Ratio of Baseline Monocyte Counts to Apolipoprotein A1 is Associated with Long-Term Mortality in Patients with Coronary Artery Disease After Percutaneous Coronary Intervention

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Research

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Abstract

Background: The relationship between the ratio of monocytes to apolipoprotein A1 (MAR) and the long-term prognosis of patients with coronary artery disease (CAD) after PCI has not been investigated.

Methods: A total of 5678 patients with CAD after PCI were recruited for the present study from the First Affiliated Hospital of Xinjiang Medical University. The patients were divided into 3 groups according to the MAR tertiles: lower group (MAR<0.34, n=1881), medium group (0.34≤MAR<0.50, n=1859), and higher group (MAR≥0.50, n=1938). The primary endpoint was long-term mortality, including all-cause death (ACM) and cardiac death (CM). The mean follow-up time was 35.9 ± 22.6 months.

Results: There were 78 (4.1%) deaths in the lower group, 90 (4.8%) deaths in the medium group, and 125 (6.4%) deaths in the higher group. The difference was significant (*P*=0.004). We also found significant differences among these three groups in the incidence of CM (*P*=0.012), MACE (*P*=0.008), and MACCE (*P*=0.012). Using 0.535 as an optimal cutoff value, we found that patients with MARs ≥0.535 had 40.5% and 39.9% increased risks of ACM and CM, respectively, compared to patients with an MAR<0.535. The differences remained significant after adjustment for confounders (ACM, HR=1.447, 95%CI: 1.139-1.838, *P*=0.003; CM, HR=1.424, 95%CI: 1.089-1.862, *P*=0.010).

Conclusion: This study demonstrated that the baseline MAR was an independent predictor of long-term mortality in CAD patients who underwent PCI.

Introduction

The inflammatory response plays an important role in the development of coronary atherosclerotic disease [1–3]. Inflammatory factors and adhesion molecules mediate the entry of monocytes into the arterial intima, which is a major pathophysiological change in the early stages of the atherosclerotic disease, and these monocytes interact with platelets and endothelial cells to cause inflammation and thrombosis [4]. Chapman et al. found that monocytes play a key role in new carotid plaque formation in sub-healthy populations [5]. Elevated monocyte counts in leukocyte subtypes independently predict cardiovascular events in patients with stable coronary heart disease [6]. High monocyte counts were a risk factor for cardiovascular death and coronary plaque formation in elderly Korean populations, and monocyte count may be an independent predictor of cardiovascular death [7]. A recent study confirmed that a high monocyte count and low hemoglobin were associated with poor prognosis in patients with CAD [8].

A previous study suggested a negative correlation between high-density lipoprotein (HDL) levels and atherosclerosis [9]. Apolipoprotein a1 (ApoA1) is the main component of HDL, and it may affect the anti-inflammatory and anti-oxidative effects of HDL via various mechanisms [10]. A large number of animal studies confirmed that high ApoAI expression reduced the volume of atherosclerotic plaques [11–14].

Accumulated evidence suggests that increased monocyte counts and decreased ApoA1 level are associated with a poor prognosis of CAD patients. However, the relationship between the ratio of monocyte counts to ApoA1 and outcomes of CAD patients who underwent PCI is not clear.

Methods

Subjects

This study was a large single-center retrospective cohort study conducted at the First Affiliated Hospital of Xinjiang Medical University from January 2008 to December 2016. The details of the study design have been registered at http://www.chictr.org.cn (Chictr-ORC-16010153). Inclusion criteria: CAD was confirmed by coronary angiography (CAG), which showed at least one main coronary artery stenosis ≥ 70%. Patients meeting the diagnostic criteria of CAD and who were treated with at least one stent were recruited for the present study. We excluded subjects with no baseline monocyte counts and/or ApoA1, hematological disease, malignancy, active infection, renal or hepatic insufficiency, severe valvular disease, hyperthyroidism and hypothyroidism. Finally, we enrolled 5678 patients in the present study. The research protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University.

Definitions

Hypertension was defined as patients who were taking antihypertensive medication or who exhibited 3 blood pressure measurements of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg[15–16]. Diabetes was defined as patients who were taking hypoglycemic agents or who exhibited fasting blood glucose ≥ 7.0 mmol/L, random blood glucose ≥ 11.1 mmol/L or an oral glucose tolerance test for 2 hours of blood glucose ≥ 11.1 mmol/L[17]. Hyperlipidemia was defined in accordance with the "Chinese Adult Diabetes Management Guide (2016) [18]". Smoking was defined as regular smoking over the past 6 months.

Pci Procedure

All patients received 300 mg of clopidogrel, 300 mg of aspirin and 100 U/kg of heparin before PCI. PCI was performed using a standard radial or femoral approach, and all patients had at least one successful stent implant. Surgeons determined the need for pre-expansion, post-expansion, and glycoprotein IIb/IIIa receptor inhibitors according to the patients' conditions. Experienced cardiac intervention specialists performed all procedures, and the numbers and the characteristics of lesions were recorded. All patients received beta-blockers, angiotensin-converting enzyme inhibitors, and statins in the absence of contraindications. After PCI, all the patients took 75 mg of clopidogrel and 100 mg of aspirin daily for at least 12 months.

Endpoints

The primary endpoint was long-term mortality, including ACM and CM. The secondary endpoints were major cardiovascular adverse events (MACE), which were defined as the combination of nonfatal myocardial infarction, cardiac death and target vessel revascularization, and major cardiovascular and cerebrovascular adverse events (MACCE) were defined as non-fatal myocardial infarction, nonfatal stroke, cardiac death, and target vessel revascularization.

Blood Detection

All of the indicators of blood tests were measured in the center laboratory of the First Affiliated Hospital of Xinjiang Medical University according to a unified standard protocol, including blood cell tests and serum concentrations of blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), total cholesterol (TC), triglycerides (TG), glucose (GLU), high-density lipoprotein-C (HDL-C), low-density lipoprotein-C (LDL-C), apolipoprotein A1 (ApoAI), apolipoprotein B (ApoB) and lipoprotein A (Lp(a)).

Results

Baseline data

As shown in Fig. 1, 5678 patients were included and divided into three groups according to the MAR ratio: lower group (MAR < 0.34, n = 1881), medium group (0.34 ≤ MAR < 0.50, n = 1859), and higher group (MAR ≥ 0.50, n = 1938). As shown in Table 1, there were significant differences in age, male ratio, smoking, alcohol consumption, creatinine, uric acid, urea nitrogen, TC, HDL, LDL, ApoB, ApoA1, diastolic blood pressure, and multivessel disease among the three groups (all *Ps* < 0.05). There were no significant differences in the use of clopidogrel, aspirin, new generation of stents, or in the assessment of diabetes, hypertension, systolic blood pressure, post-expansion, pre-expansion, left main lesions, blood glucose, triglycerides, or lipoprotein a (*P* > 0.05) among the groups.

Table 1
Characteristics of participants of the three groups

Variables	Lower group (n = 1881)	Medium group (n = 1859)	Higher group (n = 1938)	X^2	*P*
Clopidogrel, n(%)	547(29.4)	571(30.9)	607(31.5)	2.071	0.355
Aspirin, n(%)	1287(69.1)	1258(68.0)	1263(65.5)	5.792	0.055
Sex, Male, n(%)	1232(65.5)	1399(75.3)	1590(82.0)	138.212	**< 0.001**
Smorking, n(%)	643(34.2)	764(41.1)	874(45.1)	48.292	**< 0.001**
Alcohol drinking, n(%)	469(24.9)	542(29.2)	655(33.8)	36.222	**< 0.001**
Diabetes, n(%)	459(24.4)	460(24.7)	468(24.1)	0.184	0.912
Hypertension, n(%)	796(42.3)	802(43.1)	827(42.7)	0.261	0.878
Mutivessel disease, n(%)	1161(61.8)	1238(66.6)	1284(66.3)	12.060	**0.002**
CTO, n(%)	382(20.3)	405(21.8)	531(27.4)	30.009	**< 0.001**
DES use, n(%)	1766(93.9)	1752(94.2)	1830(94.4)	0.429	0.807
Post-dilatation, n(%)	1161(61.8)	1166(62.7)	1235(63.7)	1.585	0.453
Pre-dilatation, n(%)	1631(86.8)	1607(86.4)	1674(86.4)	0.132	0.936
LM disease, n(%)	120(6.4)	141(7.6)	150(7.7)	3.106	0.212
Age, years	60.42 ± 10.30	59.64 ± 10.94	58.41 ± 11.01	16.972	**< 0.001**
SBP,mmHg	127.24 ± 18.99	127.50 ± 18.68	126.50 ± 18.62	1.467	0.231
DBP,mmHg	75.72 ± 11.28	76.53 ± 11.22	76.64 ± 11.43	3.801	**0.022**
Cr,mmol/L	73.26 ± 20.15	76.27 ± 19.41	78.30 ± 21.34	29.538	**< 0.001**
GLU,mmol/L	6.50 ± 3.15	6.64 ± 3.18	6.67 ± 3.07	1.599	0.202
UA,mmol/L	313.00 ± 87.30	327.45 ± 90.47	329.04 ± 92.14	18.196	**< 0.001**
BUN,mmol/L	5.44 ± 1.59	5.55 ± 1.66	5.56 ± 1.75	3.295	**0.037**
TG,mmol/L	1.89 ± 1.23	1.92 ± 1.29	1.89 ± 1.29	0.410	0.663

Variables	Lower group (n = 1881)	Medium group (n = 1859)	Higher group (n = 1938)	X^2	*P*
TC,mmol/L	4.11 ± 1.10	3.99 ± 1.12	3.80 ± 1.09	38.726	< 0.001
HDL-C,mmol/L	1.10 ± 0.45	1.02 ± 0.50	0.94 ± 0.49	53.426	< 0.001
LDL-C,mmol/L	2.55 ± 0.94	2.47 ± 0.90	2.37 ± 0.90	18.825	< 0.001
ApoB,mmol/L	0.88 ± 0.44	0.86 ± 0.40	0.82 ± 0.35	11.847	< 0.001
ApoA1,mmol/L	1.32 ± 0.41	1.16 ± 0.20	1.03 ± 0.22	476.785	< 0.001
Lp(a),mmol/L	221.92 ± 178.37	218.48 ± 170.82	220.49 ± 180.93	0.178	0.837

Clinical Outcomes

Table 2 shows the incidence of the primary and secondary endpoints, which were significantly higher in the high MAR group compared to the low MAR group (all *Ps* < 0.05).

Table 2
Outcomes comparison between each group

Outcomes	Lower group (n = 1881)	Medium group (n = 1859)	Higher group (n = 1938)	χ^2	P values
ACM, n(%)	78(4.1)	90(4.8)	125(6.4)	10.92	0.004
CM, n(%)	64(3.4)	70(3.8)	101(5.2)	8.845	0.012
MACCE, n(%)	238(12.7)	258(13.9)	312(16.1)	9.569	0.008
MACE, n(%)	217(11.5)	235(12.6)	285(14.7)	8.77	0.012

Note: ACM, All-cause mortality; CM, Cardiac mortality;MACCE, Major cardiovascular and cerebrovascular adverse events; MACE, Major cardiovascular adverse events

ROC curve analyses suggested an optimal cut-off value of 0.535 for the MAR, which exhibited a sensitivity and specificity of 50.5% and 58.7%, respectively. Patients with a MAR ≥ 0.535 had 40.5%, and 39.9% increased risks of ACM and CM, respectively, compared to patients with an MAR < 0.535. The differences remained significant after adjustment for confounders (ACM, HR = 1.447, 95%CI: 1.139–1.838, *P* = 0.003; CM, HR = 1.424, 95%CI: 1.089–1.862, *P* = 0.010), as shown in Table 3.

Table 3
Clinical outcomes and MAR as bisection variable

Outcomes	HR (95%CI)	*P* values	Adjusted HR (95%CI)	*P* values
ACM				
MAR ≥ 0.535 vs. <0.535	1.405 (1.109–1.781)	0.005	1.447 (1.139–1.838)	0.003
CM				
MAR ≥ 0.535 vs. <0.535	1.399 (1.074–1.823)	0.013	1.424 (1.089–1.862)	0.010
MACCEs				
MAR ≥ 0.535 vs. <0.535	1.158 (1.000-1.341)	0.050	1.157 (0.997–1.341)	0.054
MACEs				
MAR ≥ 0.535 vs. <0.535	1.154 (0.990–1.346)	0.067	1.147 (0.982–1.340)	0.082

The Cox proportional hazards model demonstrated a decreased adverse event-free survival rate in the high MAR group compared to the low MAR group during the up-to 10 years of follow up (Fig. 2).

Discussion

The main finding of this study was that elevated MAR was an independent predictor for long-term mortality in CAD patients who underwent PCI. This report is the first study to evaluate the association of MAR with long-term mortality in CAD patients after PCI.

Monocytes are important immune system cells that play an irreplaceable role in the inflammatory response and participate in the pathophysiological processes of various stages of atherosclerosis [1–3]. The role of monocytes in atherosclerosis has been clearly demonstrated [19–21]. ApoA1 is the main protein component of HDL, and it binds to the ATP-binding transporter (ABCA1) on the surface of macrophages and vascular smooth muscle cells to remove excess cholesterol from cells, which prevents foam cell formation with macrophages in atherosclerotic plaques. ABCA1 expression was significantly reduced in vascular smooth muscle cells, which, in turn, reduced ApoA1-mediated reverse cholesterol transport [22–25].

In the present study, we found that increased MAR was an independent predictor for long-term mortality in CAD patients after PCI. Although several variables were significantly different between the low MAR and high MAR groups, the elevated MAR remained an independent predictor for mortality in this population after adjustment for confounders using multivariable Cox regression analysis.

This study has several limitations. First, this study was a single-center retrospective cohort study, and there might be some unknown confounding factors that affected the study results. Second, this study only evaluated baseline MAR and did not assess postoperative changes over time. Finally, other markers

of inflammation and oxidative stress, which may affect the clinical outcome of patients with CAD after PCI, were not considered.

In conclusion, our study found that MAR was an independent predictor of long-term mortality after PCI in patients with CAD.

Abbreviations

CAD
Coronary artery disease
AMI
Acute myocardial infarction
CAG
Coronary angiography;
LVEF
Left ventricular ejection fraction;
IRA
Infarct-related artery;
ACM
All-cause mortality;
MACE
Major adverse cardiovascular events

Declarations

Ethics approval and consent to participate

The research protocol was approved by the ethics committee or review committee of the First Affiliated Hospital of Xinjiang Medical University. Because the study was a retrospective cohort study based on real-world situations, there was no need to obtain informed consent from the patients.

Consent to publish

All authors aggree to publish this work.

Availability of data and materials

Due to confidentiality policies, data will not be shared.

Competing interests

No potential conflicts of interest relevant to this article were reported by any of the authors. None of the funding sources played a role in the design, collection, analysis or interpretation of the data or in the

decision to submit the manuscript for publication. The authors declare that they have no competing interests.

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Authors' Contributions

ZC and TTW made substantial contributions to study conception and design and to the drafting and critical revision of the manuscript for important intellectual content.

XGH, YY, XM, and YTM made substantial contributions to the study conception and design and critical revision of the manuscript for important intellectual content.

XX and YYZ made substantial contributions to study conception and design, drafting and critical revision of the manuscript for important intellectual content, including study supervision.

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Figures

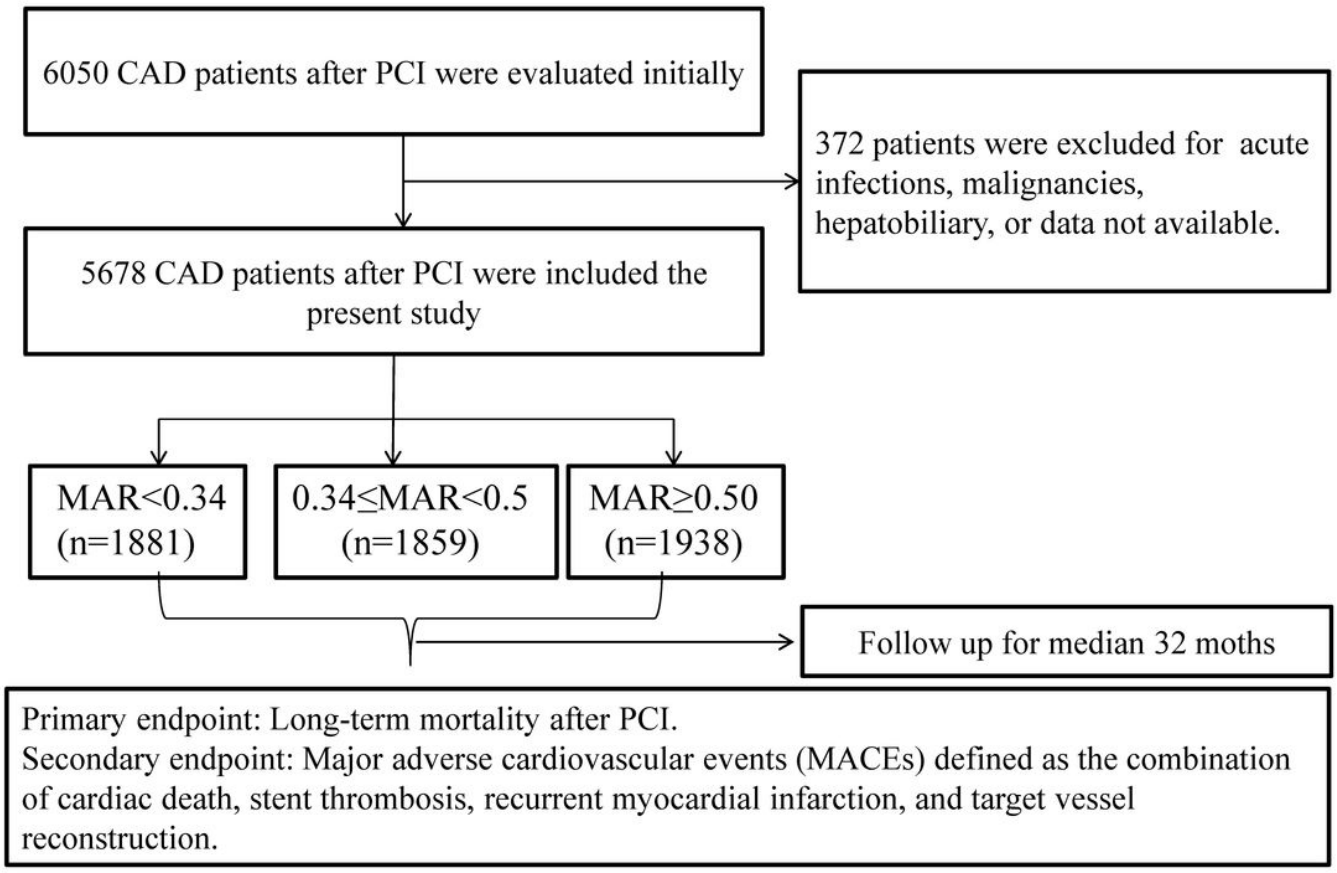

Figure 1

The flow chart of patients inclusion.

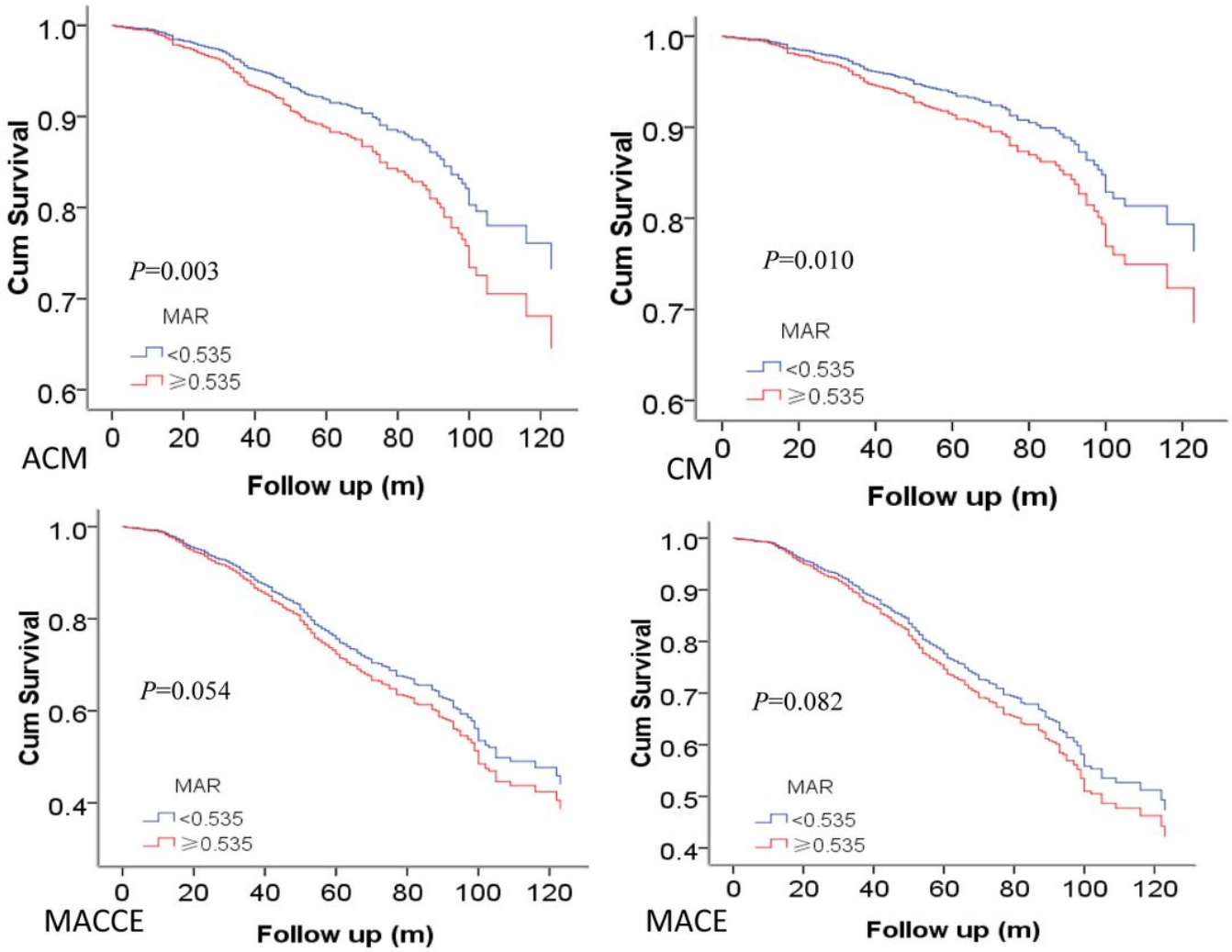

Figure 2

Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of primary endpoint and secondary endpoints.