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High-density lipoprotein cholesterol to apolipoprotein A-1 ratio is an important indicator predicting in-hospital death in patients with acute coronary syndrome

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High-density lipoprotein cholesterol to apolipoprotein A-1 ratio is an important indicator predicting in-hospital death in patients with acute coronary syndrome

Zhenjun Ji et al., The role of HDL-C/ApoA-I ratio in acute coronary syndrome

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Abstract

Background: Dyslipidemia plays a pivotal role in the pathogenesis of acute coronary syndrome (ACS). This study aims to investigate the value of two indices associated with lipid metabolism, low-density lipoprotein cholesterol to apolipoprotein B ratio (LBR) and high-density lipoprotein cholesterol to apolipoprotein A-1 ratio (HAR), to predict in-hospital death in patients with ACS.

Methods: This single-center, retrospective, observational study included 3,366 consecutive ACS patients in Zhongda Hospital, Southeast University from July 2013 to January 2018. The clinical and laboratory data were extracted, and the in-hospital death and hospitalization days were also recorded.

Results: All patients were equally divided into four groups according to quartiles of

HAR: Q1 (HAR < 1.0283), Q2 (1.0283 ≤ HAR < 1.0860), Q3 (1.0860 ≤ HAR < 1.1798), and Q4 (HAR ≥ 1.1798). Overall, HAR was positively associated with the counts of neutrophils and monocytes, whereas negatively correlated to lymphocyte counts. HAR was negatively correlated to left ventricular ejection fraction (LVEF). Compared to other three groups, in-hospital mortality (vs. Q1, Q2, and Q3, $p < 0.001$) and hospitalization length (vs. Q1, Q2, and Q3, $p < 0.001$) were significantly higher in the Q4 group. When grouped by LBR, however, there was no significant difference in LVEF, in-hospital mortality, and hospitalization length among groups. After adjusting potential impact from age, systolic blood pressure, creatine, lactate dehydrogenase, albumin, glucose, and uric acid, multivariate analysis indicated that HAR was an independent factor predicting in-hospital death among ACS patients.

Conclusions: HAR had good predictive value for patients' in-hospital death after the occurrence of acute coronary events, but LBR was not related to in-hospital adverse events.

Key words: low-density lipoprotein cholesterol to apolipoprotein B ratio, high-density lipoprotein cholesterol to apolipoprotein A-I ratio, acute coronary syndrome, in-hospital death

Introduction

Acute coronary syndrome (ACS), mainly caused by atherosclerotic plaque rupture, erosion or calcified nodule, is characterized as acute myocardial ischemia, cardiomyocyte necrosis, and subsequent inflammation [1, 2]. Dyslipidemia is known as an important risk factor for the occurrence of ACS, and lipid management plays a pivotal role in the secondary prevention after the occurrence of ACS to improve patient prognosis. There are more studies are focused on blood lipids of ACS patients [3].

The components of blood lipids consist of triglycerides, cholesterol, phospholipids, free fatty acids and cholesterol esters. Among plasma lipoproteins,

low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are widely studied in cardiovascular diseases. The main function of LDL is to transport endogenous cholesterol from the liver to other organs [4], and the function of HDL is to reverse the process of cholesterol being transported from outside to inside the liver. The protein part of plasma lipoprotein is called apolipoprotein (Apo), and up until now, more than 20 apolipoproteins have been isolated from human plasma [4]. HDL contains 70% ApoA-I, 20% ApoA-II, and lecithin-cholesterol transferase (LCAT) [5]. ApoA-I mainly recognizes HDL receptors and activates LCAT. LDL owns a receptor that specifically recognizes ApoB-100. After the LDL in plasma binds to the LDL receptor through ApoB-100, it is endocytosed by the cells to exert its effect [4].

There is an apolipoprotein B (ApoB) molecule in each LDL particle. Therefore, the level of ApoB represents the number of LDL particles in the plasma. The LDL particle size can be estimated indirectly through LDL-C/ApoB ratio (LBR) [6]. The optimal cut-off value of LBR is 1.2, which corresponds to the LDL diameter of 25.5 nm and also distinguishes small dense LDL (sdLDL) from large buoyant LDL [6, 7]. The Québec Cardiovascular Study has shown that patients with sdLDL (LDL diameters ≤ 25.5 nm) have a significant increase in the incidence of coronary heart disease (CHD) [8]. Plasma concentration of sdLDL is significantly associated with risk of atherosclerotic cardiovascular disease (ASCVD) [9].

Plasma level of HDL cholesterol (HDL-C) is inversely related to the risk of CHD [10], and a higher concentration of ApoA-I is also associated with reduced cardiovascular disease (CVD) risk [11]. HDL containing major protein ApoA-I is beneficial for vascular protection, and the beneficial cardiovascular effects of HDL and ApoA-I infusion therapy have been previously reported [12–14].

However, in the inflammatory response, the role of HDL as an anti-inflammatory may transform into that of pro-inflammatory particles [15]. HDL can be modified by inflammatory proteins such as acute-phase proteins and complement factors, further leading to impaired antioxidant capacity, which is associated with increased oxLDL levels [16]. Such HDL with function impairment is commonly called “dysfunctional

HDL". The increased HDL-C/apoA-I ratio (HAR) may reflect the impaired ability of cholesterol-rich HDL particles to absorb excess cholesterol from peripheral tissues and progressive atherosclerotic plaques [17].

This study aims to study the roles of LBR and HAR in predicting the in-hospital death of ACS patients.

Methods

Study design and population

This single-center, retrospective, observational study was approved by the Ethics Committee of Zhongda Hospital affiliated to Southeast University (2020ZDSYLL164-P01). The requirement of informed consents was waived due to the retrospective nature. In total, 3,366 patients were included from Zhongda Hospital, Southeast University from July 2013 to January 2018, including 761 unstable angina, 1,325 ST-segment elevation myocardial infarction (STEMI) and 1,280 non-STEMI patients (Fig. 1). Inclusion criteria included: (1) age > 18 years old; (2) Diagnosed as ACS according to the guideline for diagnosis and treatment of ACS [18]. Exclusion criteria included: (1) Lactating and pregnant women; (2) Suffering from serious diseases with a life expectancy < 6 months, such as advanced malignant tumors; (3) Acute and chronic inflammatory diseases, such as chronic obstructive pulmonary disease, hepatitis, rheumatic and rheumatoid diseases.

Data collection

The demographic data, medical history, laboratory and imaging examination results at admission were all extracted from the electronic medical record system (Yidu Cloud, China). Collected variables included age, sex, smoking history, hypertension history (HBP), diabetes history, Killip classification, systolic blood pressure (SBP), alamine aminotransferase (ALT), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), blood urea nitrogen (BUN), uric acid (UA), TnI, albumin (ALB), direct bilirubin (DBil), creatine, glucose (GLU), neutrophils,

lymphocytes, monocytes, white blood cells (WBC), platelet (PLT), hemoglobin (Hb), D-dimer, glycosylated hemoglobin (HbA1C), and left ventricular ejected fraction (LVEF). Lipid profile was also recorded, including total cholesterol (TC), triglyceride (TG), HDL-C, LDL cholesterol (LDL-C), ApoA1, ApoB1, and Lpa. In-hospital death and hospitalization days were recorded.

Statistical analysis

Data was analyzed by SPSS 23.0 and GraphPad Prism 8. The Shapiro-Wilk test was used for judging normality. Continuous numerical variables conforming to the normal distribution were expressed as mean ± standard deviation (SD), and one-way ANOVA analysis was used for comparison among multiple groups. Data following the non-normal distribution was described as median (interquartile range), and the Mann-Whitney U test was used for comparison between multiple groups. The Chi-square test was used for comparison of binary variables. The Pearson analysis was used for correlation analysis between HAR and other variables. Univariate and multivariate logistic regression analyses were used for adjusting potential confounding factors to determine indepdent factors of in-hospital death.

Results

Basic characteristics of patients

This study enrolled 3366 patients with a diagnosis of ACS, which were subsequently divided into four groups according to quartiles of HAR, Q1 (Quartile 1, < 1.0283), Q2 (Quartile 2, 1.0283–1.0860), Q3 (Quartile 3, 1.0860–1.1798), Q4 (Quartile 4, ≥ 1.1798). As age increased, the HAR also increased ($p < 0.001$). Age in Q4 group was significantly higher than the Q1 group (73.17 ± 13.21 vs. 69.85 ± 12.85). Neutrophil and WBC counts were also markedly increased, whereas lymphocyte count was decreased in Q4 group, compared with Q1 group ($p < 0.001$ for all). The level of D-dimer and BUN in Q4 group were also higher than in Q1 group ($p < 0.001$), while levels of ALB and Hb were significantly decreased ($p <$

0.001). There was no significance in GLU (p = 0.132), HbA1C (p = 0.120) and diabetes history (p = 0.316) among these groups (Table 1).

The population was also divided into four groups according to quartiles of LBR (**Suppl. Table S1**), Q1: < 3.1094, Q2: 3.1094–3.3317, Q3: 3.3317–3.5620, Q4: ≥ 3.5620. In contrast, age was gradually lower in the higher LBR group. There was no significance in WBC count in different LBR groups, although lymphocyte count was increased in the higher LBR group. Despite no significance in GLU levels among the four groups (p = 0.549), the proportion of patients with diabetes history declined gradually as the LBR increased (p = 0.017).

Pearson correlation analysis of HAR

HAR was positively correlated to age (r = 0.073, p < 0.001), ALT (r = 0.046, p = 0.006), BUN (r = 0.161, p < 0.001), UA (r = 0.0563, p = 0.001), creatinine (Cr) (r = 0.122, p < 0.001), D-dimer (r = 0.140, p < 0.001). HAR was negatively related to SBP (r = –0.055, p = 0.001), ALB (r = –0.169, p < 0.001), Hb (r = –0.140, p < 0.001) (Table 2, Fig. 2). Regarding inflammatory markers, HAR was positively associated with high sensitivity C-reactive protein (hsCRP) (r = 0.297, p < 0.001), neutrophils (r = 0.138, p < 0.001), and WBC (r = 0.119, p < 0.001), while it was negatively correlated to lymphocyte counts (r = –0.130, p < 0.001) (Table 2, Fig. 2). HAR was not associated with diabetes related indicators, such as HbA1C (r = –0.024, p = 0.163) and GLU (r = –0.008, p = 0.655) (Table 2). By contrast, LBR was negatively related to age (r = –0.085, p < 0.001), BUN (r = –0.080, p < 0.001), ALB (r = 0.134, p < 0.001), Cr (r = –0.055, p = 0.001), hsCRP (r = –0.103, p < 0.001) and D-dimer (r = –0.060, p = 0.005), and positively associated with SBP (r = 0.039, p = 0.023) and lymphocyte count (r = 0.075, p < 0.001) (Table 2).

High HAR was associated with adverse cardiac function and longer hospitalization periods

Left ventricular ejection fraction was gradually decreased as HAR increased,

reaching the lowest ejection fraction in Q4 group ($p < 0.001$) (Table 1). Meanwhile, Pearson analysis showed that HAR was negatively related to LVEF ($r = –0.121$, $p < 0.001$) (Table 2). Therefore, higher HAR may indicate the deterioration of cardiac function. Compared to other three groups, hospitalization days ($p < 0.001$) were also higher in Q4 group, which demonstrated that high HAR was associated with longer hospitalization periods. The in-hospital mortality ($p = 0.014$) and hospitalization days ($p < 0.001$) were both increased in Q4 group, compared to the other three groups (Table 1, 2). Univariate and variate linear regression were used for determing the role of HAR in predicting in-hospital days. Significant variables in univariate regression were enrolled into multilinear regression by “Stepwise” methods . Finally, HAR was an independent predictor of hospitalizaition time after ACS (hazard ratio [HR]: 2.221, 95% confidence interval [CI]: 0.888–3.553, $p = 0.001$), which meant the in-hospital days prolonged 2 days when HAR increased by 1 unit (Table 3). When grouped by LBR, there was no significance in LVEF ($p = 0.221$), in-hospital mortality ($p = 0.05$) and hospitalization days ($p = 0.226$) (**Suppl. Table S1**).

HAR, rather than LBR, was an independent factor predicting in-hospital death in ACS patients

Next, predictors of in-hospital death in ACS patients were analyzed. Univariate logistic regression showed that sex (female), age, SBP (90–140 mmHg), SBP (≥ 140 mmHg), Cr (> 81 μmol/L), ALT, LDH, AST, ALB (≥ 40 g/L) , GLU, UA, PT, LVEF, cardiac arrest, Killip (≥ II), percutaneous coronary intervention treatment, antidiabetic drugs, antihypertensive drugs, antiplatelet drugs, beta-blocker drugs, statins, nitrates and HAR were all important variables predicting in-hospital death (Table 4). Significant variables in univariate analysis were enrolled and analyzed in variate logistic regression by “Forward Likelyhood Ratio”. Variate analysis showed that HAR was an important factor predicting in-hospital death after adjusting for age (HR: 1.068, 95% CI: 1.050–1.087, $p < 0.001$), SBP (90–140 mmHg) (HR: 0.243, 95% CI: 0.121–0.488, $p < 0.001$), SBP (≥ 140 mmHg) (HR: 0.134, 95% CI: 0.063–0.286, $p <$

0.001), Cr (> 81 μmol/L) (HR: 3.525, 95% CI: 2.266–5.483, p < 0.001), LDH (HR: 1.000, 95% CI: 1.000–1.000, p = 0.007), ALB (≥ 40 g/L) (HR: 0.580, 95% CI: 0.356–0.945, p = 0.029), GLU (HR: 1.055, 95% CI: 1.026–1.084, p < 0.001), LVEF (HR: 0.041, 95% CI: 0.011–0.158, p < 0.001) and antiplatelet drugs (HR: 0.468, 95% CI: 0.234–0.935, p = 0.031) (Table 4). These results indicated that HAR was an independent predictor of in-hospital death after ACS. Univariate regression analysis showed that LBR can predict in-hospital death (HR: 0.630, 95% CI: 0.435–0.913, p = 0.015), however, variate regression analysis showed no significance in LBR for predicting in-hospital death (**Suppl. Table S2**).

Discussion

In this study, it was found that HAR was positively related to inflammatory cells counts and negatively correlated to LVEF. Moreover, the proportion of acute myocardial infarction, the hospitalization days and the in-hospital mortality in the high HAR group were significantly increased. LBR, as an indicator of LDL particle size, had no significant correlation with WBC and neutrophil counts. LBR had no significance with LVEF, hospitalization days and in-hospital mortality. HAR was an important predictor of in-hospital death after ACS, rather than LBR, which may result from the impaired ability of HDL particles to absorb excess cholesterol indicated by the increased level of HAR.

The ARIC study found that HDL-C was negatively associated with the incidence of CHD in a 10 year follow-up of 12,339 residents from 4 communities [19]. However, dal-OUTCOMES study showed that dalcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, can increase the HDL-C level, but failed to reduce the risk of adverse outcomes in patients with a recent ACS [20]. It has been reported that HDL-C was an indicator of HDL quantity, and the quality was more important than the quantity due to the loss of anti-atherosclerosis function [20]. ApoA-I is an important protein component of HDL with anti-atherosclerosis function. Changes in the quantity and type of proteins and lipids bound by HDL particles and oxidative

modification of the components can lead to the loss of this function, becoming “dysfunctional HDL” [21]. HAR may reflect the change in the cholesterol content of each HDL particle [22].

Mainly explored herein, was the predictive ability of HAR in predicting the prognosis of ACS patients. In the present study, it was found that HAR was positively correlated with inflammatory cell counts, hsCRP and LDH, emerging as a potential marker of inflammation. LDH is closely associated with myocardial injury diseases and liver injury, and hsCRP is a common marker of inflammatory diseases. The LBR was not significantly correlated with inflammatory cell counts. HAR was also related to the in-hospital mortality and hospitalization days. After adjusting for age, sex, SBP, Cr, LDH, ALB, GLU, LVEF, and antiplatelet drugs, HAR was shown to be an important factor in predicting in-hospital mortality.

The PRIME study showed that in France and Northern Ireland, HDL-C was not associated with CHD incidence and only ApoA-I could predict the incidence of CHD after adjusting for lipid and non-lipid parameters [11]. A Mendelian randomization study showed HDL characteristics (such as size and cholesterol content) were associated with CHD, instead of HDL-C and ApoA-I levels [23]. These previous studies supported that HAR is not a valuable biomarker for CHD. However, in the current study, it was demonstrated that HAR was associated with the risk of in-hospital death in the ACS population. In a retrospective study of 2,566 patients receiving assessment of atherosclerotic plaque with intravascular ultrasound, plaque progression measured by percent atheroma volume and total atheroma volume was attenuated in patients with higher HAR [24]. In the IDEAL study, higher HDL-C was consistent with a higher risk of CHD when adjusting for age, gender, smoking, ApoB and ApoA-I [25]. An occupational cohort study involved 263,340 people showed that increasing HAR ratio quartiles was positively associated with mortality of CVD ($p = 0.016$), and the adjusted HR of CVD in the highest HAR ratio quartile to the lowest was 2.37 (95% CI: 0.89–6.37), which demonstrated that increasing HAR was an important risk factor for CVD [22].

Since HAR and LBR were both similarly important ratios in CVDs, further study compared the role of LBR in ACS patients. It has been reported that LBR was negatively associated with CHD [26]. In a case-cohort study, LBR ≤ 1.2 can predict CHD in patients with type 2 diabetes after adjusting confounders [27]. CHD and diabetes mellitus status were both independent factors predicting the minimum LBR, and LBR may play an important role in risk stratification in diabetic patients with CHD [28]. In a prospective cohort study with 9.9 ± 4.6 years follow-up of 1,687 patients with established atherosclerosis, Cox regression showed that LBR can predict major adverse cardiac events after adjusting some variables such as age, gender, smoking history, body mass index, etc. [29]. However, the relationship between LBR and ACS has rarely been reported. The present study showed LBR was not related to hospitalization days of ACS patients. Incidence of in-hospital death gradually decreased with the increase of LBR quartiles, although without any statistical significance. Different from HAR, LBR was not an independent predictor of in-hospital death.

Limitations of the study

There are some limitations of the current study. First, this study did not actually measure the particle size of LDL and the proportion of dysfunctional HDL. Instead, representative related markers (HAR and LBR) were used to evaluate the relationship between the quality and type of lipids in the blood and the prognosis of ACS. Second, as a retrospective study, confounding factors have an influence on the results, but variate logistic regression was used to eliminate the influence of confounding factors as much as possible.

Conclusions

In conclusion, it was found that HAR had an important predictive value in the in-hospital death after ACS, while the LBR, which represents the size of the LDL particle size, was not related to the adverse prognosis. These results show that more

attention needs to be paid to HDL-C and ApoA-I in coronary artery disease, not only LDL-C and ApoB.

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Conflict of interest: None declared

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Table 1. Basic characteristics of patients.

Characteristics	Quartile 1 (n = 841)	Quartile 2 (n = 842)	Quartile 3 (n = 842)	Quartile 4 (n = 841)	P
Age [years]	69.85 ± 12.85	71.05 ± 12.75	72.10 ± 13.06	73.17 ± 13.21	< 0.001***
Sex, male	581 (69.08%)	643 (76.37%)	580 (68.88%)	550 (65.40%)	< 0.001***
Smoking	349 (41.50%)	359 (42.64%)	350 (41.67%)	303 (36.03%)	0.025*
SBP [mmHg]	134.22 ± 21.11	133.45 ± 21.00	131.41 ± 22.31	131.09 ± 22.79	0.060
Laboratory examination:					
WBC [10^9/L]	8.29 ± 3.34	8.42 ± 3.77	8.73 ± 3.79	9.67 ± 4.98	< 0.001***
Neutrophils [10^9/L]	6.14 ± 3.27	6.32 ± 3.67	6.66 ± 3.67	7.66 ± 4.61	< 0.001***
Lymphocytes [10^9/L]	1.54 ± 0.66	1.51 ± 0.68	1.46 ± 0.62	1.33 ± 0.66	< 0.001***
ALT [U/L]	27.00 (17.00, 43.50)	26.00 (17.00, 41.00)	26.00 (16.00, 42.00)	27.00 (16.00, 48.00)	0.343
AST [U/L]	31.00 (21.00, 86.00)	30.00 (20.00, 70.00)	35.00 (20.00, 92.00)	42.00 (22.00, 115.00)	< 0.001***
LDH [U/L]	233.00 (183.73, 380.00)	215.00 (169.89, 350.25)	243.00 (175.00, 432.36)	292.00 (190.50, 563.56)	< 0.001***
TnI [ng/mL]	0.86 (0.15, 5.06)	0.79 (0.12, 4.77)	1.29 (0.21, 7.78)	1.81 (0.27, 9.49)	< 0.001***
LDL-C [mmol/L]	2.62 ± 0.83	2.63 ± 0.88	2.77 ± 0.86	2.67 ± 0.95	0.003**
HDL-C [mmol/L]	1.02 ± 0.25	1.07 ± 0.18	1.16 ± 0.23	1.13 ± 0.32	< 0.001***
BUN [mmol/L]	6.58 ± 3.95	6.81 ± 4.51	7.01 ± 4.59	8.86 ± 7.72	< 0.001***
Uric acid [μmol/L]	345.32 ± 110.22	350.08 ± 114.22	347.65 ± 112.93	363.99 ± 144.26	0.007**
TC [mmol/L]	4.19 ± 1.07	4.30 ± 1.10	4.53 ± 1.19	4.42 ± 1.29	< 0.001***
Triglyceride [mmol/L]	1.76 ± 1.14	1.78 ± 1.29	1.67 ± 1.38	1.65 ± 1.56	0.111
Albumin [g/L]	38.06 ± 4.62	37.60 ± 4.79	37.80 ± 4.89	36.21 ± 5.34	< 0.001***
Direct bilirubin [μmol/L]	3.30 (2.35, 4.70)	3.30 (2.40, 4.53)	3.30 (2.20, 4.50)	3.10 (2.00, 4.60)	0.177
Creatinine [μmol/L]	78.00 (66.00, 97.00)	83.00 (69.00, 103.00)	84.00 (69.00, 107.00)	90.00 (71.00, 126.00)	< 0.001***
Lipoprotein a [mg/L]	319.93 ± 300.74	320.39 ± 267.35	335.08 ± 241.660	351.75 ± 288.33	0.057
Glucose [mmol/L]	8.36 ± 4.29	8.01 ± 3.98	8.11 ± 3.98	8.42 ± 4.50	0.132
ApoB [g/L]	0.78 ± 0.23	0.78 ± 0.22	0.81 ± 0.21	0.79 ± 0.23	0.005**
ApoA-I [g/L]	1.10 ± 0.29	1.01 ± 0.17	1.03 ± 0.21	0.87 ± 0.27	< 0.001***
Platelet [10^9/L]	199.23 ± 63.15	196.69 ± 63.43	197.73 ± 62.91	198.58 ± 68.90	0.865
Hemoglobin [g/L]	132.51 ± 19.99	133.11 ± 20.67	131.21 ± 21.12	124.48 ± 23.92	< 0.001***
HbA1C [%]	7.06 ± 1.17	6.97 ± 0.99	7.00 ± 0.98	7.08 ± 1.04	0.120
D-dimer [ug/L]	132.14 (61.50, 301.25)	164.00 (98.84, 330.12)	196.00 (107.00, 424.19)	257.67 (123.80, 620.50)	< 0.001***
LVEF	0.60 ± 0.11	0.60 ± 0.11	0.58 ± 0.12	0.57 ± 0.12	< 0.001***
Cardiac arrest	38 (4.52%)	45 (5.34%)	66 (7.84%)	71 (8.44%)	0.002**
Hospitalization days	7.00 (5.00, 10.00)	7.00 (5.00, 11.00)	7.00 (5.00, 11.00)	8.00 (5.00, 13.00)	< 0.001***
Death	32 (3.80%)	39 (4.63%)	63 (7.48%)	65 (7.73%)	< 0.001***
Killip (≥ II)	124 (14.74%)	126 (14.96%)	175 (20.78%)	217 (25.80%)	< 0.001***
Previous history:					
Diabetes	292 (34.72%)	267 (31.71%)	263 (31.24%)	288 (34.24%)	0.316
Hypertension	584 (69.44%)	600 (71.26%)	580 (68.88%)	578 (68.73%)	0.657
Number of affected coronary vessels:					0.061
Single vessel	140 (16.65%)	131 (15.56%)	150 (17.81%)	102 (12.13%)	
Double vessels	201 (23.90%)	199 (23.63%)	194 (23.04%)	200 (23.78%)	
Triple vessels	500 (59.45%)	512 (60.81%)	498 (59.15%)	539 (64.09%)	
ACS types:					< 0.001***
Unstable angina	218 (25.92%)	222 (26.37%)	183 (21.73%)	138 (16.41%)	
STEMI	317 (37.69%)	307 (36.46%)	334 (39.67%)	367 (43.64%)	
NSTEMI	306 (36.39%)	313 (37.17%)	325 (38.60%)	336 (39.95%)	
PCI treatment	714 (84.90%)	711 (84.44%)	772 (91.69%)	785 (93.34%)	< 0.001***
Medication on admission:					
Antidiabetic drugs	207 (24.61%)	180 (21.45%)	181 (21.65%)	172 (20.45%)	0.194
Antihypertensive drugs	606 (72.06%)	619 (73.78%)	594 (71.05%)	588 (69.92%)	0.344
Antiplatelet drugs	819 (97.38%)	818 (97.50%)	806 (96.41%)	816 (97.03%)	0.549
Beta-blocker drugs	663 (78.83%)	678 (80.81%)	661 (79.07%)	685 (81.45%)	0.454
Statins	809 (96.20%)	804 (95.83%)	778 (93.06%)	784 (93.22%)	0.003**
Nitrates	641 (76.22%)	650 (77.47%)	626 (74.88%)	637 (75.74%)	0.655

Continuous data, conforming to normal distribution and homogeneity of variance, was described as mean ± standard deviation (M ± standard deviation); otherwise, it was described by quartiles (median (25%, 75%)). Categorical data was presented as frequency (percentage); *p < 0.05; **p < 0.01; ***p < 0.001; SBP — systolic blood pressure; WBC — white blood cells; ALT — alanine aminotransferase; AST — aspartate aminotransferase; LDH — lactate dehydrogenase; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; BUN — blood urea nitrogen; TC — total cholesterol; HbA1C — glycosylated hemoglobin; LVEF — left ventricular ejected fraction; ACS — acute coronary syndrome; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention

Table 2. Correlation among high density lipoprotein cholesterol/ApoA-I, low density lipoprotein cholesterol/ApoB and common variables.

*p < 0.05; **p < 0.01; ***p < 0.001; SBP — systolic blood pressure; ALT — alanine aminotransferase; LDH — lactate dehydrogenase; BUN — blood urea nitrogen; WBC — white blood cells; HbA1C — glycosylated hemoglobin; hsCRP — high sensitivity C reactive protein; LVEF — left ventricular ejected fraction

Variables	**Pearson analysis of HDL-C/ApoA-I**		**Pearson analysis of LDL-C/ApoB**	
	r	**p**	**r**	**p**
Age [years]	0.073	< 0.001***	–0.085	< 0.001***
SBP [mmHg]	–0.055	0.001**	0.039	0.023*
ALT [U/L]	0.046	0.006**	–0.026	0.126
LDH [U/L]	0.069	< 0.001***	0.001	0.968
BUN [mmol/L]	0.161	< 0.001***	–0.080	< 0.001***
Uric acid [μmol/L]	0.063	< 0.001***	0.008	0.638
Albumin [g/L]	–0.169	< 0.001***	0.134	< 0.001***
Creatinine [μmol/L]	0.122	< 0.001***	–0.055	0.001**
Glucose [mmol/L]	0.008	0.655	–0.011	0.511
WBC [10^9/L]	0.119	< 0.001***	–0.012	0.492
Neutrophil [10^9/L]	0.138	< 0.001***	–0.024	0.172
Lymphocyte [10^9/L]	–0.130	< 0.001***	0.075	< 0.001***
Hemoglobin [g/L]	–0.140	< 0.001***	0.109	< 0.001***
D-dimer [ug/L]	0.140	< 0.001***	–0.060	0.005**
HbA1C [%]	0.024	0.163	0.014	0.421
hsCRP [mg/L]	0.297	< 0.001***	–0.103	< 0.001***
LVEF	–0.121	< 0.001***	–0.017	0.321

Table 3. Multiple linear regression of high density lipoprotein cholesterol (HDL-C)/ApoA-I predicting in-hospital days in acute coronary syndrome patients.

*p < 0.05; **p < 0.01; ***p < 0.001; HR — hazard ratio; CI — confidence interval; LVEF — left ventricular ejected fraction

Parameters	**Univariate linear regression**			**Multiple linear regression**		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age [years]	0.118	0.097–0.139	< 0.001***	0.074	0.052–0.096	< 0.001***
Uric acid [μmol/L]	0.003	0.001–0.006	0.006**	–	–	–
Albumin [g/L]	–0.342	–0.397 – –0.288	< 0.001***	-0.176	–0.236 – –0.115	< 0.001***
Creatinine [μmol/L]	0.011	0.009–0.014	< 0.001***	0.007	0.004–0.009	< 0.001***
LVEF	–12.252	–14.610 – –9.894	< 0.001***	–8.164	–10.540 – –5.788	< 0.001***
HDL-C/ApoA-I	4.287	2.933–5.640	< 0.001***	2.221	0.888–3.553	0.001**

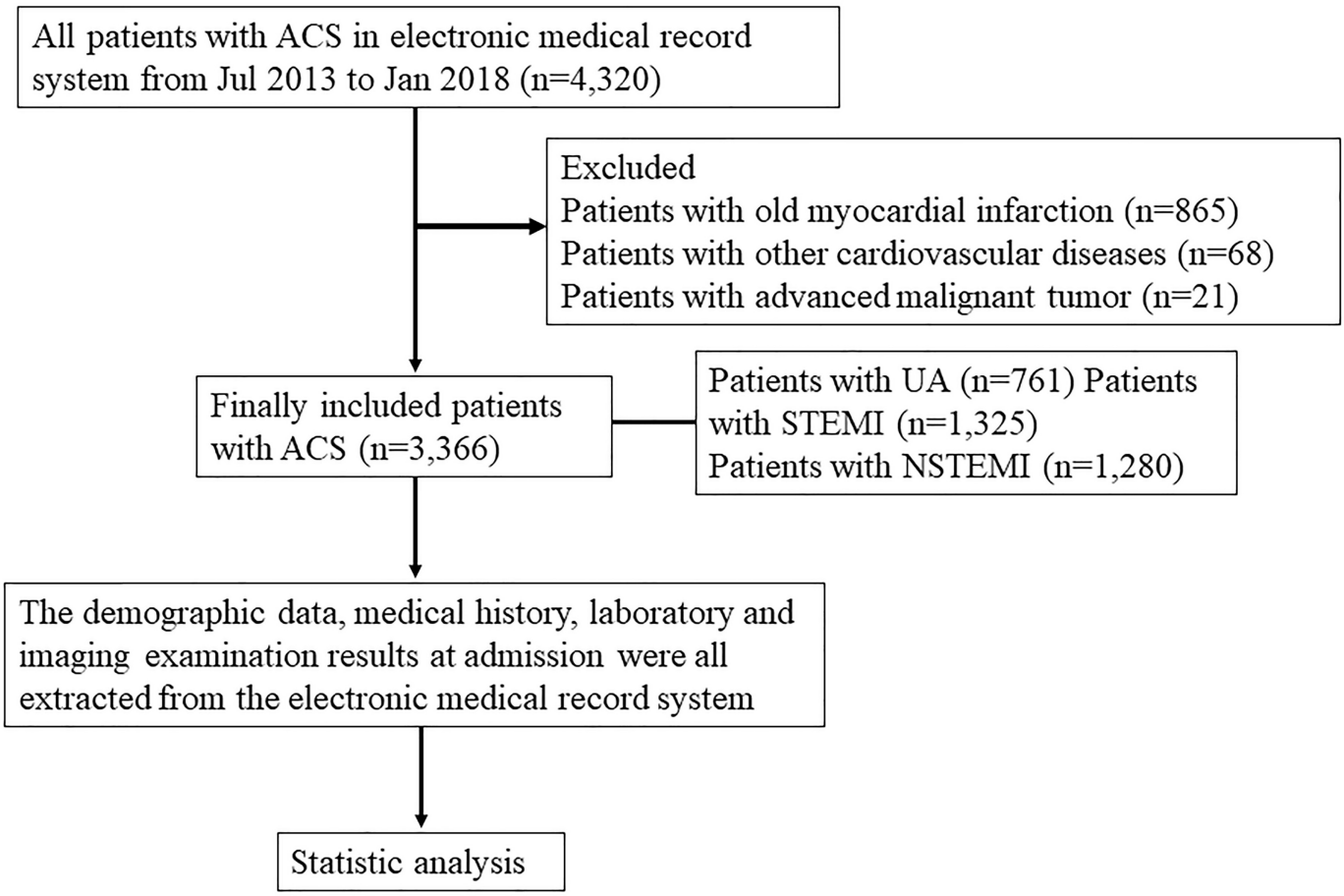
Table 4. Logistic regression of high density lipoptotein cholesterol (HDL-C)/ApoA-I predicting in-hospital death in acute coronary syndrome patients.

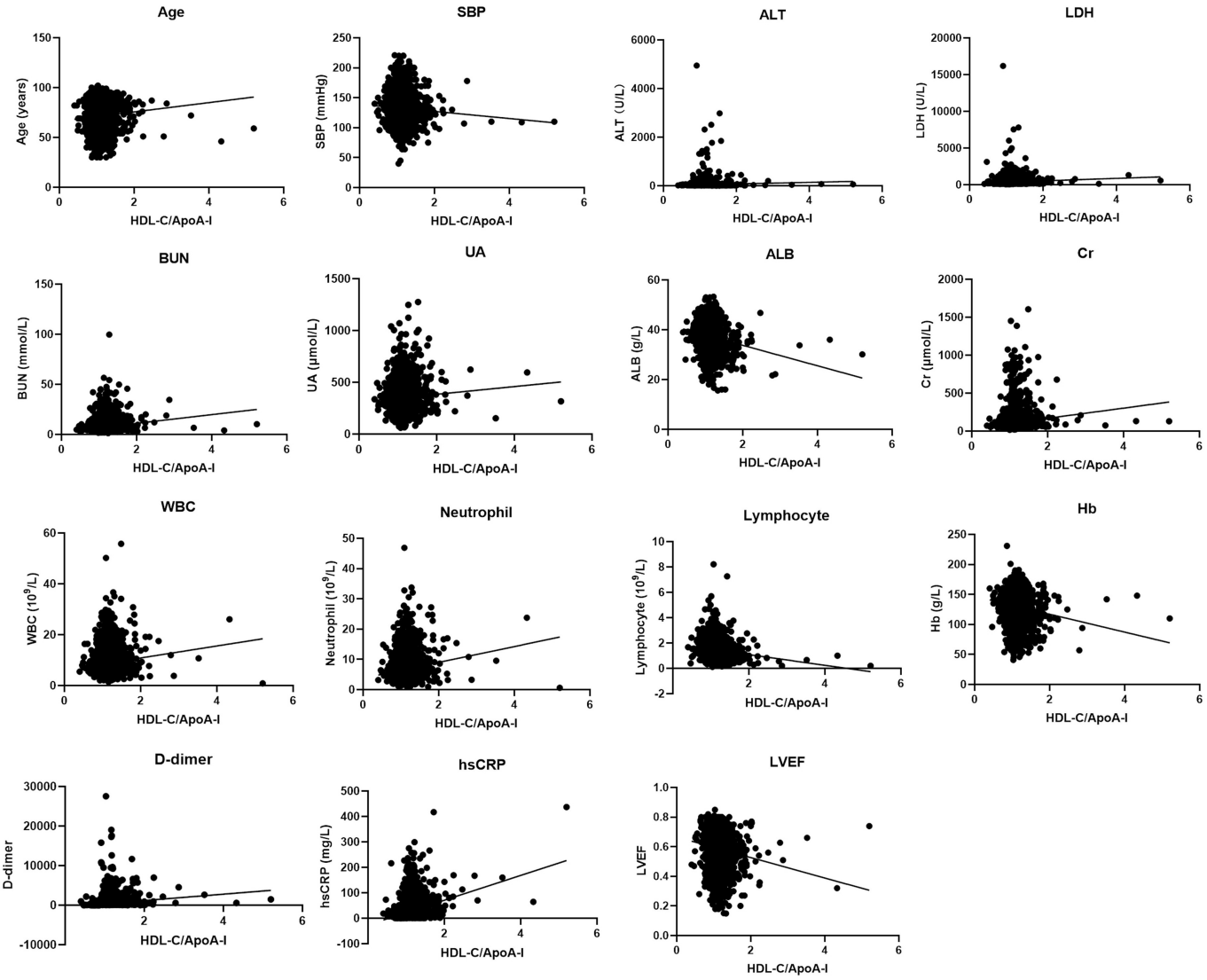
*p < 0.05; **p < 0.01; ***p < 0.001; HR — hazard ratio; CI — confidence interval; SBP — systolic blood pressure; ALT — alanine aminotransferase; LDH — lactate dehydrogenase; AST — aspartate aminotransferase; LVEF — left ventricular ejected fraction; PCI — percutaneous coronary intervention

Parameters	Univariate logistic regression			Variate logistic regression		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Sex (female)	1.762	1.317–2.359	< 0.001***	1.848	1.327–2.575	< 0.001***
Age [years]	1.086	1.070–1.102	< 0.001***	1.068	1.050–1.087	< 0.001***
SBP (< 90 mmHg)						
SBP 90–140 mmHg	0.122	0.068–0.219	< 0.001***	0.243	0.121–0.488	< 0.001***
SBP ≥ 140 mmHg	0.078	0.041–0.149	< 0.001***	0.134	0.063–0.286	< 0.001***
Albumin (< 40 g/L)						
Albumin ≥ 40g/L	0.236	0.149–0.373	< 0.001***	0.580	0.356–0.945	0.029*
Creatinine (≤ 81μmol/L)						
Creatinine > 81 μmol/L	6.122	4.056–9.240	< 0.001***	3.525	2.266–5.483	< 0.001***
ALT [U/L]	1.001	1.000–1.002	0.001**	–	–	–
AST [U/L]	1.000	1.000–1.001	0.083	–	–	–
LDH [U/L]	1.000	1.000–1.001	< 0.001***	1.000	1.000–1.000	0.007**
Glucose [mmol/L]	1.077	1.051–1.104	< 0.001***	1.055	1.026–1.084	< 0.001***
Uric acid [μmol/L]	1.003	1.002–1.004	< 0.001***	–	–	–
Prothrombin time [s]	1.023	1.010–1.037	0.001**	–	–	–
HDL-C/ApoA-I	2.600	1.565–4.320	< 0.001***	1.831	1.010–3.321	0.046*
LVEF	0.005	0.002–0.014	< 0.001***	0.041	0.011–0.158	< 0.001***
Killip (≥ II)	2.645	1.955–3.579	< 0.001***	–	–	–
Cardiac arrest	0.000	0.000–0.000	0.974	–	–	–
PCI treatment	1.351	0.898–2.034	0.149	–	–	–
Antidiabetic drugs	1.106	0.786–1.556	0.564	–	–	–
Antihypertensive drugs	0.541	0.402–0.727	< 0.001***	–	–	–
Antiplatelet drugs	0.424	0.228–0.790	0.007**	0.468	0.234–0.935	0.031*
Statins	0.665	0.384–1.152	0.146	–	–	–
Nitrates	0.804	0.582–1.113	0.189	–	–	–
Beta-blocker drugs	0.610	0.441–0.844	0.003**	–	–	–

Figure 1. The flow chart of enrolled patients. The total number of patients with acute coronary syndrome (ACS) in electronic medical record system from July 2013 to January 2018 was 4,320. Among them, 865 patients were diagnosed as old myocardial infarction, and 68 patients were diagnosed as other cardiovascular diseases such as coronary heart disease and myocarditis. There were also 21 patients with advanced malignant tumor who were excluded. Finally, 3,366 patients with ACS were included in this study.

Figure 2. Pearson correlation analysis of HDL-C/apoA-I ratio (HAR). HAR was positively correlated to age (r = 0.073, p < 0.001; **A**), alamine aminotransferase (r = 0.046, p = 0.006; **B**), lactate dehydrogenase (r = 0.069, p < 0.001; **C**), blood urea nitrogen (r = 0.161, p < 0.001; **D**), uric acid (r = 0.063, p < 0.001; **E**), creatinine (r = 0.122, p < 0.001; **F**), white blood cells (r = 0.119, p < 0.001; **G**), neutrophil (r = 0.138, p < 0.001; **H**), high sensitivity C reactive protein (r = 0.297, p < 0.001; **I**), D-dimer (r = 0.140, p < 0.001; **J**). HAR was negatively related to systolic blood pressure (r = –0.055, p = 0.001), albumin (r = –0.169, p < 0.001), lymphocyte (r = –0.130, p < 0.001), hemoglobin (r = –0.140, p < 0.001) and left ventricular ejected fraction (r = –0.121, p < 0.001); *p < 0.05; **p < 0.01; ***p < 0.001.


All patients with ACS in electronic medical record system from Jul 2013 to Jan 2018 (n=4,320)
Excluded
Patients with old myocardial infarction (n=865)
Patients with other cardiovascular diseases (n=68)
Patients with advanced malignant tumor (n=21)
Finally included patients with ACS (n=3,366)
Patients with UA (n=761) Patients with STEMI (n=1,325)
Patients with NSTEMI (n=1,280)
The demographic data, medical history, laboratory and imaging examination results at admission were all extracted from the electronic medical record system
Statistic analysis


Age
Age (years)
HDL-C/ApoA-I
SBP
SBP (mmHg)
HDL-C/ApoA-I
ALT
ALT（U/L）
HDL-C/ApoA-I
LDH
LDH (U/L)
HDL-C/ApoA-I
BUN
BUN (mmol/L)
HDL-C/ApoA-I
UA
UA (μmol/L)
HDL-C/ApoA-I
ALB
ALB (g/L)
HDL-C/ApoA-I
Cr
Cr (μmol/L)
HDL-C/ApoA-I
WBC
WBC (10^9/L)
HDL-C/ApoA-I
Neutrophil
Neutrophil (10^9/L)
HDL-C/ApoA-I
Lymphocyte
Lymphocyte (10^9/L)
HDL-C/ApoA-I
Hb
Hb (g/L)
HDL-C/ApoA-I
D-dimer
D-dimer
HDL-C/ApoA-I
hsCRP
hsCRP (mg/L)
HDL-C/ApoA-I
LVEF
LVEF
HDL-C/ApoA-I