Original Article

High cholesterol concentrations as well as low cholesterol concentrations are associated with mortality at 28 days in sepsis: a retrospective cohort study

Dong-Hyun Jang[1], You Hwan Jo[2,3], Gil Joon Suh[3,4], Woon Yong Kwon[3,4], Jonghwan Shin[3,5], Kyung Su Kim[4], Huijai Lee[5], Taekyun Kim[4], Min Sung Lee[4], Changwoo Im[2], for the SNU CARE Investigators

[1]Department of Emergency Medicine, Korea University Anam Hospital, Seoul, Republic of Korea; [2]Department of Emergency Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [3]Department of Emergency Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea; [4]Department of Emergency Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [5]Department of Emergency Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Republic of Korea

Contributions: (I) Conception and design: YH Jo, GJ Suh; (II) Administrative support: YH Jo, WY Kwon; (III) Provision of study materials or patients: YH Jo, GJ Suh, J Sin; (IV) Collection and assembly of data: DH Jang, T Kim, MS Lee, C Im; (V) Data analysis and interpretation: DH Jang, KS Kim, H Lee; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: You Hwan Jo, MD, PhD. Department of Emergency Medicine, Seoul National University Bundang Hospital, 82, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, 13620, Republic of Korea. Email: emdrjyh@gmail.com.

Background: Low serum cholesterol is known to be associated with poor prognosis in sepsis patients. On the other hand, there have been few studies on the association between high serum cholesterol, one of the major risk factors for cardiovascular adverse events, and prognosis of sepsis patients. We investigated the relationship between the serum total cholesterol concentration and outcome of sepsis patients.

Methods: We conducted a multicenter retrospective cohort study at the emergency departments (EDs) of three urban tertiary teaching hospitals. Patients were divided into three groups according to the initial serum total cholesterol concentration: low cholesterol (cholesterol <120 mg/dL), normal cholesterol (cholesterol 120–200 mg/dL), and high cholesterol (cholesterol >200 mg/dL). Multivariable Cox proportional hazard regression model was used to identify the independent association between the serum total cholesterol concentrations and mortality at 28 days.

Results: A total of 4,512 patients were included in the final analysis. The mortality at 28 days of the low, normal, and high cholesterol groups were 24.1%, 14.5%, and 20.5%, respectively (P<0.001). Both the low and high cholesterol groups had a higher risk of death than the normal cholesterol group (low cholesterol group [hazard ratio (HR), 1.46; 95% confidence interval (CIs), 1.25–1.71] and high cholesterol group (HR, 1.57; 95% CI, 1.14–2.16).

Conclusions: Both low and high serum total cholesterol concentrations were associated with higher mortality at 28 days in sepsis patients.

Keywords: Cholesterol; sepsis; prognosis; mortality

Submitted Jun 01, 2021. Accepted for publication Aug 04, 2021.
doi: 10.21037/apm-21-1461
View this article at: https://dx.doi.org/10.21037/apm-21-1461

Introduction

Sepsis is a syndrome of physiological, pathological and biochemical problems caused by infection that can induce life-threatening organ dysfunction due to a dysregulated host response (1). Although there have been many advances in the management of sepsis patients, high mortality rates remain (2).

Cholesterol is one of the major classes of lipids in the body. It is not only a major structural component of cell membranes but also serves as a precursor for the biosynthesis of essential substances in the body, such as steroid hormones, bile acid, and vitamin D (3). Although cholesterol in the body can be ingested through food or synthesized in cells, its metabolism is mainly mediated by enzymes in the liver (4). The liver maintains cholesterol homeostasis by playing a major role in the biosynthesis, uptake, degradation and conversion into bile acids and the excretion of cholesterol.

Cholesterol is not only utilized as a precursor to various substances required by the body but also downregulates the inflammatory immune response and neutralizes endotoxins in pathologic conditions (5-7). As a result, low serum cholesterol concentrations are known to be associated with a worsening inflammatory response in patients. Previous studies have shown that low serum cholesterol concentrations are associated with poor prognosis in several diseases, such as sepsis, heart failure, ischemic stroke, and cancer (8-12).

On the other hand, an excessive concentration of cholesterol in the blood vessel causes it to accumulate in the cells of the vascular wall (4). As a result, a high serum cholesterol concentration is one of the major risk factors for the development of atherosclerosis and, consequently, is a risk factor for cardiovascular disease (13,14). Familial hypercholesterolemia or chronic liver diseases, which results in cholesterol accumulation due to impaired cholesterol metabolism, is one of the major risk factors for cardiovascular events such as myocardial infarction or sudden death (15,16). On this basis, it has been generally accepted by many health care professionals that treatment for hypercholesterolemia is necessary for the prevention of cardiovascular adverse events (17).

Previous studies of sepsis patients have shown that non-survivors had lower serum cholesterol concentrations than survivors, and accordingly, low serum total cholesterol has been associated with high mortality (9,11). However, considering the cardiovascular risk that may be caused by hypercholesterolemia, it would be possible that high serum cholesterol concentrations could also have a harmful effect on sepsis patients. Therefore, we hypothesized that high serum total cholesterol as well as low serum total cholesterol might be associated with high mortality in sepsis patients. This study was conducted to evaluate the association of serum total cholesterol concentration measured at emergency department (ED) admission with mortality at 28 days in sepsis patients.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1461).

Methods

Study setting and population

We conducted a retrospective analysis of prospectively included patients (18 years old or older) with sepsis or septic shock who visited to the ED of three institutions from May 2014 to April 2018 (18,19). The three institutions (Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University Hospital, and Seoul National University Bundang Hospital) were urban teaching hospitals with approximately 50,000, 70,000, and 90,000 annual ED patient visits. Patients whose serum total cholesterol concentrations were not measured at ED admission were excluded. Patients or legal representatives who refused aggressive treatment such as admission to intensive care unit, mechanical ventilation, or administration of vasopressors were also excluded. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Seoul National University Bundang Hospital approved this retrospective analysis and waived patient informed consent (No. B-2101/660-105).

With the update of definition of sepsis in 2016, the inclusion criteria of the study populations were partially changed during the study period (19). Between May 2014 and February 2016, patients with severe sepsis and septic shock according to The Second International Sepsis Definition Consensus were included (20). Severe sepsis was defined by sepsis with organ dysfunction, and septic shock was defined by sepsis with hypotension despite adequate fluid resuscitation. Between March 2016 and April 2018, patients with sepsis and septic shock according to the Sepsis-3 definition were included (1). In this revised definition, sepsis is defined as acute change in total

Sequential Organ Failure Assessment (SOFA) score ≥2 points. Septic shock was defined as a clinical construct of sepsis with persisting hypotension requiring vasopressors and having a serum lactate level greater than 2 mmol/L despite adequate fluid resuscitation.

Patients received treatment according to the guidelines recommended by the Survival Sepsis Campaign (2,21). Adequate fluid resuscitation using crystalloids was performed, in the absence of any contraindications, and antibiotics were administered immediately after appropriate culture specimens were obtained. Medications such as vasoactive agents, corticosteroids, and insulin were administered according to the judgment of the attending physician.

The serum total cholesterol concentration was included in the routine serum chemistry panel, and the results were usually reported within 1 hour at all three institutions and were measured in the central laboratory of each institution. The upper limit of the normal range of the serum total cholesterol concentration was 200 mg/dL, and there was no absolute lower limit.

Data collection and processing

Standardized data collection forms were used for data extraction. The data collection forms included demographic data such as age, sex, and comorbidities; initial hemodynamic parameters such as blood pressure, heart rate, respiratory rate, and body temperature; Laboratory data, such as complete blood count (CBC) and serum chemistry. Presumed or confirmed primary site of infection and outcome variables such as mortality were also collected. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score and SOFA score were calculated from the data collected. The missing data in the registry was obtained from the relevant information of the electrical medical record and filled in.

Mortality at 28 days after ED admission was the primary outcome of this study. A structured telephone follow-up was conducted for patients who were discharged before 28 days after hospitalization. During the study period, 39 patients were lost to follow-up and excluded from the cohort.

Statistical analysis

Patients were divided into survivors and non-survivors at 28 days, and baseline characteristics were compared between the two groups. Continuous variables are expressed as the median (25th and 75th percentile). Differences of continuous variables between survivors and non-survivors were evaluated with the Student's *t* test or the Mann-Whitney U test, as appropriate. Categorical variables are expressed as numbers (percentages), and differences were compared with the χ^2 test or Fisher's exact test, as appropriate.

To determine the approximate association of the serum total cholesterol concentration with mortality at 28 days, a restricted cubic spline curve adjusted for age, sex, body mass index, the APACHE II score, and the variables considered to be associated with cholesterol metabolism, such as chronic liver disease and total bilirubin concentration, was used. After that, we divided the patients into three groups based on the results of previous studies and the restricted cubic spline curve to compare the difference in mortality according to the serum total cholesterol concentration: low cholesterol group (cholesterol <120 mg/dL), normal cholesterol group (cholesterol 120–200 mg/dL), and high cholesterol group (cholesterol >200 mg/dL). We defined a high cholesterol concentration based on a cutoff value of 200 mg/dL, the upper limit of the total cholesterol concentration in the normal range. Since there is no clear consensus on the definition of hypocholesterolemia and many studies have regarded hypolipidemia as less than 120–150 mg/dL (22), we set 120 mg/dL as the cutoff value for a low total cholesterol concentration. Differences of continuous variables between groups were evaluated with the One-way analysis of variance or the Kruskal-Wallis test, as appropriate. Categorical variables were compared with the χ^2 test or Fisher's exact test, as appropriate. The Bonferroni correction method was used for multiple comparisons.

Kaplan-Meier plot was used to compare survival over time between the three groups according to the serum total cholesterol concentrations, and differences between curves were assessed by the log-rank test. Multivariable Cox proportional hazard regression analysis was used to identify the independent association between serum total cholesterol concentrations and mortality at 28 days, and the results were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). In the multivariable analysis, age, sex, body mass index, APACHE II score, and variables considered to be associated with cholesterol metabolism, such as chronic liver disease and total bilirubin concentration were included.

All data processing and statistical analyses were performed with R package software, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). A

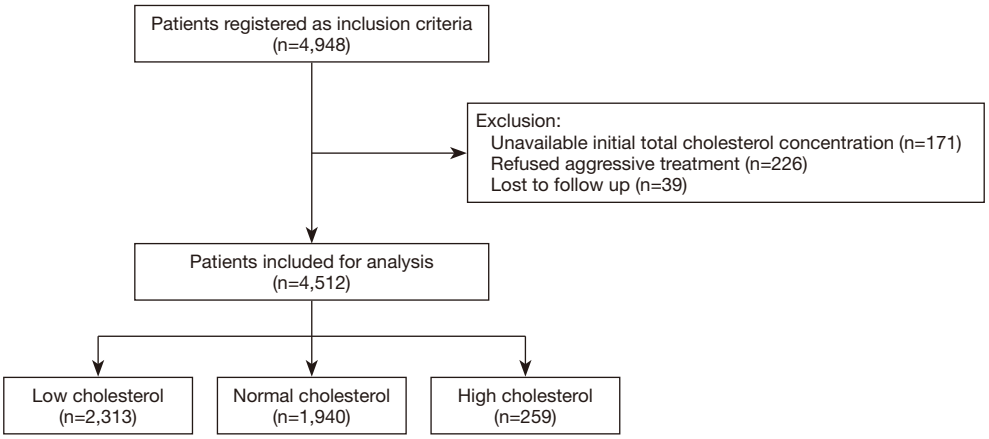

Figure 1 Flow chart for patient inclusion.

two-tailed P value less than 0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

During the study period, a total of 4,948 patients were diagnosed and treated with sepsis or septic shock in the EDs. Of these patients, 171 were excluded because the serum total cholesterol concentration was not measured at ED admission, 226 were excluded because they refused aggressive treatment, and 39 were lost to follow-up. As a result, 4,512 patients were included in the final analysis (*Figure 1*).

Table 1 shows the clinical characteristics of the study population. The median age of the patients was 73 [63–80] years, 2,709 (60.0%) were male, and the overall mortality rate was 19.8%. The non-survivors were older, more male, and showed a lower body mass index than the survivors. The median serum total cholesterol concentrations were lower in the non-survivors than in the survivors, at 103.0 (74.0–138.0) mg/dL (P<0.001) *vs.* 121.0 (95.0–152.0) mg/dL.

Serum total cholesterol concentrations and mortality

In the restricted cubic spline curve between the total serum cholesterol concentration and the adjusted odds for death on 28 days, the mortality was lowest between 120 and 200 mg/dL cholesterol (*Figure 2*). The curve showed higher mortality in both low and high serum total cholesterol concentrations than in normal serum total cholesterol concentration. *Table 2* presents the clinical characteristics of the three groups divided by serum total cholesterol concentrations. The low cholesterol group had a lower body mass index than the other groups, and the high cholesterol group was younger than the other groups. Among the initial hemodynamic variables, the mean arterial pressure was lower in the low cholesterol group and higher in the high cholesterol group than in the normal cholesterol group. The low cholesterol group had higher APACHE II scores and SOFA scores than the other groups. There was no statistically significant difference in the APACHE II score or SOFA score between the normal cholesterol group and the high cholesterol group.

The mortality at 28 days of the low cholesterol group, normal cholesterol group, and high cholesterol group were 24.1%, 14.5%, and 20.5%, respectively (P<0.001). The Kaplan-Meier curve with the log-rank test showed a higher mortality rate in both the low and high cholesterol groups than in the normal cholesterol group (P<0.001; *Figure 3*).

In the multivariable Cox proportional hazards regression analysis summarized in *Table 3*, age, sex, body mass index, underlying chronic liver disease, total bilirubin, and the APACHE II score were independently associated with mortality at 28 days. The HRs of the low cholesterol group and the high cholesterol group were 1.46 (95% CI, 1.25–1.71) and 1.57 (95% CI, 1.14–2.16), respectively.

Discussion

In this study of sepsis patients, the median serum total cholesterol concentration was lower in non-survivors than in survivors. However, when patients were divided

Table 1 Clinical characteristics of patients according to 28-day mortality

Variables	Total (N=4,512)	Survivors (N=3,620)	Non-survivors (N=892)	P
Age	73.0 (63.0–80.0)	72.5 (62.0–79.0)	74.0 (65.0–81.5)	<0.001
Male	2,709 (60.0)	2,126 (58.7)	583 (65.4)	<0.001
Body mass index	21.3 (18.5–24.0)	21.5 (18.6–24.2)	20.7 (18.0–23.5)	<0.001
Comorbidity				
Hypertension	1,972 (43.7)	1,586 (43.8)	386 (43.3)	0.785
Diabetes	1,484 (32.9)	1,185 (32.8)	299 (33.5)	0.695
Chronic liver disease	395 (8.8)	286 (7.9)	109 (12.2)	<0.001
Congestive heart failure	86 (1.9)	64 (1.8)	22 (2.5)	0.219
Chronic lung disease	510 (11.3)	412 (11.4)	98 (11.0)	0.782
Chronic kidney disease	430 (9.5)	338 (9.3)	92 (10.3)	0.409
Initial hemodynamic variables				
Mean arterial pressure (mmHg)	69.0 (59.0–87.0)	70.0 (60.0–87.0)	67.0 (57.0–84.0)	<0.001
Heart rate (beat/min)	104.0 (88.0–121.0)	102.0 (87.0–120.0)	110.0 (95.0–127.0)	<0.001
Respiratory rate (breath/min)	21.0 (18.0–25.0)	20.0 (18.0–24.0)	24.0 (20.0–28.0)	<0.001
Body temperature (℃)	37.2 (36.6–38.2)	37.3 (36.7–38.2)	37.0 (36.4–37.9)	<0.001
Laboratory results				
Total cholesterol (mg/dL)	118.0 (91.0–150.0)	121.0 (95.0–152.0)	103.0 (74.0–138.0)	<0.001
White blood cell (10^3/μL)	11.2 (6.3–16.8)	11.3 (6.8–16.8)	10.5 (4.1–16.6)	<0.001
Hemoglobin (g/dL)	11.0 (9.3–12.6)	11.2 (9.5–12.7)	10.5 (8.7–12.1)	<0.001
Platelet (10^3/μL)	173.0 (102.0–254.0)	177.0 (109.0–256.0)	148.0 (72.0–248.0)	<0.001
Creatinine (mg/dL)	1.2 (0.9–2.1)	1.2 (0.8–2.0)	1.5 (1.0–2.5)	<0.001
Albumin (g/dL)	3.0 (2.6–3.5)	3.1 (2.7–3.5)	2.7 (2.3–3.1)	<0.001
Total bilirubin (mg/dL)	0.9 (0.6–1.7)	0.9 (0.6–1.6)	1.0 (0.6–2.0)	<0.001
CRP (mg/dL)	12.8 (5.7–21.2)	12.2 (5.3–20.6)	14.8 (7.5–22.5)	<0.001
Lactate (mmol/L)	2.4 (1.5–4.3)	2.1 (1.4–3.7)	3.8 (2.0–7.2)	<0.001
Infection site				
Lung	2,041 (45.2)	1,534 (42.4)	507 (56.8)	<0.001
Urogenital	838 (18.6)	758 (20.9)	80 (9.0)	<0.001
Intra-abdomen	1,208 (26.8)	996 (27.5)	212 (23.8)	0.026
Others	469 (10.4)	366 (10.1)	103 (11.5)	0.231
Medications				
Vasopressors	2,163 (48.7)	1,626 (45.6)	537 (61.2)	<0.001
Steroids	345 (7.8)	214 (6.0)	131 (15.0)	<0.001
APACHE II score	21.0 (15.0–28.0)	19.0 (14.0–26.0)	28.0 (20.0–37.0)	<0.001
SOFA score	7.0 (4.0–9.0)	6.0 (4.0–9.0)	9.0 (6.0–12.0)	<0.001

Data are expressed as median (interquartile range) or n (%) as appropriate. CRP, C-reactive protein; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

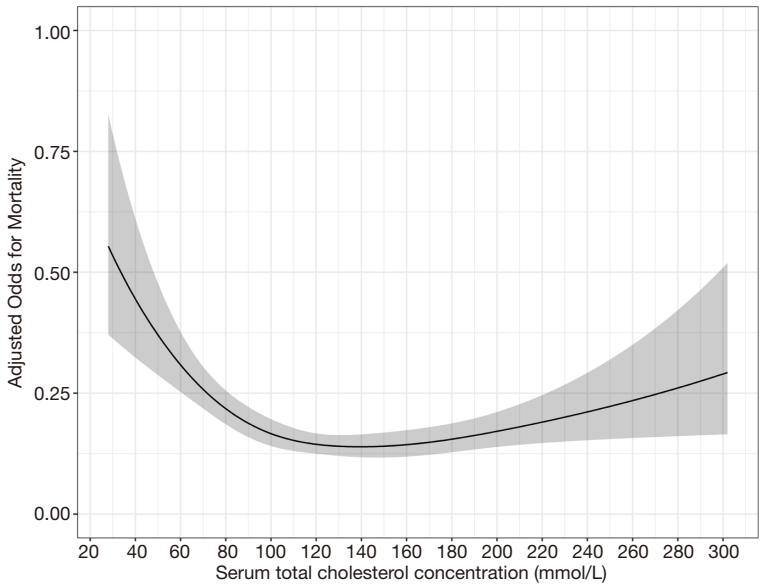

Figure 2 The restricted cubic spline curve of mortality at 28 days according to the serum total cholesterol concentrations. The model was fit with four knots and adjusted for age, sex, body mass index, the Acute Physiology and Chronic Health Evaluation II score, and the variables considered to be associated with cholesterol metabolism, such as chronic liver disease and total bilirubin concentration. The black line indicates the adjusted odds ratios for mortality at 28 days, and the gray shaded area represents the 95% confidence interval.

into three groups according to the serum total cholesterol concentrations, we found that both low and high total cholesterol concentrations were associated with high mortality at 28 days. In the multivariable analysis, both high and low cholesterol concentrations were independently associated with mortality at 28 days in sepsis patients.

Several studies have reported low initial total cholesterol concentrations in sepsis patients (11,23). In our study, the median serum total cholesterol concentration of all included patients was 118 (91.0–150.0) mg/dL, which was lower than the normal range. Among the three groups divided by total cholesterol concentration, the number of patients in the low cholesterol group was the highest, with only 259 (5.7%) in the high cholesterol group. The low total cholesterol concentration in sepsis patients may be due to the low premorbid total cholesterol concentration of patients, but a decrease in total cholesterol concentrations under inflammatory conditions is more likely (24). However, premorbid total cholesterol concentrations of the patients were not available in our study.

In previous studies, both low and high cholesterol concentrations have been reported to be associated with poor prognosis in patients with special conditions. Liu *et al.* (25) investigated the association between serum cholesterol concentration and mortality in dialysis patients according to the presence or absence of malnutrition or inflammatory conditions. In this study, only the low cholesterol group showed higher mortality than the other groups in all patients. However, in the subgroup with inflammation or malnutrition, mortality caused by cardiovascular disease was high at both low and high cholesterol concentrations. In another study that investigated the association between cholesterol concentration and mortality caused by cardiovascular disease, mortality was lowest in the 160–199 mg/dL group, with higher mortality rates observed in both the lower and higher cholesterol groups (26). Similarly, in a study examining the association between cholesterol concentration and disease severity in acute pancreatitis patients, both low and high total cholesterol concentrations were associated with the possibility of greater disease severity (27). In the present study, the low cholesterol group showed higher mortality than the normal cholesterol group, which is consistent with other studies in sepsis patients (9,11). In addition, the high cholesterol group also showed higher mortality than the normal cholesterol group. The results of our study suggest that although an association between total cholesterol concentration and poor prognosis

Table 2 Clinical characteristics of patients according to the serum total cholesterol concentration

Variables	Low cholesterol (N=2,313)	Normal cholesterol (N=1,940)	High cholesterol (N=259)	P
Age	73.0 (64.0–80.0)	73.0 (63.0–80.0)	69.0 (59.5–79.0)	0.008
Male	1,494 (64.6)	1,087 (56.0)	128 (49.4)	<0.001
Body mass index	21.1 (18.3–23.7)	21.6 (18.7–24.3)	21.7 (19.3–24.4)	<0.001
Comorbidity				
Hypertension	1,041 (45.0)	836 (43.1)	95 (36.7)	0.028
Diabetes	819 (35.4)	597 (30.8)	68 (26.3)	<0.001
Chronic liver disease	275 (11.9)	104 (5.4)	16 (6.2)	<0.001
Congestive heart failure	51 (2.2)	33 (1.7)	2 (0.8)	0.189
Chronic lung disease	240 (10.4)	242 (12.5)	28 (10.8)	0.096
Chronic kidney disease	235 (10.2)	177 (9.1)	18 (6.9)	0.179
Initial hemodynamic variables				
Mean arterial pressure (mmHg)	66.0 (57.0–82.0)	72.0 (61.0–90.0)	79.0 (62.0–95.0)	<0.001
Heart rate (beat/min)	102.0 (88.0–121.0)	105.0 (89.0–121.0)	106.0 (90.0–121.0)	0.066
Respiratory rate (breath/min)	21.0 (18.0–25.0)	20.0 (18.0–25.0)	20.0 (18.0–26.0)	0.759
Body temperature (℃)	37.1 (36.5–38.0)	37.4 (36.7–38.4)	37.3 (36.6–38.4)	<0.001
Laboratory results				
Total cholesterol (mg/dL)	92.0 (73.0–106.0)	146.0 (131.0–167.0)	218.0 (207.0–237.5)	<0.001
White blood cell (10^3/μL)	11.1 (5.9–17.8)	11.3 (6.7–15.9)	11.2 (7.8–15.9)	0.420
Hemoglobin (g/dL)	10.4 (8.8–12.0)	11.6 (10.0–13.1)	12.4 (10.9–14.2)	<0.001
Platelet (10^3/μL)	151.0 (84.0–240.0)	187.0 (120.0–261.0)	225.0 (166.5–297.5)	<0.001
Creatinine (mg/dL)	1.4 (1.0–2.4)	1.1 (0.8–1.8)	1.1 (0.8–1.7)	<0.001
Albumin (g/dL)	2.8 (2.4–3.2)	3.3 (2.9–3.6)	3.6 (3.2–4.0)	<0.001
Total bilirubin (mg/dL)	0.9 (0.6–1.8)	0.9 (0.6–1.5)	1.0 (0.6–1.6)	0.036
CRP (mg/dL)	15.5 (8.0–23.7)	10.3 (4.3–18.2)	6.5 (2.7–14.4)	<0.001
Lactate (mmol/L)	2.6 (1.5–4.9)	2.1 (1.4–3.9)	2.5 (1.7–4.3)	<0.001
Infection site				
Lung	1,031 (44.6)	885 (45.6)	125 (48.3)	0.477
Urogenital	408 (17.6)	391 (20.2)	39 (15.1)	0.036
Intra-abdomen	669 (28.9)	469 (24.2)	70 (27.0)	0.002
Others	226 (9.8)	213 (11.0)	30 (11.6)	0.355
Medications				
Vasopressors	1,271 (55.8)	801 (42.0)	91 (35.7)	<0.001
Steroids	232 (10.2)	103 (5.4)	10 (4.0)	<0.001
APACHE II score	22.0 (16.0–30.0)	20.0 (14.0–27.0)	19.0 (12.0–27.0)	<0.001
SOFA score	7.0 (5.0–10.0)	6.0 (4.0–8.0)	5.0 (3.0–8.0)	<0.001
28-day mortality	557 (24.1)	282 (14.5)	53 (20.5)	<0.001

Data are expressed as median (interquartile range) or n (%) as appropriate. CRP, C-reactive protein; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

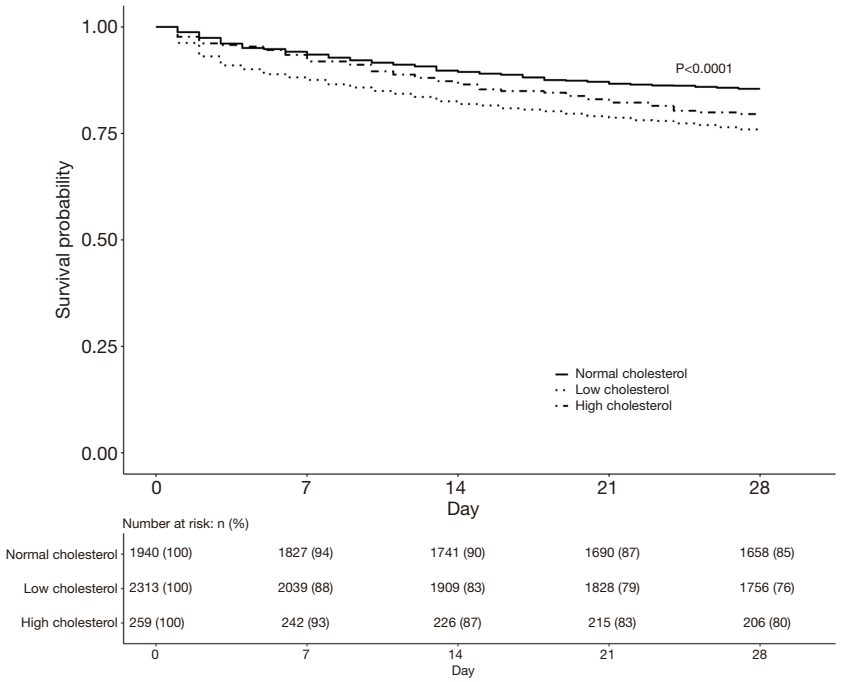

Figure 3 Kaplan-Meier curve of the three groups divided by serum total cholesterol concentration.

Table 3 Multivariable Cox regression analysis for 28-day mortality

Variables	Hazard ratio	95% CI	P value
Age	1.01	1.00–1.01	0.035
Male	0.84	0.72–0.98	0.026
Body mass index	0.97	0.95–0.99	0.001
Chronic liver disease	1.41	1.13–1.76	0.002
Total bilirubin	1.06	1.04–1.07	<0.001
APACHE II score	1.07	1.07–1.08	<0.001
Normal cholesterol	Ref	Ref	Ref
Low cholesterol	1.46	1.25–1.71	<0.001
High cholesterol	1.57	1.14–2.16	0.006

CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation.

has been previously reported in sepsis patients, a high cholesterol concentration does not have a protective effect.

The mechanisms underlying the association between low cholesterol concentration and mortality and between high cholesterol concentration and mortality in sepsis patients differ. The association between low cholesterol concentration and mortality has been reported to be associated with changes in cholesterol metabolism and the neutralizing capacity of endotoxins in inflammatory conditions. According to a previous study on sepsis, endotoxins and cytokines influence cholesterol metabolism under inflammatory conditions, and the resulting decrease in cholesterol concentration is also associated with disease severity (24). Several other studies have shown that inflammatory conditions such as sepsis cause a decrease in cholesterol concentration, and a decrease in cholesterol is associated with changes in the inflammatory response, leading to a poor prognosis (6,9,28). In the present study, the low cholesterol group showed lower initial mean arterial pressure and higher APACHE II score and SOFA score than the other groups. These findings suggest that the low cholesterol group had a higher severity at the time of admission and consequently resulted in higher mortality than the normal cholesterol group.

On the other hand, the mechanism underlying association between high cholesterol concentration and mortality has not yet been elucidated. However, it might be associated with the possibility of cardiovascular complications. In the study conducted by Liu *et al.* (25), mortality due to cardiovascular events in patients with inflammation or malnutrition was higher in the group with high cholesterol concentrations than in the group

with normal cholesterol concentrations. In a recent study that investigated the relationship between the pre-illness lipid profile and mortality in sepsis patients, a higher concentration of low-density lipoprotein was associated with high mortality, which might be associated with adverse cardiovascular events (29). In the present study, the high cholesterol group showed lower age and higher initial mean arterial pressure than the other groups, and the APACHE II score and SOFA score were not significantly different from those of the normal cholesterol group. In addition, in the Kaplan-Meier curve of the three groups divided by serum total cholesterol concentration, the high cholesterol group and the normal cholesterol group showed similar mortality for the first week, but as time progressed, the high cholesterol concentration group showed higher mortality. In contrast, the low cholesterol group showed higher initial severity and had higher mortality at the early stage of hospitalization. These findings suggest that although the patients in the high cholesterol group did not have higher severity at admission compared to the other groups, they became worse while in the hospital. Further studies are warranted to elucidate the mechanism underlying the association between high serum cholesterol and mortality in sepsis patients.

There are some limitations that should be noted. First, this study is a retrospective analysis of data from three institutions making it difficult to generalize these results to other institutions. Second, the definitions of sepsis updated during the study period, so there may be some differences in the composition of the study population. However, the association of total cholesterol concentration with 28-day mortality and baseline characteristics were not different between the patients before and after the update of sepsis definition (Figure S1, Figure S2, and Table S1). Third, the fasting time was not examined at the time when the initial serum total cholesterol concentration was measured. However, in several previous studies that investigated the difference in lipid profiles between fasting and non-fasting states, there were few differences in serum total cholesterol concentrations in the fasting state (30,31). Fourth, as more detailed information on the lipid profile was not investigated, it is not known which cholesterol component had a major association with patient prognosis.

Conclusions

Both low and high serum total cholesterol concentrations were associated with greater mortality at 28 days in patients with sepsis or septic shock and could be used as a prognostic factor in sepsis or septic shock.

Acknowledgments

Funding: This study was partly supported by Grant No. 16-2016-0004 from the Seoul National University Bundang Hospital Research Fund. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1461

Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-1461

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1461). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Seoul National University Bundang Hospital (No. B-2101/660-105) and individual consent for this retrospective analysis was waived.

References

1. Singer M, Deutschman CS, Seymour CW, et al. The

Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
2. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017;43:304-77.
3. Myant NB. The biology of cholesterol and related steroids. Butterworth-Heinemann, 2014.
4. Trapani L, Segatto M, Pallottini V. Regulation and deregulation of cholesterol homeostasis: The liver as a metabolic "power station". World J Hepatol 2012;4:184-90.
5. Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. Lancet 2000;356:930-3.
6. Gordon BR, Parker TS, Levine DM, et al. Relationship of hypolipidemia to cytokine concentrations and outcomes in critically ill surgical patients. Crit Care Med 2001;29:1563-8.
7. Goldfarb RD, Parker TS, Levine DM, et al. Protein-free phospholipid emulsion treatment improved cardiopulmonary function and survival in porcine sepsis. Am J Physiol Regul Integr Comp Physiol 2003;284:R550-7.
8. Horwich TB, Hamilton MA, Maclellan WR, et al. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. J Card Fail 2002;8:216-24.
9. Memi D, Gursoy O, Tasdogan M, et al. High C-reactive protein and low cholesterol levels are prognostic markers of survival in severe sepsis. J Clin Anesth 2007;19:186-91.
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. Yamano 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. Kannel WB, Castelli WP, Gordon T. Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study. Ann Intern Med 1979;90:85-91.
14. Carmena R, Duriez P, Fruchart JC. Atherogenic lipoprotein particles in atherosclerosis. Circulation 2004;109:III2-7.
15. Min HK, Kapoor A, Fuchs M, et al. Increased hepatic synthesis and dysregulation of cholesterol metabolism is associated with the severity of nonalcoholic fatty liver disease. Cell Metab 2012;15:665-74.
16. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478-90a.
17. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285-350.
18. Kim KS, Suh GJ, Kim K, et al. Quick Sepsis-related Organ Failure Assessment score is not sensitive enough to predict 28-day mortality in emergency department patients with sepsis: a retrospective review. Clin Exp Emerg Med 2019;6:77-83.
19. Kim JH, Jang DH, Jo YH, et al. Serum total carbon dioxide as a prognostic factor for 28-day mortality in patients with sepsis. Am J Emerg Med 2021;44:277-83.
20. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003;29:530-8.
21. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008;34:17-60.
22. Elmehdawi R. Hypolipidemia: a word of caution. Libyan J Med 2008;3:84-90.
23. Chien JY, Jerng JS, Yu CJ, et al. Low serum level of high-density lipoprotein cholesterol is a poor prognostic factor for severe sepsis. Crit Care Med 2005;33:1688-93.
24. Fraunberger P, Schaefer S, Werdan K, et al. Reduction of circulating cholesterol and apolipoprotein levels during sepsis. Clin Chem Lab Med 1999;37:357-62.
25. Liu Y, Coresh J, Eustace JA, et al. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. JAMA 2004;291:451-9.
26. Bae JM, Yang YJ, Li ZM, et al. Low cholesterol is associated with mortality from cardiovascular diseases: a dynamic cohort study in Korean adults. J Korean Med Sci 2012;27:58-63.
27. Hong W, Zimmer V, Basharat Z, et al. Association of total

cholesterol with severe acute pancreatitis: A U-shaped relationship. Clin Nutr 2020;39:250-7.
28. Lee HY, Lee DH, Lee BK, et al. The association between lipid profiles and the neurologic outcome in patients with out-of-hospital cardiac arrest. Resuscitation 2019;145:26-31.
29. Maile MD, Sigakis MJ, Stringer KA, et al. Impact of the pre-illness lipid profile on sepsis mortality. J Crit Care 2020;57:197-202.
30. Sidhu D, Naugler C. Fasting time and lipid levels in a community-based population: a cross-sectional study. Arch Intern Med 2012;172:1707-10.
31. Langsted A, Nordestgaard BG. Nonfasting versus fasting lipid profile for cardiovascular risk prediction. Pathology 2019;51:131-41.

Cite this article as: Jang DH, Jo YH, Suh GJ, Kwon WY, Shin J, Kim KS, Lee H, Kim T, Lee MS, Im C, for the SNU CARE Investigators. High cholesterol concentrations as well as low cholesterol concentrations are associated with mortality at 28 days in sepsis: a retrospective cohort study. Ann Palliat Med 2021;10(10):10338-10348. doi: 10.21037/apm-21-1461

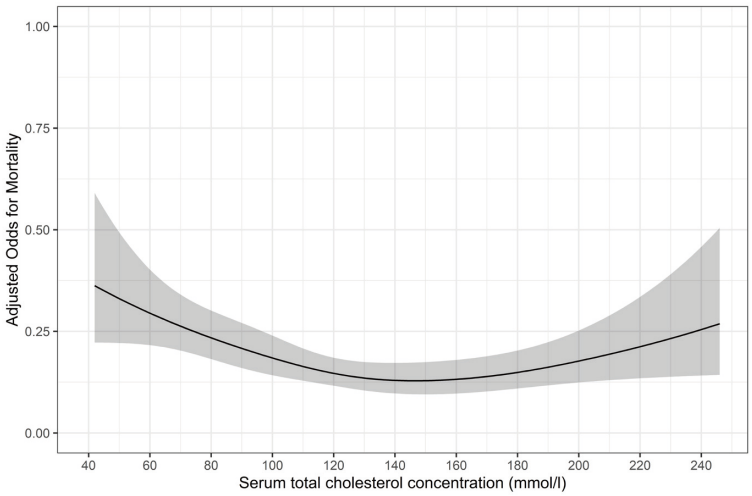

Figure S1 The restricted cubic spline curve of mortality at 28 days according to the serum total cholesterol concentrations in patients enrolled from May 2014 to February 2016. Patients with severe sepsis and septic shock according to The Second International Sepsis Definition Consensus were enrolled during this period. The black line indicates the adjusted odds ratios for mortality at 28 days, and the gray shaded area represents the 95% confidence interval.

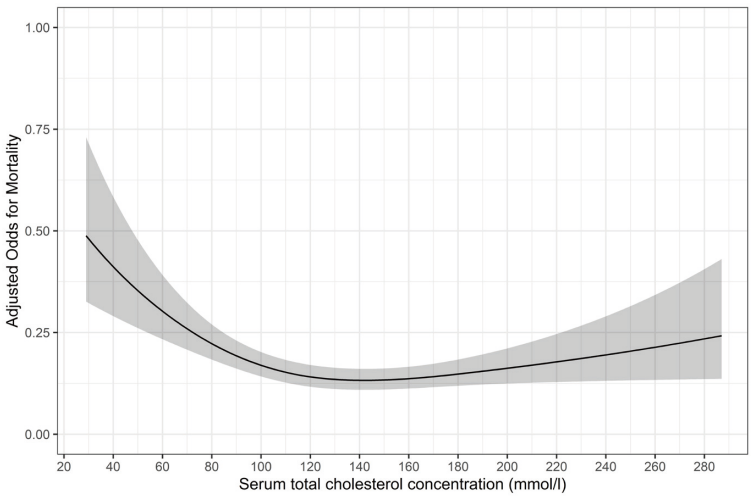

Figure S2 The restricted cubic spline curve of mortality at 28 days according to the serum total cholesterol concentrations in patients enrolled from March 2016 to April 2018. Patients with sepsis and septic shock according to the Sepsis-3 definition were enrolled during this period. The black line indicates the adjusted odds ratios for mortality at 28 days, and the gray shaded area represents the 95% confidence interval.

https://dx.doi.org/10.21037/apm-21-1461

Table S1 Baseline characteristics of patients according to the study period

Variables	From May 2014 to February 2016 (N=1,616)	From March 2016 to April 2018 (N=2,896)	p
Age	73.0 (62.0–79.0)	73.0 (63.0–80.0)	0.037
Male	985 (61.0)	1724 (59.5)	0.366
Body mass index	21.3 (18.5–24.0)	21.3 (18.5–24.0)	0.813
Comorbidity			
Hypertension	678 (42.0)	1294 (44.7)	0.077
Diabetes	519 (32.1)	965 (33.4)	0.414
Chronic liver disease	165 (10.2)	230 (7.9)	0.011
Congestive heart failure	31 (1.9)	55 (1.9)	1.000
Chronic lung disease	194 (12.0)	316 (10.9)	0.290
Chronic kidney disease	142 (8.8)	288 (9.9)	0.224
Malignant disease	597 (36.9)	1138 (39.3)	0.127
Initial hemodynamic variables			
Mean arterial pressure (mmHg)	66.0 (58.0–80.0)	72.0 (60.0–90.0)	<0.001
Heart rate (beat/min)	107.0 (89.0–124.0)	102.0 (87.0–119.0)	<0.001
Respiratory rate (breath/min)	22.0 (18.0–26.0)	20.0 (18.0–24.0)	<0.001
Body temperature (℃)	37.2 (36.5–38.1)	37.3 (36.7–38.2)	<0.001
Laboratory results			
Total cholesterol (mg/dL)	116.0 (88.5–145.0)	120.0 (92.0–152.0)	0.002
White blood cell (10^3/μL)	11.3 (6.6–17.3)	11.1 (6.2–16.5)	0.186
Hemoglobin (g/dL)	10.9 (9.2–12.5)	11.1 (9.4–12.7)	0.031
Platelet (10^3/μL)	168.0 (99.5–246.0)	176.0 (102.0–259.0)	0.038
Creatinine (mg/dL)	1.3 (0.9–2.1)	1.2 (0.8–2.0)	0.081
Albumin (g/dL)	3.0 (2.6–3.4)	3.1 (2.6–3.5)	<0.001
Total bilirubin (mg/dL)	0.9 (0.6–1.5)	0.9 (0.6–1.7)	0.004
CRP (mg/dL)	13.1 (6.7–21.8)	12.4 (5.2–20.7)	0.004
Lactate (mmol/L)	2.5 (1.5–4.7)	2.4 (1.4–4.2)	0.012
Infection site			
Lung	746 (46.2)	1295 (44.7)	0.366
Urogenital	288 (17.8)	550 (19.0)	0.353
Intra-abdomen	440 (27.2)	768 (26.5)	0.631
Others	142 (8.8)	327 (11.3)	0.010
APACHE II score	23.0 (17.0–31.0)	19.0 (14.0–26.0)	<0.001
SOFA score	7.0 (5.0–10.0)	6.0 (4.0–9.0)	<0.001
28-day mortality	333 (20.6)	559 (19.3)	0.310

Data are expressed as median (interquartile range) or n (%) as appropriate. CRP, C-reactive protein; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation.

https://dx.doi.org/10.21037/apm-21-1461