Lipid Paradox in Acute Myocardial Infarction—The Association With 30-Day In-Hospital Mortality

Kai-Hung Cheng, MD[1,2,3]; Chih-Sheng Chu, MD, PhD[1,2,3]; Tsung-Hsien Lin, MD, PhD[1,2,3]; Kun-Tai Lee, MD[1,2]; Sheng-Hsiung Sheu, MD[1,2]; Wen-Ter Lai, MD[1,2]

Objectives: Elevated low-density lipoprotein cholesterol and triglycerides are major risk factors for coronary artery disease. However, fatty acids from triglycerides are a major energy source, low-density lipoprotein cholesterol is critical for cell membrane synthesis, and both are critical for cell survival. This study was designed to clarify the relationship between lipid profile, morbidity as assessed by Killip classification, and 30-day mortality in patients with acute myocardial infarction.

Design: A noninterventional observational study.

Setting: Coronary care unit in a university hospital.

Patients: Seven hundred twenty-four patients with acute myocardial infarction in the coronary care program of the Bureau of Health Promotion were analyzed.

Interventions: None.

Measurements and Main Results: Low-density lipoprotein cholesterol and triglyceride levels were significantly lower in high-Killip (III + IV) patients compared with low-Killip (I + II) patients and in those who died compared with those who survived beyond 30 days (both $p < 0.001$). After adjustment for risk factors, low-density lipoprotein cholesterol less than 62.5 mg/dL and triglycerides less than 110 mg/dL were identified as optimal threshold values for predicting 30-day mortality and were associated with hazard ratios of 1.65 (95% CI, 1.18–2.30) and 5.05 (95% CI, 1.75–14.54), and the actual mortality rates were 23% in low low-density lipoprotein, 6% in high low-density lipoprotein, 14% in low triglycerides, and 3% in high triglycerides groups, respectively. To test the synergistic effect, high-Killip patients with triglycerides less than 62.5 mg/dL and low-density lipoprotein cholesterol less than 110 mg/dL had a 10.9-fold higher adjusted risk of mortality than low-Killip patients with triglycerides greater than or equal to 62.5 mg/dL and low-density lipoprotein cholesterol greater than or equal to 110 mg/dL ($p < 0.001$). The lipid paradox also improved acute myocardial infarction short-term outcomes prediction on original Killip and thrombolytic in myocardial infarction scores.

Conclusions: Low low-density lipoprotein cholesterol, low triglycerides, and high Killip severity were associated with significantly higher 30-day in-hospital mortality in patients presenting with acute myocardial infarction. The initial lipid profile of patients with acute myocardial infarction may therefore hold prognostic value. (*Crit Care Med* 2015; 43:1255–1264)

Key Words: Killip classification; low-density lipoprotein cholesterol; mortality; myocardial infarction; triglycerides

Elevated low-density lipoprotein (LDL) is an important risk factor for cardiovascular disease (CVD) (1–3), and the concept of "LDL—the lower, the better" has been proposed in many statin studies to improve major cardiovascular outcomes and mortality (4–10). Elevated triglyceride-rich lipoprotein species or lipoprotein changes associated with altered triglyceride metabolism have also been reported to influence the development of CVD (7, 11). However, fatty acids from triglyceride-rich lipoproteins serve as a source of energy for tissues and are important for cell survival. Low-density lipoprotein cholesterol (LDL-C) is critical for the synthesis of cellular membranes and steroid hormones (12). In addition, lipid-free apolipoprotein B has been reported to induce apoptosis (13). This lipid paradox with respect to CVD has similarly been reported in elderly patients and those with rheumatoid arthritis (14), heart failure, stroke, and atrial fibrillation (15–20). The Killip(-Kimball) classification has also been used for acute myocardial infarction (AMI) risk stratification (21). Poor 12-month clinical outcomes have been reported in patients with low LDL-C with AMI, although it was not an independent predictor of 12-month mortality (22). The association between lipid profile, Killip classification, and 30-day in-hospital mortality remains unknown, and this study aims to clarify those associations in patients with AMI.

[1]Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.

[2]Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.

[3]Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: wtlai@cc.kmu.edu.tw

DOI: 10.1097/CCM.0000000000000946

MATERIALS AND METHODS

Study Population and Design

A total of 724 patients with AMI participating in the coronary care program of the Bureau of Health Promotion at Kaohsiung Medical University Hospital between February 2010 and April 2012 were analyzed. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital and conformed to the Declaration of Helsinki. All subjects provided informed consent before participation. The inclusion criteria for patients with ST-elevation myocardial infarction (STEMI) were as follows: 1) duration of persistent angina from onset to arrival to the emergency department less than 6 hours, 2) ST-segment elevation greater than 1 mm in two or more limb leads or greater than 2 mm in two or more contiguous precordial leads, 3) confirmed diagnosis of MI based on persistent angina greater than 20 minutes, electrocardiogram findings, and cardiac enzyme changes, and 4) coronary angiography performed within 12 hours of the onset of chest pain (23). For patients with non–ST-elevation myocardial infarction (NSTEMI), the inclusion criteria were as follows: 1) onset of chest discomfort in the preceding 48 hours, 2) new horizontal or down-sloping ST depression greater than or equal to 0.05 mm in two contiguous leads and/or T inversion greater than or equal to 0.1 mm in two contiguous leads with prominent R wave or R/S ratio greater than 1, and/or 3) elevated troponin I (> 1.0 ng/dL) with a rising and/or falling pattern (24–26). Ninety-five percent of the patients were treated with unfractionated heparin or low-molecular-weight heparin. However, individual heparin dosing was calculated by body weight (kg), and the information is not available in this study.

Clinical data including demographic information, medical history (hypertension, diabetes, smoking status, alcohol use, dyslipidemia, previous use of statins, and end-stage renal disease [ESRD]), and the number of coronary arteries with significant luminal stenosis (> 70%) by angiography were collected. Hypertension was defined as a systolic blood pressure (SBP) of greater than or equal to 140 mm Hg, diastolic blood pressure of greater than or equal to 90 mm Hg, or current antihypertensive therapy. Dyslipidemia was defined as a total cholesterol level of greater than or equal to 200 mg/dL, triglyceride level of greater than or equal to 200 mg/dL, or current antilipidemic therapy. Diabetes was diagnosed when the fasting blood glucose (FBG) was greater than or equal to 126 mg/dL or current treatment with oral hypoglycemic agents or insulin. ESRD was the last stage (stage five) of chronic kidney disease which required dialysis or a kidney transplant to live. Subjects were classified as alcohol drinkers or cigarette smokers if they had regularly consumed any alcoholic beverage greater than or equal to 1 time per week or smoked greater than or equal to 10 cigarettes per week during the preceding 6 months (27, 28). In-hospital cardiovascular events, including death, recurrent nonfatal AMI, and life-threatening arrhythmia, were also recorded. Standard medical care consisting of dual antiplatelet therapy, renin-angiotensin system blockade, and β-blockers was administered to most patients unless absolutely contraindicated. Statins were administered after obtaining a fasting blood specimen on the morning after admission according to the Taiwan National Health Insurance Guidelines (LDL-C > 100 mg/dL or already use) and/or revised Adult Treatment Panel III of the National Cholesterol Education Program guidelines (LDL-C > 70 mg/dL or already use).

Biochemistry Data and Killip Score

Peripheral venous blood samples were collected into pyrogen-free tubes both in the emergency department and after more than 8 hours of overnight fasting the following morning. FBG, fasting lipid panel, and routine biochemical profiles were analyzed. Killip classification was determined as follows: Killip class I, no clinical signs of heart failure; Killip class II, rales or crackles in the lungs, an S_3, and elevated jugular venous pressure; Killip class III, frank acute pulmonary edema; and Killip class IV, cardiogenic shock or hypotension and evidence of peripheral vasoconstriction (21). According to Killip severity, patients were divided into high-Killip (I + II) and low-Killip (III + IV) groups.

Statistical Analysis

All data are presented as mean ± SD or *n* (%). Baseline characteristics were compared between groups with the Student *t* test for continuous variables and Pearson chi-square test or Fisher exact test for categorical variables. Cox regression was used to estimate hazard ratios. The multivariate logistic model was further adapted to determine the independent risk factors after adjusting for dichotomized risk factors. This model included age, gender, initial SBP, initial heart rate, B-type natriuretic peptide (BNP), creatinine, body mass index (BMI), diabetes mellitus, hypertension, dyslipidemia, smoking status, family history of premature coronary artery disease, and statin treatment, as have been traditionally controlled for in other studies (22). Receiver operating characteristic (ROC) curve analysis was performed to obtain areas under the ROC curve (ROC-AUC) and optimal cutoff points by maximal values of Youden index (Youden index = sensitivity + specificity − 1) between disease severity with LDL-C and triglyceride. For each patient, beyond the TIMI (thrombolytic in myocardial infarction or TIMI Study Group) risk score (29), additional risk scores were calculated as the simple arithmetic sum of point values assigned to each risk factor based on the multiple covariate adjusted risk relationship: similar values for similar odds ratios (ORs). The discriminatory capacity of the risk scores was assessed by using the ROC-AUC (*c*-statistic) as an index of model performance (30). The *c*-statistic reflected the concordance of predictions with actual outcomes in rank order, with a *c*-statistic of 1.0 indicating perfect discrimination. A *p* value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS software version 14.0 (SPSS, Chicago, IL).

RESULTS

Patient Baseline Clinical and Biological Characteristics

In total, 724 patients were enrolled, and their baseline characteristics and biochemistry variables stratified by Killip class, LDL, and triglyceride were summarized in **Tables 1–3**,

TABLE 1. Baseline Characteristics of the Patients With Low- and High-Killip Groups

	Low-Killip Group (I + II) (*n* = 509)	High-Killip Group (III + IV) (*n* = 215)	*p*
Age (yr)	63.8 ± 14.2	69.9 ± 12.7	< 0.001[a]
Male, *n* (%)	390 (76.6)	157 (73.1)	0.580
Diabetes mellitus, *n* (%)	197 (38.7)	110 (51.2)	0.002[a]
Hypertension, *n* (%)	298 (58.5)	139 (64.7)	0.135
Dyslipidemia, *n* (%)	107 (21.0)	50 (23.3)	0.554
Previous statin treatment, *n* (%)	50 (11.6)	31 (14.4)	0.324
Smoking, *n* (%)	183 (36.0)	54 (25.1)	0.004[a]
Family history of premature coronary artery disease, *n* (%)	9 (1.8)	2 (0.9)	0.521
Alcohol consumption, *n* (%)	19 (3.7)	8 (3.7)	1.000
End-stage renal disease, *n* (%)	24 (4.7)	21 (9.8)	0.017[a]
ST-elevation myocardial infarction, *n* (%)	249 (49)	174 (48.4)	0.934
Hospital stay (d)	11.1 ± 19.7	18.6 ± 29.9	< 0.001[a]
Blood biochemistry			
Total cholesterol (mg/dL)	176.0 ± 46.8	152.5 ± 49.2	< 0.001[a]
Low-density lipoprotein cholesterol (mg/dL)	109.6 ± 54.3	90.5 ± 41.6	< 0.001[a]
HDL-C (mg/dL)	38.8 ± 15.2	41.7 ± 36.4	0.272
Triglyceride (mg/L)	134.5 ± 90.7	110.2 ± 66.2	< 0.001[a]
Total cholesterol/HDL-C	5.2 ± 3.6	4.5 ± 3.6	0.029[a]
Abdominal girth (cm)	91.7 ± 69.4	77.3 ± 30.5	0.069
Body mass index	25.1 ± 7.4	23.9 ± 4.05	0.038[a]
C-reactive protein (g/L)	6.3 ± 45.4	9.3 ± 49.6	0.482
B-type natriuretic peptide (μg/mL)	1341.3 ± 3004.9	2182.4 ± 2997.0	0.007[a]
Fasting blood glucose (mg/dL)	125.3 ± 50.7	157 ± 62.7	0.002[a]

HDL-C = high-density lipoprotein cholesterol.
[a]$p < 0.05$.
Data are displayed as mean ± SD or *n* (%).

respectively. LDL and triglyceride cutoffs were derived from the ROC analysis for high and low Killip (see *The Association Between LDL-C and Triglyceride With 30-Day In-Hospital Mortality* section). Those with higher Killip, low LDL, and low triglyceride were significantly older, had a lower prevalence rate of currently smoking, longer hospital stay, lower levels of total cholesterol (Chol(T)), LDL-C, triglyceride, and BMI but higher BNP. Significantly higher prevalence rates of STEMI and higher Killip were noted in both low LDL and low triglyceride groups, and significantly higher prevalence rates of diabetes, ESRD, and higher ratios of Chol(T)/HDL-C were found in patients with high-Killip class. Similar differences were also found between those who expired compared with those who survived over 30 days (**Table 4**). Interestingly, there was a lipid paradox with significantly lower Chol(T), LDL-C, triglyceride, and BMI in the high-Killip patients and in those who died.

The Association Between LDL-C and Triglyceride With 30-Day In-Hospital Mortality

Overall, initially low LDL-C and triglyceride were associated with a significantly higher in-hospital mortality rate within 30 days when taking both LDL-C and triglyceride less than 60 mg/dL as a reference. Hazard ratios for 30-day in-hospital mortality as a function of LDL and triglyceride levels are depicted in **Table 5**. ROC curves for LDL-C and triglyceride and AMI severity (high-Killip group vs low-Killip group) were constructed to choose the optimal cutoff points. The AUC was 0.64 (95% CI, 0.59–0.69) for LDL-C and 0.59 (95% CI, 0.54–0.63) for triglyceride. The optimal cutoff point (sensitivity, specificity) for high and low Killip was 62.5 mg/dL (0.25, 0.88) for LDL-C and 110 mg/dL (0.54, 0.63) for triglyceride by the maximum of each Youden index. Cumulative survival over 30 days of follow-up showed a significantly higher mortality rate in the LDL-C less than 62.5 mg/dL

TABLE 2. Baseline Characteristics of the Patients With Acute Myocardial Infarction With High and Low Low-Density Lipoprotein Cholesterol

	High (≥ 62.5 mg/dL) LDL-C (*n* = 509)	Low (< 62.5 mg/dL) LDL-C (*n* = 215)	*p*
Age (yr)	64.1 ± 14.1	71.9 ± 12.0	< 0.001[a]
Male, *n* (%)	386 (75.8)	158 (73.5)	0.829
Killip III + IV, *n* (%)	132 (25.9)	103 (47.9)	< 0.001[a]
Diabetes mellitus, *n* (%)	201 (39.5)	130 (60.5)	< 0.001[a]
Hypertension, *n* (%)	294 (57.8)	160 (74.4)	0.005[a]
Dyslipidemia, *n* (%)	104 (20.4)	51 (23.7)	0.210
Previous statin treatment, *n* (%)	51 (10)	49 (22.7)	< 0.001[a]
Smoking, *n* (%)	184 (36.1)	39 (18.3)	< 0.001[a]
Alcohol consumption, *n* (%)	19 (3.7)	10 (4.7)	0.530
End-stage renal disease, *n* (%)	25 (4.9)	28 (13.0)	0.007[a]
ST-elevation myocardial infarction, *n* (%)	264 (51.9)	67 (31.2)	0.001[a]
Hospital stay (d)	11.8 ± 19.4	21.7 ± 38.8	0.011[a]
Blood biochemistry			
Total cholesterol (mg/dL)	178.7 ± 44.1	117.5 ± 38.9	< 0.001[a]
LDL-C (mg/dL)	115.3 ± 48.0	43.0 ± 14.4	< 0.001[a]
High-density lipoprotein cholesterol (mg/dL)	39.8 ± 24.2	37.9 ± 16.5	0.426
Triglyceride (mg/L)	130.3 ± 85.5	111.8 ± 79.9	0.039[a]
Fasting glucose (mg/dL)	133.9 ± 58.5	130.2 ± 38.3	0.794
Abdominal girth (cm)	87.2 ± 54.1	103.8 ± 123.7	0.406
Body mass index	25.1 ± 7.0	23.2 ± 4.2	0.009[a]
C-reactive protein (g/L)	6.9 ± 51.5	10.3 ± 23.7	0.544
B-type natriuretic peptide (μg/mL)	1459.0 ± 2628.7	2588.3 ± 4335.8	0.028[a]

LDL-C = low-density lipoprotein cholesterol.
[a]$p < 0.05$.
Data are displayed as mean ± SD or *n* (%).

and triglyceride less than 110 mg/dL groups (hazard ratios, 1.65 and 5.05; 95% CI, 1.18–2.30 and 1.75–14.54, respectively) (**Fig. 1**). To investigate the further potential for lipid paradox, we compared patterns of LDL and Killip class and found that low LDL-C (< 62.5 mg/dL) in high-Killip group had an approximately six-fold higher adjusted risk than high LDL-C (≥ 62.5 mg/dL) in low-Killip group ($p < 0.001$). In addition, similar risks were found between the low LDL in low-Killip and high LDL in high-Killip (hazard ratio, 0.57; 95% CI, 0.22–1.47; $p = 0.25$). For triglyceride, the low triglyceride in high-Killip had an approximately eight-fold higher adjusted risk than the high triglyceride in low-Killip group ($p < 0.001$) but no significant differences among other three groups (**Fig. 2**). The high AMI Killip severity group had a 2.5-fold higher risk of mortality than the low group, whereas the group with both low LDL-C and triglyceride had a 10.9-fold higher risk of mortality than the group with both high LDL-C and triglyceride after adjustment (**Fig. 3**). Therefore, in addition to Killip classification, the initial lipid profile had prognostic value in this patient population.

Predictors of Mortality: Risk Factors Associated With Mortality to Develop a New Risk Score for Myocardial Infarction

A multivariate modeling was performed using all clinical and biochemical variables that were significantly different on univariate analysis between the high- and low-Killip patient groups or deceased and surviving groups (**Table 6**). Lipid variables, including both low LDL-C (< 62.5 mg/dL) and triglyceride (< 110 mg/dL), were independently significantly associated with 30-day in-hospital mortality. The ORs with 95% CI were 2.795 (1.280–6.104) for low LDL-C, 4.313 (1.425–13.053) for low triglyceride, and 2.576 (1.181–5.620) for Killip score (III + IV vs I + II).

TABLE 3. Baseline Characteristics of the Patients With Acute Myocardial Infarction With High and Low Triglyceride

	High (≥ 110 mg/dL) Triglyceride (*n* = 355)	Low (< 110 mg/dL) Triglyceride (*n* = 369)	*p*
Age (yr)	60.7 ± 14.1	69.7 ± 12.6	< 0.001[a]
Male, *n* (%)	277 (78.0)	273 (74.0)	0.337
Killip III + IV, *n* (%)	80 (22.5)	135 (36.6)	< 0.001[a]
Diabetes mellitus, *n* (%)	151 (42.5)	158 (42.8)	0.948
Hypertension, *n* (%)	208 (58.6)	226 (61.2)	0.480
Dyslipidemia, *n* (%)	81 (22.8)	73 (19.8)	0.275
Previous statin treatment, *n* (%)	43 (12.1)	43 (11.7)	0.322
Smoking, *n* (%)	146 (41.1)	97 (26.3)	< 0.001[a]
Alcohol consumption, *n* (%)	17 (4.8)	11 (3.0)	0.384
End-stage renal disease, *n* (%)	18 (5.1)	27 (7.3)	0.497
ST-elevation myocardial infarction, *n* (%)	170 (47.9)	192 (52.0)	0.001[a]
Hospital stay (d)	11.5 ± 23.6	15.2 ± 24.1	0.044[a]
Blood biochemistry			
Total cholesterol (mg/dL)	184.4 ± 52.2	154.6 ± 40.3	< 0.001[a]
Low-density lipoprotein cholesterol (mg/dL)	115.3 ± 62.2	93.8 ± 36.7	< 0.001[a]
High-density lipoprotein cholesterol (mg/dL)	37.4 ± 28.9	41.6 ± 15.8	0.018[a]
Triglyceride (mg/L)	185.5 ± 86.0	71.4 ± 25.8	< 0.001[a]
Fasting glucose (mg/dL)	143.3 ± 67.0	123.5 ± 40.7	0.036[a]
Abdominal girth (cm)	85.1 ± 21.4	93.3 ± 89.8	0.224
Body mass index	26.1 ± 8.7	23.7 ± 3.9	< 0.001[a]
C-reactive protein (g/L)	6.9 ± 51.5	10.3 ± 23.7	0.544
B-type natriuretic peptide (μg/mL)	1459.0 ± 2628.7	2588.3 ± 4335.8	0.028[a]

[a]$p < 0.05$.
Data are displayed as mean ± SD or *n* (%).

Effects of Lipid Paradox on Improvements in Model Performance

We derived, weighed, and integrated this information into a model similar to the TIMI risk score for the prediction of short-term outcomes in AMI (**Table 7**). Low LDL-C improved the *c*-statistic of the original TIMI risk score and Killip classification from 0.723 to 0.754 and from 0.702 to 0.765, whereas low triglyceride improved the *c*-statistic of the original TIMI risk score and Killip classification from 0.723 to 0.747 and from 0.702 to 0.762. The combination of both low LDL and triglyceride improved the *c*-statistic even further to 0.774 in TIMI risk score and to 0.801 in Killip classification. The addition of Killip classification criteria yielded even further improvement in the *c*-statistic. For direct comparison, the LDL + triglyceride alone, with *c*-statistic of 0.748 (0.681–0.814), is a better predictor than TIMI risk score and Killip classification ($p_{(trend)} < 0.001$).

DISCUSSION

This study supports a lipid paradox in patients presenting with AMI, with significantly lower TC, LDL, and triglyceride in patients with severe Killip classification and in those who died in the hospital within 30 days (Tables 1–4). Cumulative survival showed significantly higher mortality rates in patients with LDL less than 62.5 mg/dL and triglyceride less than 110 mg/dL (optimal cutoff points by each lipid ROC curve with severity) groups (Fig. 1). The synergistic effects of both low LDL-C and low triglyceride in addition to Killip classification on AMI patients were demonstrated in Figure 2. The high-Killip group had a 2.5-fold higher risk of mortality than the low severity group, whereas the group with both low LDL and low triglyceride had a 10.9-fold higher risk than the group with both high LDL and high triglyceride (Fig. 3). After adjustments using multivariate model, lipid variables including low

TABLE 4. Baseline Characteristics of the Patients With Acute Myocardial Infarction Who Died or Were Alive Within 30 Days

	Alive ($n = 659$)	Expired ($n = 65$)	p
Age (yr)	64.8 ± 13.8	69.9 ± 12.7	< 0.001[a]
Male, *n* (%)	504 (76.5)	43 (66.2)	0.070
Diabetes mellitus, *n* (%)	274 (41.6)	33 (50.8)	0.188
Hypertension, *n* (%)	394 (59.8)	43 (66.2)	0.354
Dyslipidemia, *n* (%)	143 (21.7)	14 (21.5)	1.000
Previous statin treatment, *n* (%)	82 (12.4)	8 (12.3)	1.000
Smoking, *n* (%)	225 (34.1)	12 (18.5)	0.012[a]
Family history of premature coronary artery disease, *n* (%)	11 (1.7)	0 (0)	0.612
Alcohol consumption, *n* (%)	24 (3.6)	3 (4.6)	0.727
End-stage renal disease, *n* (%)	36 (5.5)	9 (13.8)	0.014[a]
ST-elevation myocardial infarction, *n* (%)	319 (48.4)	34 (52.3)	0.436
Blood biochemistry			
Total cholesterol (mg/dL)	172.4 ± 47.8	132.9 ± 43.2	< 0.001[a]
Low-density lipoprotein cholesterol (mg/dL)	106.6 ± 52.0	75.1 ± 32.3	< 0.001[a]
HDL-C (mg/dL)	40.0 ± 24.1	35.6 ± 13.1	0.153
Triglyceride (mg/L)	130.5 ± 85.9	92.0 ± 64.3	< 0.001[a]
Total cholesterol/HDL-C	5.1 ± 3.8	4.1 ± 1.9	0.052
Abdominal girth (cm)	89.1 ± 64.0	67.0 ± 44.9	0.492
Body mass index	24.9 ± 6.8	23.0 ± 3.19	0.037[a]
C-reactive protein (g/L)	6.3 ± 45.4	9.3 ± 49.6	0.482
B-type natriuretic peptide (μg/mL)	1498.6 ± 2865.3	2778.6 ± 3848.6	0.005[a]

HDL-C = high-density lipoprotein cholesterol.
[a]$p < 0.05$.
Data are displayed as mean ± SD or *n* (%).

LDL-C and low triglyceride as well as Killip severity were all independently significantly associated with 30-day in-hospital mortality (Table 6). Regarding lipid paradox on improvements in model performance, LDL-C and triglyceride modestly improved the *c*-statistics of the original TIMI risk score separately and together (LDL-C + triglyceride) to 0.774, and the improvements were best when added together to the Killip classification (0.801). For direct comparison, the LDL + triglyceride alone, with *c*-statistics of 0.748, is better than TIMI risk score and Killip classification (all $p_{(trend)} < 0.001$) (Table 7).

Epidemiological studies have shown that high LDL-C and triglyceride are important risk factors for CVD (1–3, 5–7, 31), but only play a minor role in the acute phase of AMI. To the best of our knowledge, this study is the first to show an association

TABLE 5. The Associations Between Low-Density Lipoprotein Cholesterol and Triglyceride With 30-Day In-Hospital Mortality

Low-Density Lipoprotein Cholesterol (mg/dL)	HR	95% CI	p	Triglyceride (mg/dL)	HR	95% CI	p
< 60	1			< 60	1		
60–120	0.310	0.179–0.539	< 0.001[a]	60–120	0.758	0.416–1.382	0.366
≥ 120	0.131	0.056–0.306	< 0.001[a]	≥ 120	0.196	0.087–0.444	< 0.001[a]

HR = hazard ratio.
[a]$p < 0.05$.

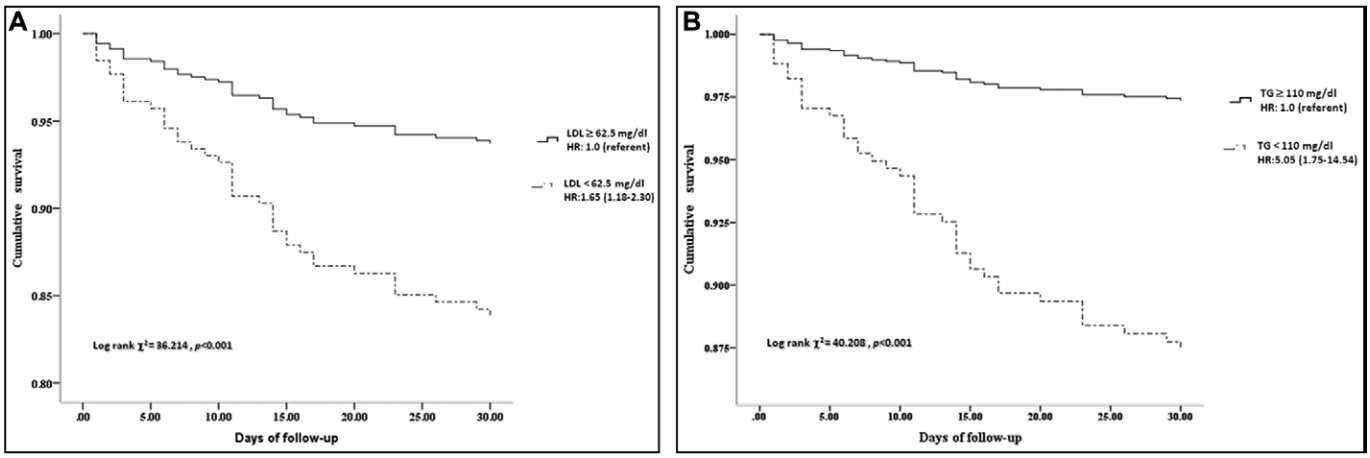

Figure 1. The associations between low-density lipoprotein cholesterol (LDL-C) (categories divided by acute myocardial infarction [AMI] severity) and triglyceride (TG) with 30-day in-hospital mortality. The optimal cutoff points of LDL-C (62.5 mg/dL) and TG (109.5 mg/dL) were assessed by receiver operating characteristic curves for high Killip (III + IV) and low Killip (I + II) patients with AMI. Cumulative survival from the first day to 30 days of follow-up showed significantly more mortality in the LDL-C < 62.5 mg/dL and TG < 110 mg/dL groups (both $p < 0.001$). The hazard ratios (HRs) with 95% CIs by Cox regression were 3.8 (2.20–6.63) and 3.61 (1.80–7.27), respectively. Initial low levels of LDL-C and TG predicted significantly higher 30-day in-hospital mortality.

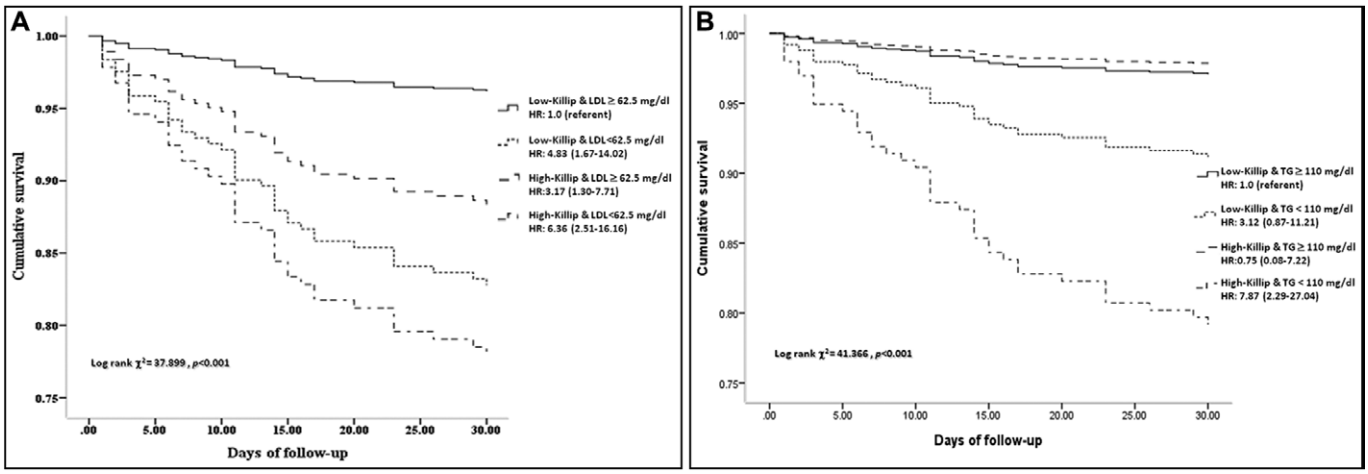

Figure 2. 30-Day in-hospital mortality among patients with acute myocardial infarction (AMI) according to baseline lipid profile (in terms of low-density lipoprotein cholesterol [LDL-C] and triglyceride [TG], respectively) and AMI severity (low Killip vs high Killip). For TG, the reference value for hazard ratio (HR) calculation was the group with stable AMI and TG ≥ 110 mg/dL. For LDL-C, the reference value for HR calculation was the group with stable AMI and LDL-C ≥ 62.5 mg/dL.

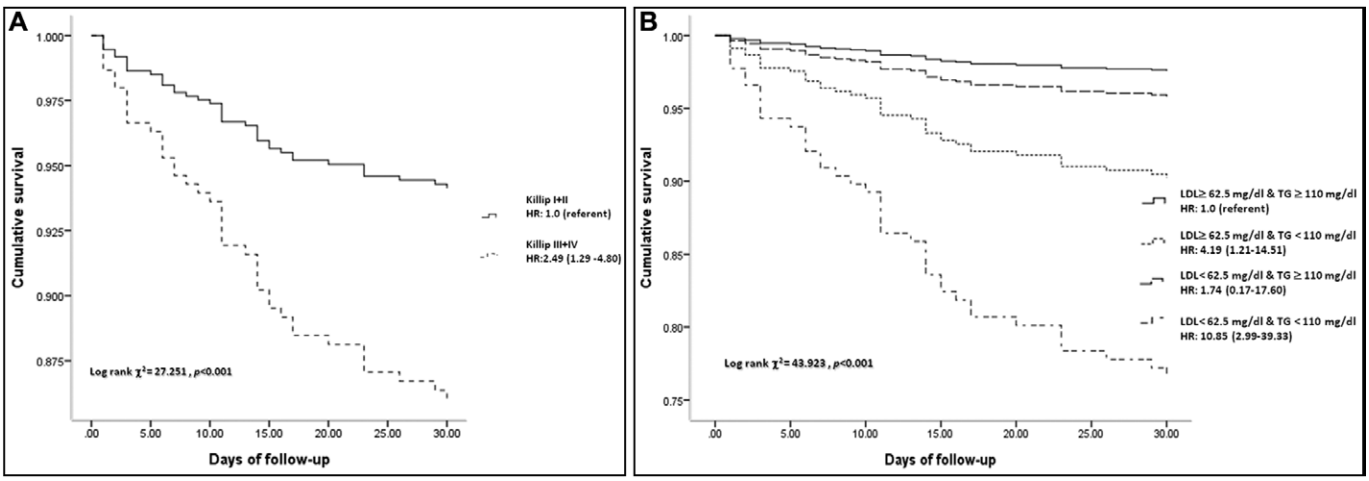

Figure 3. 30-Day in-hospital mortality among patients with acute myocardial infarction (AMI) according to AMI severity (low Killip vs high Killip) and lipid profile (combining both low-density lipoprotein cholesterol [LDL-C] and triglyceride [TG]). The reference value for hazard ratio (HR) calculation was the group with LDL-C ≥ 62.5 mg/dL and TG ≥ 110 mg/dL.

TABLE 6. Risk Factors From Baseline Characteristics of 30-Day Mortality Analyzed for Development of New Risk Score for Myocardial Infarction

Variables	OR (95% CI)	*p*
Low triglyceride	4.313 (1.425–13.053)	0.010[a]
Low-density lipoprotein cholesterol	2.795 (1.280–6.104)	0.010[a]
Killip	2.576 (1.181–5.620)	0.017[a]
Age	1.029 (0.994–1.066)	0.109
Body mass index	1.001 (0.925–1.083)	0.982
B-type natriuretic peptide	1.000 (1.000–1.000)	0.173
Initial heart rate	0.999 (0.986–1.013)	0.927
Initial systolic blood pressure	0.998 (0.988–1.008)	0.703
Creatinine	0.996 (0.927–1.069)	0.906
Gender	0.977 (0.434–2.200)	0.956

OR = odds ratio.

[a]$p < 0.05$.

Adjusted OR of the variables including age, initial systolic blood pressure, initial heart rate, gender (male), body mass index, B-type natriuretic peptide, creatinine, Killip (I + II vs. III + IV), low-density lipoprotein cholesterol (cutoff: 62.5 mg/dl), triglyceride (110 mg/L), and traditional categorical risk factors including diabetes mellitus, hypertension, smoking, family history of premature coronary artery disease, and statin treatment between the patients with acute myocardial infarction (AMI) who died or were alive within 30 days in the multivariate regression model of AMI.

between low initial admission levels of Chol(T), LDL-C, and triglyceride with high AMI Killip severity (Tables 1–3). The novel findings of this study are that low admission levels of Chol(T), LDL-C, and triglyceride were associated with a high short-term (30-day) in-hospital mortality rate (Tables 4 and 5). Such a lipid paradox has been founded in the elderly, in some major CVDs (15–19) and rheumatoid arthritis (14). By contrast, however, in a large population of patients with AMI, lipids were not an independent predictor of 12-month mortality (22). Physiologically, LDL-C is critical for the cell and hormones (12), and LDL-C less than 30 mg/dL has been reported to result in an increase in psychiatric and hepatobiliary disorders (32). Another large population study also revealed that patients with NSTEMI and with a history of hypercholesterolemia were associated with lower in-hospital mortality (33), which was consistent with the results in our study. LDL-C may be crucial for cell survival during initial 30-day in-hospital phase when facing life-threatening stress of AMI with ischemia and fulminate reactive inflammatory response, which makes cells and their membrane vulnerable. LDL-C needs to be posttranslationally modified or oxidized to become pathogenic (34, 35). These are plausible reasons for the discrepancy of 30-day in-hospital phase and 12-month phase. According to the 2013 American College of Cardiology/American Heart Association dyslipidemia guideline, an appropriate intensity of statin therapy should be used to reduce the atherosclerotic cardiovascular risk in those most likely to benefit, but not for specific lipid targets as there is currently no randomized control trial evidence to support this (36). Therefore, future goal-oriented studies are needed to answer these questions. In addition, the decrease of plasma triglyceride during the acute phase of unstable angina or non-STEMI has been reported as a marker of recurrent ischemia (37). Triglyceride is an important energy source for peripheral tissues, and those messages provide our study results the reasons why LDL-C and triglyceride are important in the life-threatening AMI status. In addition, high triglyceride advantage is also found in our study. The higher severity it is in AMI, the greater sympathetic activity spurs the synthesis and activation of lipoprotein lipase, which then breaks down circulating triglyceride to glycerol and fatty acids (38–41). The current study provides further information that low levels of LDL-C and triglyceride on initial admission are predictive of short-term (30-day) in-hospital adjusted mortality (Fig. 1 and Table 7), particularly when both LDL and triglyceride are integrated (Fig. 3*B*). The lipid paradox also improves modal performance of prediction (Table 7).

There are several limitations to this study. First, the number of patients might be still insufficient compared to large trials.

TABLE 7. Performance of 30-Day In-Hospital Mortality Prediction Models Using *c*-Statistics

Models	*c*-Statistics (Receiver Operating Characteristic index)	95% CI	SE	$p_{(trend)}$
TIMI RS	0.723	0.652–0.794	0.036	< 0.001[a]
TIMI RS + LDL-C	0.754	0.688–0.820	0.034	< 0.001[a]
TIMI RS + triglyceride	0.747	0.680–0.815	0.035	< 0.001[a]
TIMI RS + LDL-C + triglyceride	0.774	0.710–0.838	0.032	< 0.001[a]
Killip	0.702	0.627–0.777	0.038	< 0.001[a]
Killip + LDL-C	0.765	0.697–0.832	0.035	< 0.001[a]
Killip + triglyceride	0.762	0.697–0.828	0.034	< 0.001[a]
Killip + LDL-C + triglyceride	0.801	0.741–0.861	0.031	< 0.001[a]
LDL-C + triglyceride	0.748	0.681–0.814	0.034	< 0.001[a]

TMI = thrombolytic in myocardial infarction, RS = risk score, LDL-C = low-density lipoprotein cholesterol.

[a]$p < 0.05$.

Second, this is a single-center study. Further nationwide, multicenter prospective cohort studies enrolling patients with AMI should be conducted to clarify our findings.

CONCLUSIONS

The paradoxically low levels of LDL-C and triglyceride during the acute phase of MI were significantly associated with high AMI Killip severity and 30-day in-hospital mortality rate. Initial lipid profiles should be taken into consideration to predict the prognosis.

ACKNOWLEDGMENTS

We thank Ms. Fang-Zhi Lin for her help to hold the coronary care program and perform data collection.

REFERENCES

1. Kannel WB, Castelli WP, Gordon T: Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study. *Ann Intern Med* 1979; 90:85–91
2. Wilson PW: High-density lipoprotein, low-density lipoprotein and coronary artery disease. *Am J Cardiol* 1990; 66:7A–10A
3. Stamler J, Neaton JD: The Multiple Risk Factor Intervention Trial (MRFIT)—Importance then and now. *JAMA* 2008; 300:1343–1345
4. Genser B, März W: Low density lipoprotein cholesterol, statins and cardiovascular events: A meta-analysis. *Clin Res Cardiol* 2006; 95:393–404
5. Grundy SM, Cleeman JI, Merz CN, et al; Coordinating Committee of the National Cholesterol Education Program: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Arterioscler Thromb Vasc Biol* 2004; 24:e149–e161
6. Stone NJ, Bilek S, Rosenbaum S: Recent National Cholesterol Education Program Adult Treatment Panel III update: Adjustments and options. *Am J Cardiol* 2005; 96:53E–59E
7. Abdel-Maksoud M, Sazonov V, Gutkin SW, et al: Effects of modifying triglycerides and triglyceride-rich lipoproteins on cardiovascular outcomes. *J Cardiovasc Pharmacol* 2008; 51:331–351
8. Barter PJ, Rye KA: Is there a role for fibrates in the management of dyslipidemia in the metabolic syndrome? *Arterioscler Thromb Vasc Biol* 2008; 28:39–46
9. Preiss D, Sattar N: Lipids, lipid modifying agents and cardiovascular risk: A review of the evidence. *Clin Endocrinol (Oxf)* 2009; 70:815–828
10. Martin SS, Blumenthal RS, Miller M: LDL cholesterol: The lower the better. *Med Clin North Am* 2012; 96:13–26
11. Krauss RM: Triglycerides and atherogenic lipoproteins: Rationale for lipid management. *Am J Med* 1998; 105:58S–62S.
12. Stancu CS, Toma L, Sima AV: Dual role of lipoproteins in endothelial cell dysfunction in atherosclerosis. *Cell Tissue Res* 2012; 349:433–446
13. Morita SY, Deharu Y, Takata E, et al: Cytotoxicity of lipid-free apolipoprotein B. *Biochim Biophys Acta* 2008; 1778:2594–2603
14. Myasoedova E, Crowson CS, Kremers HM, et al: Lipid paradox in rheumatoid arthritis: The impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. *Ann Rheum Dis* 2011; 70:482–487
15. Güder G, Frantz S, Bauersachs J, et al: Reverse epidemiology in systolic and nonsystolic heart failure: Cumulative prognostic benefit of classical cardiovascular risk factors. *Circ Heart Fail* 2009; 2:563–571
16. Rauchhaus M, Clark AL, Doehner W, et al: The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol* 2003; 42:1933–1940
17. Schatz IJ, Masaki K, Yano K, et al: Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: A cohort study. *Lancet* 2001; 358:351–355
18. Charach G, George J, Roth A, et al: Baseline low-density lipoprotein cholesterol levels and outcome in patients with heart failure. *Am J Cardiol* 2010; 105:100–104
19. Markaki I, Nilsson U, Kostulas K, et al: High cholesterol levels are associated with improved long-term survival after acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2014; 23:e47–e53
20. Lopez FL, Agarwal SK, Maclehose RF, et al: Blood lipid levels, lipid-lowering medications, and the incidence of atrial fibrillation: The atherosclerosis risk in communities study. *Circ Arrhythm Electrophysiol* 2012; 5:155–162
21. Killip T III, Kimball JT: Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol* 1967; 20:457–464
22. Cho KH, Jeong MH, Ahn Y, et al; Korea Acute Myocardial Infarction Registry Investigators: Low-density lipoprotein cholesterol level in patients with acute myocardial infarction having percutaneous coronary intervention (the cholesterol paradox). *Am J Cardiol* 2010; 106:1061–1068
23. Cheng KH, Chu CS, Lee KT, et al: Electrocardiographic algorithms for predicting the complexity of coronary artery lesions in ST-segment elevation myocardial infarction in ED. *Am J Emerg Med* 2008; 26:10–17
24. Thygesen K, Mair J, Katus H, et al; Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care: Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J* 2010; 31:2197–2204
25. de Lemos JA, Drazner MH, Omland T, et al: Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010; 304:2503–2512
26. Thygesen K, Alpert JS, Jaffe AS, et al; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction; Authors/Task Force Members Chairpersons; Biomarker Subcommittee; ECG Subcommittee; Imaging Subcommittee; Classification Subcommittee; Intervention Subcommittee; Trials & Registries Subcommittee; Trials & Registries Subcommittee; Trials & Registries Subcommittee; Trials & Registries Subcommittee; ESC Committee for Practice Guidelines (CPG); Document Reviewers: Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; 60:1581–1598
27. Cheng KH, Hsi E, Liu CC, et al: The associations of novel vitamin D3 metabolic gene CYP27A1 polymorphism, adiponectin/leptin ratio, and metabolic syndrome in middle-aged Taiwanese males. *Int J Endocrinol* 2015; 2015:658151
28. Cheng KH, Huang SP, Huang CN, et al: The impact of estradiol and 1,25(OH)2D3 on metabolic syndrome in middle-aged Taiwanese males. *PLoS One* 2013; 8:e60295
29. Morrow DA, Antman EM, Charlesworth A, et al: TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation* 2000; 102:2031–2037
30. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; 143:29–36
31. Schwandt P: Triglyceride-rich lipoproteins and atherosclerosis. *Drugs* 1990; 40(Suppl 1):38–41
32. Everett B, Mora S, Grossbard J, et al: Safety profile of statin-treated patients with LDL-C < 30 mg/dl. *J Am Coll Cardiol* 2012; 59:E1619–E1619
33. Wang TY, Newby LK, Chen AY, et al: Hypercholesterolemia paradox in relation to mortality in acute coronary syndrome. *Clin Cardiol* 2009; 32:E22–E28
34. Estruch M, Sánchez-Quesada JL, Ordóñez Llanos J, et al: Electronegative LDL: A circulating modified LDL with a role in inflammation. *Mediators Inflamm* 2013; 2013:181324
35. Delporte C, Van Antwerpen P, Vanhamme L, et al: Low-density lipoprotein modified by myeloperoxidase in inflammatory pathways and clinical studies. *Mediators Inflamm* 2013; 2013:971579
36. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report

of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129:S1–S45

37. Correia LC, Magalhães LP, Braga JC, et al: Decrease of plasma triglycerides during the acute phase of unstable angina or non-ST elevation myocardial infarction is a marker of recurrent ischemia. *Atherosclerosis* 2004; 177:71–76
38. Festuccia WT, Blanchard PG, Richard D, et al: Basal adrenergic tone is required for maximal stimulation of rat brown adipose tissue UCP1 expression by chronic PPAR-gamma activation. *Am J Physiol Regul Integr Comp Physiol* 2010; 299:R159–R167
39. Klingenspor M, Ebbinghaus C, Hülshorst G, et al: Multiple regulatory steps are involved in the control of lipoprotein lipase activity in brown adipose tissue. *J Lipid Res* 1996; 37:1685–1695
40. Pecquery R, Leneveu MC, Giudicelli Y: In vivo desensitization of the beta, but not the alpha 2-adrenoreceptor-coupled-adenylate cyclase system in hamster white adipocytes after administration of epinephrine. *Endocrinology* 1984; 114:1576–1583
41. Lefebvre P, Luyckx C, Bacq ZM: Effects of denervation on the metabolism and the response to glucagon of white adipose tissue of rats. *Horm Metab Res* 1973; 5:245–250