Observational Study

Medicine

OPEN

Serum total cholesterol level as a potential predictive biomarker for neurological outcomes in cardiac arrest survivors who underwent target temperature management

Changjoo Ahn, MD[a], Changshin Kang, MD, PhD[a], Hong Joon Ahn, MD, PhD[a,b,*], Yeonho You, MD, PhD[a], Jung Soo Park, MD, PhD[a,b], Jin Hong Min, MD, PhD[b,c], Wonjoon Jeong, MD, PhD[a], Yongchul Cho, MD[a], Seung Ryu, MD, PhD[a], Yong Nam In, MD, PhD[b,c]

Abstract

Cholesterol is an essential substance to maintain cell membranes. Low levels of total cholesterol (TC) are associated with poor prognosis in critically ill patients. Cardiac arrest-induced whole-body ischemia and reperfusion injury cause a *sepsis-like* syndrome. The Cholesterol level in post-cardiac arrest patients may indicate the degree of endotoxemia or inflammation caused by ischemic and reperfusion injury. We aimed to investigate the association of TC levels with neurologic outcome of out-of-hospital cardiac arrest (OHCA) survivors who underwent target temperature management (TTM). This was a retrospective single-center observational study from May 2018 to April 2021 on a cohort of 106 patients. TC levels were determined in samples obtained immediately and at 24, 48, and 72 hours after the return of spontaneous circulation (ROSC). The primary outcome was poor neurologic outcome at 3 months after ROSC. Poor neurologic outcome was defined by cerebral performance categories 3 to 5. Sixty patients had a poor neurologic outcome. TC levels were significantly lower in the poor neurologic outcome group at each time point. The TC levels for predicting poor neurologic outcome had a sensitivity of 80.8%, with 67.6% specificity at 48 hours (TC_{48}) after ROSC. The areas under the curve value of TC_{48} was 0.771 (0.670–0.853), with a cutoff value of 114 mg/dL. TC level at 48 hours after ROSC was a helpful marker for the 3-month poor neurologic outcome. This might be an easily accessible predictive marker of neurologic outcome in OHCA survivors treated with TTM.

Abbreviations: AUROC = area under the ROC curve, CI = confidence interval, CPC = cerebral performance category, CPR = cardiopulmonary resuscitation, IL-6 = interleukin-6, NSE = neuron-specific enolase, OHCA = out-of-hospital cardiac arrest, PCAS = post-cardiac arrest syndrome, ROC = receiver operating characteristic, ROSC = return of spontaneous circulation, TC = total cholesterol, TTM = target temperature management.

Keywords: cholesterol, heart arrest, post-cardiac arrest syndrome

1. Introduction

During cardiac arrest, whole-body ischemia occurs followed by reperfusion injury after the return of spontaneous circulation (ROSC).[1,2] Cardiac arrest-induced whole-body ischemia and reperfusion injury cause a *sepsis-like* syndrome.[3,4] This ongoing ischemia-reperfusion injury persists for days with the formation of free radical species, systemic inflammation with cytokine production, disseminated endothelial damage, and apoptosis, leading to multi-systemic organ damage defined as post-cardiac arrest syndrome (PCAS).[1,2]

Cholesterol is an essential substance that maintains the structural integrity and fluidity of cell membranes.[5] Cholesterol may play an important role in combating systemic inflammation in critically ill patients. Approximately 90% of circulating cholesterol is incorporated into lipoproteins, such as high-density lipoprotein and low-density lipoprotein. Lipoproteins can neutralize and remove bacterial toxins and endotoxins.[6–8] They also exhibit anti-inflammatory properties.[8,9] The association between lipid profiles and various pathological conditions has also been investigated in several

CA and CK contributed equally to this work.

This work was supported by research fund of Chungnam National University Hospital.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

[a] Department of Emergency Medicine, Chungnam National University Hospital, Jung-gu, Daejeon, Republic of Korea, [b] Department of Emergency Medicine, College of Medicine, Chungnam National University School of Medicine, Jung-gu, Daejeon, Republic of Korea, [c] Department of Emergency Medicine, Chungnam National University Sejong Hospital, Sejong, Republic of Korea.

**Correspondence: Hong Joon Ahn, Department of Emergency Medicine, Chungnam National University Hospital, 282, Munhwa-ro, Jung-gu, Daejeon, Republic of Korea (e-mail: jooniahn@daum.net).*

How to cite this article: Ahn C, Kang C, Ahn HJ, You Y, Park JS, Min JH, Jeong W, Cho Y, Ryu S, In YN. Serum total cholesterol level as a potential predictive biomarker for neurological outcomes in cardiac arrest survivors who underwent target temperature management. Medicine 2022;101:46(e31909).

Received: 2 November 2021 / Received in final form: 28 October 2022 / Accepted: 28 October 2022

http://dx.doi.org/10.1097/MD.0000000000031909

studies. Low cholesterol levels have been associated with a poor prognosis in cancer, sepsis, and ischemic stroke.[10–13] Additionally, in a large cohort population-based study, high cholesterol levels were associated with reduced all-cause mortality.[14]

We hypothesized that *sepsis-like* syndrome after cardiac arrest would differentially affect total cholesterol (TC) levels based on neurological outcomes; thus, TC could be used as a prognostic tool for cardiac arrest survivors. Hence, we aimed to investigate the association between serum TC level and neurological outcomes in out-of-hospital cardiac arrest (OHCA) survivors who underwent target temperature management (TTM).

2. Materials and methods

This study was approved by the Institutional Review Board of Chungnam National University Hospital (CNUH IRB-2017-10-027). Approval and consent from the patients' next of kin were obtained before enrollment.

2.1. Study design and population

This was a retrospective single-center observational study of adult comatose OHCA survivors treated with TTM at a tertiary academic hospital (a 1365-bed tertiary care referral center in Daejeon, Korea) from May 2018 to April 2021. The inclusion criterion comprised OHCA patients aged ≥ 18 years who had been treated using TTM. The exclusion criteria for this study were as follows: age < 18 years, traumatic cardiac arrest or interrupted TTM (due to hemodynamic instability), not eligible for TTM (i.e., intracranial hemorrhage, active bleeding, known terminal illness, or poor pre-arrest neurological status), apparent previous brain parenchymal disease, extracorporeal membrane oxygenation, or further treatment refusal by the next of kin.

2.2. The TTM protocol

TTM was performed using cooling devices (Arctic Sun ® Energy Transfer Pads TM, Medivance Corp., Louisville). The target temperature of 33°C was maintained for 24 hours with rewarming to 37°C at a rate of 0.25°C/h and was monitored using an esophageal and bladder temperature probe. ADMS™ (Anaesthetic Depth Monitor for Sedation, Unimedics Co., Ltd., Seoul, Korea) was used to monitor the anesthesia depth. Midazolam (0.05 mg/kg intravenous bolus, followed by a titrated intravenous continuous infusion at a dose between 0.05 and 0.2 mg/kg/h) and cisatracurium (0.15 mg/kg intravenous bolus, followed by an infusion of up to 0.3 mg/kg/h) were administered for sedation and control of shivering. All other aspects of patient management involved standard intensive care, in accordance with our institutional intensive care unit protocol.

2.3. Data collection and measurement

We collected the following data: age, sex, presence of a witness on collapse, bystander cardiopulmonary resuscitation (CPR), first monitored rhythm, etiology of cardiac arrest, time from collapse to CPR (no-flow time), time from CPR to ROSC (low-flow time), mean arterial pressure, partial pressure of oxygen, partial pressure of carbon dioxide, sequential organ failure assessment, weight-based mean norepinephrine dose, TC, serum interleukin-6 (IL-6), and serum neuron-specific enolase (NSE) levels. Neurological outcomes were assessed using the Glasgow-Pittsburgh cerebral performance category (CPC) scale. A CPC of 1 to 2 demonstrated good neurological outcomes, while a CPC of 3 to 5 was related to poor neurological outcomes.

2.4. Obtaining serum samples

We obtained samples for measuring TC (normal value 125–220 mg/dL) and IL-6 (normal value ≤ 7.0 pg/mL) via venipuncture. We obtained the samples (TC_0 and IL-6_0) immediately after ROSC and at 24 hours (TC_{24}, IL-6_{24}), 48 hours (TC_{48}, IL-6_{48}), and 72 hours (TC_{72}, IL-6_{72}) after ROSC, and defined the *immediate* time point as the time of first blood draw after ROSC.

2.5. Statistical analyses

We presented categorical variables as frequencies and percentages. We compared categorical variables using Chi-squared or Fisher's exact tests as appropriate and presented continuous variables as median values with interquartile range values or means and standard deviations. We conducted the Mann–Whitney test to compare serum TC and IL-6 levels among neurological outcome groups. For each time point, we plotted the receiver operating characteristic (ROC) curves and determined the corresponding areas under the curve (AUCs) to evaluate the predictive performance of TC and IL-6 levels in the poor neurological outcome group. We determined an optimal cutoff value for predicting poor neurological outcome by 3 months post-OHCA using the maximal Youden index (sensitivity + specificity - 1). Subsequently, we used the Delong test to determine the differences in prognostic performance between poor neurological outcomes and each of the time points.[15] We performed statistical analyses using SPSS software, version 18 (SPSS Inc., Chicago, IL) and calculated ROC curves using MedCalc version 15.2.2 (MedCalc Software, Mariakerke, Belgium). Statistical significance was set at $P < .05$.

3. Results

3.1. Patient characteristics

ROSC was achieved in 118 post-OHCA patients, of which 106 were enrolled in the study. The poor neurological outcome groups consisted of 60 (56.6 %) patients, 3 months after ROSC (Fig. 1). The demographic and clinical characteristics stratified by neurological outcomes are shown in Table 1. Survivors with good neurological outcomes had a higher incidence of witnessed arrest and bystander CPR and were more likely to have a shockable rhythm and cardiac etiology. Moreover, they had shorter no- and low-flow times, higher mean arterial pressures with lower weight-based mean norepinephrine doses, lower sequential organ failure assessment scores, and lower serum NSE levels than patients with poor neurological outcomes.

3.2. Comparison of serum TC and IL-6 levels between the good and poor neurological outcome groups

The TC levels were significantly lower, and IL-6 levels were higher at all times in the poor neurological outcome group than in the good neurological outcome group (Table 2).

3.3. Prognostic performance of serum TC and IL-6

The capacity of TC and IL-6 to predict poor neurological outcomes (CPC 3–5) was determined using ROC analysis. The AUC value of TC_{48} (area under the response operator characteristic [AUROC]: 0.771 [95% confidence interval [CI]: 0.670–0.853]) was the highest among those of TC (Fig. 2). The TC levels for predicting poor neurological outcomes had a sensitivity of 67.6%, with 80.8% specificity at TC_{48}. The cutoff value was 114 mg/dL. The IL-6 levels for predicting poor neurological outcomes had a sensitivity of 52.3.0%, with 94.3% specificity at IL-6_0. The cutoff value was 733.2 pg/mL (AUROC: 0.747 [95% CI: 0.637–0.838]) (Table 3).

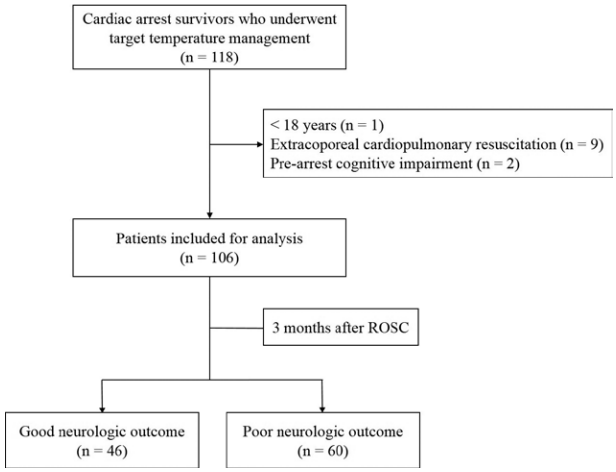

Figure 1. Schematic flow diagram of patients included in the study. ROSC = return of spontaneous circulation.

4. Discussion

In this retrospective observational study, we investigated the association between serum TC level and neurological outcomes in OHCA survivors who underwent TTM and found that the TC levels at 48 hours after ROSC were significantly different between the poor and good neurological outcome groups. Furthermore, TC showed a reasonable prognostic performance 48 hours after ROSC.

Cholesterol and lipoproteins play critical roles during systemic inflammation in various critical situations.[13] These are involved in the removal of endotoxins by binding to lipopolysaccharide and lipoteichoic acid to neutralize the inflammatory process, leading to monocyte and cytokine reduction.[9,13,16] Windler E. et al[17] reported that hospitalized patients who had cholesterol levels < 100 mg/dL had tenfold higher mortality than the average of all hospital patients. The degree of endotoxemia is associated with increased severity scores and haemodynamic instability.[4] γ-Glutamyltransferase plays a role in amino acids uptake and transport, and high cholesterol levels result in increased γ-glutamyltransferase activity. Therefore high serum cholesterol level may reduce the neurotoxic effects of excitotoxic amino acids in ischemia-reperfusion injury.[18] And several animal studies have shown that cholesterol attenuates the toxicity of free radicals through oxidation and increases tolerance to anoxia and oxidative stress.[19–21] Moreover, Muldoon M. F. et al[22] reported that the low serum cholesterol level group showed

Table 1

Baseline demographics and clinical characteristics.

Characteristics	Cohort (N = 106)	Good outcome (N = 46)	Poor outcome (N = 60)	*P*
Demographic characteristics				
Age, yrs	57.0.0 (40.8–70.0)	57.0 (38.8–68.3)	57.5 (41.3–71.5)	.686
Sex, male, N (%)	77 (72.6)	36 (78.3)	41 (68.3)	.180
Cardiac arrest characteristics				
Witness arrest, N (%)	71 (67.0)	37 (80.4)	34 (56.7)	.008*
Bystander CPR, N (%)	76 (71.7)	39 (84.8)	37 (61.7)	.010*
Shockable rhythm, N (%)	27 (25.4)	23 (50.0)	4 (6.7)	<.001*
Cardiac etiology, N (%)	38 (35.8)	26 (56.5)	12 (20.0)	<.001*
No flow time, min, median (IQR)	2.0 (0.0–13.0)	0.5 (0.0–4.8)	5.0 (0.0–23.0)	.001*
Low flow time, min, median (IQR)	20.0 (9.5–31.0)	10.0 (8.0–19.0)	28.5 (19.0–43.0)	<.001*
Clinical characteristics, median (IQR)				
MAP (mm Hg)	90.0 (74.0–106.3)	98.5 (81.5–110.5)	85.5 (71.0–102.0)	.032*
PaO_2 (mm Hg)	140.5 (91.5–237.0)	146.5 (81.8–237.5)	137.0 (96.0–238.8)	.936
$PaCO_2$ (mm Hg)	38.2 (35.7–41.4)	39.0 (36.2–41.9)	38.2 (34.9–41.1)	.075
SOFA score	10.0 (8.0–12.0)	8.0 (6.8–10.3)	10.5 (9.0–12.0)	.002*
Norepinephrine (μg/kg/min)	0.0570 (0.0–0.3)	0.02 (0.0–0.1)	0.1 (0.04–0.36)	<.001*
$S\text{-}NSE_{48}$ (ng/mL)	34.6 (20.4–121.3)	22.4 (14.7–24.9)	100.6 (50.9–294.7)	<.001*
$S\text{-}NSE_{72}$ (ng/mL)	35.3 (17.3–165.0)	18.3 (13.7–27.1)	122.0 (37.4–274.3)	<.001*

CPR = cardiopulmonary resuscitation, IQR = interquartile range, MAP = mean arterial pressure, PaO_2 = partial pressure of oxygen, $PaCO_2$ = partial pressure of carbon dioxide, serum neuron-specific enolase at 48 h after return of spontaneous circulation = $S\text{-}NSEO_{72}$, serum neuron-specific enolase at 72 h after return of spontaneous circulation, SOFA = sequential organ failure assessment; $S\text{-}NSE_{48}$.
**P* values are significant at $P < .05$.

Table 2

Comparison of TC and IL-6 levels between the neurologic outcome groups.

Sample	Time	Cohort (N = 106)	Good outcome (N = 46)	Poor outcome (N = 60)	*P*
TC (mg/dL)	TC_0	146.0 (114.0–177.3)	157.5 (130.3–183.8)	139.0 (110.0–170.5)	.005*
	TC_{24}	121.0 (95.5–157.5)	146.5 (119.3–165.5)	108.0 (82.0–130.5)	<.001*
	TC_{48}	109.0 (83.0–133.5)	130.0 (106.0–147.3)	95.0 (71.5–111.0)	<.001*
	TC_{72}	110.0 (84.5–131.0)	128.5 (104.8–136.8)	97 (77.0–119.0)	<.001*
IL-6 (pg/mL)	$IL\text{-}6_0$	346.7 (70.2–1750.0)	126.0 (57.3–386.2)	854.7 (117.5–5000.0)	<.001*
	$IL\text{-}6_{24}$	71.1 (26.1–847.0)	49.0 (17.2–142.3)	243.3 (37.9–1941.8)	.003*
	$IL\text{-}6_{48}$	77.2 (26.6–851.7)	59.9 (18.0–291.8)	117.9 (43.9–1215.3)	.032*
	$IL\text{-}6_{72}$	75.1 (20.5–99.6)	36.9 (15.5–352.3)	175.7 (42.1–874.1)	.010*

Continuous variables are expressed as median (interquartile range). TC and IL-6 levels were immediately (TC0, IL-60), and at 24 h (TC24, IL-624), 48 h (TC48, IL-648), and 72 h (TC72, IL-672) after return of spontaneous circulation.
IL-6 = interleukin-6, TC = total cholesterol.
**P* values are significant at $P < .05$.

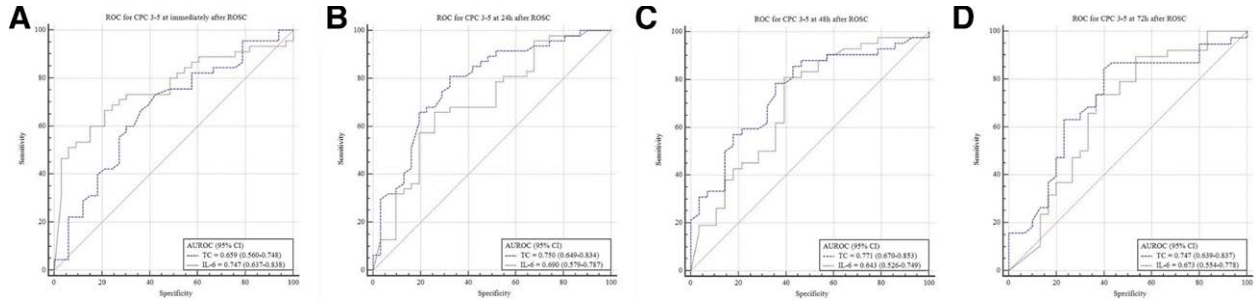

Figure 2. AUROC curves for predicting poor neurological outcomes 3 months after ROSC between TC and IL-6. a: ROC curve for TC & IL-6 values immediately after ROSC. Delong test for comparison of TC and IL-6 levels. The ROC curve difference in area (95% CI) for TC_0 vs $IL\text{-}6_0$ was 0.071 (–0.075 to 0.217), $P = .339$. b: ROC curve for TC & IL-6 values at 24 h after ROSC. Delong test for comparison of TC and IL-6 levels. The ROC curve difference in area (95% CI) for TC_{24} vs $IL\text{-}6_{24}$ was 0.015 (–0.115 to 0.145), $P = .823$. c: ROC curve for TC & IL-6 values at 48 h after ROSC. Delong test for comparison of TC and IL-6 levels. The ROC curve difference in area (95% CI) for TC_{48} vs $IL\text{-}6_{48}$ was 0.086 (–0.056 to 0.227), $P = .236$. d: ROC curve for TC & IL-6 values at 72 h after ROSC. Delong test for comparison of TC and IL-6 levels. The ROC curve difference in area (95% CI) for TC_{72} vs $IL\text{-}6_{72}$ was 0.050 (–0.123 to 0.223), $P = .574$. AUROC = area under the response operator characteristic, IL-6 = interleukin-6, ROC = receiver operating characteristic, ROSC = return of spontaneous circulation, TC = total cholesterol.

Table 3

Association of TC and IL-6 levels with poor neurological outcome.

Sample	Time	AUROC (95% CI)	*P* value	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV/NPV
TC	TC_0	0.659 (0.560–0.748)	.003*	152 (mg/dL)	70.0 (56.8–81.2)	60.9 (45.4–74.9)	70.0/60.9
	TC_{24}	0.750 (0.649–0.834)	<.001*	114 (mg/dL)	61.5 (47.0–74.7)	82.9 (67.9–92.8)	82.1/63.0
	TC_{48}	0.771 (0.670–0.853)	<.001*	114 (mg/dL)	80.8 (67.5–90.4)	67.6 (50.2–82.0)	77.8/71.4
	TC_{72}	0.747 (0.639–0.837)	<.001*	109 (mg/dL)	68.9 (53.4–81.8)	75.7 (58.8–88.2)	77.5/66.7
IL-6	$IL\text{-}6_0$	0.747 (0.637–0.838)	<.001*	733.2 (pg/mL)	52.3 (36.7–67.5)	94.3 (80.8–99.3)	92.0/61.1
	$IL\text{-}6_{24}$	0.690 (0.579–0.787)	.002*	162.6 (pg/mL)	58.3 (43.2–72.4)	80.0 (63.1–91.6)	80.0/58.3
	$IL\text{-}6_{48}$	0.643 (0.526–0.749)	.029*	35.2 (pg/mL)	81.8 (67.3–91.8)	48.5 (30.8–66.5)	67.9/66.7
	$IL\text{-}6_{72}$	0.673 (0.554–0.778)	.008*	52.1 (pg/mL)	74.4 (57.9–87.0)	62.9 (44.9–78.5)	69.0/68.7

TC and IL-6 levels were immediately (TC0, IL-60), and at 24 h (TC24, IL-624), 48 h (TC48, IL-648), and 72 h (TC72, IL-672) after return of spontaneous circulation.

AUROC = area under the receiver-operating characteristic curve, CI = confidence interval, IL-6 = interleukin-6, NPV = negative predictive value, PPV = positive predictive value, TC = total cholesterol.

*P values are significant at $P < .05$.

decreased total serum antioxidant activity compared with the high cholesterol level group.

Inflammatory reactions to acute ischemic injuries are mediated by cytokines that increase in the central nervous system and systemic circulation.[23,24] Banks WA et al[25] reported that the penetration of IL-6 from cerebrospinal fluid into serum may occur as a result of BBB disruption or by an active transport mechanism when the blood brain barrier. Increased serum IL-6 levels have been observed in patients with neurological disorders (Alzheimer's disease, Parkinson's disease, brain tumor, and multiple sclerosis), brain injury, and stroke.[26–28] Cardiac arrest-induced whole-body ischemia and reperfusion injury produce systemic inflammation with an increase in IL-6 and endotoxemia.[3,4] In a canine CPR model study, TC levels were significantly decreased 10 min after ROSC compared with the pre-arrest baseline level.[29] In another study, the group of patients with PCAS had significantly lower TC levels than those in the control group.[30] Cholesterol levels are inversely proportional to the concentration of proinflammatory cytokines.[31] In the present study, the TC level was inversely proportional to the concentration of IL-6, according to the poor and good neurological outcome groups, 3 months after ROSC. This suggests that the cholesterol level in post-cardiac arrest patients may indicate the degree of endotoxemia or inflammation caused by ischemic and reperfusion injury.[32] Lipoprotein consumption from neutralizing abundant endotoxins can occur, and cholesterol levels can be decreased by the severity of inflammation after cardiac arrest.[4,13] Previous studies have investigated the relationship between initial TC levels and neurological outcomes in OHCA patients. In one study with 200 PCAS patients, initial serum levels of TC after ROSC were significantly higher in patients with a good neurological outcome (170 [121.5–193] mg/dL vs 128 (102–153) mg/dL, $P < .01$). The AUC for prognosis prediction of good neurological outcome using initial TC was 0.69 (95% CI: 0.61–0.77).[30] Another study on lipid profiles in PCAS patients by Lee et al[32] investigated the association between initial lipid profiles after ROSC and the neurological outcome in OHCA survivors. They reported that the AUC of initial TC after ROSC was 0.742 (95% CI: 0.672–0.803) with 71.9% (95% CI: 58.5–83.0) sensitivity and 68.8% (95% CI: 59.9–76.8) specificity for predicting good neurological outcome. In the present study, serial serum TC levels were obtained, showing that TC levels measured at all times were higher with good neurological outcomes.

In 2021, the European Resuscitation Council recommends the use of multimodal prognostication rather than a single modality for the prediction of poor neurological outcomes; NSE is the only blood biomarker included in the guidelines for the prediction of poor neurological outcomes (NSE > 60 μg/L at 48 h and/or 72 h).[33] In this study, the AUC of TC_{48} for prognosis prediction at 48 hours after ROSC was 0.771, with 80.8% (95% CI: 67.5–90.4) sensitivity and 67.6% (95% CI: 50.2–82.0) specificity with respect to poor neurological outcome. The AUC of TC_{48} for predicting poor neurological outcomes showed reasonable prognostic performance. Therefore, it may not be appropriate to use TC level as a single modality to assess the prognosis of post-cardiac arrest survivors. TC level is an easy, quick, and inexpensive measurable biomarker, but NSE analysis has limited availability in routine laboratories. Thus, TC may be included in multimodal prognostication methods used for the prediction of neurological outcomes in cardiac arrest survivors.

This study has some limitations. First, this was a single-center, retrospective study, which limits its generalizability to other hospitals. Second, the self-fulfilling prophecy of a poor neurological outcome could not be excluded because the results of TC levels were available to the physicians participating in the study. Third, 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 are treated with lipid-lowering agents[34]; generally, TC is not a target of lipid-lowering drugs. Thus, the impact of not receiving medication is likely to be modest. Fourth, other lipid profiles (high-density lipoprotein, low-density lipoprotein, and triglycerides) were not measured. Thus, we could not speculate on the changes in these parameters. Multicenter studies are needed in the future to establish the generalisability of these results.

5. Conclusion

This study demonstrated that low TC levels at 48 h after ROSC in cardiac arrest survivors who underwent TTM were associated with poor neurological outcomes. Therefore, the TC level at 48 h after ROSC might be an easily obtainable and useful early predictor of neurologic outcome in cardiac arrest survivors.

Author contributions

Conceptualization: Changjoo Ahn, Changshin Kang, Hong Joon Ahn.
Data curation: Changjoo Ahn, Changshin Kang, Hong Joon Ahn, Yeonho You, Wonjoon Jeong.
Formal analysis: Changjoo Ahn, Changshin Kang, Hong Joon Ahn, Jung Soo Park, Seung Ryu.
Funding acquisition: Hong Joon Ahn.
Writing – original draft: Changjoo Ahn, Changshin Kang, Hong Joon Ahn, Jin Hong Min.
Writing – review & editing: Hong Joon Ahn, Yongchul Cho, Yong Nam In.

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