

[ ORIGINAL ARTICLE ]

# A Low Early High-density Lipoprotein Cholesterol Level Is an Independent Predictor of In-hospital Death in Patients with Acute Coronary Syndrome

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## Abstract:

**Objective** In patients with acute coronary syndrome (ACS), low high-density lipoprotein cholesterol (HDL-C) levels in samples collected after an overnight fast are diagnostic indicators and well-established predictors of adverse outcomes. However, the relationship between the HDL-C levels in samples collected just after arrival (early HDL-C) and in-hospital mortality remains unknown. The purposes of the present ACS study were to (1) evaluate the association between the early HDL-C levels of patients and in-hospital mortality and (2) compare the early HDL-C level with other well-known determinants associated with in-hospital mortality.

**Methods** This retrospective study surveyed 638 consecutive ACS patients and then assessed the possible determinants of in-hospital mortality. All initial blood samples, including that for early HDL-C, were drawn within one hour of arrival.

**Results** In the present study, the overall in-hospital mortality was 5.9%. A multivariable analysis showed that a low early HDL-C [odds ratio (OR) 2.53, 95% confidence interval (CI) 1.14-5.62], elevated troponin T (OR 4.40, 95% CI 1.26-15.29) and high Killip class (OR 15.41, 95% CI 7.29-32.59) were independent predictors of in-hospital mortality. A Kaplan-Meier survival analysis indicated that there the in-hospital outcome for the low early HDL-C group was significantly worse than that for the high early HDL-C group (age- and gender-adjusted hazard ratio 2.40, 95% CI 1.15-5.00,  $p=0.02$ ).

**Conclusion** ACS patients with low early HDL-C levels had higher in-hospital mortalities than those who did not have low early HDL-C levels. In addition to the already well-known determinants, low early HDL-C should also be considered as an independent predictor of in-hospital mortality in ACS patients who present to a cardiac care unit.

**Key words:** HDL-cholesterol, acute coronary syndrome, in-hospital mortality, early detection

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## Introduction

Being able to predict the in-hospital mortality of patients with acute coronary syndrome (ACS) at the time of admission is of great importance when trying to determine treatments. Therefore, many large registries have tried to evaluate possible predictors of in-hospital mortality in ACS patients.

The Global Registry of Acute Coronary Events (GRACE)

risk score, which is used as a predictor of the risk for death in ACS, is determined based on age, vital signs, creatinine and Killip class (1). However, when trying to determine the mortality in these patients, other laboratory data are not usually included in this score. Furthermore, with the exception of elevated creatinine kinase MB or troponin T, the Thrombolysis in Myocardial Infarction (TIMI) risk score, which is a risk score for patients with non-ST elevated ACS, does not include any other biomarkers used in the calculation of the risk (2). Since it is very difficult to simply and rapidly per-

form tests for serum laboratory data, with the exception of those for cardiac biomarkers, other laboratory data are not widely used to evaluate the ACS patient prognosis.

A low level of high-density lipoprotein cholesterol (HDL-C) has been shown to be a strong predictor for cardiovascular events (3-9). However, while many survivors of ACS have been enrolled in prospective interventional studies performed to examine the use of statins for the secondary prevention of ACS, randomized-control trials have not recorded the baseline lipid profile data of ACS patients who died before enrollment. The CRUSADE study (6) and ACTION Registry-GWTG (8), two large-scale registry studies that examined the non-ST-segment elevation in ACS patients, assessed the HDL-C levels on admission. Although both studies showed that the patients with low HDL-C levels exhibited a greater risk of in-hospital mortality than those with normal and high HDL-C levels, the baseline data were missing in more than half of the patients in these registry studies. In addition, similar studies analyzing the initial lipid profiles in ACS patients failed to mention the interval between the arrival time and blood sampling time (4, 7). Thus, the relationship between the in-hospital mortality and the HDL-C levels of samples drawn just after arrival (early HDL-C) remains unclear and poorly studied.

The purposes of our present ACS study were to evaluate the association between the early HDL-C levels and in-hospital mortality and to compare the early HDL-C levels with other well-known determinants.

## Materials and Methods

### Patients and study design

This study enrolled 638 consecutive ACS patients admitted to our emergency department or cardiac care unit between October 2009 and July 2013. In this ACS study, the patient group included subjects with ST-elevated myocardial infarction (STEMI), non-ST-elevated myocardial infarction (NSTEMI) and unstable angina. After excluding 15 patients because of data deficiency, 623 patients were retrospectively surveyed and then assessed for possible determinants associated with in-hospital mortality. After having their history taken at the time of admission, all patients underwent a physical examination, electrocardiogram, echocardiography and a qualitative analysis of troponin T, as well as a determination of their serum creatinine, fasting plasma glucose, low-density lipoprotein cholesterol (LDL-C), HDL-C and triglyceride (TG) levels. All initial blood samples for the present study were taken within one hour of arrival. All biochemistry data, including lipid profiles, were measured using a Conductor Etch System 9000 Series device (Hitachi High-Technologies Corporation, Tokyo, Japan).

The diagnostic criteria for ACS were as follows: 1) exhibiting symptoms compatible with ACS within 24 hours of hospital presentation, and 2) exhibiting any or all of abnormal cardiac biomarkers, electrocardiographic changes and/or

a documented history of coronary artery disease. The study protocol was developed based on the code of the Ethics Committee of Iwate Medical University. Informed consent was obtained from each patient after admission, and this study was performed in accordance with the Declaration of Helsinki. The primary endpoint of the present study was the in-hospital death due to any cause.

### Statistical analyses

The baseline data were presented as the median values (25th and 75th percentiles). Categorical or dichotomous variables expressed as absolute values and percentages were compared using a Fisher's exact test. Continuous variables were compared by either an unpaired Student's *t*-test or Mann-Whitney U test. A receiver operating characteristic (ROC) curve analysis was performed to establish the cut-off values of the predictive factors. A multivariate logistic regression model was used to evaluate the independent contribution of the in-hospital mortality in the ACS patients. A Mantel-Haenszel chi-squared test was used to test for an interaction between the HDL-C levels and gender. Univariate predictors of potential significance values were included in the multivariate analysis. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for these analyses, with  $p < 0.05$  considered to be significant. Cox regression was used to estimate the age- and gender-adjusted hazard ratios. All data were analyzed using the SPSS software program, version 21, for Windows (SPSS, Chicago, USA).

## Results

Over 70% of our ACS population consisted of STEMI patients, with an overall in-hospital mortality of 5.9%. The cause of death in all of our patients was cardiac death due to multiple organ failure caused by cardiogenic shock. Table 1 presents the baseline characteristics for the patients. Compared with the deceased patients, those who survived were significantly younger and were more likely to be smokers. The surviving group also contained a smaller percentage of STEMI patients and a larger percentage of patients with a Killip class greater than 2 in the deceased patients. Of the cardiac catheterizations performed, 605 patients (97.1%) underwent coronary angiography, while 488 (78.3%) underwent coronary intervention within 24 hours of onset. Because of unstable hemodynamics, 177 patients (28.4%) were given catecholamine and/or assist devices. Compared to the patients who survived, the deceased patients exhibited a higher prevalence of left main trunk disease and a lower rate of urgent percutaneous coronary intervention (PCI).

Table 2 shows the baseline lipid profile and incidence of statin pretreatment in the present study. Compared with the surviving patients, the deceased patients showed significantly lower HDL-C levels at the time of arrival. However, there was no significant difference between the two groups

**Table 1. Baseline Patient Characteristics.**

Characteristic	Surviving patients (n=586)	Deceased patients (n=37)	p value
Age (years)	69 (59-77)	76 (64-80)	0.02
Male sex, n (%)	459 (78.3%)	30 (81.1%)	0.84
Body length (cm)	163.0 (156.0-169.0)	160.6 (151.2-170.0)	0.50
Body weight (kg)	62.5 (55.0-72.0)	61.2 (50.9-71.5)	0.24
Body mass index	23.9 (21.9-26.2)	23.7 (20.7-26.7)	0.53
Hypertension, n (%)	413 (70.5%)	24 (64.9%)	0.46
Dyslipidemia, n (%)	269 (45.9%)	14 (37.8%)	0.40
Diabetes, n (%)	210 (35.8%)	19 (51.4%)	0.08
Current Smoker, n (%)	349 (59.6%)	13 (35.1%)	0.01
Previous MI, n (%)	63 (10.8%)	2 (5.4%)	0.41
Previous PCI, n (%)	61 (10.4%)	2 (5.4%)	0.57
Previous CABG, n (%)	14 (2.4%)	1 (2.7%)	0.61
Elevated troponin T, n (%)	443 (75.6%)	29 (78.4%)	0.84
Killip class $\geq 3$ , n (%)	74 (12.6%)	25 (67.6%)	<0.0001
Defibrillation out-of-hospital, n (%)	19 (3.2%)	1 (2.7%)	1.00
ST elevation, n (%)	412 (70.3%)	33 (89.2%)	0.01
LV ejection fraction (%)	50.1 $\pm$ 10.8	40.7 $\pm$ 13.8	<0.0001
Chronic kidney disease, n (%)	212 (36.2%)	8 (21.6%)	0.08
Usage of HD, n (%)	18 (3.1%)	5 (13.5%)	<0.0001
Catheterization within 24 hours from onset, n (%)	525 (89.6%)	31 (83.8%)	0.27
Culprit vessel			<0.005
LM, n (%)	14 (2.4%)	5 (13.5%)	
LAD, n (%)	267 (45.6%)	12 (32.4%)	
LCX, n (%)	96 (16.4%)	6 (16.2%)	
RCA, n (%)	172 (29.4%)	10 (27.0%)	
Multi-vessel disease, n (%)	344 (58.7%)	24 (64.9%)	0.50
Urgent PCI, n (%)	469 (80.0%)	19 (51.4%)	<0.0005
Catecholamine administration and/or usage of assist devices, n (%)	144 (24.6%)	33 (89.2%)	<0.0001

CABG: coronary-artery bypass surgery, HD: hemodialysis, LAD: left anterior descending artery, LCX: left circumflex artery, LM: left main, MI: myocardial infarction, PCI: percutaneous coronary intervention, RCA: right coronary artery

**Table 2. Baseline Lipid Profile and Incidence of Statin Pretreatment.**

Variable	Surviving patients (n=586)	Deceased patients (n=37)	p value
HDL-C level (mg/dL)	49.0 $\pm$ 13.0	43.7 $\pm$ 12.5	0.01
LDL-C level (mg/dL)	116.6 $\pm$ 39.2	106.1 $\pm$ 38.8	0.13
TG level (mg/dL)	121.1 $\pm$ 94.2	99.9 $\pm$ 50.4	0.38
L/H ratio	2.53 $\pm$ 1.05	2.60 $\pm$ 1.15	0.78
Statin pretreatment (%)	122 (20.8%)	10 (27.0%)	0.41

HDL-C: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, L/H ratio: low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio, TG: triglyceride

in the LDL-C or TG levels at the time of arrival. Although 20% of patients were using statins before suffering from ACS, no significant differences were found between the two groups.

The results of the univariate analysis shown in Table 3 indicated that an old age, smoking, an elevated troponin T level, a high Killip class and a low early HDL-C level were associated with in-hospital death. Furthermore, the multivariate analysis also showed that there was an association between in-hospital death and an elevated troponin T level, a high Killip class and a low early HDL-C level (Table 4).

The Mantel-Haenszel chi-squared test showed there was an interaction between gender and a low early HDL-C level ( $p=0.57$ ). Based on this result and after taking the gender differences into consideration, we defined the cut-off points for “low early HDL-C” for both men and women. The ROC curve analysis indicated that the optimal cut-off point for low early HDL-C in the men was 44.5 mg/dL (Fig. 1). However, due to the low statistical power of the analysis, the optimal cut-off point for low early HDL-C in the women could not be definitively determined. Thus, low early HDL-C was defined as <45 mg/dL for men and <55 mg/dL for

**Table 3. Univariate Analysis for In-hospital Deaths in ACS Patients.**

Variable	p value	OR	95% CI
Age	0.03	1.035	1.004-1.066
Male sex	0.69	1.286	0.509-2.763
Smoking	0.005	0.368	0.184-0.737
Elevated Troponin T	0.03	3.830	1.159-12.652
Killip class $\geq 3$	<0.001	14.414	6.945-29.917
Defibrillation out-of-hospital	0.86	0.829	0.108-6.368
ST elevation	0.10	1.980	0.889-4.410
Chronic kidney disease	0.30	1.427	0.728-2.794
Low early HDL-C level	0.008	2.718	1.293-5.717

ACS: acute coronary syndrome, CI: confidence interval, HDL-C: high-density lipoprotein cholesterol, OR: odds ratio

women in the present study. Fig. 2 shows the Kaplan-Meier survival curves for the ACS patients with and without low early HDL-C levels. Patients with low early HDL-C had a significantly lower in-hospital survival rate than those without low early HDL-C (age- and gender-adjusted hazard ratio 2.40, 95% CI 1.15-5.00,  $p=0.02$ ).

Table 5 shows the associations between low early HDL-C and the patients' characteristics. Patients with low early HDL-C had a higher incidence rate of male sex, multi-vessel disease, catecholamine administration and/or the usage of assist devices than those without low early HDL-C.

## Discussion

In the present study, low early HDL-C was significantly associated with in-hospital death in ACS patients. This association was independent of both a high Killip class rate and a positive rate of cardiac troponin T. These results suggest that, similar to other well-known predictors, a low early HDL-C can predict a poor in-hospital outcome. Furthermore, a low early HDL-C was correlated with the severity of the coronary stenosis, catecholamine administration and/or the use of an assist device.

The average HDL-C level in the present study was slightly higher than that reported for registries established in other countries (5, 6, 8, 10, 11). However, despite differences in the treatments, countries and study designs, all of the studies came to the same conclusion: a low HDL-C level was a predictor of a poor clinical outcome in ACS patients. In addition, the mortality rate in the present study was slightly higher than the currently reported Japanese mortality rates (12). This may be because our cohort included a relatively large number of severely ill patients who could not be treated at their local hospitals due to needing intensive care, complex PCI procedures or CABG. In the present study, paradoxically, subjects in the surviving group were more likely to be smokers, which is a well-known coronary risk factor. However, this paradox has also been commonly observed in other ACS studies comparing smokers and non-smokers (13, 14). Based on these previous reports, we con-

**Table 4. Multivariate Analysis for In-hospital Deaths in ACS Patients.**

Variable	p value	OR	95% CI
Elevated troponin T	0.02	4.40	1.26-15.29
Killip class $\geq 3$	<0.001	15.41	7.29-32.59
Low early HDL-C level	0.02	2.53	1.14-5.62

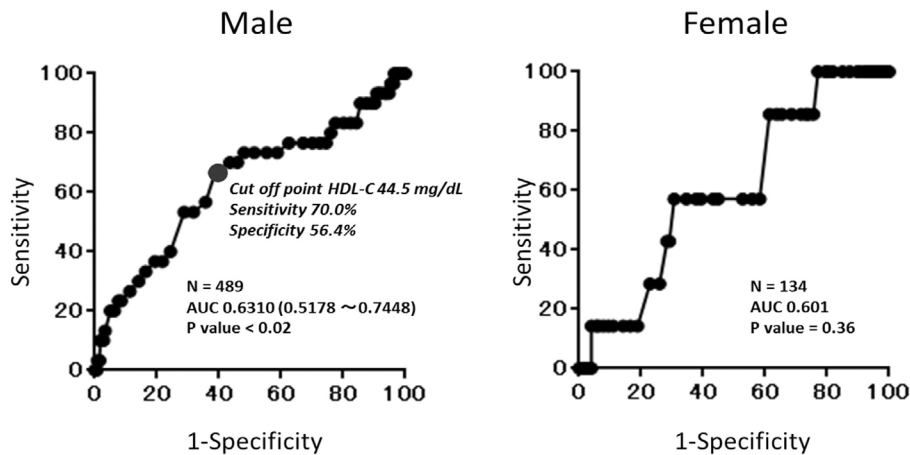
ACS: acute coronary syndrome, CI: confidence interval, HDL-C: high-density lipoprotein cholesterol, OR: odds ratio

cluded that this result was associated with the so called "smoker's paradox".

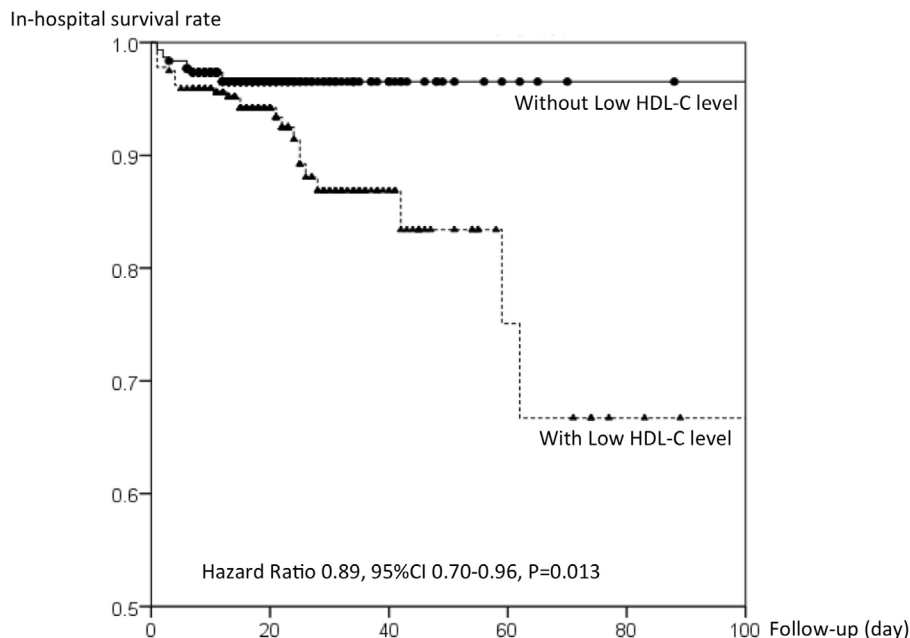
In the MIRACL study, which showed that low HDL-C levels predicted the risk of recurrent cardiovascular events over the ensuing 16 weeks, all of the blood samples were collected after a 12- to 14-hour fast among the ACS patients (3). Similarly, the low HDL-C levels shown to be associated with a significantly higher risk of in-hospital mortality in Asian STEMI patients who underwent successful PCI were also obtained from samples collected in an overnight fasting state (15). The LUNAR trial, which specifically focused on the timing of the sample collection, reported that there was relatively little variance in the HDL-C levels during the four days after an ACS event (16). Based on the results of the LUNAR trial, the early HDL-C levels found in our present study appear to be roughly equal in value to those reported for the MIRACL study.

The reason for the correlation between low HDL-C levels and an adverse short-term prognosis in ACS patients remains unknown. Regarding angiographic findings, several examinations of data from ACS patients have identified an inverse relationship between the rate of multi-vessel coronary disease and the HDL-C level (5, 6, 8, 15). In addition, ACS patients with a low HDL-C level more often exhibited severe heart failure than those without low HDL-C level (5, 15). These results suggest that a low HDL-C level is associated with the severity of the diseased coronary artery and worsening of the cardiac hemodynamics as a result of multi-vessel coronary disease. Furthermore, recent studies in STEMI patients with multi-vessel disease have shown that complete revascularization significantly reduces the risk of future events compared with revascularization of only the infarct-related artery (17, 18). Thus, stratification according to early HDL-C might aid in determining whether or not an assist device should be prepared in advance of cardiogenic shock.

In contrast to the present study, another recent study that examined the initial lipid profile of ACS patients who presented to a cardiac care unit found that low LDL-C levels (not HDL-C levels) were associated with a significantly higher rate of 30-day in-hospital mortality (19). However, the initial blood samples analyzed in that study were not drawn at the time of arrival but instead in the morning following an overnight fast of more than 8 hours. Due to the large variation in the LDL-C levels that has been reported in the fasting state (20), the association between the early



**Figure 1.** An ROC curve analysis for HDL-C prediction of in-hospital mortality. The optimal cut-off point for HDL-C in men was 44.5 mg/dL. However, based on our data, the optimal cut-off point for HDL-C could not be definitively defined in the women. When taking gender differences into consideration in the present study, a low HDL-C level was defined as <45 mg/dL for men and <55 mg/dL for women.



**Figure 2.** Kaplan-Meier survival curves in ACS patients with and without low early HDL-C levels. In the present study, the cut-off for low early HDL-C was defined as <45 mg/dL for men and <55 mg/dL for women.

LDL-C levels of ACS patients and in-hospital mortality remains unclear. In addition, data analyzed from the National Registry of Myocardial Infarction (NORMI), which collected blood samples within 24 hours of admission, demonstrated the presence of "the lipid paradox". This paradox showed that the in-hospital mortality in patients with ACS was associated with low HDL-C levels rather than low LDL-C levels (9). Therefore, with regard to the early lipid profiles in ACS patients who present to a cardiac care unit, early HDL-C levels might be a more useful predictor of in-hospital mortality than early LDL-C levels.

Furthermore, our study showed that, in addition to ele-

vated cardiac troponin and a higher Killip class, a low early HDL-C level was also an independent predictor of a poor in-hospital outcome in ACS patients. Thus, when an ACS patient is admitted to an emergency department or a cardiac care unit, risk assessments derived from the patient's data may be useful for evaluating their risk of in-hospital death. The GRACE (1) score, which is a well-known and classical predictor of in-hospital mortality, involves checking several items related to a patient's baseline physical data that can be analyzed within the emergency department. However, only one laboratory value (serum creatinine level) is required for this classical risk score. Of note, during the enrollment pe-

**Table 5. Association between Low Early HDL-C Levels and Patient Background.**

Variable	Without low early HDL-C level (n=304)	With low early HDL-C level (n=319)	p value
Age	68 (59-76)	71 (60-78)	0.06
Male sex, n (%)	257 (84.5%)	232 (72.7%)	<0.0005
Smoking, n (%)	186 (61.2%)	208 (65.2%)	0.32
Elevated troponin T level, n (%)	234 (77.9%)	238 (74.6%)	0.51
Killip class $\geq 3$ , n (%)	43 (14.1%)	56 (17.6%)	0.28
Multi-vessel disease, n (%)	166 (54.6%)	202 (63.3%)	<0.05
Catecholamine administration and/or usage of assist device, n (%)	74 (24.3%)	101 (31.7%)	<0.05

HDL-C: high-density lipoprotein cholesterol

riod for the GRACE registry, the efficacy of aggressive lipid lowering therapy for ACS patients (21, 22) and the utility of highly sensitive cardiac biomarkers in improving the accuracy of the ACS diagnosis (23, 24) had yet to be definitively established and applied to ACS patients.

Several studies comparing the classical risk score with the risk assessment based on the results of biomarkers have suggested that C-reactive protein (25) or troponin T (26) levels can provide a better prognostic accuracy than the GRACE risk score. However, several verification studies that examined the GRACE risk score have reported finding similar accuracies despite differences in the study period, the countries involved and the risk assessments used (26-30). Given the potential utility of these factors in clinical practice, a further study that compares the classical predictors with the added items to be checked, including early HDL-C levels and several other biomarkers, will need to be performed. However, given that C-reactive protein and cardiac troponins can vary greatly depending on the duration of time from the onset of ACS to the time of the sampling (31, 32), when ACS patients are admitted to an emergency department or a cardiac care unit, we recommend that high-risk patients be stratified according their early HDL-C levels, which are stable during the acute phase of ACS.

### Limitations

The present study had several limitations. First, our single-center study only assessed a relatively small number of patients compared to the established registries used to create and validate the classical risk score. Second, the TIMI and GRACE score were not calculated from our data. In the present study, 413 (66.3%) of the 623 total patients had been transferred from other clinics or hospitals. As some of these patients lacked initial medical findings for use in calculating the TIMI and GRACE score, it was not possible to compare the early HDL-C levels with the classical risk scores. Third, our study only included Japanese patients. Thus, the backgrounds of our patients differed from those of the patients who were evaluated during the development of the GRACE risk score and other registries. However, given that the overall in-hospital mortality of our study was similar to that of a Japanese registry used to confirm the diag-

nostic accuracy of the GRACE risk score (33), our population may adequately represent the spectrum of patients with ACS. Fourth, both STEMI and NSTEMI cases were included in our study. Because the in-hospital mortality of STEMI patients was higher than that for the NSTEMI patients, the results of our prognostic analysis may differ depending on the prevalence of STEMI in the patient group examined. Finally, the HDL-C levels and the ACS incidence rate can differ according to the gender (34) or race (35). Thus, the cut-off value for the level of HDL-C that can be used to predict the in-hospital mortality in ACS patients can be difficult to define. A larger clinical study that compares the classical risk items with the early HDL-C levels will need to be performed in order to identify high-risk patients.

### Conclusion

The present study confirmed that a low early HDL-C level was an independent predictor of in-hospital death in ACS patients. For risk stratification at the time of ACS patient admission, the integration of the early HDL-C level with the classical predictors might help improve the risk classification.

### Author's disclosure of potential Conflicts of Interest (COI).

Tomonori Itoh: Honoraria, Daiichi Sankyo, Otsuka Pharm and Abbott Vascular Japan. Yoshihiro Morino: Honoraria, Abbott Vascular, Daiichi Sankyo and Bayer.

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