

Association Between Hypcholesterolemia and Mortality in Critically Ill Patients With Sepsis: A Systematic Review and Meta-Analysis

OBJECTIVE: To ascertain the association between cholesterol and triglyceride levels on ICU admission and mortality in patients with sepsis.

DATA SOURCES: Systematic review and meta-analysis of published studies on PubMed and Embase.

STUDY SELECTION: All observational studies reporting ICU admission cholesterol and triglyceride levels in critically ill patients with sepsis were included. Authors were contacted for further data.

DATA EXTRACTION: Eighteen observational studies were identified, including 1,283 patients with a crude overall mortality of 33.3%. Data were assessed using Revman (Version 5.1, Cochrane Collaboration, Oxford, United Kingdom) and presented as mean difference (MD) with 95% CIs, p values, and I^2 values.

DATA SYNTHESIS: Admission levels of total cholesterol (17 studies, 1,204 patients; MD = 0.52 mmol/L [0.27–0.77 mmol/L]; $p < 0.001$; $I^2 = 91\%$), high-density lipoprotein (HDL)-cholesterol (14 studies, 991 patients; MD = 0.08 mmol/L [0.01–0.15 mmol/L]; $p = 0.02$; $I^2 = 61\%$), and low-density lipoprotein (LDL)-cholesterol (15 studies, 1,017 patients; MD = 0.18 mmol/L [0.04–0.32 mmol/L]; $p = 0.01$; $I^2 = 71\%$) were significantly lower in eventual nonsurvivors compared with survivors. No association was seen between admission triglyceride levels and mortality (15 studies, 1,070 patients; MD = 0.00 mmol/L [–0.16 to 0.15 mmol/L]; $p = -0.95$; $I^2 = 79\%$).

CONCLUSIONS: Mortality was associated with lower levels of total cholesterol, HDL-cholesterol, and LDL-cholesterol, but not triglyceride levels, in patients admitted to ICU with sepsis. The impact of cholesterol replacement on patient outcomes in sepsis, particularly in at-risk groups, merits investigation.

KEYWORDS: cholesterol levels; intensive care unit; lipids; sepsis; triglycerides

Cholesterol is integral to several key physiologic processes including physical properties of the cell membrane, maintenance of cell membrane integrity, signaling pathways, immunity, and as a precursor for the synthesis of hormones, Vitamin D, and bile acids (1). The association between sepsis—the life-threatening organ dysfunction caused by a dysregulated host response to infection (2)—and hypocholesterolemia was first recognized a century ago (3). Many subsequent studies have demonstrated an association between the magnitude of decrease in serum cholesterol in sepsis and mortality, in particular the component of cholesterol bound to high-density lipoprotein (HDL-C) (4–7). The association between outcome and serum levels of cholesterol bound to low-density lipoprotein (LDL-C) or triglyceride (TG) appears less consistent.

Little mechanistic work has been performed to date to understand the pathophysiological mechanisms underlying hypocholesterolemia, nor clinical implications beyond the association with poor outcomes (1). Nonetheless, the

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KEY POINTS

Question: Does an association exist between cholesterol and triglyceride levels on ICU admission and mortality in patients with sepsis?

Findings: In a systematic review and meta-analysis, admission levels of total cholesterol, HDL-cholesterol, and LDL-cholesterol significantly differed between eventual nonsurvivors and survivors. No association was seen between admission triglyceride levels and mortality.

Meaning: Cholesterol levels are associated with mortality in sepsis. Effects of cholesterol replacement in sepsis need to be determined in future studies, particularly in at-risk groups.

therapeutic possibilities of lipoprotein administration or modifying the cholesterol pathway in sepsis are generating increasing interest. A recent review article noted that high-density lipoproteins (HDLs) display antioxidant, antiapoptotic, antithrombotic, anti-inflammatory, and anti-infectious properties (8). Improved organ function and survival were noted in animal models of sepsis infused with reconstituted HDL or an apolipoprotein A1 mimetic (apolipoprotein A1 being the major lipoprotein in HDL) (9, 10). A small pilot study of a cholesterol-sphingomyelin liposome given to patients with pneumococcal pneumonia showed good safety and tolerability and an encouraging reduction in organ dysfunction (11). A clinical trial with an anti-inflammatory intravenous fish oil emulsion is ongoing (12).

It is, thus, timely to perform a systematic review and meta-analysis on the association between mortality and ICU admission levels of cholesterol (total, HDL, and low-density lipoprotein [LDL]) and TG levels in critically ill patients with sepsis and septic shock. This systematic review was registered on the PROSPERO (International prospective register of systematic reviews, National Institute for Health Research NIHR, United Kingdom) database (registration number: CRD42021286120).

MATERIALS AND METHODS

Search Strategy

A systematic search of PubMed and Embase was conducted on July 20, 2022. Controlled vocabulary

(MeSH) and key words were used when possible. Date restrictions were not applied. Our Boolean search strategy included the following search terms: (cholesterol OR triglyceride OR HDL OR high-density lipoprotein OR LDL OR low-density lipoprotein OR lipoprotein) AND (sepsis OR septic OR septicemia OR intensive care OR critical care OR critical illness OR intensive care unit OR ICU). Where cholesterol levels were not stratified according to mortality status, the corresponding author was contacted for this information in order to reduce reporting bias.

Eligibility Criteria

Inclusion and exclusion criteria were determined a priori. All observational studies reporting ICU admission serum cholesterol (including total cholesterol, HDL-C, and LDL-C) and TG levels in critically ill adult patients (≥ 18 yr old) with sepsis were considered.

Study Selection

Both titles and abstracts were independently screened by two investigators (D.A.H., P.A.). A designated third author (N.A.) resolved discrepancies. Applying the predefined inclusion criteria, all relevant full-text publications were subsequently analyzed for eligibility.

Data Collection and Analysis

Two investigators (D.A.H., P.A.) independently extracted information from the selected publications using a standardized data collection form. Data were collected on year of publication, total number of included patients, ICU admission cholesterol (total cholesterol, HDL-C, and LDL-C) and TG levels, origin of sepsis, mortality, and preadmission statin use. Where reported, normal laboratory ranges cited for these variables were also collected. When not reported in metric units, cholesterol and TG units were converted from mg/dL to mmol/L (multiplication by 0.02586 and 0.01129 for cholesterol and TG units, respectively). Unclear data were not processed. As studies were observational, no risk of bias assessment was performed.

Outcome

Associations were sought between serum levels of cholesterol, its constituents (HDL-C and LDL-C) and

TG at ICU admission, and subsequent mortality. ICU mortality was primarily analyzed, where available. Otherwise, 28 or 30-day mortalities were used, unless stated otherwise.

Statistical Analysis

Mean and SD of the relevant variables were collected for outcome analysis. Where data were reported as median and interquartile range with CIs, we followed published and online Cochrane recommendations to approximate the values of mean and SD. Outcome differences were analyzed using an inverse variance model with 95% CIs. Summary values are reported using mean difference (MD). The association between cholesterol and TG levels and survival was assessed using area under the receiver operating characteristic curve (AUROC). Statistical analyses were conducted using Review Manager ("Revman") for Mac (Version 5.1, Cochrane Collaboration, Oxford, United Kingdom) and GraphPad Prism (Version 9.0, GraphPad Software, San Diego, CA). Statistical heterogeneity was assessed using the I^2 methodology. I^2 values greater than 50% and greater than 75% were considered to indicate moderate and significant heterogeneities among studies, respectively. All p values were two-tailed and considered statistically significant if below 0.05. Data are presented as MD with 95% CIs, p values, and I^2 values.

No subgroup or sensitivity analyses were performed.

RESULTS

Included Trials

The search strategy identified 9,454 titles and abstracts, 1,055 of which were duplicates (**Fig. 1**). Following screening of the remaining 8,399 titles and abstracts, 47 articles were identified for full-text review. Thirteen studies included data on cholesterol but were not stratified by mortality (5, 6, 13–23). Of these studies, the corresponding authors were contacted by e-mail, of whom seven responded and provided the relevant data (13–19). The remaining six studies were excluded (5, 6, 20–23). Of the remaining 34 studies, a further 23 were excluded as 10 studies included patients outside the ICU (24–33), three had a randomized, interventional design investigating selenium infusions, glycemic control, and antithrombin III application possibly confounding analysis (34–36), three included diagnoses

other than sepsis (37–39), four were in a language other than English (40–43), and three were obtained from a pediatric cohort (44–46). Eighteen studies were, therefore, included in the final analysis (7, 13–19, 47–56).

Study Characteristics

Eighteen observational studies including 1,283 patients with sepsis reporting ICU admission cholesterol and/or TG levels were identified. Sources of sepsis varied among studies and are presented in groups in **Supplemental Table 1** (<http://links.lww.com/CCX/B143>). Mortality was reported as ICU mortality in 15 studies, and 28- or 30-day mortalities in three studies. Crude overall mortality was 33.3%. Preadmission statin use was reported in six studies according to eventual ICU nonsurvivors and survivors (**Supplemental Table 1**, <http://links.lww.com/CCX/B143>).

ICU Admission Cholesterol and Triglyceride Levels in Septic Nonsurvivors and Survivors

Figure 2 demonstrates overall mean and SD of admission cholesterol and TG levels in septic nonsurvivors and survivors for the included studies.

Overall, total admission cholesterol levels were 2.7 mmol/L (SD, 0.94 mmol/L) in survivors and 2.44 mmol/L (SD, 0.89 mmol/L) in nonsurvivors. Overall HDL-C was 0.56 mmol/L (SD, 0.36 mmol/L) in survivors and 0.54 mmol/L (SD, 0.36 mmol/L) in nonsurvivors. LDL-C was 1.24 mmol/L (SD, 0.63 mmol/L) in survivors and 1.22 mmol/L (SD, 0.74 mmol/L) in nonsurvivors. TG levels were 1.58 mmol/L (SD, 0.96 mmol/L) in survivors and 1.51 mmol/L (SD, 0.89 mmol/L) in nonsurvivors. Individual lipid admission levels were available for a total number of 518 patients (13–19). Of these 518 patients, HDL-C at admission was below the lower limit of normal in 476 patients (91.9%). Of these, 376 patients (79%) eventually survived. In contrast, corresponding numbers with admission levels below the lower limit of normal were less pronounced for total cholesterol values, where only 58.1% (301/518 patients) had levels below the normal range at admission. Of these 301 patients, 232 patients (77%) eventually survived. Admission TGs were below the normal laboratory range in three of 518 (0.6%) patients. Calculations were not performed for LDL-C, as differing cardiovascular risk profiles influence target ranges in individual patients.

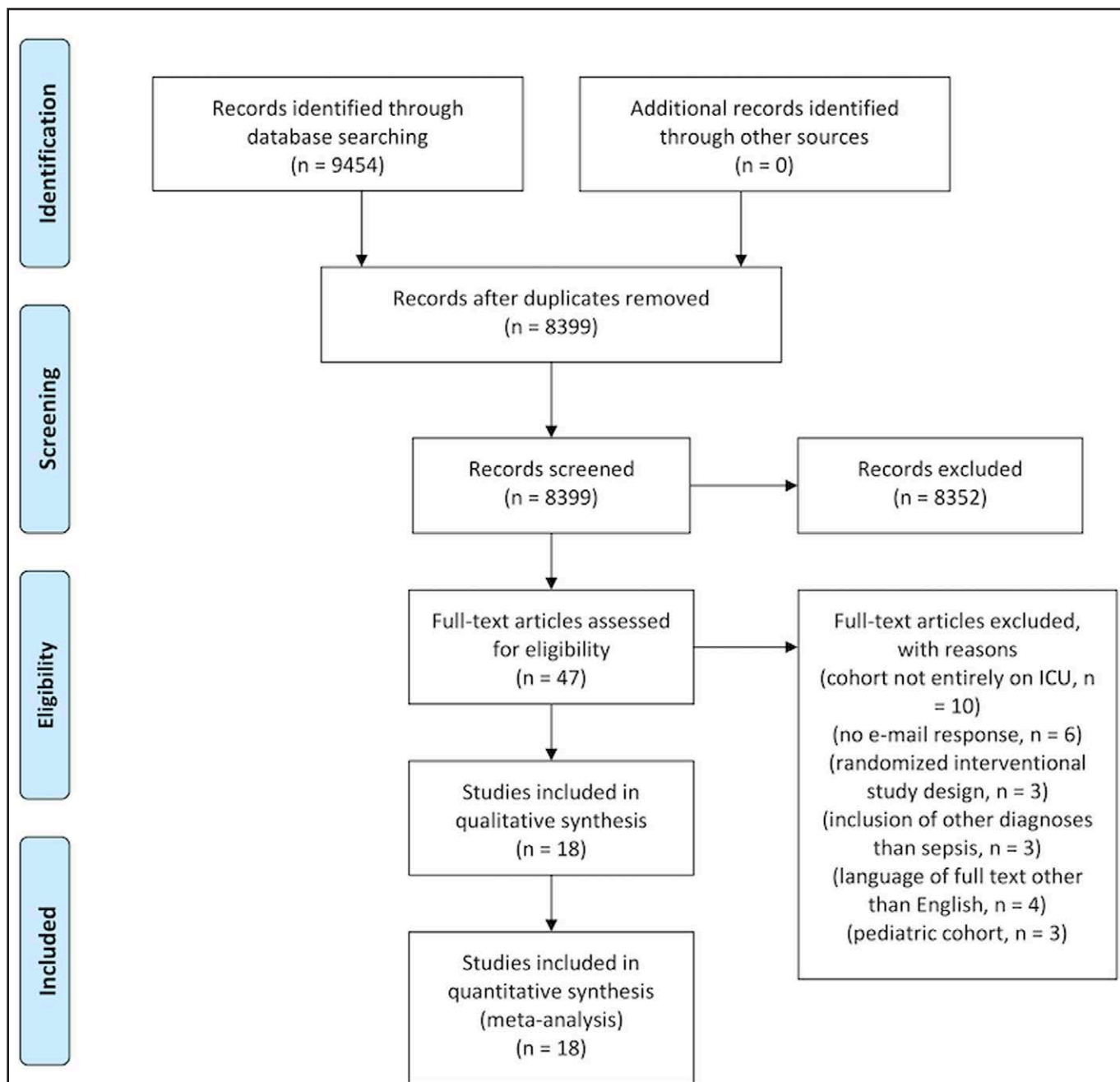


Figure 1. PRISMA flowchart.

Mean Difference of ICU Admission Cholesterol and Triglyceride Levels Between Nonsurvivors and Survivors

ICU admission levels of total cholesterol (17 studies, 1,204 patients; MD = 0.52 mmol/L [0.27–0.77 mmol/L]; $p < 0.001$; $I^2 = 91\%$), HDL-cholesterol (14 studies, 991 patients; MD = 0.08 mmol/L [0.01–0.15 mmol/L]; $p = 0.02$; $I^2 = 61\%$), and LDL-cholesterol (15 studies, 1,017 patients; MD = 0.18 mmol/L [0.04–0.32 mmol/L]; $p = 0.01$; $I^2 = 71\%$) were significantly lower

in eventual nonsurvivors compared with survivors (Figs. 3–5). There was no association between admission TG levels and mortality (15 studies, 1,070 patients; MD = 0.00 mmol/L [–0.16 to 0.15 mmol/L]; $p = -0.95$; $I^2 = 79\%$) (Fig. 6).

Area Under the Receiver Operating Characteristic Curves

Supplemental Figure 1 (<http://links.lww.com/CCX/B143>) depicts AUROCs showing the association

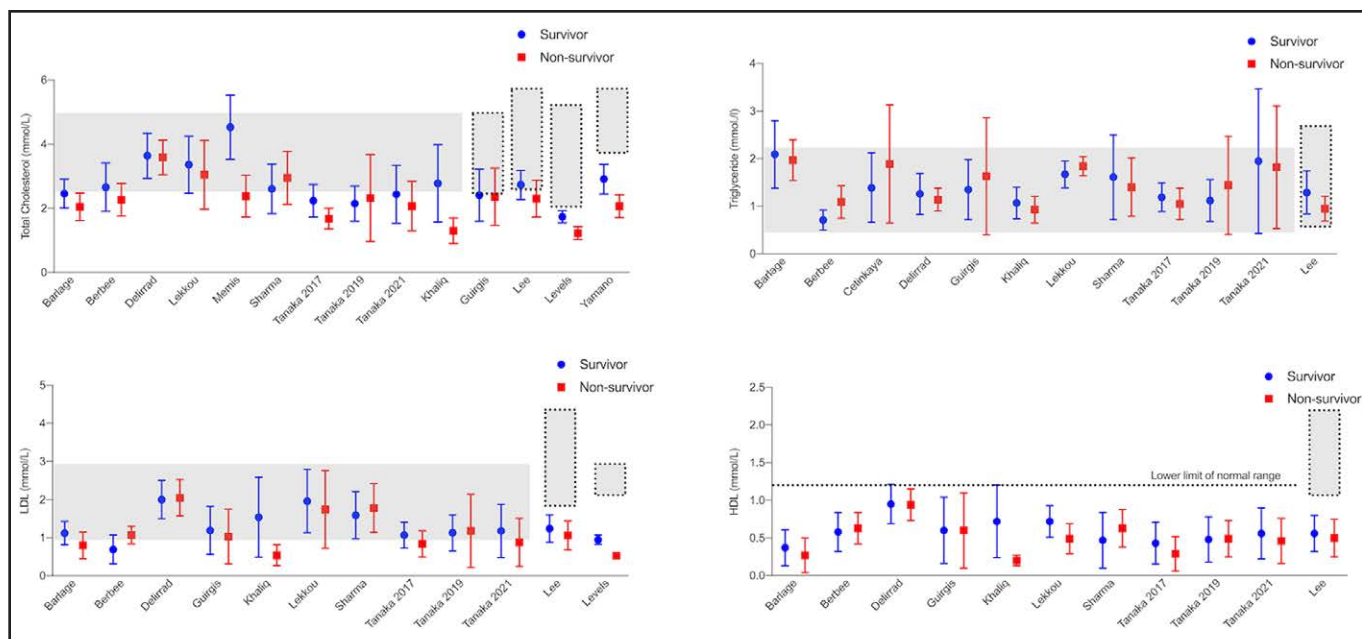


Figure 2. Comparison of total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglyceride levels in eventual survivors and nonsurvivors by study. *Dotted lines* represent normal laboratory ranges, where reported in the studies. *Horizontal gray bars* represent normal laboratory ranges of the author's institution. All values are demonstrated as mean and sd.

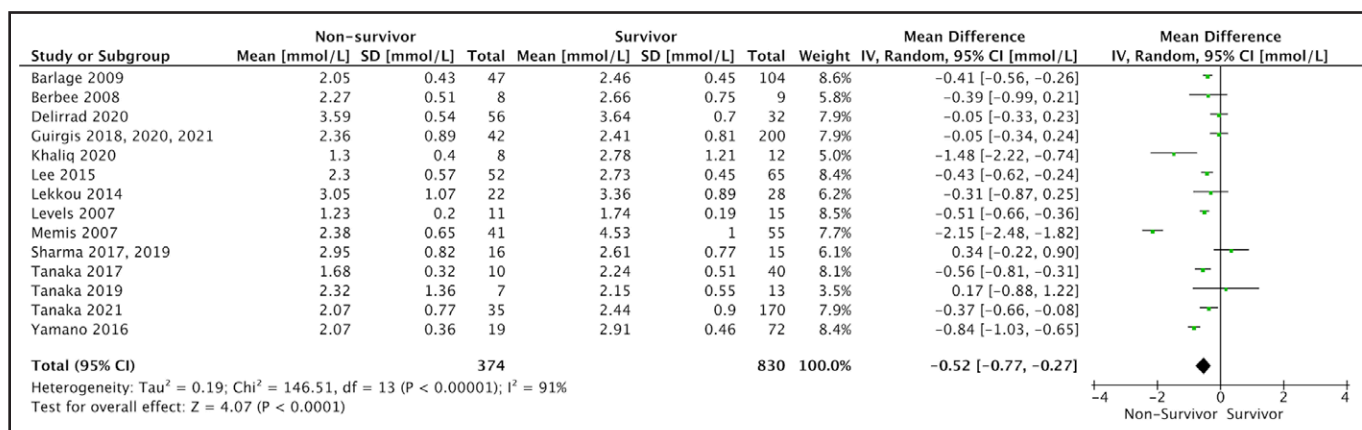


Figure 3. Forest plot—total cholesterol by study. Forest plots representing observational studies and effects on lipid alterations. *Horizontal bars* represent 95% CIs.

between ICU admission cholesterol and TG levels and survival combined for all studies where individual patient parameters were available and provided by the corresponding authors.

DISCUSSION

Our meta-analysis shows an association between a greater degree of hypocholesterolemia (applying to total cholesterol, HDL-C, and LDL-C) at ICU admission and eventual mortality in patients with sepsis, but no association between mortality and admission TG levels.

Alterations in serum lipids are a well-characterized feature in critical illness including sepsis, trauma, and burns (1, 57). A large review by Golucci et al (4) including patients with systemic inflammatory response syndrome and sepsis highlighted changes in lipid metabolism of greater than 30,000 patients and demonstrated profound alterations in total cholesterol, and HDL-C and LDL-C levels. However, this article did not stratify according to survivor status and also included diagnoses other than sepsis.

A recently published meta-analysis analyzed lipid levels in COVID-19 patients and did seek associations

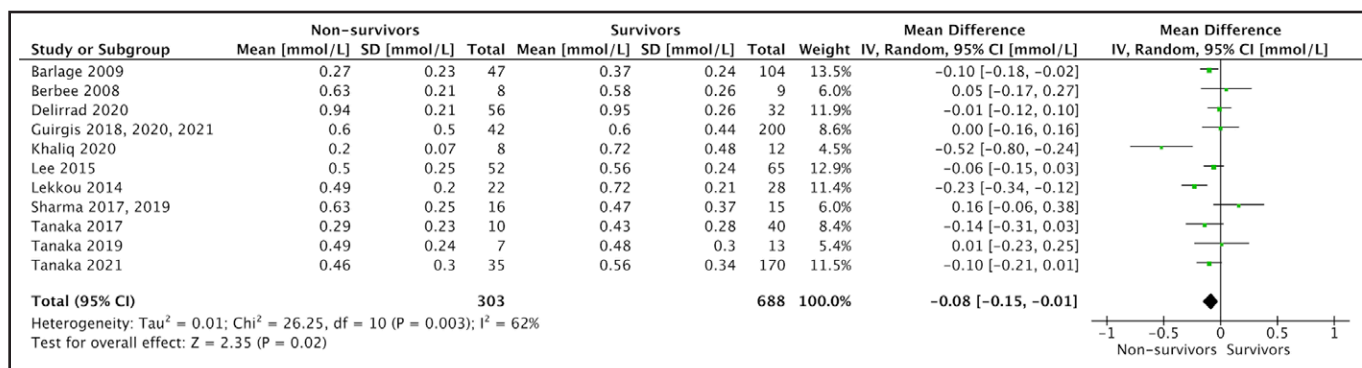


Figure 4. Forest plot—high-density lipoprotein cholesterol by study. Forest plots representing observational studies and effects on lipid alterations. *Horizontal bars* represent 95% CIs.

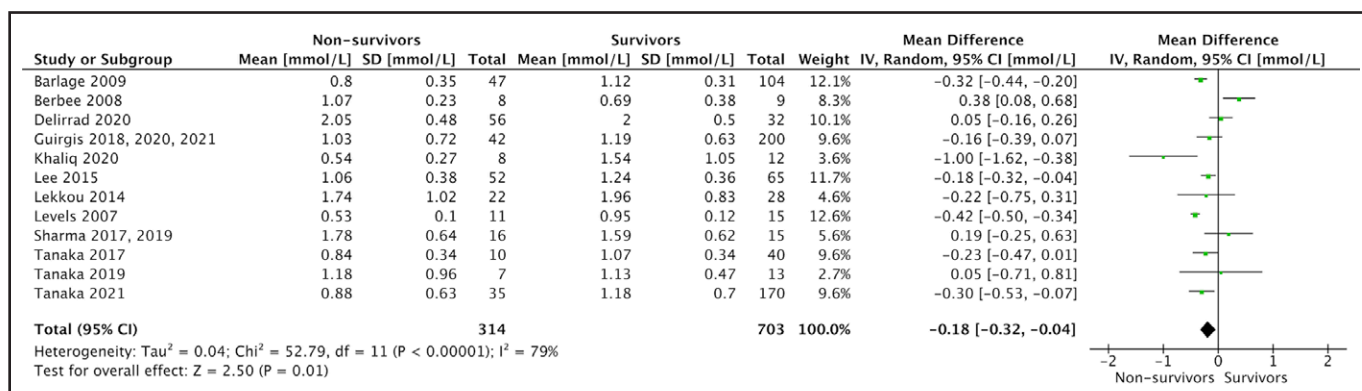


Figure 5. Forest plot—low-density lipoprotein cholesterol by study. Forest plots representing observational studies and effects on lipid alterations. *Horizontal bars* represent 95% CIs.

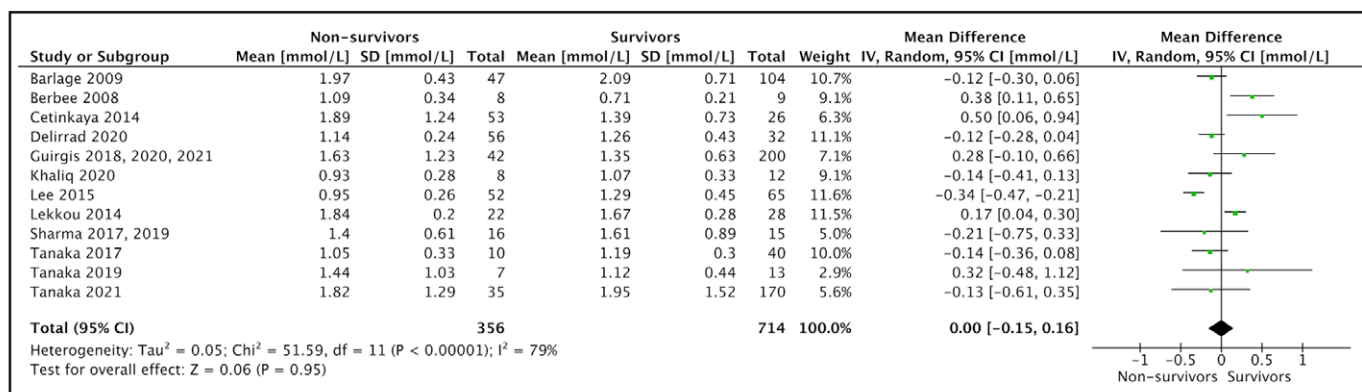


Figure 6. Forest plot—triglycerides by study. Forest plots representing observational studies and effects on lipid alterations. *Horizontal bars* represent 95% CIs.

with disease severity and outcomes (58). Comparable with our findings, the authors were able to demonstrate that patients with severe disease or eventual non-survival exhibited lower cholesterol (total, HDL-C, and LDL-C) but not TG levels, with effect sizes similar to our study. These findings highlight possible similarities in the host response toward bacterial and viral triggers.

From a pathophysiological point of view, diverse biological mechanisms leading to hypocholesterolemia

in sepsis have been proposed, including impaired cholesterol synthesis and reverse cholesterol transport (1). Decreased intake and intestinal absorption and upregulation of the scavenger receptor class B type 1 have also been characterized during critical illness (1). Given the association between low cholesterol and critical illness and, in our present analysis, with sepsis-related mortality, it can be postulated that elevating cholesterol levels could be a beneficial adjunct treatment in

critical illness. Clearly, this relationship may simply be epiphenomenal. However, the multiple roles played by cholesterol in the body do suggest otherwise. A cholesterol-containing liposomal preparation has been trialed in patients with pneumococcal pneumonia as a toxin-binding agent (11), whereas an ongoing clinical study of a fish oil-containing lipid emulsion is being conducted in septic patients with the rationale that the constituents provide substrate for cholesterol synthesis and may, thus, stabilize cholesterol levels (12). Although a large randomized study failed to detect reduced mortality or organ dysfunction after a phospholipid infusion containing phosphatidylcholine, soybean oil, and cholate (but containing no cholesterol) (59), a secondary analysis suggested possible benefits in patients with low HDL levels (60). This work follows on from encouraging laboratory studies, showing various strategies aimed at increasing cholesterol levels in animal, and cell models of infection or sepsis offer outcome benefits. Such strategies include liposome administration (61), pharmacological inhibition of cholesterol ester transfer protein (CETP) (33), and intracellular delivery of cholesterol using nanocarriers (62). As important effects of cholesterol might also be mediated by lipoproteins, which are often dysfunctional in inflammatory states, application of functional lipoproteins might be an interesting approach during sepsis. Preclinical studies applying recombinant HDL without containing cholesterol have shown convincing results (63, 64). Clearly, we await large randomized trials demonstrating safety, tolerability, and efficacy, with identification of subgroups of patients who may benefit most from cholesterol and/or lipoprotein supplementation.

A limitation of our study is the infrequent reporting of preillness use of statins and/or other lipid-lowering agents. One could speculate that preillness statin use may be deleterious because of their lipid-lowering properties. However, statins themselves have anti-inflammatory properties and, notably, also increase both HDL-cholesterol and apolipoprotein A1 to a modest degree, an effect probably mediated by reductions in CETP activity (65). Possible outcome benefits in septic patients have been suggested from preexisting statin use and continuation throughout the septic episode (66–68). Although a randomized trial in patients with acute respiratory distress syndrome showed no overall benefit (69), in a post hoc analysis, the subset of patients with a hyperinflammatory phenotype showed

a significant mortality reduction (70). The difficulty to detect reliable results from statin use in sepsis may be largely due to significant patient heterogeneity. Other limitations include possible publication bias with studies failing to report a lack of association between lipid alterations in sepsis and outcome. Different health-care settings and patient demographics could also reduce the generalizability of our findings, and preillness baseline levels are not reported. However, we consider our obtained I^2 values (especially for HDL-C and LDL-C) adequate, adding strength to this study. Any confounding impact from concurrent use of nutrition and lipid-containing drugs such as the sedative agent propofol has not been reported.

Finally, it is worth reflecting on the utility of the results from this meta-analysis and possible clinical applications. Although these findings sit alongside many other clinical and biochemical prognosticators of poor outcomes in septic patients (71), the baseline serum cholesterol level (total, HDL, or LDL) could be used to enrich trial design by prestratifying patients into higher and lower mortality risk groups. The underlying rationale is that those with low cholesterol levels are most at risk of poor outcomes and would likely benefit most from augmentation of cholesterol levels. A further theranostic application may be achieved by titrating therapy to an optimal serum level. Fixed dosing regimens of immunomodulatory and other interventions have been traditionally used in prospective randomized controlled trials without cognizance of the impact on the individual patient whose baseline pathobiology and response to the therapy will be highly heterogeneous. Arguably, the consistently disappointing results of these studies are due in large part to a combination of nonspecific patient selection and inadequate titration to prime effect.

CONCLUSIONS

In conclusion, our study demonstrated that mortality was associated with lower total cholesterol, HDL, and LDL, but not TG levels among patients admitted to ICU with sepsis. The impact of cholesterol replacement on patient outcomes in sepsis has yet to be determined but merits study, especially in at-risk groups.

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The authors have disclosed that they do not have any potential conflicts of interest.

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The review protocol and raw data are available from the corresponding author upon reasonable request.

Registration: PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42021286120).

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