	0.068	1.15
LVEF (per 5% decrease)	1.16	1.04–1.29	0.008	1.32
ApoB/A1 ratio (per 0.1 increase)	1.12	1.06–1.19	<0.001	1.28
eGFR (per 10 mL/min/1.73m^2 decrease)	1.09	1.01–1.18	0.032	1.41
hs-CRP (per 1 mg/L increase)	1.05	1.02–1.09	0.042	1.22
NT-proBNP (per 100 pg/mL increase)	1.03	1.01–1.05	0.006	1.38
SYNTAX score (per 5 points)	1.14	1.03–1.26	0.012	1.35
Complete revascularization	0.71	0.52–0.96	0.028	1.19
Statin intensity			0.018	1.12
High-intensity	Reference	—	—	
Moderate-intensity	1.35	1.01–1.82	0.046	
Low-intensity or none	1.68	1.12–2.52	0.012	

Abbreviations: ApoB/A1, apolipoprotein B to apolipoprotein A1; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LASSO, least absolute shrinkage and selection operator; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VIF, variance inflation factor.

To assess the risk stratification capability of the nomogram, patients were divided into three risk groups based on the predicted probability of MACE: low-risk, intermediate-risk, and high-risk groups. Kaplan-Meier survival analysis revealed significant differences in MACE-free survival among the three groups (Figure 3B, log-rank P<0.001). The 5-year MACE-free survival rates were 93.0% (95% CI: 91.2–94.8%) for the low-risk group, 89.9% (95% CI: 87.8–92.0%) for the intermediate-risk group, and 83.1% (95% CI: 80.7–85.5%) for the high-risk group. Patients in the high-risk group had a 2.4-fold higher cumulative incidence of MACE compared with those in the low-risk group (16.9% vs. 7.0%), suggesting that the nomogram effectively identifies patients who may benefit from intensified secondary prevention strategies.

Subgroup and Sensitivity Analyses

Subgroup analyses were performed to evaluate the consistency of the association between ApoB/A1 ratio and MACE across clinically relevant patient subgroups (Figure 4). The prognostic value of ApoB/A1 ratio was consistent across subgroups stratified by age (<65 vs. ≥65 years), sex, diabetes status, and statin intensity, with no significant interactions detected (all *P* for interaction > 0.05). However, a significant interaction was observed between clinical presentation and the effect of ApoB/A1 ratio on MACE risk (*P* for interaction = 0.029). In patients presenting with ACS, elevated ApoB/A1 ratio was significantly associated with increased MACE risk (HR 1.14 per 0.1 increase, 95% CI 1.09–1.19), whereas this association was not observed in patients with stable CAD (HR 1.00, 95% CI 0.89–1.12). This finding suggests that the predictive value of ApoB/A1 ratio may be more pronounced in the setting of acute plaque instability.

Sensitivity analyses confirmed the robustness of the primary findings (Table 3). The association between ApoB/A1 ratio and MACE remained consistent after excluding patients without statin therapy (HR 1.11, 95% CI 1.06–1.16), excluding early events within 30 days (HR 1.12, 95% CI 1.07–1.17), and when analyzed separately in the training cohort (HR 1.12, 95% CI 1.06–1.18) and validation cohort (HR 1.11, 95% CI 1.03–1.20).

Discussion

The primary findings of this study demonstrated that the ApoB/A1 ratio may serve as an independent predictor of hard cardiovascular endpoints, including all-cause death, myocardial infarction, and stroke, even after adjustment for statin therapy intensity. The developed nomogram exhibited satisfactory discriminative ability and calibration in both the training and validation cohorts. DCA confirmed that the nomogram provides clinical net benefit across a range of

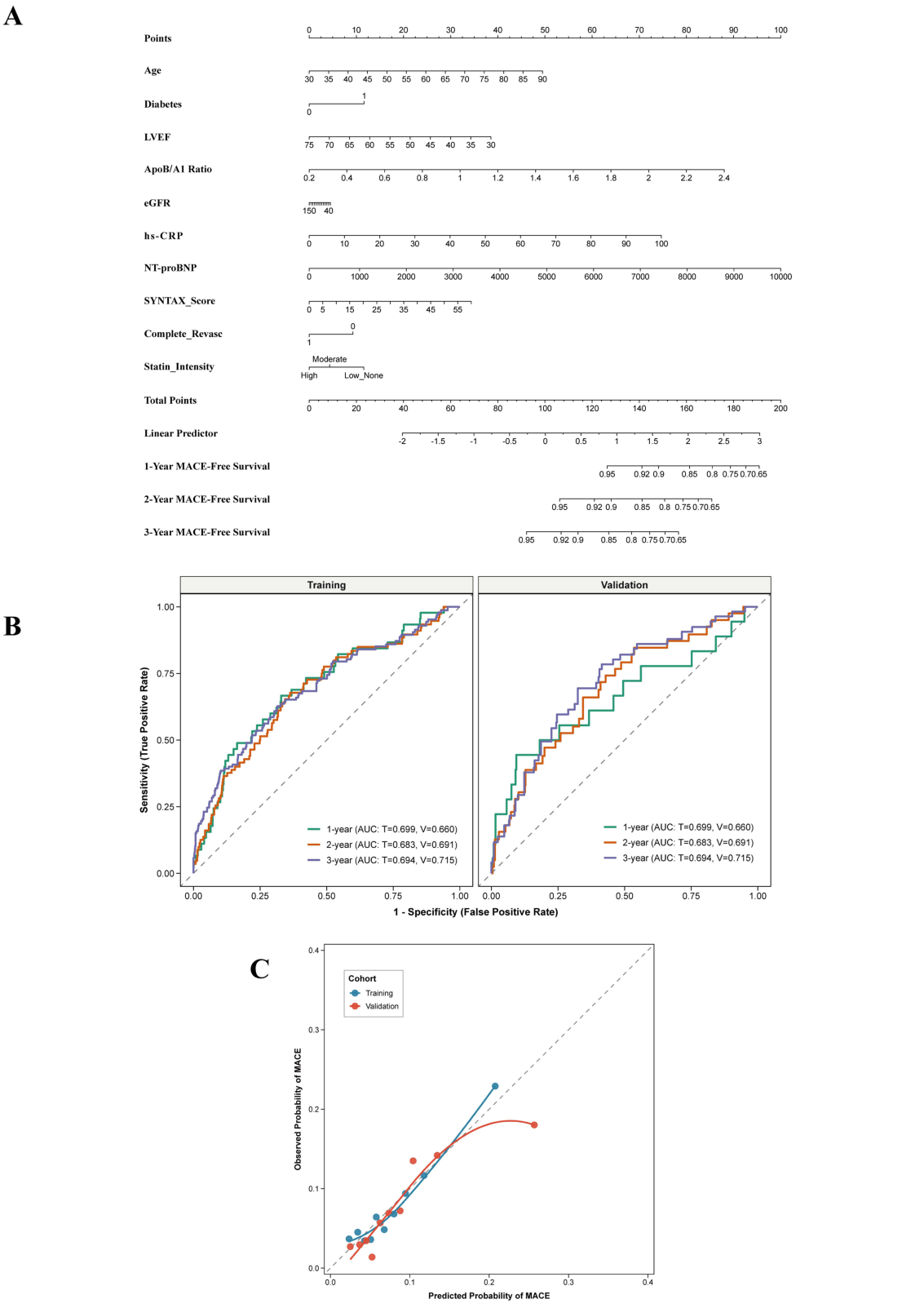

Figure 2 Nomogram for Predicting Major Adverse Cardiovascular Events and Model Performance. (**A**) Nomogram for predicting 1-, 2-, and 3-year probability of major adverse cardiovascular events. (**B**) Time-dependent receiver operating characteristic curves for predicting MACE at 1 year (green), 2 years (Orange), and 3 years (blue) in the training and validation cohorts. The area under the curve (AUC) values are shown for each time point (T, training cohort; V, validation cohort); (**C**) Calibration curves comparing the predicted probability and observed probability of MACE in the training cohort (blue) and validation cohort (red). The dashed diagonal line represents perfect calibration.

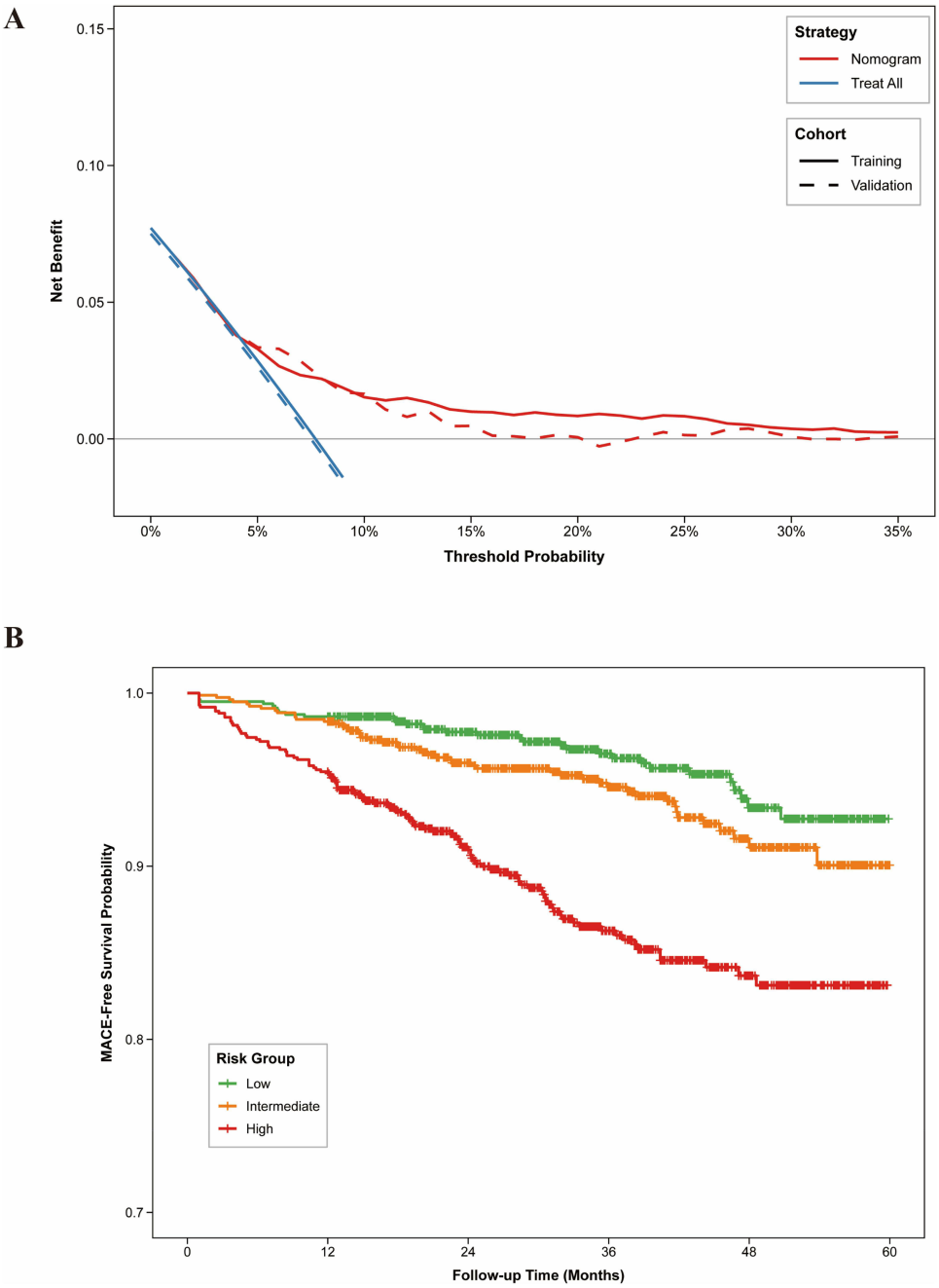

Figure 3 Clinical Utility and Risk Stratification of the Nomogram. (**A**) Decision curve analysis comparing net benefit of the nomogram with treat-all and treat-none strategies. The red lines represent the nomogram, and the blue lines represent the treat-all strategy. Solid lines indicate the training cohort, whereas dashed lines indicate the validation cohort. (**B**) Kaplan-Meier curves for event-free survival stratified by nomogram risk score. The green line indicates the low-risk group, the Orange line indicates the intermediate-risk group, and the red line indicates the high-risk group.

threshold probabilities, supporting its practical utility in risk stratification. Subgroup analyses further revealed that the predictive value of the ApoB/A1 ratio remained consistent across different statin intensity categories, age groups, and sex, and diabetes, suggesting its robustness as a risk marker independent of lipid-lowering treatment status. The present study extends prior work by adding the ApoB/A1 ratio within a comprehensive 10-predictor nomogram that simultaneously accounts for hemodynamic status, angiographic complexity, revascularization completeness, and statin intensity. The cohort comprised 2459 patients with a median follow-up of 33.8 months, and the model underwent formal bootstrap internal validation, yielding a clinically deployable risk stratification tool.

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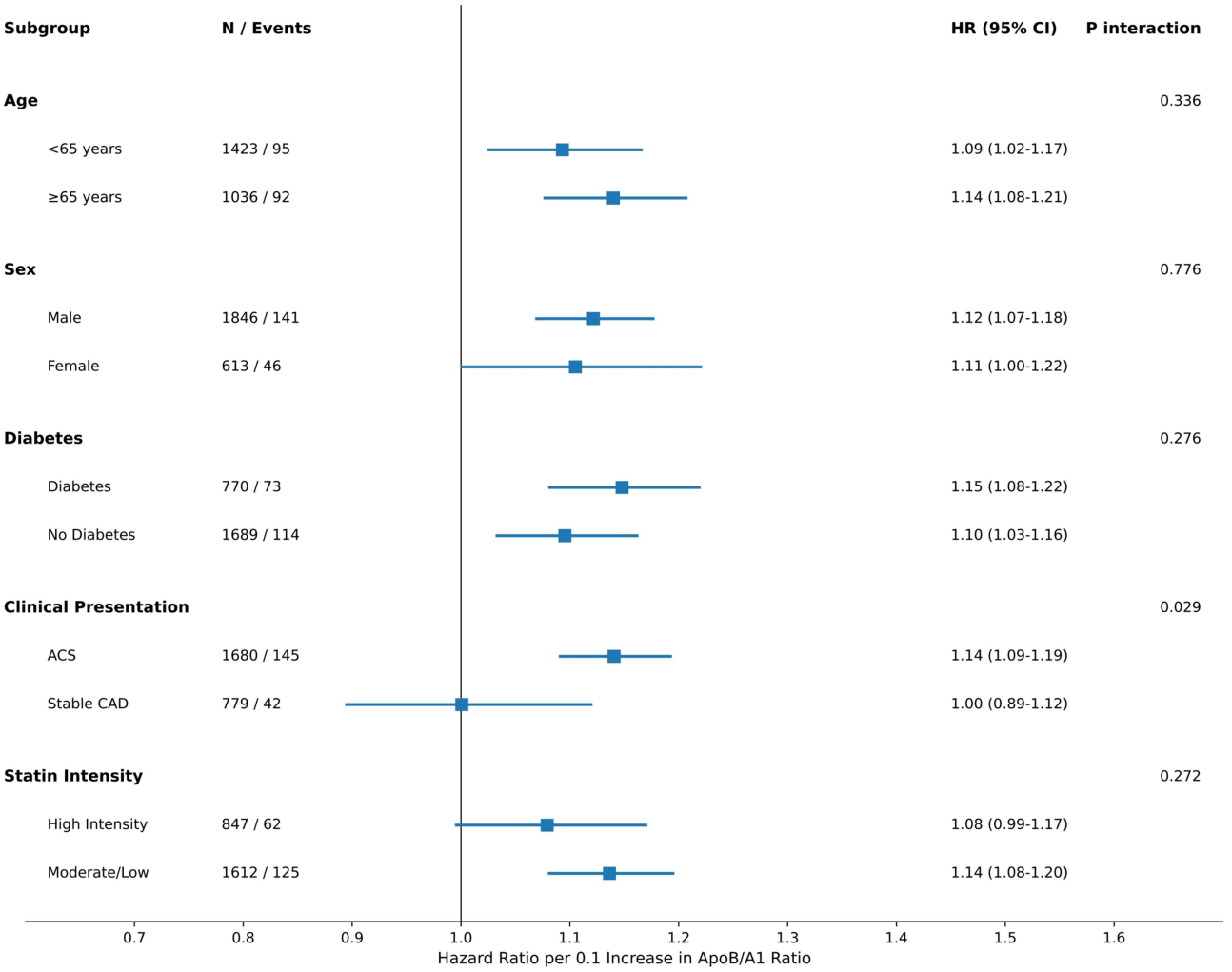

Figure 4 Subgroup Analyses for the Association Between Apolipoprotein B/A1 Ratio and MACE. Forest plot depicting the hazard ratios (HR) and 95% confidence intervals (CI) for the association between ApoB/A1 ratio (per 0.1 increase) and MACE across prespecified subgroups. Subgroups were defined by age (<65 vs. ≥65 years), sex (male vs. female), diabetes status (yes vs. no), clinical presentation (acute coronary syndrome vs. stable coronary artery disease), and statin intensity (high vs. moderate/low). The squares represent the point estimates of HR, and the horizontal lines indicate the 95% CI. The vertical line at HR = 1.0 represents the null effect. P values for interaction were calculated using likelihood ratio tests comparing models with and without the interaction term.

The prognostic significance of the ApoB/A1 ratio can be explained by its biological representation of the balance between proatherogenic and antiatherogenic lipoprotein particles. ApoB reflects the total burden of atherogenic particles, including low-density lipoprotein, very-low-density lipoprotein, intermediate-density lipoprotein, and lipoprotein(a),

Table 3 Sensitivity Analyses for the Association Between Apolipoprotein B/A1 Ratio and Major Adverse Cardiovascular Events

Analysis	N	Events	HR (95% CI)	*P* value
Primary analysis (all patients)	2459	187	1.12 (1.06–1.19)	<0.001
Excluding patients without statin therapy	2380	182	1.11 (1.06–1.16)	<0.001
Excluding early events (≤30 days)	2449	177	1.12 (1.07–1.17)	<0.001
Excluding severe renal dysfunction (eGFR <30)	2459	187	1.12 (1.07–1.17)	<0.001
Training cohort only	1721	130	1.12 (1.06–1.18)	<0.001
Validation cohort only	738	57	1.11 (1.03–1.20)	0.004
ACS patients only	1680	145	1.14 (1.09–1.19)	<0.001

Note: Hazard ratios are expressed per 0.1 increase in ApoB/A1 ratio.
Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

while ApoA1 represents the atheroprotective capacity of high-density lipoprotein through reverse cholesterol transport.[8,15] The current findings aligned with prior epidemiological study: in 137,100 individuals followed for 17.8 years, the highest decile of ApoB/A1 ratio was associated with HR of 1.7 for MACE and 2.7 for myocardial infarction compared with the lowest decile.[9] Similarly, in type 2 diabetes patients, elevated ApoB/A1 ratio was associated with increased macrovascular events (HR= 1.13) and microvascular events (HR= 1.19).[10] A recent study in 1938 post-PCI patients reported that high ApoB/A1 ratio was significantly associated with one-year MACE.[14] Mendelian randomization analyses have further confirmed the causal relationship between elevated ApoB/A1 ratio and MACE, supporting biological plausibility.[16] In patients with recent acute coronary syndrome, achieved ApoB was predictive of MACE after adjustment for achieved LDL cholesterol, but not vice versa, indicating that ApoB provides incremental prognostic information beyond traditional lipid markers.[17] Even modest discordance between ApoB and LDL particle number was associated with elevated cardiovascular risk, with hazard ratios reaching 2.5 for coronary artery disease at 30% discordance.[18] The present investigation extends these observations by establishing a validated prediction tool specifically for the post-PCI population receiving contemporary guideline-directed therapy.

It is worth noting that ApoB structurally incorporates the apolipoprotein B-100 moiety present on Lp(a) particles, and elevated Lp(a) levels may therefore partially contribute to a higher ApoB/A1 ratio.[8] Lp(a) is an established independent cardiovascular risk factor with particular relevance in the post-PCI setting. A meta-analysis of 18 studies encompassing 18,168 ACS patients confirmed that elevated Lp(a) independently predicts MACE and all-cause mortality.[19] JACC data further demonstrated significant associations between Lp(a) biomarkers and MACE in patients undergoing coronary angiography, even after multivariable adjustment.[20] Although the ApoB/A1 ratio may partially capture Lp(a)-related atherogenic risk through its ApoB component, the two markers are not interchangeable. Lp(a) additionally confers prothrombotic and pro-inflammatory effects that operate independently of standard lipid metabolism pathways. Given that Lp(a) was not systematically measured in the present cohort, its independent contribution to MACE risk could not be disentangled from the broader ApoB-mediated atherogenic burden reflected by the ApoB/A1 ratio.

The high prevalence of statin use in the study population reflects real-world clinical practice patterns following PCI. Despite the beneficial effects of statins on lowering ApoB-containing lipoproteins, the ApoB/A1 ratio continued to predict adverse outcomes in this statin-treated cohort. In 13,015 statin-treated patients from the Copenhagen general population study with 8-year follow-up, elevated ApoB but not LDL cholesterol was associated with increased all-cause mortality (HR=1.21) and myocardial infarction (HR=1.49) when there was discordance between these markers.[21] Statins predominantly reduce ApoB through hepatic LDL receptor upregulation while having modest effects on ApoA1.[22] Serial optical coherence tomography demonstrated that achieving ApoB <65 mg/dL was associated with greater plaque stabilization, including increased fibrous cap thickness and lower prevalence of thin-cap fibroatheroma, directly linking ApoB reduction to favorable plaque remodeling.[23] Consequently, post-treatment ApoB/A1 ratio may capture residual lipid-related cardiovascular risk not reflected by LDL cholesterol targets. The National Lipid Association Expert Consensus emphasized that ApoB and non-HDL cholesterol are stronger predictors of residual risk than LDL cholesterol in statin-treated patients.[24]

Beyond lipid-related risk, the present model highlights the complementary prognostic contribution of hemodynamic biomarkers. In the multivariable Cox regression analysis, both decreased LVEF and elevated NT-proBNP emerged as independent predictors of MACE. These findings are consistent with their well-established roles in cardiovascular risk stratification. NT-proBNP reflects myocardial wall stress and neurohormonal activation. It has been demonstrated to independently predict long-term MACE in post-PCI patients, including in the context of left main coronary artery intervention.[25] Data from the PARADISE-MI trial further confirmed that NT-proBNP identifies patients with hemodynamically more significant myocardial infarction. Such patients face elevated risks of subsequent heart failure and recurrent coronary events, independent of high-sensitivity troponin levels.[25] Prior prediction models have tended to focus on either lipid metabolism or cardiac function in isolation. The concurrent inclusion of the ApoB/A1 ratio alongside LVEF and NT-proBNP within a single nomogram addresses this gap. This integration may better reflect the dual pathophysiological pathways driving long-term adverse events after PCI, namely ongoing atherogenic burden and underlying left ventricular dysfunction.

Subgroup analyses revealed that the predictive value of ApoB/A1 ratio was consistent across most pre-specified subgroups, including age, sex, diabetes status, and statin therapy intensity, with no significant effect modification observed. However, a significant interaction was identified between clinical presentation and the prognostic effect of ApoB/A1 ratio. In patients presenting with acute coronary syndrome, elevated ApoB/A1 ratio was significantly associated with increased MACE risk, whereas this association was attenuated in patients with stable coronary artery disease. Acute coronary syndrome is characterized by vulnerable plaques with thin fibrous caps, large lipid cores, and active inflammation.[26] Optical coherence tomography studies have demonstrated that ApoB/A1 ratio is significantly higher in acute coronary syndrome patients compared with chronic coronary syndrome patients, and correlates with vulnerable plaque features including plaque rupture and erosion.[11] In this inflammatory milieu, elevated atherogenic lipoprotein particles may more readily penetrate the dysfunctional endothelium and accelerate plaque destabilization, explaining the stronger prognostic association observed in acute coronary syndrome patients.[27] The sensitivity analyses, including different cutoff values for ApoB/A1 ratio, yielded consistent results, further strengthening the robustness of these findings.

The developed nomogram addresses important gaps in existing risk prediction tools. The GRACE score, while achieving C-statistics of 0.82–0.84 for acute coronary syndrome outcomes, primarily targets short-term mortality and does not incorporate apolipoprotein-based markers.[5] A systematic review of 23 MACE prediction models after PCI found that most achieved C-indices between 0.65 and 0.80, with few incorporating lipid metabolism biomarkers beyond conventional cholesterol measurements.[11] Recent nomograms incorporating novel lipid-related indices have shown improved performance: a model using triglyceride-glucose index achieved C-index of 0.77–0.79 in STEMI patients, while another incorporating HbA1c/ApoA1 ratio demonstrated C-index of 0.77–0.79.[12,28] A nomogram for chronic total occlusion PCI incorporating conventional variables achieved C-index of 0.715.[13] The current model, by integrating ApoB/A1 ratio with clinical, hemodynamic and procedural variables, provides individualized long-term risk estimation. The clinical utility of this nomogram extends to guiding secondary prevention intensification. Patients identified as high-risk may benefit from PCSK9 inhibitors, which reduce MACE by approximately 15–20% in high-risk populations.[29,30] Meta-analyses have demonstrated that each 10 mg/dL reduction in ApoB is associated with 5–7% reduction in cardiovascular mortality.[31] Lifestyle interventions including dietary modification and weight reduction can favorably modulate the ApoB/A1 ratio and should be emphasized in high-risk individuals.[32]

Several limitations of this study warrant consideration. The single-center retrospective design introduces potential selection bias and limits generalizability. Although internal validation was performed using bootstrapping, independent external validation in multicenter cohorts is necessary to confirm transportability. The high statin utilization rate resulted in small numbers of patients not receiving statins, limiting statistical power for this specific subgroup comparison. The number of patients with severely reduced left ventricular ejection fraction (LVEF <40%) was limited, which precluded adequately powered subgroup analysis in this stratum. The study did not incorporate emerging biomarkers such as lipoprotein(a) or serial high-sensitivity C-reactive protein measurements, which have been recognized as contributors to residual cardiovascular risk. Troponin measurements at admission, post-PCI, and over serial time points were not systematically available in the retrospective database, precluding analysis of periprocedural myocardial injury as a potential predictor of long-term MACE. Serial apolipoprotein measurements were not available, precluding analysis of the relationship between longitudinal changes in ApoB/A1 ratio and outcomes. Outcome ascertainment relied primarily on electronic medical records and telephone follow-up, which may have introduced information bias for events occurring outside the index hospital.

Conclusion

In summary, this study developed and validated a practical nomogram incorporating the ApoB/A1 ratio for predicting MACE in patients with CAD undergoing PCI. The model demonstrated good discrimination, calibration, and clinical utility, with consistent performance across different statin intensity subgroups. This tool may facilitate individualized residual risk stratification and guide intensification of lipid-lowering therapy. These findings are derived from a single-center cohort, and external validation in prospective multicenter studies is needed before broader clinical implementation.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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