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

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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)\textsuperscript{[1,2]}. Cardiac arrest-induced whole-body ischemia and reperfusion injury cause a sepsis-like syndrome\textsuperscript{[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)\textsuperscript{[1,2]}.

Cholesterol is an essential substance that maintains the structural integrity and fluidity of cell membranes\textsuperscript{[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\textsuperscript{[6–8]}. They also exhibit anti-inflammatory properties\textsuperscript{[6–8]}. The association between lipid profiles and various pathological conditions has also been investigated in several
studies. Low cholesterol levels have been associated with a poor prognosis in cancer, sepsis, and ischemic stroke.\textsuperscript{10–13} Additionally, in a large cohort population-based study, high cholesterol levels were associated with reduced all-cause mortality.\textsuperscript{14}

We hypothesized that \textit{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 $\geq$ 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 \textsuperscript{\textregistered} 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\textsuperscript{TM} (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 scores, and lower serum NSE levels. 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. 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\%, with 94.3\% specificity at IL-6. The cutoff value was 733.2 pg/mL (AUROC: 0.747 [95\% CI: 0.637–0.838]) (Table 3).
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. 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. Windler E. et al. 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. 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. And several animal studies have shown that cholesterol attenuates the toxicity of free radicals through oxidation and increases tolerance to anoxia and oxidative stress. Moreover, Muldoon M. F. et al. reported that the low serum cholesterol level group showed a higher risk of adverse outcomes compared to patients with normal cholesterol levels.

**Table 1**

| Characteristics                        | Cohort (N = 106) | Good outcome (N = 46) | Poor outcome (N = 60) | P   |
|----------------------------------------|------------------|-----------------------|-----------------------|-----|
| Demographic characteristics           |                  |                       |                       |     |
| Age, yrs                               | 57.0 (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 arrest, 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*|
| PaO2 (mm Hg)                           | 140.5 (91.5–237.0)| 146.5 (118.2–237.5)   | 137.0 (96.0–238.5)    | .936|
| PaCO2 (mm Hg)                          | 38.2 (35.8–41.4) | 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-NSE48 (ng/mL)                        | 34.6 (20.4–121.3)| 22.4 (13.7–27.1)      | 100.6 (50.9–294.7)    | <.001*|
| S-NSE72 (ng/mL)                        | 35.3 (17.3–165.0)| 18.3 (13.7–27.1)      | 122.0 (37.4–274.3)    | <.001*|

**Table 2**

| Sample | Time  | Cohort (N = 106) | Good outcome (N = 46) | Poor outcome (N = 60) | P    |
|--------|-------|------------------|-----------------------|-----------------------|------|
| TC (mg/dL) |       |                  |                       |                       |     |
| TC0    | 146.0 (114.0–177.3) | 157.5 (130.3–183.8) | 139.0 (110.0–170.5)   | .005*|
| TC24   | 121.0 (95.5–157.5)  | 146.5 (119.3–165.5) | 108.0 (82.0–130.5)    | <.001*|
| TC48   | 109.0 (83.0–133.5)  | 130.0 (106.0–147.3) | 95.0 (71.5–111.0)     | <.001*|
| TC72   | 110.0 (84.5–131.0)  | 128.5 (104.8–136.8) | 97 (77.0–119.0)       | <.001*|
| IL-6 (pg/mL) |     |                  |                       |                       |     |
| IL-60  | 346.7 (70.2–1750.0)| 126.0 (57.3–386.2)  | 854.7 (117.5–5000.0)  | <.001*|
| IL-624 | 71.1 (26.1–847.0)   | 49.0 (17.2–142.3)   | 243.3 (37.9–1914.1)   | .003*|
| IL-648 | 77.2 (26.6–851.7)   | 59.9 (18.0–291.8)   | 117.9 (49.9–1215.3)   | .022*|
| IL-672 | 75.1 (20.5–90.6)    | 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), at 24 h (TC24, IL-624), 48 h (TC48, IL-648), and 72 h (TC72, IL-672) after return of spontaneous circulation.

**Table 3**

| Sample | Time  | Cohort (N = 106) | Good outcome (N = 46) | Poor outcome (N = 60) | P    |
|--------|-------|------------------|-----------------------|-----------------------|------|
| TC (mg/dL) |       |                  |                       |                       |     |
| TC0    | 146.0 (114.0–177.3) | 157.5 (130.3–183.8) | 139.0 (110.0–170.5)   | .005*|
| TC24   | 121.0 (95.5–157.5)  | 146.5 (119.3–165.5) | 108.0 (82.0–130.5)    | <.001*|
| TC48   | 109.0 (83.0–133.5)  | 130.0 (106.0–147.3) | 95.0 (71.5–111.0)     | <.001*|
| TC72   | 110.0 (84.5–131.0)  | 128.5 (104.8–136.8) | 97 (77.0–119.0)       | <.001*|
| IL-6 (pg/mL) |     |                  |                       |                       |     |
| IL-60  | 346.7 (70.2–1750.0)| 126.0 (57.3–386.2)  | 854.7 (117.5–5000.0)  | <.001*|
| IL-624 | 71.1 (26.1–847.0)   | 49.0 (17.2–142.3)   | 243.3 (37.9–1914.1)   | .003*|
| IL-648 | 77.2 (26.6–851.7)   | 59.9 (18.0–291.8)   | 117.9 (49.9–1215.3)   | .022*|
| IL-672 | 75.1 (20.5–90.6)    | 36.9 (15.5–352.3)   | 175.7 (42.1–874.1)    | .010*|

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 vs IL-6, was 0.071 (−0.075 to 0.227), *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, vs IL-6, 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, vs IL-6, 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, vs IL-6, 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     | 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    | 0.771 (0.670–0.860) | <.001* | 114 (mg/dL) | 61.5 (47.0–74.7) | 82.9 (67.9–92.8) | 82.1/63.0 |
| TC    | 0.747 (0.639–0.847) | <.001* | 109 (mg/dL) | 80.8 (67.5–90.4) | 77.8 (60.2–82.0) | 77.8/71.4 |
| IL-6  | 0.745 (0.650–0.841) | <.001* | 733.2 (pg/mL) | 52.3 (36.7–67.5) | 94.3 (80.8–99.3) | 92.0/61.1 |
| IL-6  | 0.690 (0.579–0.878) | .029* | 80.5 (mg/dL) | 43.2 (72.4) | 80.0 (63.1–91.6) | 80.0/58.3 |
| IL-6  | 0.643 (0.526–0.740) | .029* | 35.2 (pg/mL) | 81.8 (67.3–91.8) | 48.5 (30.8–66.5) | 67.9/66.7 |
| IL-6  | 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 |

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.

Values are significant at *P < .05.

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.

A 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. Banks WA et al 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 systemic circulation. Banks WA et al 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)[13]. In this study, the AUC of TC48 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 TC48 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 generalizability 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.

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References
[1] Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Stroke. Resuscitation. 2008;79:75–97.
[2] Mongardon N, Dumas F, Ricome S, et al. Post-cardiac arrest syndrome: from immediate resuscitation to long-term outcome. Ann Intensive Care. 2011;1:45.
[3] Adrie C, Laurent I, Monchi M, et al. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome. Curr Open Crit Care. 2004;10:208–12.
[4] Adrie C, Adib-Conquy M, Laurent I, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a “sepsis-like” syndrome. Circulation. 2002;106:562–8.
[5] Cox RA, Garcia-Palmeri MR. Cholesterol, triglycerides, and associated lipoproteins. In: Clinical methods: the history, physical, and laboratory examinations. 3rd ed. Boston: Butterworths; 1990:153–60.
[6] Girstea M, Walley KR, Russell JA, et al. Decreased high-density lipoprotein cholesterol level is an early prognostic marker for organ dysfunction and death in patients with suspected sepsis. J Crit Care. 2017;38:289–94.
[7] Nagase M, Sakurai A, Sugita A, et al. Oxidative stress and abnormal cholesterol metabolism in patients with post-cardiac arrest syndrome. J Clin Biochem Nutr. 2017;61:108–17.
[8] Lekkou A, Mouzaki A, Siagris D, et al. Serum lipid profile, cytokine production, and clinical outcome in patients with severe sepsis. J Crit Care. 2014;29:723–7.
[9] Guirgis FW, Donnelly JP, Dodani S, et al. Cholesterol levels and long-term rates of community acquired sepsis. Crit Care. 2016;20:408.
[10] Kitahara CM, Berrington de González A, Freedman ND, et al. Total cholesterol and cancer risk in a large prospective study in Korea. J Clin Oncol. 2011;29:1592–8.
[11] Yamanouchi S, Shimizu K, Ogura H, et al. Low total cholesterol and high total bilirubin are associated with prognosis in patients with prolonged sepsis. J Crit Care. 2016;31:36–40.
[12] Zhao W, An Z, Hong Y, et al. Low total cholesterol level is the independent predictor of poor outcomes in patients with acute ischemic stroke: a hospital-based prospective study. BMC Neurol. 2016;16:36.
[13] Son YS, Kim KS, Sul GJ, et al. Admission levels of high-density lipoprotein and apolipoprotein A-1 are associated with the neurologic outcome in patients with out-of-hospital cardiac arrest. Clin Exp Emerg Med. 2017;4:232–7.
[14] Liang Y, Vetrano DL, Qu C. Serum total cholesterol and risk of cardiovascular and non-cardiovascular mortality in old age: a population-based study. BMC Geriatr. 2017;17:294.
[15] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837–45.
[16] Berbee JP, Havekes LM, Rensen PC. Apolipoproteins modulate the inflammatory response to lipopolysaccharide. J Endotoxin Res. 2005;11:97–103.
[17] Windler E, Ewers-Grabov U, Thiery J, et al. The prognostic value of hypocholesterolemia in hospitalised patients. Clin Invest. 1994;92:839–43.
[18] Eryurek FG, Surmen E, Oner P, et al. Gamma-glutamyl transpeptidase and acetylcholinesterase activities in brain capillaries of cholesterol-fed rabbits. Res Commun Chem Pathol Pharmacol. 1990;69:245–8.
[19] Biller K, Fae P, Germann R, et al. Cholesterol rather than procalcitonin or C-reactive protein predicts mortality in patients with infection. Shock. 2014;42:129–32.
[20] Bastiaanse EM, van der Valk-Kokshoorn LJ, Egas-Kennphaas JM, et al. Low total cholesterol level is the independent predictor of neurologic outcome in cardiac arrest survivors. J Neurol Sci. 2021: post-resuscitation care. Intensive Care Med. 2021;47:369–421.
[21] Ahsan et al. • Medicine (2022) 101:46 www.md-journal.com