Original Article

Effects of cholesterol levels on outcomes of out-of-hospital cardiac arrest: a cross-sectional study

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Objective High cholesterol level is a risk factor for coronary artery disease, and coronary artery disease is a major risk factor for out-of-hospital cardiac arrest (OHCA). However, the effect of cholesterol level on outcomes of OHCA has been poorly studied. This study aimed to determine the effect of cholesterol level on outcomes of OHCA.

Methods This cross-sectional study used the CAPTURES (Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiologic Surveillance) project database in Korea. Multivariable conditional logistic regression analysis was performed to estimate the effect of cholesterol level on outcomes in OHCA.

Results In all, 584 cases of OHCA were analyzed; those with cholesterol levels < 120 mg/dL were classified as having low total cholesterol (TC) (n = 197), those with levels ranging from 120–199 mg/dL as middle TC (n = 322), and those with ≥ 200 mg/dL as high TC (n = 65). Compared to low TC, more patients with middle TC and high TC survived to discharge (9.1% vs. 22.0% and 26.2%, respectively, P = 0.001). The good cerebral performance category also increased in that order (4.1 % vs. 14.6% and 23.1%, respectively, P ≤ 0.001). Comparing middle TC and high TC with low TC, adjusted odds ratios (95% confidence intervals) were 1.97 (1.06 to 3.64) and 2.53 (1.08 to 5.92) for survival to discharge, respectively, and 2.53 (1.07 to 5.98) and 4.73 (1.63 to 13.71) for good neurological recovery, respectively.

Conclusion Higher cholesterol is associated with better outcomes in OHCA; cholesterol level is a good predictor of outcomes of OHCA.

Keywords Heart arrest; Cholesterol; Outcome; Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiologic Surveillance

Capsule Summary

What is already known
Cholesterol is a risk factor for coronary artery disease, and coronary artery disease is one of the major risk factors of out-of-hospital cardiac arrest (OHCA). However, the effect of cholesterol on outcomes of OHCA has been poorly studied.

What is new in the current study
Higher cholesterol is associated with better outcomes in OHCA; cholesterol level is the good predictor of outcomes of OHCA.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is the leading cause of death worldwide. OHCA occurs in 13 out of every 10,000 people in the United States (326,000 cases/yr), with a survival rate of 8% when treated.[1,2] The survival rate is low and the prognosis is often poor, despite intra-resuscitation and post-resuscitation efforts for OHCA.[2] The burden of public medical treatment due to the occurrence of OHCA is increasing.[3,4]

Cholesterol is an alcohol with a steroid skeleton and is an essential substance that maintains the structural integrity and fluidity of cell membranes.[5] It is also a precursor of steroid hormones, bile acid, vitamin D, as well as constituents of the cell membrane.[6] Cholesterol levels are recommended to be below 200 mg/dL for normal adults, are considered borderline high between 200 and 239 mg/dL and high above 240 mg/dL.[7,8] Hypocholesterolemia refers to serum cholesterol levels less than 120 mg/dL, concerning mostly those individuals in the 5th percentile of the distribution of normal adults.[9]

In general, higher cholesterol levels are a risk factor for coronary artery disease (CAD), and CAD is a major risk factor for OHCA.[10-14] However, the effects of cholesterol level on the outcomes of OHCA have not been extensively studied, apart from rat studies or a limited number of human studies.[15-19] According to several studies, adverse events that cause severe damage to the human body, such as cerebral infarction, cerebral hemorrhage, major burns, surgery, and sepsis, show better outcomes in individuals with higher cholesterol levels.[20-26]

In this study we aimed to determine the association of cholesterol level with outcomes of OHCA.

METHODS

Study design and setting
This cross-sectional study used the Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiologic Surveillance (CAP-TURES) project database in Korea. Emergency medical technicians operate ambulances at the request of the dispatcher. If there is no physician stopping emergency treatment or declaring death online, cardiopulmonary resuscitation (CPR) continues, and the patient would be transferred to the emergency department (ED). EDs are divided into three levels, with more resources and facilities at levels 1 and 2, and resident emergency physicians present 24 hours a day, 365 days a year. Please refer to the reports for the characteristics of the emergency medical service (EMS) and emergency medical technicians, and the characteristics of the OHCA protocols and the EDs.[27,28]

The study was performed at 27 hospitals, where the 2010 CPR guidelines were generally accepted as a standard protocol, including hypothermia treatments. Standard advanced life support including airway management, chest compression, and circulatory support at the emergency room were used in each hospital. However, details of CPR drugs, fluid therapy, and ventilatory care modules were selected according to the physicians' preference. Hypothermia treatment followed the target temperature of 32°C to 34°C in the study period. The cooling methods, duration of initiation, maintenance and rewarming of cooling differed according to the hospital but generally adhered to the 2010 guidelines. Details of cooling methods were selected by hospital and the physicians' preference. EMS CPR was recommended by the national fire department on the basis of the EMS medical direction guideline.

Study participants
Patients were enrolled in this study from January to December 2014; the study comprised adults over 18 years of age transferred to the hospital by the EMS after cardiac arrest. Patients without a cardiac etiology or who had been transferred from another hospital were excluded; patients with unknown cholesterol levels and those with traumatic OHCA were excluded.

Data collection and protocols

The CAPTURES project was designed to identify the risk factors for OHCA and their prognoses. This project was a hospital-based prospective cohort study conducted in 27 EDs from January to December 2014 (9 level one EDs and 18 level two EDs). Patients with OHCA of cardiac etiology having undergone resuscitation by the EMS and transportation to the ED were included in the study. Patients with terminal illness, pregnancy, requiring hospice care, homeless, and carrying 'Do Not Resuscitate' cards were excluded. The CAPTURES registry uses Utstein templates and laboratory tests to record social, physical, emotional, medical history, and outcomes from the EMS and ED. These data were collected by ED physicians through structured survey papers directly provided to the family, or by study coordinators from each ED reviewing medical records and investigating long-term outcomes over the telephone over 6 to 12 months. The collected data were inputted and transmitted to the central data server using EpiData ver. 3.1 (Filefacts, USA; http://www.filefacts.com) and was filtered using this data entry system. A quality management committee, consisting of emergency physicians, cardiologists and statisticians, trained all ED physicians and coordinators prior to the project and gave feedback to the coordinators every month.

Measurement of variables

The main exposure was total cholesterol (TC) level, which corresponded to the blood test value at the time of CPR recorded in the CAPTURES database. Cholesterol groups were defined according to TC levels as low TC ($0 \leq$ TC ≤ 119 mg/dL), middle TC ($120 \leq$ TC ≤ 199 mg/dL), and high TC (≥ 200 mg/dL). The cut-off values followed the international guidelines.[7-9]

It was anticipated that fasting before the blood test would not significantly affect the test results.[29] Patients with physician-diagnosed dyslipidemia or who were taking anti-hyperlipidemic drugs were included regardless. Confounders included age, sex,

co-morbidities (hypertension and diabetes), Utstein factors (arrest location, witnessed, bystander CPR, and initial shockable rhythm), EMS factors (response time, scene time, and transport time), and serum laboratory factors (hemoglobin, albumin, and protein levels).

Measurement of outcomes

The primary endpoint was survival to discharge and the secondary endpoint was good cerebral performance category (CPC) level. Survival to discharge was defined as being alive and going home, or to a nursing home or extended care facility.[30] CPC is the gold standard for determining the neurological outcomes of cardiac arrest, and good CPC encompasses CPC1 and CPC2 patients.[31]

Statistical analysis

Demographic variables were described by the distribution of potential risk factors for outcomes between low TC, middle TC, and high TC. Categorical variables were compared using the chi-square test, and continuous variables were compared using the Wilcoxon rank-sum test.

A multivariable logistic regression analysis was performed to test the association between low TC, middle TC, and high TC groups and outcomes, adjusting for potential confounders such as age, sex, co-morbidities (hypertension and diabetes), Utstein factors (arrest location, witnessed, bystander CPR, and initial shockable rhythm), and EMS factors (response time, scene time, and transport time). Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated (reference: low TC). A multivariable logistic regression analysis was performed to test the association between shockable rhythm and the outcomes, adjusting for potential confounders to calculate adjusted ORs and 95% CIs (reference: non-shockable rhythm).

Potential confounders were selected from the univariate analysis using P < 0.20 level for a strong association. Some factors such as bystander CPR or witness which were already known to
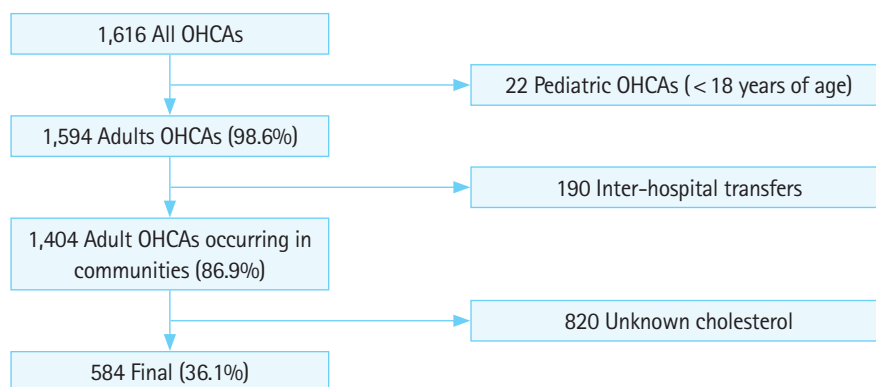

Fig. 1. Study population flow chart. OHCA, out-of-hospital cardiac arrest.

be strongly associated with outcome were included even though the P-value was over 0.02. We put the potential variables into the final multivariable logistic analysis model and tested the collinearity diagnostics among variables in particular laboratory results using a condition index of less than 20. The final model had no collinearity among variables. We tested the goodness-of-fit using the Hosmer-Lemeshow method in the final model and the level of fitness was acceptable when the Hosmer-Lemeshow-chi was less than 15 and P-value > 0.05.

An interaction analysis was performed to compare the effect size of TC according to initial electrocardiogram (ECG) rhythm using the same model with adjustments for interaction terms (analysis based on TC group when initial ECG is shockacle or nonshockable), in addition to potential confounders in the above main analysis.

Ethics statement

The study complied with the tenets of the Declaration of Helsinki and the study protocol was approved by all institutional review boards of the 27 participating study institutions with a waiver of informed consent.

RESULTS

Study population

The total number of cases of OHCA available for this study was 1,616 and, of these, 584 were ultimately analyzed, after exclud-

Table 1. Characteristics and outcomes of the study population classified by total cholesterol level

	Total	Low total cholesterol[a]	Middle total cholesterol[b]	High total cholesterol[c]	P-value
All	584 (100)	197 (100)	322 (100)	65 (100)	
Sex					0.020
Male	404 (69.2)	125 (63.5)	226 (70.2)	53 (81.5)	
Female	180 (30.8)	72 (36.5)	96 (29.8)	12 (18.5)	
Age (yr)					<0.001
18–54	156 (26.7)	29 (14.7)	100 (31.1)	27 (41.5)	
55–74	226 (38.7)	68 (34.5)	132 (41.0)	26 (40.0)	
≥75	202 (34.6)	100 (50.8)	90 (28.0)	12 (18.5)	
Median (IQR)	58 (49–70)	75 (66–82)	63.5 (53–76)	58 (49–70)	
Diabetes					0.001
No	170 (29.1)	44 (22.3)	102 (31.7)	24 (36.9)	
Yes	137 (23.5)	68 (34.5)	61 (18.9)	8 (12.3)	
Unknown	277 (47.4)	85 (43.1)	159 (49.4)	33 (50.8)	
Hypertension					0.003
No	136 (23.3)	35 (17.8)	79 (24.5)	22 (33.8)	
Yes	217 (37.2)	90 (45.7)	114 (35.4)	13 (20.0)	
Unknown	231 (39.6)	72 (36.5)	129 (40.1)	30 (46.2)	

(Continued to the next)

Table 1. Continued

	Total	Low total cholesterol[a]	Middle total cholesterol[b]	High total cholesterol[c]	P-value
Witness					0.995
No	206 (35.3)	70 (35.5)	113 (35.1)	23 (35.4)	
Yes	378 (64.7)	127 (64.5)	209 (64.9)	42 (64.6)	
Location					<0.001
Private	424 (72.6)	163 (82.7)	222 (68.9)	39 (60.0)	
Public	160 (27.4)	34 (17.3)	100 (31.1)	26 (40.0)	
Bystander CPR					0.829
No	334 (57.2)	116 (58.9)	182 (56.5)	36 (55.4)	
Yes	250 (42.8)	81 (41.1)	140 (43.5)	29 (44.6)	
ECG at EMS					<0.001
Non-shockable	443 (75.9)	174 (88.3)	229 (71.1)	40 (61.5)	
Shockable	141 (24.1)	23 (11.7)	93 (28.9)	25 (38.5)	
Response time (min)					0.745
0< ≤4	111 (19.0)	30 (15.2)	68 (21.1)	13 (20.0)	
4< ≤8	305 (52.2)	105 (53.3)	167 (51.9)	33 (50.8)	
8< ≤12	113 (19.3)	43 (21.8)	58 (18.0)	12 (18.5)	
>12	55 (9.4)	19 (9.6)	29 (9.0)	7 (10.8)	
Scene time (min)					0.020
0< ≤4	153 (26.2)	61 (31.0)	70 (21.7)	22 (33.8)	
4< ≤8	202 (34.6)	58 (29.4)	117 (36.3)	27 (41.5)	
8< ≤12	133 (22.8)	45 (22.8)	75 (23.3)	13 (20.0)	
>12	96 (16.4)	33 (16.8)	60 (18.6)	3 (4.6)	
Transport time (min)					0.076
0< ≤4	70 (12.0)	27 (13.7)	38 (11.8)	5 (7.7)	
4< ≤8	205 (35.1)	65 (33.0)	119 (37.0)	21 (32.3)	
8< ≤12	128 (21.9)	39 (19.8)	65 (20.2)	24 (36.9)	
>12	181 (31.0)	66 (33.5)	100 (31.1)	15 (23.1)	
Hemoglobin (g/dL)					<0.001
0< ≤10.3	140 (24.0)	90 (45.7)	49 (15.2)	1 (1.5)	
10.3< ≤14.6	297 (50.9)	90 (45.7)	175 (54.3)	32 (49.2)	
>14.6	147 (25.2)	17 (8.6)	98 (30.4)	32 (49.2)	
Protein (g/dL)					<0.001
0< ≤5.6	138 (23.6)	78 (39.6)	58 (18.0)	2 (3.1)	
5.6< ≤6.8	287 (49.1)	87 (44.2)	173 (53.7)	27 (41.5)	
>6.8	159 (27.2)	32 (16.2)	91 (28.3)	36 (55.4)	
Albumin (g/dL)					<0.001
0< ≤3.0	132 (22.6)	91 (46.2)	39 (12.1)	2 (3.1)	
3.0< ≤4.0	295 (50.5)	92 (46.7)	180 (55.9)	23 (35.4)	
>4.0	157 (26.9)	14 (7.1)	103 (32.0)	40 (61.5)	
Outcomes					
Prehospital ROSC	61 (10.4)	8 (4.1)	41 (12.7)	12 (18.5)	<0.001
Survival to discharge	106 (18.2)	18 (9.1)	71 (22.0)	17 (26.2)	<0.001
Good cerebral performance category	70 (12.0)	9 (4.1)	47 (14.6)	15 (23.1)	<0.001

Values are presented as number (%).

IQR, interquartile range; CPR, cardio-pulmonary resuscitation; ECG, electrocardiogram; EMS, emergency medical services; ROSC, return of spontaneous circulation.

[a]0–119 mg/dL. [b]120–199 mg/dL. [c]200 mg/dL and higher.

ing pediatric events (n = 22), inter-hospital transfers (n = 190) and cases with unknown cholesterol levels (n = 890) (Fig. 1). Patients with low, middle and high TC levels were 197, 322, and 65, respectively.

Characteristics and outcomes of the study population

Compared to low TC, more patients survived to discharge from the middle TC and high TC groups (9.1% vs. 22.0% and 26.2%, respectively, P < 0.001). Good CPC was also higher in the same order (4.1% vs. 14.6% and 23.1%, respectively, P < 0.001) (Table 1).

Main analysis

Multivariable logistic regression analysis on the outcomes of middle TC and high TC compared with low TC (Table 2) resulted in unadjusted ORs (95% CIs) of 2.81 (1.62 to 4.88) and 3.52 (1.69 to 7.35) for survival to discharge, respectively, and 4.04 (1.87 to 8.74) and 7.09 (2.85 to 17.66) for good neurological recovery, respectively. TC, age, sex, hypertension, diabetes mellitus, witness, location, bystander cardiopulmonary resuscitation, response time,

scene time, and transport time were set as variables, resulting in adjusted ORs (95% CIs) for middle TC and high TC compared with low TC of 1.97 (1.06 to 3.64) and 2.53 (1.08 to 5.92) for survival to discharge, respectively, and 2.53 (1.07 to 5.98) and 4.73 (1.63 to 13.71) for good neurological recovery, respectively.

Due to the large effect of ECG at EMS, multivariable logistic regression analysis was performed, as well as interaction analysis for TC.

First, multivariable logistic regression analysis was performed for shockable rhythm compared with non-shockable rhythm (Table 3). Replacing the TC variable of Table 2 with the ECG at EMS variable, adjusted ORs (95% CIs) were 7.65 (4.49 to 13.05) for survival to discharge and 17.32 (8.30 to 36.15) for good neurological recovery.

Interaction analysis was performed on the outcomes between TC groups and initial ECG rhythm (Table 4). The adjusted ORs (95% CIs) for shockable rhythm were 1.51 (0.85 to 2.68) and 2.19 (1.05 to 4.56) for survival to discharge, for middle TC and high TC versus low TC, respectively, and 1.04 (0.57 to 1.91) and 2.25 (1.03 to

Table 2. Multivariable logistic regression analysis on outcomes by total cholesterol level

	Total	Outcome	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Survival to discharge				
All	584	106 (18.2)	-	-
Low total cholesterol[a]	197	18 (9.1)	1.00	1.00
Middle total cholesterol[b]	322	71 (22.0)	2.81 (1.62–4.88)	1.97 (1.06–3.64)
High total cholesterol[c]	65	17 (26.2)	3.52 (1.69–7.35)	2.53 (1.08–5.92)
Hosmer-Lemeshow test chi-square (P-value)	-	-	0.00 (0.99)	4.05 (0.85)
Good cerebral performance category				
All	582	70 (12.0)	-	-
Low total cholesterol[a]	118	8 (6.8)	1.00	1.00
Middle total cholesterol[b]	333	47 (14.1)	4.04 (1.87–8.74)	2.53 (1.07–5.98)
High total cholesterol[c]	100	15 (15.0)	7.09 (2.85–17.66)	4.73 (1.63–13.71)
Hosmer-Lemeshow test chi-square (P-value)	-	-	0.00 (0.99)	5.59 (0.69)

Values are presented as number or number (%) unless otherwise indicated.
[a]0–119 mg/dL. [b]120–199 mg/dL. [c]200 mg/dL and higher.

Table 3. Multivariable logistic regression analysis on outcomes by electrocardiogram rhythm

	Total	Outcome	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Survival to discharge				
All	584	106 (18.2)	-	-
Non-shockable	443	36 (8.1)	1.00	1.00
Shockable	141	70 (49.6)	11.14 (6.93–17.91)	7.65 (4.49–13.05)
Good cerebral performance category				
All	584	70 (12.0)	-	-
Non-shockable	443	12 (2.7)	1.00	1.00
Shockable	141	58 (41.1)	25.10 (12.91–48.77)	17.32 (8.30–36.15)

Values are presented as number or number (%) unless otherwise indicated.

Table 4. Interaction analysis on outcomes between the cholesterol group and the electrocardiogram rhythm group

	Non–shockable adjusted odds ratio (95% confidence interval)	Shockable adjusted odds ratio (95% confidence interval)
Survival to discharge		
Low total cholesterol[a]	1.00	1.00
Middle total cholesterol[b]	1.23 (0.82–1.84)	1.51 (0.85–2.68)
High total cholesterol[c]	1.31 (0.74–2.33)	2.19 (1.05–4.56)
Good cerebral performance category		
Low total cholesterol[a]	1.00	1.00
Middle total cholesterol[b]	0.90 (0.54–1.51)	1.04 (0.57–1.91)
High total cholesterol[c]	1.69 (0.85–3.36)	2.25 (1.03–4.87)

[a]0–119 mg/dL. [b]120–199 mg/dL. [c]200 mg/dL and higher.

4.87) for good neurological recovery, for middle TC and high TC versus low TC, respectively.

DISCUSSION

In this study, we found that the higher the TC levels the better the outcomes in OHCA; when TC levels were higher than 120 mg/dL, the outcomes were better than for cholesterol levels lower than 120 mg/dL. The effect of initial ECG rhythm on the outcomes and results of the interaction analysis showed that the outcomes were better with respect to shockable rhythm for TC levels higher than 200 mg/dL, compared to levels lower than 120 mg/dL. When the initial ECG rhythm was non-shockable, the pattern of outcomes changed with increasing cholesterol level, and the analysis was difficult due to the high mortality rate. Therefore, we analyzed shockable rhythms and found that outcomes were improved with increasing cholesterol level.

Some studies support these results. In humans, it has been shown that lowering cholesterol levels using drugs or food does not lower the mortality of sudden cardiac events and, in turn, cannot lower OHCA mortality.[18,19] Studies in rats have shown that abundant cholesterol at the acute phase of cardiac arrest can help the heart withstand anoxic damage to cardiomyocytes.[15-17]

There are also studies on other diseases, such as cerebral infarction, in which higher cholesterol level reflected better outcomes, and lower cholesterol level reflected worse outcomes.[20-22] Similar results were obtained for cerebral hemorrhage, major burns, surgery, and sepsis, which severely damage the human body. The reason is that lower cholesterol levels reflect greater amounts of inflammatory cytokines such as interleukin 6 and tumor necrosis factor α and worse outcomes.[23-26] The role of cholesterol (especially high-density lipoprotein cholesterol) is to bind to bacterial endotoxins (lipopolysaccharides) and neutralize them,

thereby lowering the level of inflammatory cytokines and reducing the incidence of complications.[32,33] These results were similar in older age and hospitalized patients.[34-36]

Studies on the factors that influence the outcomes of OHCA have been carried out in various fields until now.[37] However, low-density lipoprotein cholesterol, a subtype of cholesterol, has been identified as a causative agent of coronary artery disease, and studies of how TC levels affect the outcomes of OHCA are lacking.[5,38]

This study potentially suffers from various limitations. First, since the CAPTURES database records only the state at discharge and does not include the duration of hospitalization, outcomes vary depending on duration. Thus, it is necessary to additionally confirm the outcomes at 6 months and 12 months post-discharge to improve the accuracy of the results. Second, this study was designed as a cross-sectional study, not an interventional trial, and many patients were excluded; as a result, there were not enough cases with hypercholesterolemia over 240 mg/dL in the guideline. Third, this study used measurements of TC determined via different laboratory methods, making it impossible to obtain uniform and accurate test samples across all hospitals; the uniformity and accuracy were also influenced by the different conditions, including fasting status, of the patients.[39,40] Fourth, the excluded patients whose cholesterol levels were not measured comprised more than 50 percent (selection bias). If these patients were included in the analysis, the results could be different. Fifth, patients with prehospital return of spontaneous circulation also showed an increase in cholesterol levels, but it is hard to know how many of them were sustained return of spontaneous circulation and used by analysis. Finally, we did not measure the proportion of anti-lipid medications used by patients. This unmeasured bias could affect the results.

Cholesterol level is an important factor that affects the outcomes of OHCA, and cholesterol levels above 120 mg/dL are associated with better outcomes. This study was designed to uncover the role of TC level, which is routinely examined by physicians when cardiac arrest occurs in the emergency room, but has been thought of as carrying little importance in predicting outcomes of OHCA. We, on the other hand, believe that it will be very helpful in predicting outcomes of OHCA.

Based on the above studies, in order to conclude that higher cholesterol level has a positive effect on the outcomes of OHCA, we need to see how cholesterol affects the incidence of OHCA. Of course, it will also be necessary to increase the number of patients by widening the period and target. From this study, we just found an association between cholesterol level and OHCA outcomes. We expect that this study result will motivate and encourage fur-

ther research on the subgroups of cholesterol relevant to outcomes such as low-density lipoprotein and high-density lipoprotein cholesterol, molecular functions, and peptides related with CPR outcomes.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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