Nutrition Journal

RESEARCH

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Validation of the role of apolipoproteins in coronary artery disease patients with impaired kidney function for prognosis: a prospective cohort study in China

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Abstract

Objective This study aims to evaluate the relationship between apolipoproteins (ApoA1, ApoB, and the ApoB/A1 ratio) and the incidence of major adverse cardiovascular events (MACE) in patients with coronary artery disease (CAD) and impaired kidney function, assessing their potential role in secondary prevention.

Method A prospective cohort of 1,640 patients with impaired kidney function who underwent percutaneous coronary intervention in China was analyzed. Patients were categorized based on the measurements of ApoA1, ApoB, and ApoB/A1 ratio. MACE, defined as a composite of all-cause mortality, cardiovascular death, nonfatal myocardial infarctions, strokes, and unplanned revascularizations, was tracked post-procedure, with statistical analyses including Kaplan–Meier survival curves and Cox regression models to identify associations with apolipoproteins. Subgroup analyses according to kidney function were conducted.

Result During a median follow-up of 3.1 years, 324 MACE events were observed. Multivariable Cox regression analyses illustrated higher levels of ApoB and the ApoB/A1 ratio were significantly associated with increased MACE incidence (adjusted HR [95%CI] 1.668[1.044–2.666]; adjusted HR [95%CI] 2.231[1.409–3.533], respectively), while lower ApoA1 levels correlated with a higher risk (adjusted HR [95%CI] 0.505[0.326–0.782]). ROC curve analyses indicated comparable predictive performances to traditional risk factors like LDL cholesterol. Subgroup analysis revealed that the above association was not statistically significant in the moderate-to-severe renal impairment CAD patients (eGFR < 45 mL/min/1.73 m^2).

Conclusion Our findings illustrate that apolipoproteins, specifically ApoA1 and ApoB, along with their ratio, are significant predictors of major adverse cardiovascular events in CAD patients with impaired kidney function. These results emphasize the need for incorporating apolipoprotein measurements in secondary prevention strategies for this high-risk population.

Keywords Apolipoprotein, Impaired kidney function, Coronary artery disease, Major adverse cardiovascular events, Secondary prevention

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Introduction

Patients with impaired renal function, characterized primarily by a reduction in estimated glomerular filtration rate (eGFR), represent a substantial population worldwide, imposing a significant burden on the World Health Organization [1]. The lipid metabolism in patients with impaired kidney function differs markedly from that of individuals with normal renal function, typically characterized by dyslipidemia manifesting as elevated triglyceride levels and decreased high-density lipoprotein cholesterol (HDL-C) levels [2]. Cardiovascular disease is the leading cause of mortality among patients with chronic kidney failure. As renal function declines, atherosclerosis accelerates, and the disturbances in lipid profiles and metabolism worsen [3, 4]. Consequently, the prognosis for patients with poor renal function and cardiovascular disease is exceedingly poor [5]. However, there is currently a lack of research focused on secondary prevention in patients with impaired kidney function and coronary artery disease (CAD).

Lipid and lipoprotein particles play a vital role in the functioning of the vasculature and the heart [6]. As a primary protein component of lipoproteins, apolipoproteins (Apos) function as structural components of lipoproteins and facilitate the transport of lipids through the bloodstream and lymphatic system. Apos also serve as ligands for cell surface receptors and as cofactors for enzymes [7]. ApoA and ApoB are two major types of apolipoproteins. ApoA1 is the most prevalent molecule among Apos, being present in both chylomicrons (CM) and HDL [8]. Recent studies have indicated that plasma ApoA1 is a protective factor against cardiovascular disease, with individuals exhibiting low levels of ApoA1 at higher risk for such conditions [9–11]. All atherogenic lipoproteins, including very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL), contain a single molecule of ApoB. ApoB is a cardiovascular metabolic risk factor and serves as a critical pathophysiological foundation for atherosclerotic cardiovascular disease [12, 13]. However, some studies have pointed out that the effects of ApoA1 and ApoB on atherosclerosis remain controversial [14]. Furthermore, the ApoB/A1 ratio has been demonstrated as a risk factor for CAD and other cardiovascular diseases [15, 16].

Previous research has predominantly focused on primary prevention, with limited knowledge regarding the role of Apos in secondary prevention for patients with CAD. Furthermore, in patients with renal insufficiency complicated by CAD, the presence of distinct lipid metabolic disorders raises questions about the potential for Apos to facilitate secondary prevention. Therefore, the objective of this study is to assess and validate the relationship between ApoA1, ApoB, and the ApoB/A1 ratio with major adverse cardiovascular events (MACE) in CAD patients with impaired kidney function, to evaluate their role in secondary prevention among this population.

Method

Study design

This study enrolled patients diagnosed with CAD and impaired kidney function who underwent percutaneous coronary intervention (PCI) at Fuwai Hospital between January 2017 and December 2018. The eligibility criteria required participants to be adults over 18 years of age with an eGFR of 60 mL/min/1.73 m^2 or lower. Patients were excluded from the study if they lacked pre-procedural serum creatinine measurements or values for Apo A1 and Apo B. Additionally, 14 patients who experienced major cardiovascular events during hospitalization and 47 patients who were lost to follow-up were also excluded. Ultimately, a total of 1,640 patients with CAD and impaired kidney function were included in the analysis (Fig. 1). The eGFR was calculated from baseline serum creatinine values obtained before PCI, employing the Chronic Kidney Disease (CKD) Epidemiology Collaboration (CKD-EPI) equation [17], with further details outlined in Supplementary Material 1. Impaired kidney function was defined as the value of eGFR less than 60 mL/min/1.73 m^2.

The research adhered to the ethical principles outlined in the Declaration of Helsinki and received approval from the Institutional Review Board of Fuwai Hospital (Approval Number 2016–847). All participants provided written informed consent before their inclusion in the study.

Study procedures

Laboratory samples were obtained from all participants following a fasting period of at least 12 h before angiography. These samples were analyzed in the clinical chemistry department of Fuwai Hospital. Serum concentrations of creatinine, ApoA1, ApoB, triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and HDL-C were determined using an automated biochemical analyzer (Hitachi 7150, Tokyo, Japan). Angiographic and procedural data were meticulously extracted from catheter records by two experienced interventional cardiologists. Any discrepancies in the interpretation of angiograms were resolved by a third independent expert.

During hospitalization, medical procedures and therapies adhered to established clinical guidelines and were carried out at the discretion of the cardiologists. Demographic information, cardiovascular risk factors, clinical parameters, laboratory results, angiographic details,

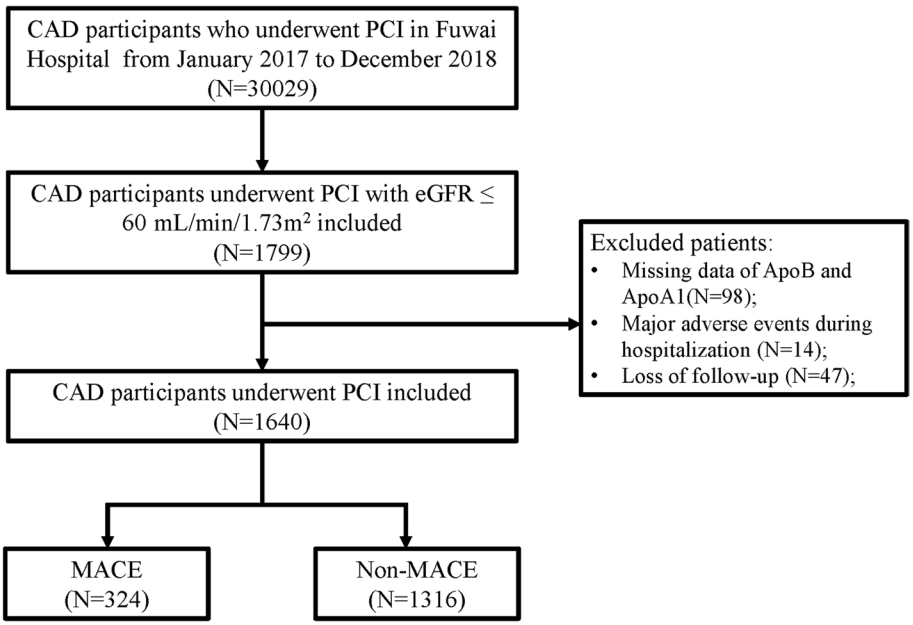

Fig. 1 Flowchart of patient selection. CAD, coronary artery disease; PCI, percutaneous coronary intervention; eGFR, estimated glomerular filtration rate; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B

procedural information, and medication data were systematically collected using standardized forms by trained research personnel.

Definition of MACE

The primary endpoint of interest was MACE, which included all-cause mortality, cardiovascular (CV) death, nonfatal myocardial infarctions (MIs), strokes, and unplanned revascularization procedures [18]. Death was classified as cardiac unless a definitive non-cardiac cause was identified. Myocardial infarction was explicitly defined by the Third Universal Definition of MI, while strokes were characterized by the emergence of a new focal neurological deficit lasting more than 24 h, confirmed through imaging studies. Unplanned revascularization was defined as any repeat PCI or surgical intervention after discharge, excluding scheduled staged PCI procedures. All events required verification via source documentation.

Statistical analysis

Continuous variables were expressed as means ± standard deviations (SD) for normally distributed data, whereas medians and interquartile ranges (IQR) were used for non-normally distributed variables. Categorical variables were summarized as frequencies and percentages. Group comparisons were conducted using one-way analysis of variance (ANOVA), the Kruskal–Wallis H test, Pearson's chi-square test, or Fisher's exact test as appropriate.

The cumulative incidence of clinical events was assessed using Kaplan–Meier survival curves, with differences analyzed using the log-rank test. Both univariable and multivariable Cox regression analyses were employed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Utilizing Schoenfeld Residuals to test whether the Cox regression model meets the proportional hazards assumption. Model 1 was unadjusted, while Model 2 was adjusted for sex, age, body mass index (BMI), acute coronary syndrome (ACS), diabetes mellitus (DM), hypertension (HTN), family history of CAD, smoking status, TG, eGFR level, lesion length, minimum lumen diameter (MLD), stent characteristics, including stent condition and stent length, and medication at discharge (including angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors [ARB/ACEI], calcium channel blockers [CCB], aspirin, clopidogrel, statin). The area under the curve (AUC) was calculated to evaluate predictive performance. The adjusted restricted cubic spline (RCS) analysis was performed to validate the linear relationship between Apos and different clinical outcomes. In instances of missing data, the VIM package in R was employed to visualize the missing values, indicating that the data were missing at random [19]. Therefore, multiple imputation was conducted utilizing the MICE package to find matches among the observed data in the predictive mean metric [20].

In the sensitivity analysis, the CKD stage 5 (eGFR < 15 mL/min/1.73 m^2) and dialysis patients were

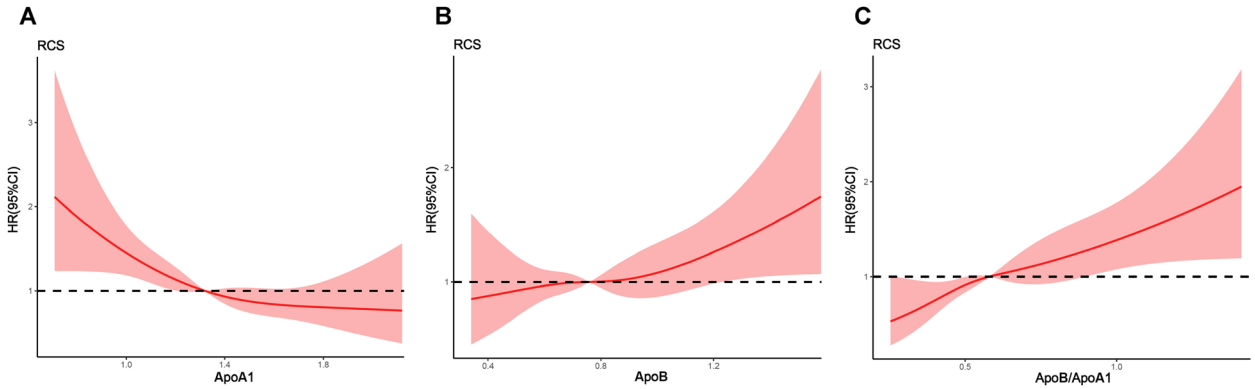

Fig. 2 Relationship between various Apos and MACE risk in patients with impaired kidney function who underwent PCI via RCS analysis (ApoA1(**A**), ApoB(**B**), and ApoB/ApoA1(**C**), cutoff values were 0.76, 1.32, and 0.58, P for nonlinear > 0.05). RCS, restricted cubic spline; MACE, major adverse cardiovascular events; HR, hazard ratio; CI, confidence interval; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B

excluded as their poorer prognosis might skew the results. Additionally, to ensure clinical relevance and to maximize comparability between the two groups in terms of sample size, patients were categorized into mild renal impairment and severe renal impairment based on an eGFR cutoff of 45 mL/min/1.73 m^2, which is considered an important threshold for assessing the severity of CKD, and the aforementioned analysis was repeated in the subgroup analysis.

Statistical analyses and calculations were performed using R software (version 4.1.3) and Python (version 3.9.12). A *p*-value threshold of less than 0.05 was considered statistically significant.

Result

Baseline characteristics

Among a cohort of 1,640 patients, 40.9% were male, with a median age of 69 years. The median eGFR was 53.16 mL/min per 1.73 m^2. Table 1 provides a comprehensive overview of the baseline characteristics of participants categorized by MACE outcomes. The prevalence of ACS and DM was found to be higher in the MACE group. Besides, there was a notable upward trend in age, creatinine levels, HbA1C, ApoB, ApoB/ApoA1, TG, LDL, white blood cells (WBC), and stent length when comparing the non-MACE group to the MACE group. Conversely, eGFR, ApoA1, HDL, and hemoglobin (HGB) showed a downward trend.

Apolipoprotein groups

According to the multivariable-adjusted RCS analysis, a linear relationship was observed between ApoA1, ApoB, and ApoB/ApoA1 levels with MACE events (P for nonlinear > 0.05). The critical threshold values were 0.76, 1.32, and 0.58, which were close to the median values used for binary classification. Based on the levels of ApoB, ApoA1, and ApoB/ApoA1, patients were stratified into two groups: low-level and high-level groups, with cut-off values set according to the RCS analysis. Survival analysis, as illustrated by KM curves, suggests that stratifying based on these thresholds effectively distinguishes between populations with CAD and impaired kidney function about MACE events, indicating a significant association between these apolipoproteins and MACE occurrences (Fig. 2).

According to Supplemental Table 1, 837 individuals were assigned to the low ApoB level group, while the remaining 803 were classified into the high ApoB level group. The mean ApoB level in the low-level group was 0.63, compared to 0.93 in the high-level group. Additionally, levels of ApoA1, ApoB/ApoA1, TC, TG, LDL, HDL, hemoglobin, and platelet (PLT) counts all increased with rising ApoB levels.

Furthermore, as indicated in Supplemental Table 1, 834 patients were placed in the low ApoA1 level group (mean ApoA1 value of 1.15), while 806 patients were in the high ApoA1 group (mean value of 1.50). Age, eGFR, ApoB, TC, TG, LDL, HDL, and successful PCI rates all increased with higher ApoA1 levels, whereas creatinine (CR), ApoB/ApoA1 ratio, and WBC counts decreased with rising ApoA1 levels.

According to Supplemental Table 2, 820 patients were grouped in the low ApoB/ApoA1 level category (mean value of 0.47), while 806 patients were assigned to the high ApoB/ApoA1 group (mean value of 0.72). The proportions of diabetes, HbA1C, PLT, WBC, ApoB, TC, TG, and LDL all increased with higher ApoB/ApoA1 levels.

Correlation of apolipoprotein levels with MACE

During a median follow-up period of 3.1 years, a total of 324 MACE events were recorded. This included 165 deaths (10.0%), 77 CV deaths (4.7%), 62 nonfatal

Table 1 Baseline characteristic of CAD patients with impaired kidney disease

		Overall	Non-MACE	MACE	*P*
n		1640	1316	324	
Male (%)		670 (40.9)	531 (40.3)	139 (42.9)	0.439
Age, y		69.40 [62.88, 75.90]	69.10 [62.40, 75.60]	70.30 [64.88, 77.32]	0.005
BMI, kg/m2		25.70 [23.53, 27.73]	25.65 [23.59, 27.68]	25.95 [23.31, 27.95]	0.469
Clinical presentation					
ACS (%)		1116 (68.0)	876 (66.6)	240 (74.1)	0.011
DM (%)		1040 (63.4)	793 (60.3)	247 (76.2)	< 0.001
Dyslipidemia (%)		1283 (78.2)	1029 (78.2)	254 (78.4)	0.996
HBP (%)		1341 (81.8)	1079 (82.0)	262 (80.9)	0.696
Family History CAD (%)		160 (9.8)	124 (9.4)	36 (11.1)	0.416
Smoking (%)		858 (52.3)	689 (52.4)	169 (52.2)	0.999
Medications at discharge					
ARB.ACEI (%)		516 (31.5)	424 (32.2)	92 (28.4)	0.207
CCB (%)		859 (52.4)	692 (52.6)	167 (51.5)	0.784
NIT (%)		1572 (95.9)	1272 (96.7)	300 (92.6)	0.002
beta (%)		1472 (89.8)	1179 (89.6)	293 (90.4)	0.73
statin (%)		1613 (98.4)	1301 (98.9)	312 (96.3)	0.003
Aspirin (%)		1624 (99.0)	1303 (99.0)	321 (99.1)	1
Clopidogrel (%)		1619 (98.7)	1303 (99.0)	316 (97.5)	0.065
Ticagrelor (%)		288 (17.6)	229 (17.4)	59 (18.2)	0.794
Laboratory data					
CR		1.36 [1.18, 1.52]	1.36 [1.18, 1.50]	1.41 [1.22, 1.58]	0.001
eGFR, mL/min/1.73 m^2		53.16 [46.58, 56.90]	53.42 [47.35, 57.03]	51.94 [41.45, 56.38]	< 0.001
HbA1C, %		6.50 [5.90, 7.50]	6.40 [5.90, 7.40]	6.80 [6.00, 8.00]	< 0.001
ApoA1, mmol/L		1.32 [1.14, 1.50]	1.34 [1.16, 1.51]	1.27 [1.11, 1.43]	< 0.001
ApoB, mmol/L		0.76 [0.63, 0.92]	0.76 [0.62, 0.91]	0.78 [0.64, 0.96]	0.06
ApoB/ApoA1		0.58 [0.47, 0.72]	0.57 [0.46, 0.70]	0.61 [0.50, 0.78]	< 0.001
TC, mmol/L		3.96 [3.36, 4.74]	3.96 [3.36, 4.68]	4.02 [3.36, 4.98]	0.159
TG, mmol/L		1.63 [1.21, 2.24]	1.63 [1.23, 2.21]	1.69 [1.17, 2.29]	0.805
LDL, mmol/L		2.31 [1.82, 2.99]	2.30 [1.81, 2.95]	2.43 [1.85, 3.18]	0.08
HDL, mmol/L		1.07 [0.89, 1.26]	1.08 [0.89, 1.26]	1.00 [0.87, 1.20]	0.003
UA, mmol/L		406.88 [345.70, 484.60]	405.00 [343.37, 484.39]	416.28 [355.95, 487.52]	0.146
HBG, g/dL		4.44 [4.03, 4.91]	4.48 [4.08, 4.92]	4.32 [3.84, 4.80]	< 0.001
PLT, K/uL		222.00 [182.00, 266.00]	222.50 [183.00, 268.00]	217.00 [181.75, 260.00]	0.185
WBC, K/uL		6.95 [5.86, 8.34]	6.81 [5.77, 8.18]	7.40 [6.28, 9.02]	< 0.001
Angiographic and PCI data					
Heavily calcified (%)		91 (5.5)	67 (5.1)	24 (7.4)	0.135
LM (%)		73 (4.5)	61 (4.6)	12 (3.7)	0.563
LAD (%)		643 (39.2)	520 (39.5)	123 (38.0)	0.654
LCX (%)		244 (14.9)	206 (15.7)	38 (11.7)	0.091
RCA (%)		642 (39.1)	502 (38.1)	140 (43.2)	0.108
Syntax		13.00 [7.00, 20.50]	13.00 [7.00, 20.00]	14.00 [8.00, 22.00]	0.076
MLD, mm		0.30 [0.04, 0.50]	0.30 [0.12, 0.50]	0.28 [0.00, 0.46]	0.002
TIMI (%)	0	336 (20.5)	246 (18.7)	90 (27.8)	0.004
	1	62 (3.8)	50 (3.8)	12 (3.7)	
	2	170 (10.4)	138 (10.5)	32 (9.9)	
	3	1072 (65.4)	882 (67.0)	190 (58.6)	
B2_C_lesion (%)		1218 (74.3)	956 (72.6)	262 (80.9)	0.003
Lesion length, mm		25.00 [15.00, 39.00]	24.00 [15.00, 39.00]	26.00 [16.00, 40.00]	0.288
Concentric (%)		264 (16.1)	219 (16.6)	45 (13.9)	0.261
Stent length, mm		28.00 [18.00, 41.25]	29.00 [18.00, 42.00]	26.00 [18.00, 38.00]	0.01
Stent (%)		1457 (88.8)	1184 (90.0)	273 (84.3)	0.005

Table 1 (continued)

BMI Body mass index, *WBC* White blood cell, *HBG* Hemoglobin, *PLT* Platelet, *eGFR* Estimated glomerular filtration rate, *ACS* Acute coronary syndrome, *DM* Diabetes mellitus, *PCI* Percutaneous coronary intervention, *TG* Triglycerides, *TC* Total cholesterol, *LDL-C* Low-density lipoprotein cholesterol, *HDL-C* High-density lipoprotein cholesterol, *MLD* Minimal lumen diameter, *TIMI* Thrombolysis In Myocardial Infarction, *LM* Left main coronary artery, *RCA* Right coronary artery, *LAD* Left anterior descending branch, *LCX* Left circumflex branch, *SYNTAX* Synergy between percutaneous coronary intervention with TAXUS and cardiac surgery

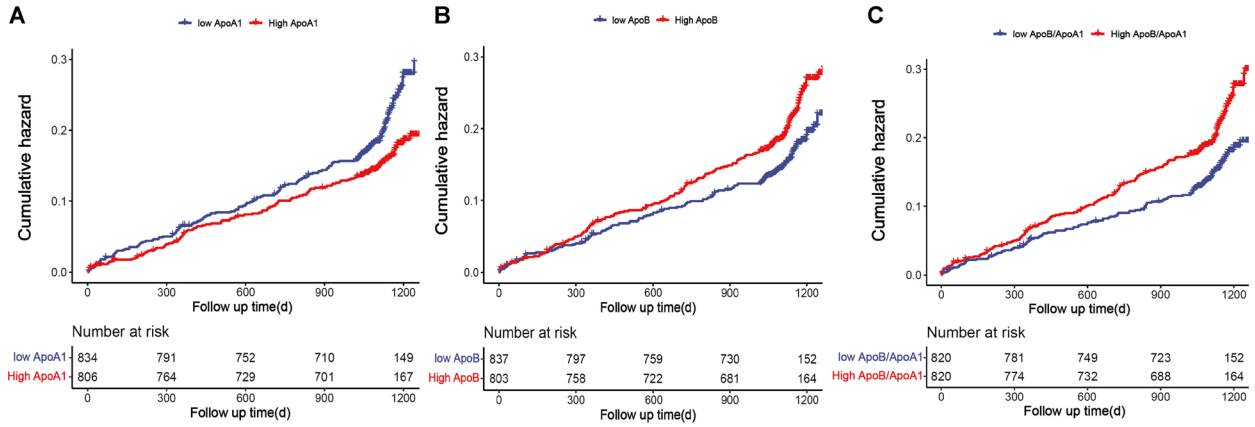

Fig. 3 The cumulative incidence for MACE in ApoA1(**A**), ApoB(**B**), and ApoB/ApoA1(**C**) illustrated by Kaplan–Meier survival curves. MACE, major adverse cardiovascular events; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B

Table 2 The relationship between various Apos and MACE risks via Cox regression

	Model1	*P*	Model2	*P*
continue				
ApoB	1.642(1.074–2.510)	0.022	1.668(1.044–2.666)	0.033
ApoA1	0.435(0.285–0.663)	0.001	0.505(0.326–0.782)	0.002
ApoB/ApoA1	2.614(1.698–4.025)	0.001	2.231(1.409–3.533)	0.001
category				
ApoB	1.222(1.072–1.434)	0.032	1.240(1.004–1.562)	0.037
ApoA1	0.716(0.574–0.894)	0.003	0.751(0.596–0.947)	0.016
ApoB/ApoA1	1.385(1.110–1.728)	0.004	1.341(1.064–1.691)	0.013

Model2 adjusted for sex, age, BMI, ACS, DM, HBP, family history CAD, smoking, Lesion length, MLD, stent, stent length, eGFR, TG, ARB/ACEI, CCB, aspirin, clopidogrel, statin

TG Triglycerides, *BMI* Body mass index, *eGFR* estimated glomerular filtration rate, *ACS* Acute coronary syndrome, *DM* Diabetes mellitus, *MLD* Minimal lumen diameter, *CAD* Coronary artery disease, *HBP* Hypertension, *CCB* Calcium channel blockers, *ARB/ACEI* Angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors

myocardial infarctions (3.8%), 19 strokes (1.2%), and 144 unplanned revascularizations (8.8%).

As shown in Fig. 3 and Table 2 both univariable and multivariable Cox regression analyses indicated a statistically significant correlation between high ApoB and ApoB/ApoA1 levels and the increased incidence of MACE (adjusted HR [95%CI] 1.668[1.044–2.666]; adjusted HR [95%CI] 2.231[1.409–3.533], respectively). In contrast, lower ApoA1 levels were also significantly associated with a higher incidence of MACE (adjusted HR [95%CI] 0.505[0.326–0.782]). Consistent results were obtained when different apolipoprotein values were analyzed as both continuous and categorical variables. Tests based on the Schoenfeld Residuals indicated that all analyses met the proportional hazards assumption, allowing for the use of the Cox proportional hazards model ($P > 0.05$, Supplementary Fig. 1).

Moreover, the results of the ROC curve analysis (Supplementary Fig. 2A) indicated that the predictive performance of ApoA1, ApoB, and ApoB/ApoA1 for MACE risk among CAD patients with impaired kidney function did not differ significantly when incorporated into predictive models. Additionally, there was no noteworthy difference in predictive capability compared to

Table 3 The subgroup analysis across various kidney functions via Cox regression

	robust HR (95%CI)	*P*	adjusted HR (95%CI)	*P*
eGFR ≤ 45 mL/min/1.73m^2				
continue				
ApoB	1.116(0.527–2.361)	0.775	1.226(0.512–2.936)	0.648
ApoA1	0.649(0.304–1.385)	0.263	0.784(0.346–1.775)	0.56
ApoB/ApoA1	1.407(0.631–3.138)	0.404	1.302(0.523–3.238)	0.571
category				
ApoB	1.003(0.664–1.456)	0.933	1.108(0.730–1.681)	0.63
ApoA1	0.725(0.484–1.087)	0.119	0.674(0.429–1.058)	0.087
ApoB/ApoA1	1.090(0.662–1.482)	0.961	1.063(0.695–1.658)	0.748
eGFR > 45 mL/min/1.73m^2				
continue				
ApoB	1.686(1.007–2.853)	0.042	1.999(1.131–3.534)	0.017
ApoA1	0.403(0.241–0.673)	0.001	0.391(0.229–0.666)	0.001
ApoB/ApoA1	2.885(1.701–4.893)	0.001	3.090(1.791–5.331)	0.001
category				
ApoB	1.313(1.007–1.711)	0.044	1.359(1.027–1.799)	0.032
ApoA1	0.742(0.568–0.968)	0.028	0.728(0.549–0.964)	0.027
ApoB/ApoA1	1.449(1.110–1.889)	0.006	1.511(1.145–1.993)	0.004

Adjusted for sex, age, BMI, ACS, DM, HBP, family history CAD, smoking, Lesion length, MLD, stent, stent length, eGFR, TG, ARB/ACEI, CCB, aspirin, clopidogrel, statin

TG Triglycerides, *BMI* Body mass index, *eGFR* Estimated glomerular filtration rate, *ACS* acute coronary syndrome, *DM* Diabetes mellitus, *MLD* Minimal lumen diameter, *CAD* Coronary artery disease, *HBP* Hypertension, *CCB* Calcium channel blockers, *ARB/ACEI* Angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors

traditional risk stratification factors such as LDL (P for DeLong test > 0.05).

Apolipoprotein levels and clinical outcomes

In various clinical outcomes, both ApoA1 levels and all-cause mortality, along with cardiovascular-related mortality, showed a statistically significant association (adjusted HR [95% CI] 0.234 [0.125–0.437] and 0.181 [0.072–0.454], respectively). There was also a notable positive correlation between ApoB/ApoA1 levels and all-cause mortality and stroke incidence (adjusted HR [95%CI] 2.839 [1.516–5.318], and 5.655 [1.056–17.327], respectively). The correlation of ApoB with various clinical outcomes was consistent with MACE results, although without significant statistical significance (Supplemental Table 4–6). The ROC curve analyses (Supplementary Fig. 2B-F) indicated that the predictive performance regarding different clinical outcomes for CAD patients with impaired kidney function did not markedly differ when ApoA1, ApoB, and ApoB / ApoA1 were included in the predictive models, respectively. Furthermore, the predictive capability remained comparable to traditional risk stratification factors such as LDL, with no significant differences noted (P for DeLong test > 0.05).

Sensitivity analysis

After excluding patients with CKD stage 5 and those on dialysis, a total of 1,633 CAD patients with impaired kidney function were included in the sensitivity analysis. The results of the Cox regression analysis were similar to those observed in the overall population (Supplemental Table 7). High levels of ApoB and the ratio of ApoB to ApoA1 were associated with an increased incidence of MACE (adjusted HR [95% CI] 1.584 [1.086–2.543] and adjusted HR [95% CI] 2.190 [1.377–3.482], respectively). Conversely, lower levels of ApoA1 were significantly associated with a higher incidence of MACE (adjusted HR [95% CI] 0.496 [0.319–0.771]).

In subgroup analysis, the associations between the aforementioned apolipoproteins (ApoA1, ApoB, and ApoB/ApoA1) and MACE persisted among patients with CAD and an eGFR greater than 45 mL/min/1.73 m^2. Specifically, the adjusted hazard ratios were as follows: ApoA1 (adjusted HR [95% CI], 0.391[0.229–0.666]), ApoB (adjusted HR [95% CI], 1.999[1.131–3.534]), and ApoB/ApoA1 (adjusted HR [95% CI] 3.090[1.791–5.331]). However, for patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), the associations between these apolipoproteins and MACE did not reach statistical significance (Table 3).

Discussion

In this retrospective analysis of a prospective cohort, we identified the correlation between serum ApoA1, ApoB, and the ApoB/ApoA1 ratio and the characteristics of patients with CAD and impaired kidney function in China. We found that lower levels of ApoA1 and higher levels of ApoB, along with a higher ApoB/ApoA1 ratio, are closely associated with an increased incidence of MACE in CAD patients with impaired kidney function undergoing PCI, demonstrating clinical relevance for secondary prevention. Apos may serve as significant risk indicators for clinicians across various fields, including those managing CAD patients with impaired kidney function. Furthermore, our study revealed that in patients with moderate to severe renal insufficiency who underwent PCI, the aforementioned associations lacked statistical significance.

Cholesterol circulates in the plasma within lipoprotein particles, where apolipoproteins serve as essential structural and functional components [21]. ApoB is a critical building block of atherogenic lipoproteins, including VLDL, intermediate-density lipoprotein (IDL), and LDL. Since each of these lipoproteins contains only a single molecule of ApoB, measuring ApoB has been employed to determine the precise quantity of atherogenic lipoproteins present in patients [22]. Previous studies have demonstrated that ApoB is a robust predictor of mortality and cardiovascular risk [23–25]. Data from the Copenhagen General Population Study indicated that in patients treated with statins, ApoB was a superior biomarker for all-cause mortality risk compared to non-HDL-C and LDL-C [26]. However, some studies and meta-analyses have noted a lack of significant statistical correlation between ApoB and all-cause as well as cardiovascular mortality in populations with normal ApoB levels and those undergoing peritoneal dialysis [14, 16, 27]. An analysis from the Study of Heart and Renal Protection (SHARP) showed higher ApoB was associated with increased risk of atherosclerotic vascular events in CKD. However, its main focus is on primary prevention. For patients with CKD, secondary prevention is crucial [28]. Our study showed a clear association between ApoB levels and the occurrence of MACE events in patients with impaired kidney function receiving PCI. This finding appeared to conflict with some previous studies; however, upon analyzing various clinical outcomes related to MACE events, our research indicated that ApoB levels did not exhibit significant statistical associations with distinct clinical outcomes, including all-cause mortality and cardiovascular mortality risk, consistent with some earlier results. Furthermore, our study found that the association between ApoB and MACE events is limited to CAD patients with eGFR levels between 45 and 60 mL/min/1.73 m^2, with no significant correlation observed in patients with eGFR below 45 mL/min/1.73 m^2. As renal function continues to deteriorate, lipid metabolism disturbances may exacerbate, indicating that the secondary preventive value of Apos in CAD patients with moderate to severe renal insufficiency necessitates further large-scale studies.

ApoA1 is the primary component of HDL. Each HDL particle contains five ApoA1 molecules, and systemic ApoA1 levels have been used as a marker of HDL cholesterol concentration [29]. ApoA1 may induce myocardial inflammation by inhibiting the activation of CD11b, a component of the CR3 heterodimer that regulates leukocyte adhesion and migration [30]. However, the relationship between ApoA1 and cardiovascular events remains controversial. Previous meta-analyses have indicated a correlation between ApoA1 levels and reduced cardiovascular mortality risk, yet the association between ApoA1 and all-cause mortality (OR = 0.97, 95% CI = 0.93–1.01) was not pronounced [14]. Additionally, conclusions from four studies suggested no significant differences between ApoA1 and cardiovascular mortality [10, 11, 31, 32]. A study from Japan illustrated that ApoA-I and renal function were independent predictors of major adverse cardiac and cerebrovascular events and all-cause death in patients undergoing intervention [33]. Our study suggests ApoA1 may serve as a protective factor for MACE events in CAD patients with impaired kidney function in China. Furthermore, lower levels of ApoA1 were significantly associated with all-cause and cardiovascular mortality, whereas no notable statistical significance was observed for non-fatal myocardial infarction, stroke, or repeat revascularization. The inconsistency in results across studies may be attributed to differences in population demographics. In our subgroup analysis, while there remained a negative correlation between ApoA1 and MACE events in CAD patients with eGFR less than 45 mL/min/1.73 m^2, this statistical difference was not significant.

The ApoB/ApoA1 ratio is a typical biomarker for assessing atherosclerosis and anti-atherosclerosis. A higher ApoB/ApoA1 ratio indicates the progression of atherosclerotic conditions and is generally considered a risk predictor for cardiovascular disease (CVD) mortality in the general population [34, 35]. The association between the ApoB/ApoA1 ratio and mortality in end-stage renal disease—specifically in dialysis patients—remains contentious. For instance, Sato et al. [16] indicated that a higher ApoB/ApoA1 ratio is associated with an increased risk of all-cause and CVD-related mortality among prevalent hemodialysis patients. Conversely, another study suggested that the baseline ApoB/ApoA1 ratio is not associated with a four-year mortality rate

[36]. Our research suggests that the ApoB/ApoA1 ratio is significantly correlated with MACE in impaired kidney function patients undergoing PCI, and it also shows statistically significant associations with all-cause mortality, cardiovascular mortality, and stroke. These findings align with previous research, highlighting the considerable differences in metabolic profiles between dialysis patients and non-dialysis chronic kidney disease patients, which may contribute to the heterogeneity of these conclusions.

The prognostic value of different Apo levels for predicting outcomes in patients with CAD and impaired renal function appears to be limited, as indicated by an AUC for MACE of less than 0.7. The factors influencing prognosis in CKD patients differ from those in the general population [37]. Traditional risk factors only partially account for the cardiovascular risk in CKD patients; even the Framingham Risk model tends to underestimate cardiovascular disease risk in this population [38]. This study adjusted only a subset of classical covariates based on clinical experience and univariate results, without thoroughly screening all risk factors. Moreover, our research suggested that the association between Apo and adverse outcomes was not statistically significant in patients with severe renal impairment. There appeared to be a paradoxical relationship between traditional risk factors and cardiovascular outcomes in patients with advanced CKD. Previous studies have indicated that, in individuals with significant renal dysfunction, established risk factors commonly found in the general population—such as hypertension, hyperlipidemia, and obesity—do not correlate with adverse outcomes, and may even show an inverse relationship [39]. This discrepancy may arise from varying time courses of different risk factors across populations, or it could be that declining renal function obscures the impact of other risk factors on adverse outcomes [40]. The premature mortality observed in CKD patients often excludes the influence of complications, which are more significant for long-term mortality. Additionally, the common occurrence of persistent inflammation and/or protein-energy wasting in advanced CKD seems to largely explain this paradoxical association [41]. This phenomenon is not limited to CKD patients but is also observed in other populations, including the elderly and those with malignancies [42].

The results of this study could aid in developing secondary prevention strategies for cardiovascular diseases by managing Apo levels for CAD patients with impaired kidney function. Furthermore, this study contributes to the enhancement of cardiovascular risk assessment by incorporating additional Apo biomarkers. However, this study has certain limitations. First, it is a single-center study, which may limit its generalizability, and selection bias is unavoidable. Second, due to the nature of the cardiovascular hospital, the number of patients with moderate to severe renal dysfunction is relatively small; further research should target patients with severe renal impairment and coexisting CAD. Third, the study did not account for changes in different Apos data and medication data during the follow-up period; long-term variations in lipid levels and medication conditions may have predictive implications for patient outcomes. Finally, potential risk factors were not fully adjusted in this cohort study, and thus, the influence of residual confounding factors could not be entirely eliminated.

Conclusion

In patients with impaired kidney function undergoing PCI, a significant association exists between Apos and MACE risks. Specifically, ApoA1, ApoB, and the ApoB/ApoA1 ratio may serve as risk biomarkers for MACE in CAD patients with impaired kidney function. However, this association requires further validation in patients with moderate to severe renal impairment and CAD.

Abbreviations

CKD	Chronic kidney disease
HDL-C	High-density lipoprotein cholesterol
CAD	Coronary artery disease
Apos	Apolipoproteins
ApoA	Apolipoprotein A
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
VLDL	Very low-density lipoprotein
LDL	Low-density lipoprotein
MACE	Major adverse cardiovascular events
Egfr	Estimated glomerular filtration rate
TG	Triglycerides
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
CV	Cardiovascular
MI	Myocardial infarction
ACS	Acute coronary syndrome
DM	Diabetes mellitus
HTN	Hypertension
BMI	Body mass index
MLD	Minimum lumen diameter
AUC	Area under the curve
CVD	Cardiovascular disease
CR	Creatinine
WBC	White blood cell
HBG	Hemoglobin
PLT	Platelet
HR	Hazard ratio
CI	Confidence interval
RCS	Restricted cubic spline
IDL	Intermediate-density lipoprotein
CCB	Calcium channel blockers
ARB/ACEI	Angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-025-01078-9.

Supplementary Material 1: CKD-EPI equations for calculating eGFR. Supplementary Table 1 Baseline characteristics of CAD patients with impaired kidney function divided by ApoB. Supplementary Table 2 Baseline characteristics of CAD patients with impaired kidney function divided by ApoA1 level. Supplementary Table 3 Baseline characteristics of CAD patients with impaired kidney function divided by ApoB/ApoA1 level. Supplementary Table 4 the relationship between ApoB and various clinical outcomes. Supplementary Table 5 the relationship between ApoA1 and various clinical outcomes. Supplementary Table 6 the relationship between ApoB/ApoA1 and various clinical outcomes. Supplementary Table 7 The relationship between various Apos and MACE risks in impaired kidney function and CAD patients exclude CKD stage 5 and dialysis patients.

Supplementary Material 2: Supplementary Fig. 1 plot of Schoenfeld Residuals showed the Cox proportional hazards model can be used. Apo, apolipoprotein. Supplementary Fig. 2 ROC curve analysis illustrated the predictive capability of different clinical outcomes in various Apos and their ratio. A: MACE; B: all-cause death; C: CV death; D: Nonfatal MI; E: Stroke; F: Revascularization. MACE, major adverse cardiovascular events; ROC, receiver operating characteristic; MI, myocardial infarction; CV, cardiovascular; Apos, apolipoproteins.

Acknowledgements
None.

Authors' contributions
Z.Y and K.D contributed to the study design. Z.Y, L.Z and E.X contributed to data collection, manuscript writing, data processing, and figure mapping. L.Z and C.S contributed to the data proofreading. R.Z contributed to formal analysis; writing—original draft preparation; B.Z and Y.H contributed to review and to edit. All authors have read and agreed to the published version of the manuscript.

Funding
This study was supported by research grants from the CAMS Innovation Fund for Medical Sciences (CIFMS) (2021-I2M-1–008), Noncommunicable Chronic Diseases-National Science and Technology Major Project (2023ZD0513900), the Fundamental Research Funds for the Central Universities (3332024033), National Natural Science Foundation of China (No. 3230050498), National High Level Hospital Clinical Research Funding (2023 - GSP - QN - 17, 2023 - GSP - QN - 21), and the project for the distinguishing academic discipline for Fuwai Hospital (2022 - FWQN05).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The research adhered to the ethical principles outlined in the Declaration of Helsinki and received approval from the Institutional Review Board of Fuwai Hospital (Approval Number 2016–847). All participants provided written informed consent before their inclusion in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 23 October 2024 Accepted: 8 January 2025
Published online: 17 January 2025

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