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Clinical paper

The association between lipid profiles and the neurologic outcome in patients with out-of-hospital cardiac arrest☆

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Abstract

Background: Lipid profiles are known to be a risk factor for development of cardiovascular disease. However, the relationship between lipid profiles and outcome in out-of-hospital cardiac arrest (OHCA) survivors remains unclear. We aimed to examine the association between lipid profiles and neurologic outcome in OHCA survivors.

Methods: This retrospective observational study included adult (≥18 years) OHCA survivors between January 2016 and December 2018. We measured patients' lipid profiles after return of spontaneous circulation (ROSC) including total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride. The primary outcome was neurologic outcome at hospital discharge. Good neurologic outcome was defined cerebral performance categories 1 and 2.

Results: A total of 182 patients were included. Of them, 57 (31.3%) were discharged with good neurologic outcomes. Median serum levels of total cholesterol (178.0 vs. 123.0 mg/dL), HDL (44.0 vs. 31.0 mg/dL), and LDL (104.0 vs. 75.0 mg/dL) were significantly higher in patients with good neurologic outcome. The area under the curves of total cholesterol, HDL, LDL, and triglyceride were 0.742 (95% confidence interval [CI], 0.672−0.803), 0.729 (95% CI, 0.658−0.792), 0.683 (95% CI, 0.610−0.750), and 0.572 (95% CI, 0.497−0.645), respectively. Total cholesterol (odds ratio [OR], 1.013; 95% CI, 1.000−1.025; p = 0.043) and HDL (OR, 1.071; 95% CI, 1.021−1.123; p = 0.005) levels were associated with good neurologic outcomes.

Conclusions: The levels of total cholesterol and HDL after ROSC were associated with good neurologic outcomes in patients with OHCA, without considering the effect of other lipid profiles simultaneously.

Keywords: Heart arrest, Prognosis, Lipid profile, Cholesterol, HDL

Introduction

The lipid profiles usually include total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides. The lipid profile is known as a risk factor for atherosclerotic disease such as acute coronary syndrome.[1] Since sudden cardiac death (SCD) accounts for one-half of all coronary heart disease-related deaths, several studies have reported on the association between lipid profile and risk of SCD.[2–4] In a study including 139 out-of-hospital cardiac arrest (OHCA) patients, cholesterol, LDL, and non-HDL levels were lower in the SCD group than in the geographic control group.[2]

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Jouven et al. reported that that high cholesterol level is associated with incidence of SCD.[3]

The association between lipid profiles and various pathologic conditions has also been investigated in several studies.[5–9] Interestingly, in contrast to "the lower, the better" cholesterol hypothesis that has been generally accepted by many health care professionals, low cholesterol level was associated with poor prognosis in cancer,[5] sepsis,[6] and ischemic stroke.[7] Additionally, in large cohort population-based study, high cholesterol level was associated with reduced all-cause mortality.[8] This may be a clue that cholesterol contributes positively to the healing or recovery from pathologic conditions, apart from the characteristics of atherogenicity and contribution of coronary artery disease development. However, the relationship between lipid level and outcomes in OHCA survivors have been investigated only in a few studies.[9]

We hypothesized that dyslipidemia is associated with neurologic outcomes in OHCA survivors. Hence, in the present study, we aimed to investigate the association between serum lipid profiles and neurologic outcome in OHCA survivors. Furthermore, we aimed to examine the prognostic performance of lipid profile for neurologic outcome.

Methods

Study design and population

We performed a retrospective observational study of adult OHCA survivors admitted in Chonnam National University Hospital in Gwangju, Korea, from January 2016 to December 2018. We included OHCA patients aged over 18 years. Patients aged under 18 years, with no return of spontaneous circulation (ROSC) after cardiac arrest, who lacked lipid profile measurements 1 h after ROSC, and with missing data were excluded. The Institutional Review Board of Chonnam National University Hospital approved this study (CNUH-2019-155).

Targeted temperature management

Comatose cardiac arrest survivors underwent targeted temperature management (TTM) in accordance with the guidelines. A target temperature of 33 °C or 36 °C was maintained for 24 h using either feedback-controlled endovascular catheters (Thermoguard, ZOLL Medical Corporation, Chelmsford, MA, USA) or surface cooling devices (Blanketrol® II; Cincinnati Subzero Products, Cincinnati, OH, USA; Artic Sun® Energy Transfer Pads™; Medivance Corp, Louisville, CO, USA). After completion of the maintenance phase in TTM, patients were rewarmed at a rate of 0.25 °C–0.5 °C/h. All patients received continuous intravenous midazolam and remifentanil (or fentanyl). All other aspects of patient management were at the discretion of the treating physicians.

Data collection and primary outcome

We obtained the following data from hospital records: age; sex; pre-existing illness; presence of a witness on collapse; bystander cardiopulmonary resuscitation (CPR); first monitored rhythm; etiology of cardiac arrest; time from collapse to ROSC; hemoglobin; serum lactate; glucose; glycated hemoglobin (HgA1c) after ROSC; CK-MB after ROSC; PaO_2 and $PaCO_2$ after ROSC; Glasgow Coma Scale (GCS) after ROSC; total cholesterol, triglyceride, HDL, and LDL after ROSC; and presence of TTM or coronary angiography.

We assessed discharge neurologic outcomes using the cerebral performance category (CPC) scale recorded as CPC 1 (good performance), CPC 2 (moderate disability), CPC 3 (severe disability), CPC 4 (vegetative state), or CPC 5 (brain death or death).[10] The primary outcome was a good neurologic outcome at discharge, defined as CPCs 1–2.

Statistical analysis

We described categorical variables as frequencies and percentages and continuous variables as median values with interquartile ranges. We compared categorical variables between groups using χ^2 or Fisher's exact tests, as appropriate. We performed a chi-square test with continuity correction in 2×2 tables. We compared continuous variables between groups using the Mann–Whitney *U* test, since all continuous variables showed non-normal distribution. Area under the receiver operating characteristics curve (AUROC) analysis was performed to examine the prognostic performance of total cholesterol, triglyceride, HDL, and LDL for good neurologic outcome. The comparison of dependent ROC curves was performed using the method of DeLong et al.[11] Optimum cut-off values were determined using Youden's index, which was calculated by deducting 1 from sum of sensitivity and specificity. Youden's index indicate the performance at a given cutoff that maximizes sensitivity and specificity.[12] In addition, cut-off values that represent 100% sensitivity were provided to differentiate good neurologic outcome.

Multivariable logistic regression analysis was performed to determine the association between lipid profiles and good neurologic outcome. All variables with p values <0.20 in univariate comparisons were included in the multivariable regression model (Supplemental Table 1). A variable with a variance inflation factor of >10 was considered problematic and was removed from the model. We used a backwards stepwise approach, sequentially eliminating variables with a threshold of $p > 0.10$ to develop a final adjusted regression model. We performed the Box–Tidwell test to verify that the continuous variables met the assumption of linearity. For the non-linear variables, we fitted the logistic model by adding quadratic terms. GCS after ROSC had non-linearity; however, the coefficient for the square of GCS after ROSC was not significant. Therefore, age, cardiac etiology, time from collapse to ROSC, and GCS after ROSC were selected as adjusted variables (Supplemental Table 1). We put one of the lipid profiles into the final model and performed the analysis separately. Lipid profiles were used as continuous variables (model 1) and categorical variables based on the cut-off value provided using Youden's index (model 2) to elucidate the type of association between lipid profiles and neurologic outcome in the different logistic models. Logistic regression analysis results were presented as odds ratio (OR) and 95% confidence interval (CI). All analyses were performed using PASW/SPSS™ software, version 18 (IBM Inc., Chicago, IL, USA) and MedCalc version 19.0 (MedCalc Software, bvba, Ostend, Belgium). A two-sided significance level of 0.05 indicates statistical significance.

Results

Characteristics of patients

A total of 524 OHCA patients were identified during the study period. Of them, 182 met the inclusion criteria as shown in Fig. 1. Supplementary Table 2 shows the results of comparison of characteristics between the excluded and included patients. There were

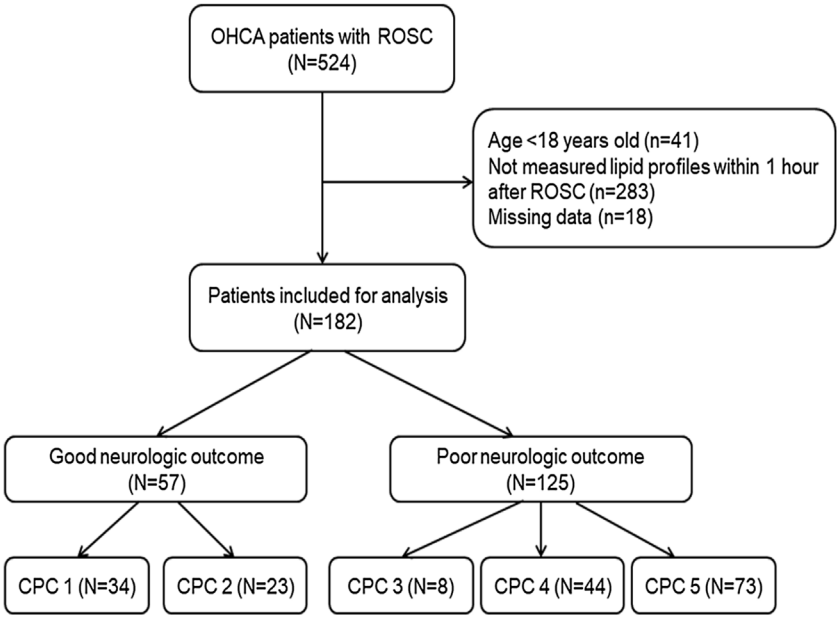

Fig. 1 – OHCA survivors between January 2016 and December 2018.
OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; CPC, cerebral performance category.

significant differences between the included and excluded patients in terms of proportion of witnessed collapse; laboratory findings including the levels of lactate, glucose, and CK-MB; and time from ROSC to blood sampling. There was no significant difference in neurologic outcome between the two groups.

Of 182 patients who met the inclusion criteria, 57 (31.3%) patients showed good neurologic outcome. Baseline characteristics stratified by neurologic outcome are presented in Table 1. Patients with good neurologic outcome were younger and had higher body mass index and lower incidence of pulmonary disease. They had higher incidence of witnessed collapse and receiving bystander CPR, were more likely to have a shockable rhythm and a cardiac etiology, and had a shorter time to ROSC. After achieving ROSC, they had a higher GCS, lower serum lactate, and lower PCO_2 level. Patients with good neurologic outcome had higher levels of total cholesterol, HDL, and LDL than those with poor neurologic outcome.

Prognostic performance of lipid profiles for neurologic outcome

Table 2shows The values of area under the curves (AUC) of lipid profiles in associated with good neurologic outcome. The AUCs of total cholesterol, HDL, LDL, and triglyceride were 0.742 (95% CI, 0.672−0.803; $p < 0.001$), 0.729 (95% CI, 0.658−0.792; $p < 0.001$), 0.683 (95% CI, 0.610−0.750; $p < 0.001$), and 0.572 (95% CI, 0.497−0.645; $p = 0.114$), respectively (Table 2). The AUC of total cholesterol was significantly different from those of LDL and triglyceride, but not those of HDL.

Association between lipid profiles and good neurologic outcome

Table 3 and Supplemental Table 3 show the association between lipid profiles and good neurologic outcome. After adjusting for confounders, total cholesterol (OR, 1.013; 95% CI, 1.000−1.025; $p = 0.043$) and HDL (OR, 1.071; 95% CI, 1.021−1.123; $p = 0.005$) levels were independently associated with good neurologic outcomes. The levels of LDL and triglyceride were not independently associated with neurologic outcomes in the multivariable analyses.

When the levels of lipid profiles were categorized, HDL > 30 mg/dL (OR, 14.29; 95% CI, 2.57−79.61; $p = 0.002$) was independently associated with neurologic outcome.

Discussion

In the present study, we found that the levels of total cholesterol and HDL after ROSC were associated with good neurologic outcomes at discharge in OHCA patients. In addition, the HDL level yielded fair performance in association with good neurologic outcomes.

HDL is well known as a "good" lipid and extensively investigated in several diseases and clinical conditions.[13] It reduces inflammatory cytokine production such as tumor necrosis factor and neutralizing endotoxin toxicity in lipopolysaccharide-induced experimental models.[14] Moreover, HDL has the ability to inactivate oxidized lipids, downregulate adhesion molecule expression, increase nitric oxide production, and inhibit NADPH oxidase activity.[15] Thus, in OHCA, where fulminant inflammation and DIC conditions are hallmarks of pathophysiology, HDL can attenuate adverse inflammatory reaction triggered by ischemia/reperfusion injuries. Recently, Son et al. demonstrated that HDL is associated with neurologic outcome in OHCA patients, which is also reported in the present study.[9] In this study, HDL level was 43.7 (39.4−47.9) mg/dL in total patients and 56.7 (49.2−64.2) mg/dL in favorable group, which were higher than those reported in the present study.[9] One possible cause of this difference may be demographic differences such as age and sex distribution between the two studies. HDL levels decreased with age and were lower in men than in women.[16,17] The present study included older

Table 1 – Baseline characteristics of patients stratified according to neurologic outcome at discharge.

	Total (n = 182)	Good (n = 57)	Poor (n = 125)	p
Age, years	61.5 (52.0–75.0)	55.5 (50.0–65.0)	66.0 (53.0–76.5)	<0.001
Male, n (%)	134 (73.6)	49 (86.0)	85 (68.0)	0.018
Body mass index, kg m^{-2}	23.4 (21.0–25.7)	24.8 (23.0–25.9)	22.8 (20.3–25.1)	<0.001
Medical history, n (%)				
Coronary artery disease	30 (16.5)	13 (22.8)	17 (13.6)	0.181
Congestive heart failure	20 (11.0)	6 (10.5)	14 (11.2)	1.000
Hypertension	73 (40.1)	18 (31.6)	55 (44.0)	0.155
Diabetes	62 (34.1)	14 (24.6)	48 (38.4)	0.097
Pulmonary disease	14 (7.7)	0 (0.0)	14 (11.2)	0.020
Renal impairment	17 (9.3)	4 (7.0)	13 (10.4)	0.651
Cerebrovascular accident	12 (6.6)	6 (10.5)	6 (4.8)	0.262
Liver cirrhosis	5 (2.7)	1 (1.8)	4 (3.2)	0.949
Malignancy	10 (5.5)	1 (1.8)	9 (7.2)	0.252
Cardiac arrest characteristics				
Witness, n (%),	117 (64.3)	51 (89.5)	66 (52.8)	<0.001
Bystander CPR, n (%)	119 (65.4)	47 (82.5)	72 (57.6)	0.002
Shockable rhythm, n (%)	58 (31.9)	38 (66.7)	20 (16.0)	<0.001
Cardiac etiology, n (%)	99 (54.4)	55 (96.5)	44 (35.2)	<0.001
Time from collapse to ROSC time, min	30.0 (16.0–45.0)	15.0 (10.0–22.5)	40.0 (23.5–52.0)	<0.001
Hospital care				
Therapeutic hypothermia	83 (45.6%)	21 (36.8%)	62 (49.6%)	0.149
Coronary angiography	72 (39.6%)	41 (71.9%)	31 (24.8%)	<0.001
Clinical characteristics after ROSC				
Glasgow Coma Scale	3 (3–5)	7 (5–12)	3 (3–3)	<0.001
Lactate, mmol/L	10.2 (6.8–14.1)	7.7 (5.1–10.4)	11.5 (8.2–14.9)	<0.001
Glucose, mg/dL	267 (193–333)	249 (185–318)	273 (201–337)	0.275
PaO_2, mmHg	125.5 (88.0–206.8)	120.0 (81.5–199.0)	129.0 (92.0–214.0)	0.424
$PaCO_2$, mmHg	45.0 (36.0–57.3)	41.0 (35.5–46.0)	51.0 (36.5–63.0)	<0.001
CK-MB, ng/mL	4.37 (2.32–11.59)	3.86 (2.11–7.52)	4.81 (2.35–12.56)	0.218
HgA1c, %	5.7 (5.4–6.7), 179[a]	5.7 (5.4–6.1)	5.8 (5.4–7.1), 122[a]	0.289
Total cholesterol, mg/dL	139.5 (108.0–179.5)	178.0 (136.0–209.0)	123.0 (101.5–157.5)	<0.001
HDL, mg/dL	35.0 (26.8–46.0)	44.0 (34.5–50.5)	31.0 (25.0–42.0)	<0.001
LDL, mg/dL	80.0 (59.0–112.0)	104.0 (71.0–125.0)	75.0 (55.5–96.0)	<0.001
Triglyceride, mg/dL	127.0 (85.8–208.0)	142.0 (94.0–229.5)	122.0 (83.5–188.5)	0.119

CPR, cardiopulmonary resuscitation; ROSC, restoration of spontaneous circulation; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a] Number of patients included in the analysis.

Table 2 – Prognostic performance of lipid profiles in association with good neurologic outcome.

	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
Total cholesterol, mg/dL	>148 (n = 80)	71.9 (58.5–83.0)	68.8 (59.9–76.8)	51.2 (43.6–58.8)	84.3 (77.7–89.2)	0.742 (0.672–0.803)
	>58 (n = 174)	100.0 (93.7–100.0)	6.4 (2.8–12.2)	32.8 (31.8–33.8)	100.0 (100.0–100.0)	
HDL, mg/dL	>30 (n = 114)	89.5 (78.5–96.0)	49.6 (40.5–58.7)	44.7 (40.0–49.6)	91.2 (58.5–83.0)	0.729 (0.658–0.792)
	>24 (n = 154)	100.0 (93.7–100.0)	22.4 (15.4–30.7)	37.0 (34.8–39.2)	100.0 (100.0–100.0)	
LDL, mg/dL	>94 (n = 68)	63.2 (49.3–75.6)	74.4 (65.8–81.8)	52.9 (44.0–61.7)	81.6 (75.6–86.3)	0.683 (0.610–0.750)
	>19 (n = 175)	100.0 (93.7–100.0)	5.6 (2.3–11.2)	32.6 (31.6–33.5)	100.0 (100.0–100.0)	
Triglyceride, mg/dL	>161 (n = 64)	47.4 (34.0–61.0)	70.4 (61.6–78.2)	42.2 (33.2–51.7)	74.6 (69.1–79.4)	0.572 (0.497–0.645)
	>57 (n = 170)	100.0 (93.7–100.0)	9.6 (5.1–16.2)	33.5 (32.3–34.8)	100.0 (100.0–100.0)	

PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

patients, and the good CPC group were mostly men. In patients with cardiovascular disease, the recommended HDL level was >40 mg/dL,[13] and HDL level below 40 mg/dL was associated with major adverse cardiac events including cardiac and all-cause mortalities.[18] However, in the present study, the cut-off value of HDL was 30 mg/dL, which was somewhat different. Thus, further study is warranted to determine whether the outcome of OHCA patients will improve by increasing the HDL levels.

Cholesterol is an essential component of cell membrane and vascular structure.[19] One large prospective cohort study showed that total cholesterol level <160 mg/dL was associated with mortality in patients with cardiovascular disease.[20] Another large cohort study reported that hospitalized patients who had cholesterol level <100 mg/dL had tenfold higher mortality than the average of all hospital patients.[21] In contrast to "the lower, the better" cholesterol hypothesis, low cholesterol concentration in

Table 3 – Multivariable logistic regression analysis in association with good neurologic outcome.

	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)[a]	p
Total cholesterol, mg/dL	1.018 (1.011–1.026)	<0.001	1.013 (1.000–1.025)	0.043
HDL, mg/dL	1.051 (1.026–1.076)	<0.001	1.071 (1.021–1.123)	0.005
LDL, mg/dL	1.016 (1.008–1.025)	<0.001	1.010 (0.994–1.027)	0.219
Triglyceride, mg/dL	1.000 (0.999–1.001)	0.899	1.001 (0.998–1.005)	0.553
Total cholesterol >148 mg/dL (n = 80)	5.06 (2.55–10.06)	<0.001	3.04 (0.92–10.04)	0.068
HDL > 30 mg/dL (n = 114)	9.30 (3.48–24.84)	<0.001	14.29 (2.57–79.61)	0.002
LDL >94 mg/dL (n = 68)	4.78 (2.45–9.33)	<0.001	3.00 (0.91–9.87)	0.070
Triglyceride >161 mg/dL (n = 64)	2.06 (1.08–3.93)	0.028	1.20 (0.38–3.80)	0.762

Each lipid profile was individually entered into the final model and analyzed separately. Each lipid profile was not adjusted for other lipid profiles.
OR, odds ratio; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a] Adjusted for age, cardiac etiology, time from collapse to return of spontaneous circulation (ROSC), and Glasgow Coma Scale after ROSC.

critically ill patients can be detrimental. We presumed that total cholesterol has several protective properties against ischemic/reperfusion injury and inflammatory condition. In ischemic/reperfusion condition such as post cardiac arrest that produces enormous free radicals, cholesterol attenuates the toxicity of free radicals through oxidation.[23] Several animal studies showed that cholesterol increases tolerance to anoxia and retards the effect of oxidative stress.[23,24] Moreover, in human studies, the low serum cholesterol level group showed decreased total serum antioxidant activity compared with the high cholesterol group.[25] Thus, cholesterol might have an antioxidant property that can protect patients against the damages induced by ischemic and reperfusion injury after ROSC.

Lipid level can be a secondary manifestation of pre-arrest clinical conditions. Several studies reported that low cholesterol level might be associated with predisposing catabolic comorbidity.[5–7] However, cardiac arrest can affect the cholesterol level. In an animal study using a canine CPR model, total cholesterol levels were significantly decreased 10 min after ROSC compared with the pre-arrest baseline level.[26] In another previous study, the group of patients with post-cardiac arrest syndrome had significantly lower total cholesterol level than the normal control group.[2] The level of cholesterol is inversely proportional to the concentration of proinflammatory cytokines.[27] This suggests that cholesterol level in post-cardiac arrest patients may indicate the degree of endotoxemia or inflammation caused by ischemic and reperfusion injury.

In the present study, triglyceride level was not associated with neurologic outcome in OHCA patients. A previous study showed that patients with high triglyceride levels had higher risk of death due to coronary artery disease, stroke, and resuscitation after cardiac arrest than those with acute coronary syndrome who achieved normal triglyceride levels after treatment with statin.[28] However, other studies showed that there was no significant difference in triglyceride levels between patients with SCD and those who survived, which is consistent with the findings of the present study.[3,4] Thus, the relationship between cardiac arrest and triglyceride levels remains controversial and further studies are needed.

High LDL level induced the occurrence of atherosclerosis and was associated with major cardiovascular events such as death from coronary heart disease and stroke.[29,30] However, the association between LDL concentration and prognosis in several diseases remained inconsistent. In a study including middle-aged male individuals, Kunutsor et al. reported that LDL was not associated with the risk of SCD.[31] In a study of intracerebral hemorrhage that could lead to global hypoxic brain injury, low LDL level was associated with 90-day mortality.[32] In the present study, the association between LDL level and neurologic outcome in OHCA survivors was discordant according to the analysis variables. Hence, further prospective studies using a large sample size are needed to elucidate the effect of LDL in OHCA survivors.

This study has several limitations. First, this was a single-center, retrospective study. Thus, to assess generalizability and causation, further multiple center studies with a larger sample size and a prospective design are warranted. Second, the proportion of patients who were eligible for the study (182 of 524) was relatively small (34.7%), and this may cause a significant selection bias. Although witnessed cardiac arrest and laboratory values including glucose, lactate, and CK-MB were different between the included and excluded patients, the other variables were not significantly different (Supplementary Table 2). Differences in laboratory findings between the two groups may be due to the differences in blood sampling time (29 min vs 86 min) after resuscitation. Third, the results of the present study are subject to a favorable bias as they were found to be optimal for the dataset on which the properties are then evaluated. Also, the threshold of HDL value (>30 mg/dL) as a marker for better neurological outcome in present study can result a high proportion of false positive cases. Therefore, the cut-off values of the given lipid profile should not be extrapolated as an optimal reference to clinical management. Fourth, we did not investigate the relationship between the serial change of lipid levels and the prognosis of OHCA patients. Thus, we could not identify whether the lipid level was the result of merely preexisting clinical condition or a subsequent change by cardiac arrest itself. Finally, we were unable to determine if the patients had a history of taking lipid-lowering medications as this might influence the level of lipid profiles. However, in Korea, only 10% of people with hypercholesterolemia were treated with lipid-lowering agents[33]; generally, total cholesterol is not a target of lipid-lowering drugs. Thus, the impact of not receiving medications is likely to be modest.

Conclusion

The serum levels of total cholesterol and HDL within 1 h after ROSC were associated with good neurologic outcomes of patients with OHCA, without considering the effect of other lipid profiles simultaneously.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.10.005.

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