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Original article

Serum malondialdehyde-modified low-density lipoprotein levels on admission predict prognosis in patients with acute coronary syndrome undergoing percutaneous coronary intervention

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ABSTRACT

Background: Malondialdehyde-modified low-density lipoprotein (MDA-LDL) is a predictive marker of cardiovascular events in patients with stable angina pectoris. However, little is known about this marker in patients with acute coronary syndrome (ACS). We investigated the prognostic relevance of MDA-LDL to cardiovascular outcomes in patients with ACS.
Methods: A total of 370 consecutive patients with ACS who underwent primary percutaneous coronary intervention (PCI) were enrolled from October 2009 to September 2014 at Mitoyo General Hospital. Serum MDA-LDL levels were measured at admission. The patients were divided into three tertile groups according to serum MDA-LDL levels. The primary outcomes were cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, revascularization, and heart failure requiring hospital admission.
Results: MDA-LDL levels in patients with acute myocardial infarction were significantly greater than those in patients with unstable angina pectoris (mean ± standard deviation: 133 ± 48 U/L vs. 157 ± 69 U/L, $p = 0.001$). During follow-up [472 (195–920) days], 82 (22%) events occurred. Kaplan–Meier analysis showed that patients in the highest MDA-LDL tertile had the worst prognosis (log-rank, $p < 0.001$). Cox regression analysis showed that serum MDA-LDL levels were an independent predictor of cardiovascular events after PCI in patients with ACS, even after adjustment for age, sex, body mass index, conventional cardiovascular risk factors, other lipid biomarkers, statin use on admission, cardiac biomarkers, and presence or absence of multivessel disease (hazard ratio: 1.80 per 1 standard deviation U/L increase, 95% confidence interval: 1.07–3.16, $p = 0.027$).
Conclusion: Serum MDA-LDL levels on admission are a significant prognostic marker in patients with ACS who undergo successful PCI.

Introduction

Accumulating evidence has shown that oxidized low-density lipoprotein (LDL) is a useful marker for cardiovascular disease. Oxidized LDL contributes to atherogenesis in a wide range of stages, such as impairing vascular endothelial cells, promoting expression of adhesion factors of vascular endothelial cells, and facilitating monocyte migration and accumulation of lipids under the vascular endothelium by being captured by macrophages [1]. Previous studies have shown that oxidized LDL levels are elevated in patients with coronary artery disease [2,3]. Oxidized LDL levels are especially increased in acute coronary syndrome (ACS) compared with stable angina pectoris [4]. Furthermore, elevated oxidized LDL levels are predictive of future cardiovascular events in healthy men and predict an increased risk of future myocardial infarction in apparently healthy people [5]. These

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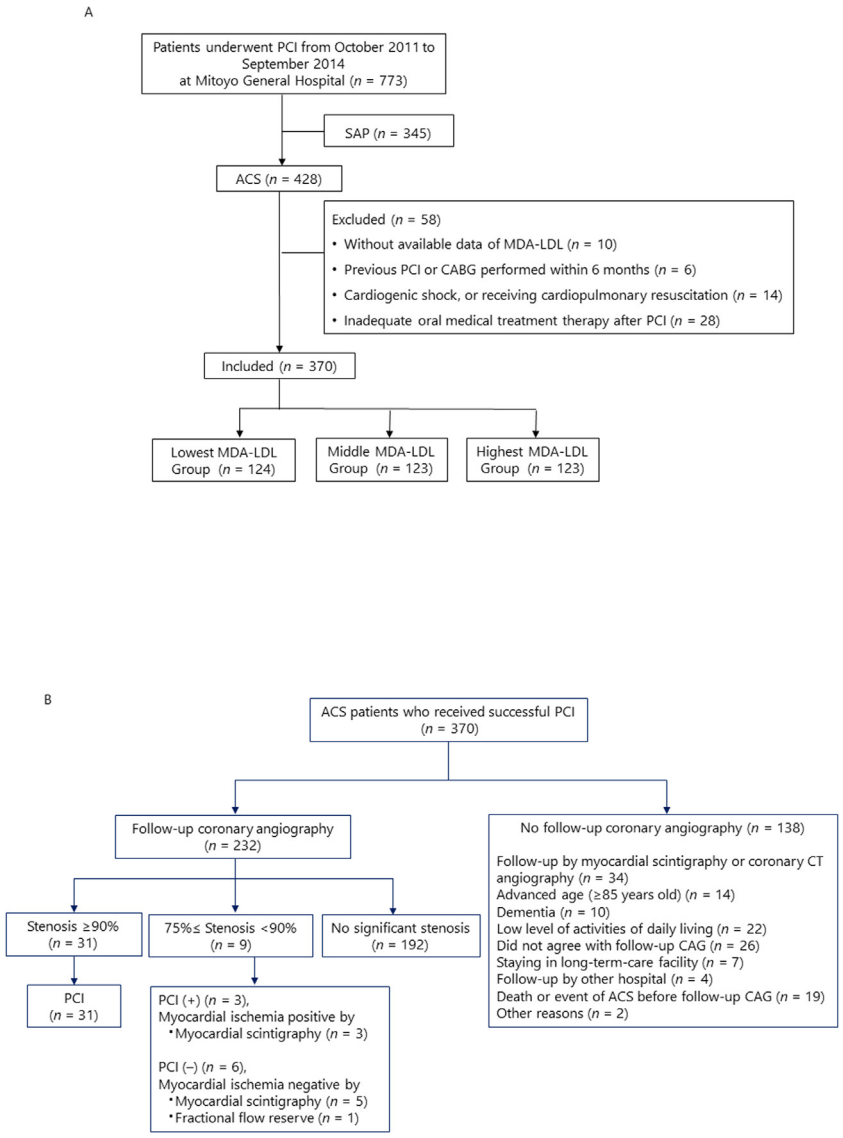

Fig. 1. Flow chart showing selection of patients in main study (A) and follow-up in coronary angiography (B).
ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CT, computed tomography; MDA-LDL, malondialdehyde-modified low-density lipoprotein; PCI, percutaneous coronary intervention; SAP, stable angina pectoris; CAG, coronary angiography.

reports suggest that oxidized LDL is not only a promoter of atherogenesis but also an important marker for the severity of cardiovascular disease and a predictor of future cardiovascular events.

Malondialdehyde-modified low-density lipoprotein (MDA-LDL) is one of the major products of lipid peroxidation and the most common form of oxidized LDL. Many reports have shown that MDA-LDL, similar to oxidized LDL, is an important marker reflecting the severity of cardiovascular disease [6]. MDA-LDL is also a predictor of future cardiac events in patients with stable angina pectoris who undergo percutaneous coronary intervention (PCI) [7]. Furthermore, MDA-LDL levels are a predictive factor for in-stent restenosis in patients with type 2 diabetes with old myocardial infarction or stable angina pectoris after PCI [8]. However, little is known about the effect of MDA-LDL on the prognosis of patients with ACS. Therefore, in this study, we aimed to investigate whether MDA-LDL levels predict cardiovascular events in patients with ACS after successful PCI.

Materials and methods

This was a retrospective, single-center study that included patients with ACS who underwent successful PCI from October 2009 to September 2014 at Mitoyo General Hospital. We defined ACS as patients with acute myocardial infarction or unstable angina pectoris. Acute myocardial infarction was defined as type 1 according to the Third Universal Definition of Myocardial Infarction [9]. Unstable angina pectoris was defined when patients had unstable symptoms of chest pain (at rest/severe and new onset/crescendo pattern) and there was no detectable release of enzymes and biomarkers of myocardial necrosis, with or without changes in electrocardiography. A successful PCI was defined according to the definition of angiographic and procedural success in the 2011 ACCF/AHA/SCAI PCI guideline [10].

The exclusion criteria of this study were as follows: stable angina pectoris; unsuccessful PCI; no available data on MDA-LDL; previous PCI or coronary artery bypass graft surgery performed

within 6 months; allergy or contraindication to antiplatelet agents or contrast media; cardiogenic shock or receiving cardiopulmonary resuscitation; comorbid conditions associated with a life expectancy of <1 year; and inadequate oral medical treatment therapy, including beta-blockers, renin–angiotensin–aldosterone system inhibitors, and statins after PCI. After screening 773 patients, 370 were included in the analysis (Fig. 1A).

This study was approved by the institutional ethics committee of Mitoyo General Hospital. All patients provided written informed consent for enrollment in this study. The study was conducted according to the principles expressed in the Declaration of Helsinki.

All patients underwent PCI by a 6Fr or 7Fr guiding catheter. The patients received dual antiplatelet agents and 7000 IU of unfractionated heparin just before the procedure, and an additional bolus of heparin was administered during PCI to achieve a target activated clotting time >250 s every 1 h. Patients received an intracoronary optimal dose of isosorbide dinitrate before coronary angiography (CAG) to prevent coronary spasm, as long as there was no hemodynamic instability. Balloons and stents were used depending on the operator's decision. The operator also decided the position and length of the angioplasty according to angiographic and intravascular ultrasound findings.

The patients received optimal medical therapy, such as dual antiplatelet agents and statins after PCI, based on Japanese and American College of Cardiology/American Heart Association guidelines [11,12].

Venous blood samples were collected just before PCI. MDA-LDL levels were measured using an enzyme-linked immunosorbent assay (Sekisui Medical Co., Tokyo, Japan) on the basis of the same principles reported by Kotani et al. [13]. For MDA-LDL measurement, inter- and intra-assay coefficients of variation were 6.5% and 9.0%, respectively [14]. Other laboratory parameters were measured using standard laboratory techniques with an automatic analyzer.

The primary endpoint of this study was major adverse cardiac and cerebrovascular events (MACCE), including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (ischemic or hemorrhagic), ischemia-driven revascularization, and heart failure requiring hospital admission. Coronary revascularization was performed in patients with severe stenosis (≥90%) or with positive ischemia shown by other modalities (i.e. myocardial scintigraphy or invasive fractional flow reserve) during follow up [15]. A scheduled PCI for residual lesions was not included as a revascularization event in this study. Follow-up data were collected by a blinded assessment team (H.O. and D.Y.) with no information on the background of the patients. Standard statistical methods were used in this study. Background data are expressed as mean ± standard deviation for normally distributed continuous variables or median (interquartile range) for non-normally distributed continuous variables. We used Student's *t*-test (between two groups) or one-way analysis of variance (among three groups) to compare normally distributed continuous variables, and Bonferroni correction was used for post hoc testing. For continuous variables with a non-normal distribution, Wilcoxon rank sum test (between two groups) or Kruskal–Wallis test (among three groups) was used to examine differences in medians. Discrete variables are presented as percentages and frequencies; comparisons were based on the chi-square test. The Kaplan–Meier method was used to estimate cumulative adverse events, and significance was evaluated by using the log-rank test. Cox proportional hazard models were used to analyze the relationship of serum MDA-LDL levels and event-free survival after adjustment for age, sex, body mass index, and the prevalence of coronary risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking), other lipid biomarkers, statin use on admission, and cardiac biomarkers, including peak creatine phosphokinase, brain natriuretic peptide, and presence or absence of multivessel disease. Logarithmic transformation was also used for non-normally distributed continuous variables to transform them to normally distributed continuous variables when we included them in Cox proportional hazard models. A receiver operating characteristic curve was constructed to demonstrate the discriminatory power of MDA-LDL levels for prespecified cardiovascular outcome. Variables were considered significant when $p < 0.05$. We performed all analyses in this study using JMP version 9.0 (SAS Institute, Tokyo, Japan) or IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA).

Results

In the main analysis, patients with ACS (n = 370) were divided into tertile groups according to serum MDA-LDL levels (U/L), with the lowest tertile at ≤118 (n = 124), the middle tertile at 119–160 (n = 123), and the highest tertile at ≥161 (n = 123).

The baseline characteristics of the study population are shown in Table 1. The mean age was 71 ± 11 years and 282 (76%) patients were men. Patients in the highest MDA-LDL group were younger and the percentage of smokers (former or current) was significantly higher in this group than in the other tertile groups. Body mass index was significantly higher in the highest MDA-LDL group compared with the lowest MDA-LDL group. Furthermore, although the highest MDA-LDL tertile group had a higher prevalence of dyslipidemia, they received significantly less statin therapy on admission compared with the other two groups. With regard to lipid profile, levels of triglyceride, total cholesterol, and low-density lipoprotein cholesterol (LDL-C), the ratio of LDL-C to high-density lipoprotein cholesterol (HDL-C), and the ratio of MDA-LDL to LDL-C (MDA-LDL/LDL-C ratio) were significantly higher in the highest MDA-LDL tertile group compared with the other two groups. The ratio of acute myocardial infarction was highest in the highest MDA-LDL tertile group, but the ratio of unstable angina pectoris was highest in the lowest MDA-LDL tertile group. MDA-LDL levels in patients with acute myocardial infarction (n = 264) were significantly higher than those in patients with unstable angina pectoris (n = 106) (133 ± 48 U/L vs. 157 ± 69 U/L, p = 0.001).

We performed follow-up CAG for 232 (63%) patients 6–12 months after PCI (Fig. 1A). Then, PCI was performed for 31 patients with severe coronary artery stenosis (≥90%) and 3 patients with borderline coronary artery stenosis (75–90%) showing positive ischemia in myocardial scintigraphy or invasive fractional flow reserve. In contrast, 138 (37%) patients did not receive follow-up CAG, detailed reasons for which are shown in Fig. 1B and Online Table 1. We detected no significant difference in the ratio of patients without follow-up CAG and reasons for not undergoing follow-up CAG among MDA-LDL tertiles. There was significant difference in the follow-up period between patients with follow-up CAG and without follow-up CAG (581 [239–1053] days and 329 [53–692], median [interquartile range], respectively, $p < 0.001$). One reason for this difference in the follow-up period is that no follow-up CAG group included patients who died or had ACS before planned follow-up CAG (n = 19) (18 [8–74] days). Another reason is that a lot of remaining patients in the no follow-up CAG group were untraceable before planned follow-up CAG.

During the follow-up (472 [195–920] days), 82 (22%) MACCE occurred (Table 2). The incidence of MACCE was highest in the tertile group with the highest MDA-LDL levels, followed by the middle and lowest tertile groups (lowest group: 12, middle group: 30, highest group: 40, $p < 0.001$). The number of revascularizations for angina pectoris (49 events) was the highest among MACCE, and the highest MDA-LDL tertile group showed the greatest number of events, followed by the middle and lowest tertile groups (lowest

Table 1
Baseline characteristics of patients with ACS in each of three groups according to tertile value of serum MDA-LDL levels.

	All ($n=370$)	Lowest MDA-LDL group (≤118 U/L) ($n=124$)	Middle MDA-LDL group (119–160 U/L) ($n=123$)	Highest MDA-LDL group (≥161 U/L) ($n=123$)	p-Value
Clinical characteristics					
Age, years	71 ± 11	75 ± 10	71 ± 11	66 ± 12[a,b]	<0.001
Male sex, n (%)	282 (76)	94 (76)	91 (74)	97 (79)	0.662
Body mass index, kg/m^2	23.4 ± 3.4	22.6 ± 3.2	23.8 ± 3.5	23.9 ± 3.4[a]	0.003
Hypertension, n (%)	249 (67)	90 (73)	84 (68)	75 (61)	0.145
Diabetes mellitus, n (%)	123 (33)	43 (35)	44 (36)	36 (29)	0.510
Dyslipidemia, n (%)	224 (61)	57 (46)	76 (62)	91 (74)[a,b]	<0.001
Smoking, n (%)	194 (52)	59 (48)	58 (47)	77 (63)[a,b]	0.022
Previous PCI, n (%)	46 (12)	16 (13)	16 (13)	14 (11)	0.911
Previous CABG, n (%)	3 (1)	2 (2)	1 (1)	0 (0)	0.369
Type of acute coronary syndrome					0.013
Acute myocardial infarction, n (%)	264 (71)	79 (64)	86 (70)	99 (80)[a]	
Unstable angina pectoris, n (%)	106 (29)	45 (36)	37 (30)	24 (20)[a]	
Angiographic characteristics					
Multi-vessel disease, n (%)	164 (44)	47 (38)	55 (45)	62 (50)	0.141
Infarct-related artery					0.368
Right, n (%)	136 (37)	41 (33)	51 (41)	44 (36)	
Left anterior descending, n (%)	184 (50)	69 (56)	51 (41)	64 (52)	
Left circumflex, n (%)	45 (12)	13 (10)	18 (14)	14 (11)	
Left main trunk, n (%)	5 (1)	1 (1)	3 (2)	1 (1)	
% stenosis of target lesion					0.163
90%, n (%)	105 (28)	43 (35)	37 (30)	25 (20)[a]	
99%, n (%)	117 (32)	36 (29)	38 (31)	43 (35)	
100%, n (%)	148 (40)	45 (36)	48 (39)	55 (45)	
TIMI grade of pre-PCI					0.338
0, n (%)	147 (40)	44 (36)	48 (39)	55 (45)	
I, n (%)	28 (8)	8 (7)	10 (8)	10 (8)	
II, n (%)	90 (24)	29 (23)	28 (23)	33 (27)	
III, n (%)	105 (28)	43 (35)	37 (30)	25 (20)[a]	
Stent use, n (%)	362(98)	119 (96)	122(99)	121 (98)	0.194
Bare metal stent, n (%)	153 (41)	49 (40)	48 (39)	56 (46)	0.514
Drug-eluting stent, n (%)	209 (56)	70 (56)	74 (60)	65 (53)	0.512
Follow up coronary angiography, n (%)	232 (63)	77 (62)	76 (62)	79 (64)	0.911
Biochemical data					
Total cholesterol, mg/dL	196 ± 36	170 ± 35	194 ± 33	222 ± 40[a,b]	<0.001
Triglyceride, mg/dL	110 (69–164)	89 (55.8–130)	110 (69–149)	136 (96–210)[a,b]	<0.001
LDL-C, mg/dL	120 ± 33	98 ± 31	119 ± 31	143 ± 38[a,b]	<0.001
HDL-C, mg/dL	49 ± 14	52 ± 14	49 ± 14	47 ± 14[a]	0.023
LDL-C/HDL-C ratio	2.6 ± 0.9	2.0 ± 0.8	2.6 ± 0.9	3.2 ± 1.0[a,b]	<0.001
MDA-LDL, U/L	150 ± 37	93 ± 18	138 ± 11	221 ± 60[a,b]	<0.001
MDA-LDL/LDL-C ratio	1.3 ± 0.5	1.0 ± 0.4	1.3 ± 0.5	1.6 ± 0.6[a,b]	<0.001
Hemoglobin A1c, %	6.3 ± 1.2	6.2 ± 1.1	6.4 ± 1.4	6.2 ± 1.3	0.349
Brain natriuretic peptide, pg/dL	79 (20–212)	117 (29–362)	40 (16–126)	68 (16–212)	0.047
Peak CPK, IU/L	1684 (522–3432)	913 (365–2500)	1797 (688–3575)	2019 (733–5270)[a]	<0.001
Peak CK-MB, IU/L	74 (17–250)	36 (13–150)	86 (17–248)	125 (32–355)[a]	0.004
eGFR, mL min^{-1} 1.73 m^{-2}	54 ± 19	52 ± 19	52 ± 19	59 ± 18[a,b]	0.006
Medications on admission					
Aspirin, n (%)	81 (22)	35 (28)	26 (21)	20 (16)	0.073
Clopidogrel, n (%)	49 (13)	19 (15)	15 (12)	15 (12)	0.704
ACEI, n (%)	19 (5)	7 (6)	7 (6)	5 (4)	0.805
ARB, n (%)	113 (31)	41 (33)	42 (34)	30 (24)	0.190
Beta-blocker, n (%)	36 (10)	14 (11)	16(13)	6 (5)	0.076
Statin, n (%)	76 (21)	29 (23)	31 (25)	16 (13)[a,b]	0.038
Insulin, n (%)	17 (5)	4 (3)	10(8)	3 (2)	0.069
Oral hypoglycemic agent, n (%)	67 (18)	25 (20)	23 (9)	19 (15)	0.616

Values are expressed as mean ± standard deviation, median and interquartile range, or absolute number of cases (relative percentage) as appropriate.
ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CK-MB, creatine kinase MB; CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDA-LDL, malondialdehyde-modified low-density lipoprotein; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.
[a] $p<0.05$ vs. the lowest group.
[b] $p<0.05$ vs. the middle group.

group: 3, middle group: 17, highest group: 29, $p<0.001$). There were no other significant differences in any type of events among the three groups.

Kaplan–Meier curves for each of the three groups after PCI showed a poorer event-free survival rate in patients with the highest tertile of MDA-LDL levels, followed by the middle and lowest tertiles (log-rank, $p<0.001$, Fig. 2A). However, there were no significant differences in other lipid biomarkers, such as total cholesterol, LDL-C, HDL-C, or triglyceride levels, among the tertile groups (Fig. 2B–E).

Multivariate Cox regression analysis showed that serum MDA-LDL level on admission was an independent predictor for MACCE

Table 2
Comparison of clinical events among three groups according to serum MDA-LDL levels in patients with ACS.

	All (n = 370)	Lowest MDA-LDL group (≤118 U/L) (n = 124)	Middle MDA-LDL group (119–160 U/L) (n = 123)	Highest MDA-LDL group (≥161 U/L) (n = 123)	p-Value
MACCE (all cause), n (%)	82 (22)	12 (10)	30 (24)	40 (33)	<0.001
Cardiovascular death, n (%)	11 (3)	1 (1)	5 (4)	5 (4)	0.219
Non-fatal myocardial infarction, n (%)	6 (2)	2 (2)	1 (1)	3 (2)	0.601
Non-fatal stroke, n (%)	6 (2)	3 (2)	2 (2)	1 (1)	0.607
Revascularization (%)	49 (13)	3 (2)	17 (14)	29 (24)	<0.001
Heart failure requiring hospital admission, n (%)	10 (3)	3 (2)	5 (4)	2 (2)	0.485

Values are expressed as absolute number of events (relative percentage).
ACS, acute coronary syndrome; MACCE, major adverse cardiovascular and cerebral events; MDA-LDL, malondialdehyde-modified low-density lipoprotein.

Table 3
Hazard ratios of MACCE for each 1 SD increase of serum MDA-LDL values in patients with ACS.

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
MDA-LDL, per 1 SD (37 U/L) increase	1.17 (1.06–1.27)	0.003	1.21 (1.08–1.34)	0.001	1.22 (1.06–1.39)	0.007	1.80 (1.07–3.16)	0.027

Model 1: unadjusted.
Model 2: adjusted for age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, and body mass index.
Model 3: adjusted for total cholesterol (per 1 SD [36 mg/dL] increase), triglycerides (*), low-density lipoprotein cholesterol (per 1 SD [33 mg/dL] increase), high-density lipoprotein cholesterol (per 1 SD [14 mg/dL] increase), and statin use (on admission), in addition to model 2.
Model 4: adjusted for peak creatine phosphokinase (*), brain natriuretic peptide (*), and presence or absence of multivessel disease, in addition to model 3.
* per 1 increase in logarithmic transformed number.
CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebral events; MDA-LDL, malondialdehyde-modified low-density lipoprotein; SD, standard deviation.

after PCI in patients with ACS (hazard ratio: 1.80 per 1 standard deviation [37 U/L] increase, 95% confidence interval: 1.07–3.16, p = 0.027) after adjustment for age, sex, body mass index, conventional cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, and history of smoking), other lipid biomarkers, statin use on admission, and cardiac biomarkers, including peak creatine phosphokinase, brain natriuretic peptide, and presence or absence of multivessel disease (Table 3).

The specificity and sensitivity of the correlation between MACCE and serum MDA-LDL levels were evaluated using receiver operating characteristic analysis to assess their predictive value. Receiver operating characteristic analysis showed that the optimal cut-off level of MDA-LDL levels was 135 U/L and the area under the curve was 0.66 (95% confidence interval: 0.60–0.73). The predictive sensitivity and specificity of MDA-LDL levels were 76% and 56%, respectively.

Additionally, we evaluated the impact of MDA-LDL in patients with acute myocardial infarction. Characteristics of patients with acute myocardial infarction are shown in Table 4. As in the main study, patients in the higher MDA-LDL group (≥142 U/L) (n = 134) were younger and had higher body mass index, higher prevalence of dyslipidemia, and significantly poorer lipid profiles, compared with patients in the lower MDA-LDL group (≤141 U/L) (n = 130). Moreover, the prevalence of multi-vessel disease was higher in the higher MDA-LDL group than in the lower MDA-LDL group. A comparison of clinical events between these two groups during follow-up (433 [186–858] days) is shown in Table 5. As in the analysis of all patients, the incidence of MACCE (n = 41 [31%]) and especially of revascularization (n = 28 [21%]) were significantly higher in the higher MDA-LDL group than in the lower MDA-LDL group (n = 14 [11%] and n = 6 [5%], respectively, $p < 0.001$). Kaplan–Meier curves showed a poorer event-free survival rate in patients in the higher MDA-LDL group than in those in the lower MDA-LDL group (Online Fig. 1). After adjustment for confounding factors, multivariate Cox regression analysis showed that serum MDA-LDL level on admission was an independent predictor for MACCE after PCI, even in patients with acute myocardial infarction (hazard ratio: 3.50 per 1 standard deviation [69 U/L] increase, 95% confidence interval: 1.27–10.5, p = 0.016) (Table 6).

Discussion

The major findings of this study were as follows: (1) MDA-LDL levels were higher in patients with acute myocardial infarction than in those with unstable angina pectoris; (2) elevation of serum MDA-LDL levels could be an independent predictor for MACCE in patients with ACS undergoing successful PCI; and (3) serum MDA-LDL on admission in patients with acute myocardial infarction was shown to be a significant factor associated with MACCE. To the best of our knowledge, this is the first study to demonstrate the relation between serum MDA-LDL levels and prognosis after successful PCI in patients with ACS.

Serum MDA-LDL level is a useful biomarker for reflecting the severity of coronary artery disease [2,16] and the presence of vulnerable plaques [17–19]. Our study showed that the acute myocardial infarction rate in patients with the highest MDA-LDL group was higher than that in patients with the lowest MDA-LDL group. These results support the clinical utility of MDA-LDL as a biomarker for the severity of coronary artery disease. Serum oxidized LDL levels, including MDA-LDL, reflect the presence of vulnerable plaques, but this is a systemic, not focal, effect. Therefore, elevated MDA-LDL levels might be the result of vulnerable plaques of other areas, such as the carotid artery, brain vessels, and arteries of the lower limbs. Additionally, our study showed poorer lipid balance and a higher body mass index in the highest MDA-LDL tertile. Recent studies have shown that MDA-LDL levels are positively correlated with LDL-C and triglyceride levels and negatively correlated with HDL-C levels [20–22]. Furthermore, Holvoet et al. reported that hyperinsulinemia and impaired glycemic control, reflecting the severity of metabolic syndrome,

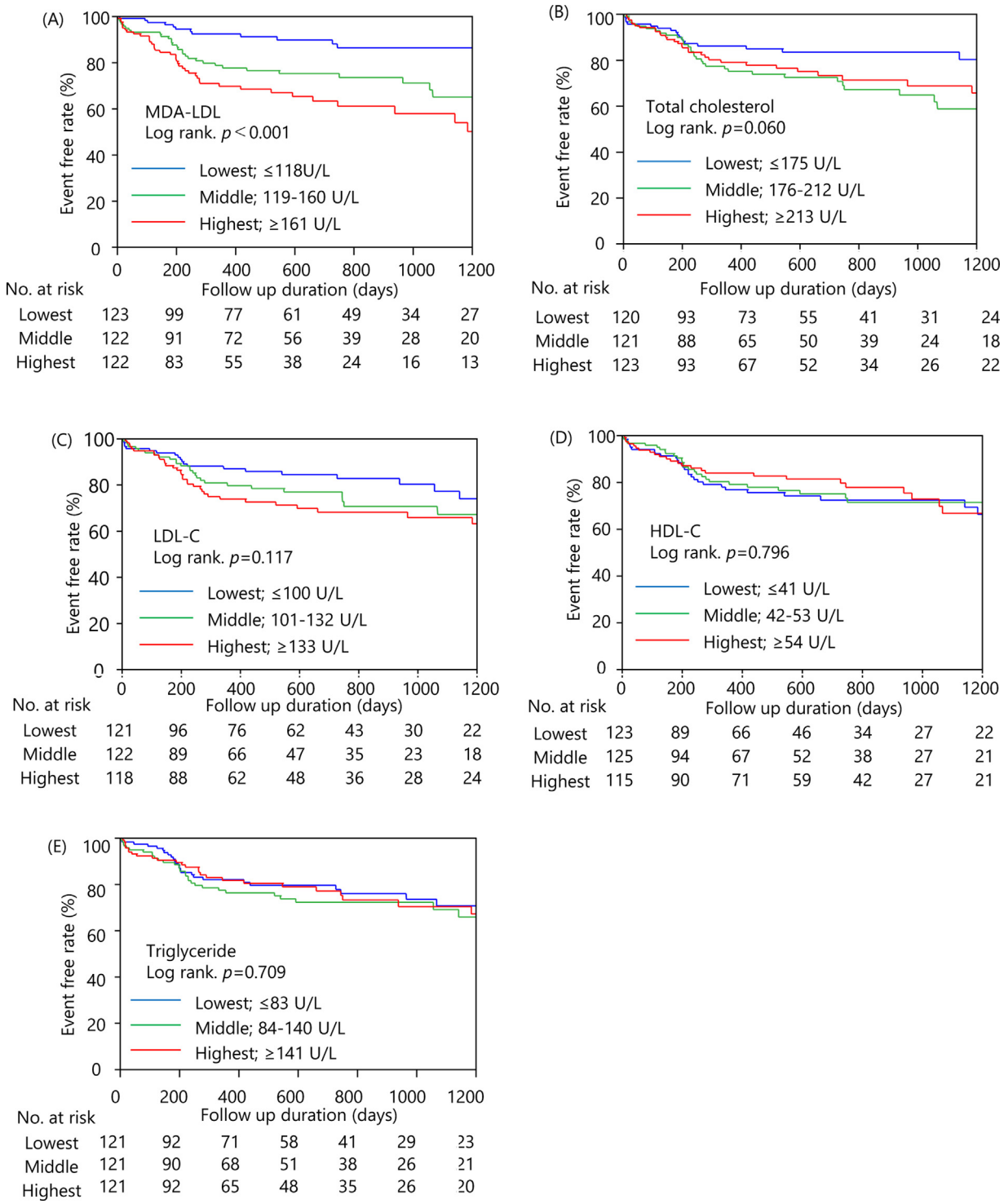

Fig. 2. Kaplan–Meier analysis of cumulative event-free rates after PCI in patients with ACS, according to tertile value of serum MDA-LDL (A), total cholesterol (B), LDL-C (C), HDL-C (D), and triglyceride (E) levels (main study).
ACS, acute coronary syndrome; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDA-LDL, malondialdehyde-modified low-density lipoprotein; PCI, percutaneous coronary intervention.

were associated with increased in vivo LDL oxidation [23]. Our results are in good agreement with these previous reports.

The MDA-LDL/LDL-C ratio, which is an indicator of the extent of LDL oxidation, was higher in patients with elevated MDA-LDL levels, especially in the highest tertile. Other reports have shown that in addition to MDA-LDL levels, the MDA-LDL/LDL-C ratio was higher in patients with coronary artery disease (CAD) compared with patients without CAD [20,24]. Our study suggested that in patients with ACS, higher MDA-LDL levels also reflected a higher MDA-LDL/LDL-C ratio, which could represent a stronger atherogenic state.

Our study also showed that the onset age of ACS was younger in the highest MDA-LDL group. This finding suggests that younger patients with ACS have poor lipid balance and strong oxidative

Table 4
Baseline characteristics of patients with AMI in each two groups according to median value of serum MDA-LDL levels.

	All patients with acute myocardial infarction (n = 264)	Lower MDA-LDL group (≤141 U/L) (n = 130)	Higher MDA-LDL group (≥142 U/L) (n = 134)	p-Value
Clinical characteristics				
Age, years	71 ± 12	74 ± 11	68 ± 11	<0.001
Male sex, n (%)	197 (75)	92 (71)	105 (78)	0.157
Body mass index, kg/m^2	23.2 ± 3.4	22.7 ± 3.5	23.7 ± 3.3	0.015
Hypertension, n (%)	163 (62)	78 (60)	85 (63)	0.566
Diabetes mellitus, n (%)	81 (31)	42 (32)	39 (29)	0.573
Dyslipidemia, n (%)	158 (60)	61 (47)	97 (72)	<0.001
Smoking, n (%)	143 (54)	67 (52)	76 (57)	0.399
Previous PCI, n (%)	26 (10)	13 (10)	13 (10)	0.935
Previous CABG, n (%)	2 (1)	1 (1)	1 (1)	0.979
Type of acute myocardial infarction				0.211
STEMI, n (%)	190 (72)	89 (68)	101 (75)	
NSTEMI, n (%)	74 (28)	41 (32)	33 (25)	
Angiographic characteristics				
Multi-vessel disease, n (%)	119 (45)	46 (35)	73 (54)	0.002
Infarct-related artery				0.390
Right, n (%)	98 (37)	46 (35)	52 (39)	
Left anterior descending, n (%)	127 (48)	60 (46)	67 (59)	
Left circumflex, n (%)	35 (13)	22 (17)	13 (10)	
Left main trunk, n (%)	4 (2)	2 (2)	2 (1)	
% stenosis of target lesion				0.283
90%, n (%)	47 (18)	28 (22)	19 (14)	
99%, n (%)	83 (31)	40 (31)	43 (32)	
100%, n (%)	134 (51)	62 (48)	72 (54)	
TIMI grade of pre-PCI				0.185
0, n (%)	133 (50)	61 (47)	72 (54)	
I, n (%)	18 (7)	6 (5)	12 (9)	
II, n (%)	66 (25)	35 (27)	31 (23)	
III, n (%)	47 (18)	28 (22)	19 (14)	
Stent use, n (%)	258 (98)	125 (96)	133 (99)	0.091
Bare metal stent, n (%)	122 (46)	59 (45)	63 (47)	0.791
Drug eluting stent, n (%)	128 (49)	66 (51)	70 (52)	0.811
Follow up coronary angiography, n (%)	169 (64)	83 (64)	86 (64)	0.955
Biochemical data				
Total cholesterol, mg/dL	199 ± 44	181 ± 38	217 ± 41	<0.001
Triglyceride, mg/dL	104 (69–160)	87 (58–127)	126 (91–200)	<0.001
LDL-C, mg/dL	124 ± 40	109 ± 34	138 ± 40	<0.001
HDL-C, mg/dL	50 ± 14	52 ± 14	48 ± 14	0.059
LDL-C/HDL-C ratio	2.6 ± 1.0	2.3 ± 0.9	3.0 ± 1.0	<0.001
MDA-LDL, U/L	157 ± 69	107 ± 24	206 ± 63	<0.001
MDA-LDL/LDL-C ratio	1.3 ± 0.6	1.0 ± 0.4	1.6 ± 0.7	<0.001
Hemoglobin A1c, %	6.3 ± 1.2	6.2 ± 1.2	6.3 ± 1.2	0.741
Brain natriuretic peptide, pg/dL	111 (25–308)	162 (43–403)	41 (13–226)	0.028
Peak CPK, IU/L	1692 (526–3451)	1035 (411–2880)	2105 (787–4554)	<0.001
Peak CK-MB, IU/L	151 (44–320)	101 (36–276)	195 (81–377)	<0.001
eGFR, mL min^{-1} 1.73 m^{-2}	55 ± 19	54 ± 19	56 ± 18	0.369
Medications on admission				
Aspirin, n (%)	39 (15)	20 (15)	19 (14)	0.783
Clopidogrel, n (%)	15 (6)	10 (8)	5 (4)	0.165
ACEI, n (%)	12 (5)	6 (5)	6 (4)	0.957
ARB, n (%)	73 (28)	37 (28)	36 (27)	0.772
Beta-blocker, n (%)	17 (6)	7 (5)	10 (7)	0.492
Statin, n (%)	45 (17)	27 (21)	18 (13)	0.113
Insulin, n (%)	9 (3)	5 (4)	4 (3)	0.700
Oral hypoglycemic agent, n (%)	42 (16)	23 (18)	19 (14)	0.435

Values are expressed as mean ± standard deviation, median and interquartile range, or absolute number of cases (relative percentage) as appropriate.
ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CK-MB, creatine kinase MB; CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDA-LDL, malondialdehyde-modified low-density lipoprotein; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.
$p < 0.05$ vs. the lowest group.
$p < 0.05$ vs. the middle group.

stress, and these factors could contribute to their younger onset of ACS. Ogawa et al. studied patients who underwent CAG, including those with CAD and normal coronary arteries [22]. These authors found that there was a negative correlation between MDA-LDL levels and age, similar to our study. However, Toshima et al. reported that there was no significant correlation between oxidized LDL levels and age in patients with CAD [25]. Additionally, Holvoet et al. reported that oxidized LDL and MDA-LDL levels were positively correlated with age in patients with ACS, stable angina pectoris, and heart transplant, as well as in controls [2]. Further

Table 5
Comparison of clinical events between the lower and higher MDA-LDL groups in patients with AMI.

	All patients with acute myocardial infarction (n = 264)	Lower MDA-LDL group (≤141 U/L) (n = 130)	Higher MDA-LDL group (≥142 U/L) (n = 134)	p-Value
MACCE (all cause), n (%)	55 (21)	14 (11)	41 (31)	<0.001
Cardiovascular death, n (%)	10 (4)	2 (2)	8 (6)	0.059
Non-fatal myocardial infarction, n (%)	3 (1)	2 (2)	1 (1)	0.544
Non-fatal stroke, n (%)	2 (1)	1 (1)	1 (1)	0.983
Revascularization (%)	34 (13)	6 (5)	28 (21)	<0.001
Heart failure requiring hospital admission, n (%)	6 (3)	3 (2)	3 (2)	0.970

Values are expressed as absolute number of events (relative percentage).
AMI, acute myocardial infarction; MACCE, major adverse cardiovascular and cerebral events; MDA-LDL, malondialdehyde-modified low-density lipoprotein.

Table 6
Hazard ratios of MACCE for each 1 SD increase of serum MDA-LDL values in patients with AMI.

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
MDA-LDL, per 1 SD (69 U/L) increase	1.29 (1.04–1.56)	0.021	1.34 (1.04–1.69)	0.023	1.41 (1.04–1.89)	0.025	3.50 (1.27–10.5)	0.016

Model 1: unadjusted.
Model 2: adjusted for age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking, and body mass index.
Model 3: adjusted for total cholesterol (per 1 SD [44 mg/dL] increase), triglycerides (*), low-density lipoprotein cholesterol (per 1 SD [40 mg/dL] increase), high-density lipoprotein cholesterol (per 1 SD [14 mg/dL] increase), and statin use (on admission), in addition to model 2.
Model 4: adjusted for peak creatine phosphokinase (*), brain natriuretic peptide (*), and presence or absence of multivessel disease, in addition to model 3.
* per 1 increase in logarithmic transformed number.
AMI, acute myocardial infarction; CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebral events; MDA-LDL, malondialdehyde-modified low-density lipoprotein; SD, standard deviation.

studies are required to determine the correlation between MDA-LDL levels and age, especially in patients with ACS.

Our study showed that in patients with ACS, elevated MDA-LDL levels were able to predict future MACCE, especially revascularization after PCI. Few other studies have focused on the relation between MDA-LDL levels and prognosis of patients with CAD [7,8]. Ito et al. reported that MDA-LDL levels were significantly associated with future cardiac events after PCI with drug-eluting stents in patients with stable angina pectoris under lipid-lowering therapy [7]. One study that used optical coherence tomography showed that MDA-LDL levels were correlated with the presence of thin-cap fibroatheromas in the culprit lesion [18]. Another report on integrated backscatter intravascular ultrasound showed that higher MDA-LDL levels suggested the presence of a plaque with greater lipid and lower fibrous content in culprit lesions [19]. Moreover, Sahara et al. reported that soft plaques, that is, lipid-rich plaques, detected on intravascular ultrasound were the strongest predictor of in-stent restenosis [26]. This was because soft plaques could be compressed more easily by stenting but also caused proliferation of the neointima and resulted in restenosis. Higher MDA-LDL levels in patients with ACS before PCI suggest the presence of soft and vulnerable plaques in the culprit lesion and/or the entire coronary artery. This could be a high-risk marker for predicting the future event of in-stent restenosis and progression of other lesions, which cause angina pectoris requiring revascularization. However, Naruko et al. reported that although oxidized LDL levels at discharge were significantly correlated with in-stent restenosis at a 6-month follow-up in patients with acute myocardial infarction, oxidized LDL levels at admission did not show a significant correlation with future cardiac events [27]. Further studies are required to conclude whether MDA-LDL levels at admission or discharge are appropriate for predicting future cardiovascular events after PCI in patients with ACS.

There are several limitations to this study. First, this was a single-center, retrospective study and the sample size was relatively small. Second, most of the differences among the tertile groups occurred in soft endpoints, such as revascularization. In our study, body mass index, the ratio of smokers, and the prevalence of dyslipidemia were higher in patients with the highest tertile of MDA-LDL compared with the other two groups. It is possible that the higher MDA-LDL levels reflected accumulation of risk factors, which resulted in a higher prevalence of MACCE, including revascularization. However, MDA-LDL levels were a significant independent risk factor for MACCE after adjustment for these factors in this study. Finally, our study design precluded the investigation of a direct causal relationship. To determine this causal relationship between MDA-LDL levels and clinical events more directly, long-term interventional studies involving therapeutic agents that reduce MDA-LDL levels are warranted.

Conclusion

In patients with ACS, elevated serum MDA-LDL levels could be an important predictor of future cardiac events, especially in patients with ACS requiring revascularization after successful PCI.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.02.012.

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