Major cardiovascular events and readmission risk of patients post percutaneous coronary intervention in one year based on ApoB/ApoA-I

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Abstract

Background: Percutaneous coronary intervention (PCI) is a practical and effective method for the treatment of coronary heart disease (CHD). The aim of this study is to assess the clinical value of ApoB/ApoA-I in predicting the major cardiovascular events (MACEs) and hospital readmission risk within one year in CHD patients post PCI.

Methods: 1938 patients who underwent PCI treatment from January 2010 to December 2018 were included in this retrospective study. Basic information, medications and biochemical indicators were recorded at admission and the one year follow-up. Univariate and multivariate Cox proportional hazards regression model were performed to determine the relationship between ApoB/ApoA-I and MACEs, as well as readmission. The Kaplan-Meier curves were plotted to illustrate the cumulative incidence of MACEs and readmission. Predictive nomograms were established to predict prognosis for MACEs and readmission.

Results: Cox regression analysis showed that ApoB/ApoA-I is an independent risk factor for MACEs in patients after PCI ($P=0.031$). The incidence of MACEs in the high-level ApoB/ApoA-I group (ApoB/ApoA-I ratio >0.824) increased within one year and the difference was statistically significant ($P=0.037$). The incidence of readmission increased within one year was not statistically significant. In addition, the nomogram predicted one year MACEs more accurately (C-index: 0.647).

Conclusions: The ratio of ApoB/ApoA-I has important predictive value for the risk of MACEs occurrence in one year for CHD patients post PCI.

1 Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in the world^{1,2}. Acute coronary syndrome (ACS) which includes unstable angina, acute non-ST-segment elevation myocardial infarction and acute ST-segment elevation myocardial infarction is a group of clinical syndromes caused by acute myocardial ischemia. It is the most dangerous and deadly form of coronary heart disease (CHD)³. Percutaneous coronary intervention (PCI) is the most common method of vascular reconstruction for CHD patients which aims to improve the symptoms of myocardial ischemia and hypoxia by dilating and dredging narrowed or occluded coronary arteries, thereby improving the survival rate of patients⁴. However, PCI can only relieve the stenotic lesions, the prognosis is still a hot topic to clarify⁵. If the risk factors for coronary heart disease continue to exist, patients will still experience heart adverse events such as recurring angina, chest pain, and recurrence after surgery and require readmission treatment. The major cardiovascular events (MACEs) incidence rate and its influencing factors are particularly important for the patients with CHD after PCI^{6,7}. The readmission of patients after PCI has also attracted more attention^{8,9}.

Dyslipidemia is one of the main risk factors for ASCVD^{2,10}. Lipid accumulation plays an important role in atherosclerosis in patients with ACS¹¹. In addition to conventional blood lipid indicators such as low-density lipoprotein (LDL-C), triglycerides (TG) and total cholesterol (TC), there is ample evidence that apolipoprotein (apo) may be a reliable predictor of primary prevention. The latest guidelines recommend Apolipoprotein B (ApoB) can be used as an alternative to LDL-C for risk assessment¹². ApoB transports all potentially atherosclerotic particles including very low-density lipoprotein, medium-density lipoprotein and low-density lipoprotein particles and it reflects the total number of atherosclerotic particles. Apolipoprotein A-I (ApoA-I) acts as the main anti-atherosclerotic protein in high-density lipoprotein (HDL) particles which transfers excess cholesterol from HDL to the liver¹³. Therefore, the ApoB/ApoA-I ratio is an indicator of the balance of atherogenic and anti-atherosclerotic cholesterol in plasma¹⁴. Studies have found that patients who suffered from more severe atherosclerotic lesions have higher level of ApoB/ApoA-I. Therefore, it is speculated that ApoB/ApoA-I is related to the progression of ACS. Previous studies have found that even if other lipids are within the normal range, the ApoB/ApoA-I ratio is significantly related to the risk of fatal myocardial infarction (MI) regardless of the traditional CVD risk factors¹⁵. In addition, a study found that the ApoB/ApoA-I ratio is a better predictor of CHD risk than Framingham Risk Score and TC/HDL-C¹⁶. The level of serum ApoB and ApoB/ApoA-I ratio can be used as risk factors for cardiovascular disease and new targets for lipid-lowering treatment strategies, which have been confirmed in related studies¹⁷.

Although various studies have discussed the close relationship between ApoB/ApoA-I ratio and cardiovascular risk, less attention was paid to the association between ApoB/ApoA-I and MACEs. The relationship between ApoB/ApoA-I and readmission post PCI is also unclear. Therefore, we performed a retrospective study to assess the association of ApoB/ApoA-I ratio with MACEs and readmission within one year post PCI treatment.

2 Methods

2.1 Study population

This retrospective study was done at Shandong Provincial Hospital affiliated to Shandong First Medical University, Jinan, China. Between January 2010 and December 2018, patients hospitalized for PCI with records in database in Shandong Provincial Hospital affiliated to Shandong First Medical University were included in this study. All patients who underwent PCI treatment were treated according to 2005 Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology¹⁸ and 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions¹⁹. The study registered on

<http://www.chictr.org.cn> (Chinese clinical trial registry). The registration number is ChiCTR2100043261. The exclusion criteria included: (1) combined thyroid disease, infectious disease, and immune system disease, (2) moderate to severe rheumatic valvular disease, (3) used anti-inflammatory drugs and antioxidant drugs recently, (4) combined with liver and kidney dysfunction and other serious systemic diseases, (5) hematological diseases and tumors and other serious acute or chronic diseases, (6) persistent or permanent atrial fibrillation, (7) mental illnesses. The study was approved by the Biomedical Research Ethic Committee of Shandong Provincial Hospital affiliated to Shandong First Medical University. The requirement for informed consent was waived by our Ethic Committee owing to the retrospective nature of the current study. The methods in the current study were performed in accordance with the relevant guidelines and regulations. The study schematic diagram is shown in Fig. 1.

2.2 Data collection

Peripheral venous blood samples of the patients were obtained at admission in ward of hospital. Lipid profiles including TC, TG, LDL-C, HDL-C, ApoA-I, ApoB and other biochemical indicators were measured in the clinical laboratory diagnostic center of Shandong Provincial Hospital affiliated to Shandong First Medical University. We obtained demographic data such as age, gender, past medical history, status of smoking and drinking, clinical characteristics, blood samples, biochemical data, medication, echocardiography, coronary angiography and surgery information from electronic medical records. Medical history including the use of aspirins, statins, clopidogrel/ticagrelor, β -blockers, diuretic and hypoglycemic agents/insulin were also obtained from medical records and follow-up period. Follow-up were implemented since the discharge date to one year. Follow-up data were collected by consulting medical records, outpatient follow-up and/or telephone interviews.

2.3 Outcomes

The primary outcome measure of this study was defined as major adverse cardiovascular events(MACEs) which included death causes by cardiovascular causes, myocardial infarction(MI), hospitalization for unstable angina pectoris, transient cerebral ischemia(TIA), transient stroke, heart failure event, PCI again, peripheral vascular therapy, and stent thrombosis. We defined secondary outcome as the incidence of hospital readmission for one year, which referred to all cause readmission within one year from the date of initial hospitalization.

2.4 Statistical analysis

All Statistical analyses were performed using R version 3.6.3, python version 3.7 and GraphPad Prism 8.0. Continuous variables were described as mean $\pm$ standard deviation and categorical variables were specified as counts and percentages. Baseline data were compared by the t-test for continuous variables and the χ^2 test for categorical variables. Pearson analyses were applied to reveal the correlation of ApoB/ApoA-I with other lipid indexes. The Kaplan–Meier curves were plotted to illustrate the cumulative incidence of MACEs and readmission over time, and they were compared by the log-rank test. Cox-regression analyses were used to identify whether ApoB/ApoA-I was an independent risk variable for

MACEs or readmission and were presented as hazard ratio(HR) and 95% confidence interval(CI). Predictive nomograms were established to predict prognosis for MACEs and readmission, and the predictive accuracy of the nomograms was determined by concordance index(C-index). A two-tailed *P* value less than 0.05 was considered statistically significant.

3 Results

3.1 Baseline clinical characteristics

After coronary angiography, a total of 2088 CHD patients who underwent PCI treatment were enrolled. Among them 1938 patients were recruited in the study. The median level of ApoB/ApoA-I ratio was 0.824 (interquartile range: 0.664–1.009). A total of 992(51.2%) patients had high ApoB/ApoA-I levels and 946(48.8%) patients had low ApoB/ApoA-I levels. We described the baseline clinical and demographic characteristics of the enrolled patients in Table 1. We stratified baseline characteristics according to median ApoB/ApoA-I ratio. Patients with high ApoB/ApoA-I ratio had more cardiovascular risk factors including diabetes, dislipidemia, myocardial infarction, multivessel diseases, occlusion existence and were less likely to be receiving statins. Besides, patients in the high level group were likely to have higher TC, TG, LDL-C, LDL-C/HDL-C ratio, Lipoprotein a (Lp(a)), ApoB, Uric acid, FPG and HbA1c, as well as lower HDL-C and ApoA-I. The baseline demographic and procedural characteristics are shown in Table 1.

Table 1
Baseline characteristics of the patients

	Total	Low APOB/ApoA-I	High APOB/ApoA-I	<i>P</i> value
N(%)	1938	992(51.2)	946(48.8)	-
Age, y	60.39 ± 9.88	61.58 ± 9.60	59.67 ± 10.04	0.002
Male, n(%)	1361(70.2)	697(70.3)	664(70.2)	0.972
Heart rate, bpm	69.47 ± 11.11	68.50 ± 10.76	70.48 ± 11.38	< 0.001
Respiratory rate	17.94 ± 1.40	17.92 ± 1.33	17.97 ± 1.47	0.484
SBP, mmHg	134.43 ± 18.97	134.21 ± 18.36	134.66 ± 19.59	0.605
DBP, mmHg	79.04 ± 12.15	78.65 ± 11.83	79.43 ± 12.47	0.158
Hospital day, d	9.74 ± 4.84	9.48 ± 4.44	10.01 ± 5.20	0.016
Medical history, n(%)				
Hypertension	1173(60.5)	602(60.7)	571(60.4)	0.883
Diabetes	615(31.7)	284(28.6)	331(35.0)	0.003
Dislipidemia	62(3.2)	17(1.7)	45(4.8)	< 0.001
Previous PCI	144(7.4)	81(8.2)	63(6.7)	0.206
Myocardial infarction	744(38.4)	335(33.8)	409(43.2)	< 0.001
Procedural characteristics, n(%)				
Multivessel disease	1773(91.5)	891(89.8)	882(93.2)	0.007
Occlusion existence	540(27.9)	245(24.7)	295(31.2)	0.001
Risk factor, n(%)				
Smoking	954(49.2)	475(47.9)	479(50.6)	0.226
Drinking	913(47.1)	460(46.4)	453(47.9)	0.504
Laboratory tests				
TC, mmol/L	4.51 ± 1.14	3.98 ± 0.86	5.06 ± 1.14	< 0.001
TG, mmol/L	1.73 ± 1.08	1.53 ± 0.97	1.95 ± 1.13	< 0.001
LDL-C, mmol/L	2.74 ± 0.89	2.29 ± 0.65	3.21 ± 0.87	< 0.001
HDL-C, mmol/L	1.11 ± 0.26	1.16 ± 0.26	1.06 ± 0.24	< 0.001

	Total	Low APOB/ApoA-I	High APOB/ApoA-I	P value
LDL-C/HDL-C ratio	2.58 ± 0.99	2.04 ± 0.65	3.15 ± 0.97	< 0.001
Lipoprotein a, g/L	0.25 ± 0.24	0.23 ± 0.23	0.28 ± 0.25	< 0.001
ApoA-I, g/L	1.11 ± 0.20	1.12 ± 0.21	1.11 ± 0.20	< 0.001
ApoB, g/L	0.94 ± 0.31	0.75 ± 0.18	1.14 ± 0.30	< 0.001
ApoB/ApoA-I ratio	0.87 ± 0.31	0.65 ± 0.13	1.10 ± 0.28	< 0.001
Creatinine, μmmol/L	71.70 ± 16.48	71.88 ± 15.83	71.51 ± 17.13	0.625
Uric acid, μmmol/L	333.94 ± 84.54	325.19 ± 82.66	343.12 ± 85.51	< 0.001
Hcy, μmmol/L	15.43 ± 7.48	15.70 ± 7.63	15.16 ± 7.30	0.110
FPG, mmol/L	6.38 ± 1.92	6.15 ± 1.69	6.62 ± 2.11	< 0.001
HbA1c, %	6.60 ± 1.16	6.47 ± 0.99	6.73 ± 1.30	< 0.001
Discharge medication, n(%)				
Aspirin	1927(99.4)	985(99.3)	942(99.6)	0.407
Statins	1811(93.4)	938(94.6)	873(92.3)	0.043
Clopidogrel/Ticagrelor	1900(98.0)	977(98.5)	923(97.6)	0.145
β-blockers	1589(82.0)	824(83.1)	765(80.9)	0.208
Diuretic	310(16.0)	146(14.7)	164(17.3)	0.116
Hypoglycemic	494(25.5)	223(22.5)	271(28.6)	0.002

3.2 Correlations between ApoB/ApoA-I and other lipid indexes

We found that ApoB/ApoA-I were moderately or strongly related with other lipid indexes(all $P < 0.001$). The strongest one was found it between LDL-C/HDL-C(Pearson $R = 0.720$). Detailed results of the Pearson correlations were shown in Fig. 2.

3.3 Results of survival analysis

Cumulative hazard curves demonstrated that patients in the high ApoB/ApoA-I ratio group had a significantly higher one year MACEs occurrence compared with those in the low ApoB/ApoA-I ratio group(log-rank $P = 0.037$; Fig. 3A). Patients in the high ApoB/ApoA-I ratio group seemed to show a higher one year readmission occurrence compared with those in the low ApoB/ApoA-I ratio group, however the difference was not statistically significant (log-rank $P = 0.065$; Fig. 3B).

3.4 Results of multivariate analyses

We used multivariate analyses to explore the effect of ApoB/ApoA-I Ratio level on MACEs and readmission after adjusting other blood lipids indexes. Adjusted HRs and 95% CI of MACEs and readmission according to the ApoB/ApoA-I ratio levels are shown in Table 2. In the unadjusted model there was an association between ApoB/ApoA-I ratio and MACEs (HR, 1.603; 95% CI, 1.134–2.266; $P = 0.007$). The association became stronger after adjusting for age, sex and other lipid covariates (HR, 3.133; 95% CI, 1.917–5.121; $P < 0.001$). There was an association between ApoB/ApoA-I ratio and readmission (HR, 1.427; 95% CI, 1.027–1.984; $P = 0.034$) in the unadjusted model. Additional adjustment for other covariates including age, sex and other lipid indexes did not change this association (HR, 2.400; 95% CI, 1.487–3.873; $P < 0.001$).

Table 2

Multivariate analyses in predicting one year MACEs and readmission occurrence according to ApoB/ApoA-I Ratio levels at baseline. Model 1 adjusted for age and sex; Model 2 adjusted for age, sex, TC, TG, LDL-C, HDL-C

End point	Category	Hazard Ratio(95%CI)		
		Unadjusted Model	Model 1	Model 2
MACEs	ApoB/ApoA-I	1.603(1.134–2.266)	1.653(1.166–2.343)	3.133(1.917–5.121)
	Low Ratio	1.0(Reference)	1.0(Reference)	1.0(Reference)
	High Ratio	1.292(1.014–1.646)	1.308(1.026–1.668)	1.544(1.142–2.089)
readmission	ApoB/ApoA-I	1.427(1.027–1.984)	1.490(1.069–2.076)	2.400(1.487–3.873)
	Low Ratio	1.0(Reference)	1.0(Reference)	1.0(Reference)
	High Ratio	1.233(0.987–1.541)	1.256(1.005–1.571)	1.425(1.080–1.881)

3.5 Results of Unadjusted and Adjusted Cox Regression to predict one year MACEs and readmission at follow-up

We used Cox Regression analyses to investigate the impact of baseline characteristics associated with one year MACEs and readmission. We incorporated the above variables into univariate and multivariate Cox regression analysis using age and gender as adjustment variables. These results demonstrated that vascular occlusion(HR: 2.016, 95%CI: 1.573–2.583, $P \leq 0.001$), ApoB/ApoA-I ratio(HR: 1.491, 95%CI: 1.037–2.142, $P = 0.031$), use of statins(HR: 0.373, 95%CI: 0.265–0.526, $P < 0.001$), use of aspirins(HR: 0.227, 95%CI: 0.093–0.554, $P = 0.001$) were independent predictors of one year MACEs. Age(HR: 1.014, 95%CI: 1.002–1.026, $P = 0.025$), Vascular occlusion(HR: 1.901, 95%CI: 1.513–2.389, $P \leq 0.001$), use of statins(HR: 0.438, 95%CI: 0.314–0.612, $P \leq 0.001$), use of aspirins(HR: 0.281, 95%CI: 0.116–0.681, $P = 0.005$) were independent predictors of one year readmission. Detailed results of the Cox regression were shown in Fig. 4A, B.

3.6 The nomograms for the Prediction of MACEs and readmission

To predict the outcome of patients after successful PCI, prognostic nomograms were established by multivariate Cox regression model according to significantly independently factors for one year MACEs and readmission (Fig. 5A, B). Each prognostic factor has multiple risk points, which can be obtained by drawing a vertical line from the corresponding value of the prognostic factor directly up to the axis with "dots". In order to determine the one year MACEs and readmission probabilities of a specific patient based on the total "total score" of the risk points, it can be marked with "365-day overall survival probabilities." The C-index of the model is 0.647 (0.613, 0.681) and 0.635 (0.603, 0.666).

4 Discussion

Lipid metabolism is a very complex process. LDL-C can not fully reflect the state of blood lipid metabolism in the body due to its own peculiarity²⁰. In recent years, the research hotspots of blood lipids point to apolipoproteins, mainly including ApoB and ApoA-I. ApoB exists in VLDL, IDL, large and round LDL and small and dense LDL particles (sd-LDL), which is the most important atherogenic particles. Compared with conventionally measured LDL-C, ApoB can reflect the number of sd-LDL especially when the LDL concentration drops to a lower level. The main function of ApoB is to promote the transport of lipoproteins to the blood vessel wall and it represents atherogenic particles²¹. ApoA-I mainly exists in HDL particles, and its main function is to take excess cholesterol from peripheral cells and then transport it to liver through HDL particles. ApoA-I represents the number of anti-atherosclerotic lipoprotein particles and the concentration of LDL²². Therefore, the ApoB/ApoA-I ratio is the simplest form of reflecting the balance of cholesterol transport in the body. The larger the ratio of ApoB/ApoA-I, the more cholesterol is present in the blood circulation, and the easier it is to deposit in the blood vessel wall, which will promote the occurrence of atherosclerosis and cardiovascular events²³⁻²⁵.

Our study analyzed patients undergoing PCI and found that among the patients grouped according to ApoB/ApoA-I ratio, biochemical indicators including TC, TG, LDL-C, HDL-C, LDL-C/HDL-C ratio, Lp(a), ApoA-I, ApoB, uric acid, fasting blood glucose, glycated hemoglobin in the high ApoB/ApoA-I group were significantly higher than those in the low ApoB/ApoA-I ratio group. The proportion of diabetes and myocardial infarction in the high ApoB/ApoA-I group was significantly higher, and the difference was statistically significant. The proportion of multivessel disease and vascular occlusion was significantly higher than that of the low ApoB/ApoA-I ratio group, and the difference was statistically significant. It shows that the level of ApoB/ApoA-I ratio is consistent with the severity of coronary artery disease in patients, and it is a valuable reference index for coronary atherosclerosis.

The INTERHEART and AMORIS studies involving 52 countries showed that the ApoB/ApoA-I ratio has the strongest predictive value for acute myocardial infarction among the nine traditional cardiovascular risk factors (smoking, drinking, abdominal obesity, high blood pressure, diabetes, psychology, low physical

activity, low fruit and vegetable intake, blood lipid), which is better than any other blood lipid and blood lipid ratio index and is independent of age, gender and race^{26,27}. Previous study also demonstrated that treatment with rosuvastatin can reduce the serum lipid level and improve cardiac function. Different dosages of rosuvastatin, age, smoking, drinking alcohol, and diabetes are independent risk factors for AF and ischemia events²⁸. Studies have found that for patients with stable angina pectoris treated with statins, the ApoB/ApoA-I ratio is positively correlated with the lipid volume percentage of the left main coronary artery plaque, suggesting that patients with a high level of ApoB/ApoA-I ratio have higher risk of left main plaque progression and plaque rupture than low-level patients. Therefore, controlling the ApoB/ApoA-I ratio at a low level is one of the important measures to prevent the rupture of the left main plaque.

In this study the analyses of the correlation between ApoB/ApoA-I ratio and other blood lipid indicators showed that TC, TG, LDL-C, LDL-C/HDL-C and Lp(a) gradually increased with the increase of ApoB/ApoA-I ratio and HDL-C showed a gradually decreasing trend. TC, TG, LDL-C, LDL-C/HDL-C, Lp(a) were positively correlated with ApoB/ApoA-I, and HDL-C was negatively correlated with ApoB/ApoA-I ratio. Multivariate Cox regression indicated that vascular occlusion, ApoB/ApoA-I ratio, aspirin, and statin were independent risk factors for one year MACEs after PCI. Age, vascular occlusion, aspirin, and statins were independent risk factors for one year readmission after PCI. The K-M curves indicated that the incidence of MACEs in the high ApoB/ApoA-I group was significantly higher than that in the low ApoB/ApoA-I group, and the difference was statistically significant. There was no statistically significant difference in the incidence of readmission between the high ApoB/ApoA-I ratio group and the low ratio group.

In summary, our study shows that ApoB/ApoA-I ratio is an independent risk factor for MACEs in patients after PCI. Therefore, the blood lipid management in ASCVD patients and deepening the understanding of ApoB/ApoA-I ratio may be have great value to the prevention and treatment of ASCVD in the future. In the course of clinical lipid-lowering treatment, ApoB/ApoA-I ratio can be used as a reference indicator for evaluating the efficacy of lipid-lowering drugs and guiding cardiovascular disease risk stratification. It is expected that more large-scale multi-center studies will further improve the clinical application value of blood lipid indicators.

Declarations

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Author contributions

J.Z performed the data analysis, and prepared the first draft of the manuscript. L.Y. and B.Z. participated in interpreting the results. M.F. reviewed and revised the manuscript. X.L. headed the supervision of technical details and edited the manuscript. P.Z. initiated the study concept and design.

Data Availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Figures

Figure 1

Flow chart of patient enrollment

Figure 2

Pearson correlations between ApoB/ApoA-I ratio and other lipid indexes. All $P < 0.001$.

Figure 3

Cumulative hazard curves of MACEs and readmission events according to ApoB/ApoA-I ratio **A**. Cumulative hazard curve of MACEs cumulative hazard rate by tertile of ApoB/ApoA-I ratio at one year follow-up **B**. Cumulative hazard curve of readmission cumulative hazard rate by tertile of ApoB/ApoA-I ratio at one year follow-up

Figure 4

Results of Cox proportional hazards model **A.** Cox proportional hazards model to predict one year MACEs **B.** Cox proportional hazards model to predict one year readmission

Figure 5

Nomogram model based on multivariate Cox regression analysis in the prediction of one year MACEs and readmission. **A.** nomogram for one year MACEs **B.** nomogram for one year readmission

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