Meta Analysis

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Omega-3 fatty acid supplementation is associated with favorable outcomes in patients with sepsis: an updated meta-analysis

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Abstract

Objectives: The efficacy of omega-3 fatty acids in the treatment of sepsis is controversial. We conducted an updated meta-analysis to clarify the efficacy of omega-3 fatty acids in patients with sepsis.

Methods: PubMed, EMBASE, and the Cochrane Library were searched for randomized clinical trials (RCTs) on omega-3 fatty acid supplementation in adults with sepsis.

Results: Twenty eligible RCTs involving 1514 patients were included in the meta-analysis. Omega-3 fatty acid supplementation was linked to reductions of mortality ($I^2 = 0$, relative risk [RR] = 0.82, 95% confidence interval [CI] = 0.69–0.97), the duration of mechanical ventilation (DMV; $I^2 = 74\%$, weighted mean difference [WMD] = −2.20, 95% CI = −4.00 to −0.40), and intensive care unit (ICU) length of stay (LOS; $I^2 = 91\%$, WMD = −3.86, 95% CI = −5.72 to −2.01). Subgroup analysis illustrated that mortality was significantly reduced in patients with sepsis and gastrointestinal dysfunction (RR = 0.5, 95% CI = 0.29–0.86, $I^2 = 0$).

Conclusion: Omega-3 fatty acid supplementation might be associated with reduced mortality in patients with sepsis, especially those with gastrointestinal dysfunction. Furthermore, omega-3 fatty acid administration could shorten DMV and ICU LOS.

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Sepsis, omega-3 fatty acids, meta-analysis, mortality, gastrointestinal dysfunction, mechanical ventilation, intensive care unit stay

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Introduction

Sepsis describes critical organ dysfunction that is caused by an uncontrolled host response to infection.[1] Despite advances in basic sciences and clinical treatment, the mortality rate of sepsis remains at 28% to 40%, and sepsis is a leading cause of death in the intensive care unit (ICU).[2] New alternative treatments must be developed to increase the survival rate of patients with sepsis. Recently, some reviews suggested that re-establishing the intestinal microenvironment and targeting the microbiota might effectively address sepsis.[3–5] Omega-3 fatty acids including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-linolenic acid, which have been revealed to improve critical conditions by modulating the composition of the intestinal microbiota, increasing the production of pro-resolving mediators and anti-inflammatory factors, inhibiting nuclear factor receptor (NF-κB) activation, and altering membrane lipid rafts.[6–10] Thus, omega-3 fatty acids may benefit patients with sepsis by altering the gut microbiome and increasing the production of anti-inflammatory mediators.

Although multiple randomized clinical trials attempted to explore the efficacy of supplementation with omega-3 fatty acids in patients with sepsis, the results were not consistent.[11–30] A previous meta-analysis[31] of 17 studies suggested that supplementation with omega-3 fatty acids did not reduce sepsis-related mortality, whereas another meta-analysis[32] of 12 studies demonstrated that parenteral supplementation with omega-3 fatty acids reduced mortality in patients with sepsis. Therefore, by incorporating the data on patients with sepsis, we conducted an updated meta-analysis to clarify the effects of omega-3 fatty acids on morality, the duration of mechanical ventilation (DMV), and ICU length of stay (LOS). Furthermore, we investigated whether with the association between omega-3 fatty acid supplementation and mortality was linked with the stage of sepsis, which was not addressed by previous meta-analyses.

Materials and methods

The present meta-analysis was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. We did not register our study with PROSPERO, but we will do so in future studies.

Search strategy

We attempted to identify all published studies exploring the efficacy of omega-3 fatty acid supplementation in patients with sepsis. We searched for all relevant trials in the Cochrane Library, EMBASE, and PubMed databases published through 30 September 2019. The search strategies are detailed in Appendices 1–3. We also meticulously checked the references of related systematic reviews to avoid missing other eligible studies.

Study selection

The eligibility of studies was first assessed independently by two authors by reading titles and abstracts. Then, the same two authors further evaluated the eligible studies by reading the full text. Any disagreement concerning eligibility was resolved by comparing notes. The inclusion criteria were as follows: (1) randomized clinical trials (RCTs); (2) adult patients diagnosed with sepsis or septic shock; (3) the intervention groups received omega-3 fatty acids (parenteral or enteral route) alone or in combination with other nutritional components; and (4) the evaluated outcomes were mortality (primary outcome), DMV, and ICU LOS (secondary outcomes). The exclusion criteria were as follows: (1) studies other than RCTs; (2) patients without sepsis or septic shock; (3) insufficient data; and (4) relevant outcomes were not reported. No language limitation was applied.

Data extraction

Two investigators independently extracted related data from eligible studies, and any dispute was resolved via discussion. The extracted information included author, publication year, country, sample size, the route of administration, details about the administration, and pertinent outcomes.

Assessment of risk of bias

Two investigators independently employed the Cochrane Collaboration tool to evaluate each study for risk of bias.[33]

Statistical analysis

The RevMan software package (version 5.3.5, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for all statistical analyses. Dichotomous outcomes were expressed as the relative risk (RR), and continuous outcomes were expressed as the weighted mean difference (WMD). Both variables were reported with 95% confidence intervals (CIs). We calculated the standard deviation (SD) using the formula recommended by the Cochrane Collaboration[34] when the value was not directly reported in a study. We also combined low-dose and high-dose intervention groups from one clinical trial into a single omega-3 fatty acid intervention group by following the formula provided in the Cochrane Handbook[34] to calculate the combined means and SDs of pertinent outcomes. The heterogeneity of the included studies was evaluated using the chi-squared test and I^2 statistic.[35] $I^2 > 50\%$ or $P < 0.05$ indicated homogeneity among the studies, and a random-effects model was used for the analysis. $I^2 \leq 50\%$ or $P \geq 0.05$ indicated that there was no homogeneity among the studies, and a fixed-effects model was used for the analysis. To clarify the stability of the results and identify potential sources of heterogeneity, sensitivity analysis was conducted. In addition, publication bias for mortality was evaluated using funnel plots. Differences were considered statistically significant at $P < 0.05$.

Results

Search results

Our search strategies yielded 232 potentially relevant articles from PubMed (82), EMBASE (79), the Cochrane Library (65), and other sources (6). After eliminating duplicates, 172 studies remained. Further reading of titles and abstracts eliminated another 138 studies. The remaining 34 studies were subjected to a full-text assessment, and 14 more studies were excluded for various reasons as explained in Figure 1. Eventually, 20 RCTs involving 1514 patients with sepsis were included in the meta-analysis.

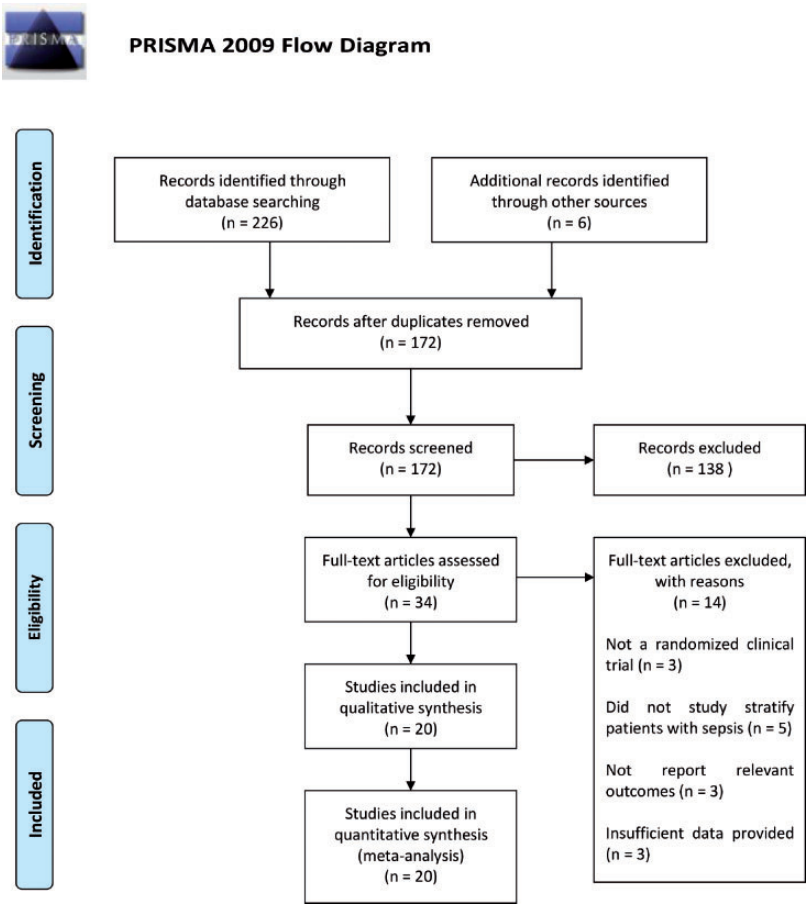

Figure 1. Flow diagram of article selection for meta-analysis.

Features of the included studies

The 20 RCTs [11–30] were published from 1995 to 2018. They were conducted principally in Asia (China, Turkey, Japan), North America (USA), South America (Brazil), Europe (Spain, Romania, Portugal, Switzerland, United Kingdom), and Africa (Egypt). The study populations were patients diagnosed with sepsis, early sepsis, abdominal sepsis, severe sepsis or septic shock, sepsis with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), and sepsis with gastrointestinal dysfunction. Eight studies[11,12,14,19,21,23,27,30] used the enteral route for omega-3 fatty acid supplementation, and the other 12 studies[13,15–18,20,22,24–26,28,29] employed the parenteral route. The risk of bias assessment is presented in Figure 2 and Figure 3. The main details of the 20 eligible studies are summarized in Table 1.

Primary outcome: mortality

The mortality analysis covered the aforementioned 20 studies[11–30] involving 1514 patients. No heterogeneity was detected among the trials ($I^2 = 0\%$, $P = 0.56$). Therefore, we used a fixed-effects model for the analysis. The results indicated that omega-3 fatty acid supplementation

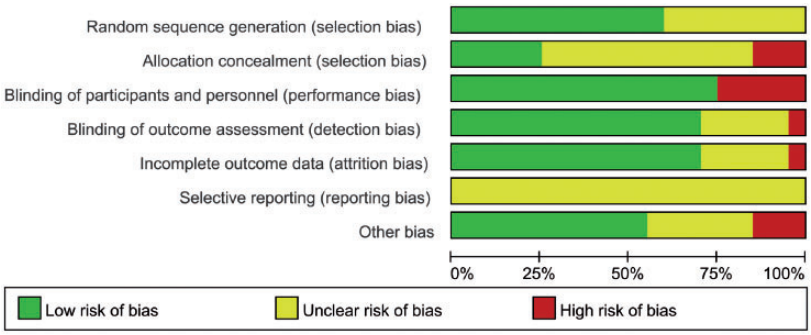

Figure 2. Risk of bias assessment of all included studies.

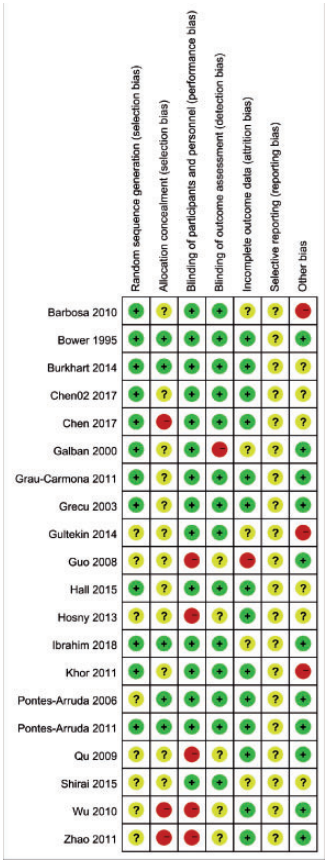

Figure 3. Risk of bias assessment of each individual study.

could lower mortality in patients with sepsis (RR = 0.82, 95% CI = 0.69 to 0.97, $P = 0.02$, Figure 4).

Secondary outcomes: DMV and ICU LOS

Effects of omega-3 fatty acids on DMV. Eight eligible[12,13,17,19,21,23,27,30] studies reported DMV as an outcome. Significant heterogeneity was detected among the trials ($I^2 = 74\%$, $P = 0.0003$), and thus, we used a random-effects model for the analysis. The results demonstrated that supplementation with omega-3 fatty acids reduced DMV (WMD = −2.20, 95% CI = −4.00 to −0.40, $P = 0.02$, Figure 5). To identify possible sources of heterogeneity, sensitivity analysis was performed. After excluding trials[17,19,21,23,27] that did not report SDs directly, no heterogeneity was detected among the remaining trials ($I^2 = 0\%$, $P = 0.41$). In addition, the effect of omega-3 fatty acids on DMV was altered after excluding the aforementioned studies (WMD = −1.29, 95% CI = −2.76 to 0.18, $P = 0.09$, Appendix 4). Thus, the result should be accepted with some caution.

Effects of omega-3 fatty acids on ICU LOS. Fifteen eligible studies[12,13,15,17–24,26–28,30]

Table 1. Characteristics of the included randomized controlled trials.

Study	Country	Population	Route of administration	Nutrition supplement		Mortality definition
				Study	Control	
Bower et al., 1995 [11]	USA	8 centers, 89 patients with sepsis	EN	Impact + RNA	Nutrition formula	NR
Galbán et al., 2000 [12]	Spain	8 centers, 176 patients with sepsis	EN	Impact + arginine, mRNA	High-protein control feed	NR
Grecu et al., 2003 [13]	Romania	1 center, 54 patients with abdominal sepsis	PN	Omegaven + LCTs	LCTs	ICU
Pontes-Arruda et al., 2006 [14]	Brazil	1 center, 103 patients with severe sepsis or septic shock	EN	EPA-GLA, antioxidants	Standard formulation	28 days
Guo et al., 2008 [15]	China	1 center, 80 patients with sepsis	PN	Omega-3 fatty acids	20% fat emulsion	28 days
Qu et al., 2009 [16]	China	1 center, 40 patients with sepsis	PN	Omega-3 fatty acids + TPN	Standard TPN	28 days
Barbosa et al., 2010 [17]	Portugal	1 center, 23 patients with sepsis or systemic inflammatory response syndrome	PN	Lipoplus + NuTRIflex Special	NuTRIflex Lipid Special	28 days
Wu et al., 2010 [18]	China	1 center, 60 patients with sepsis	PN	Omega-3 PUFAs + 20% LCTs	20% LCTs	28 days
Grau-Carmona et al., 2011 [19]	Spain	11 centers, 132 patients with sepsis and acute lung injury or acute respiratory distress syndrome	EN	Oxepa	Ensure Plus HN	28 days
Khor et al., 2011 [20]	China	1 center, 27 patients with severe sepsis	PN	Omegaven	Normal saline	28 days
Pontes-Arruda et al., 2011 [21]	Brazil	5 centers, 106 patients with early stages of sepsis	EN	Oxepa	Ensure Plus HN	28 days

(continued)

Table 1. Continued

Study	Country	Population	Route of administration	Nutrition supplement		Mortality definition
				Study	Control	
Zhao et al., 2011 [22]	China	1 center, 116 patients with sepsis	PN	Omegaven	Standard treatment	28 days
Hosny et al., 2013 [23]	Egypt	1 center, 75 patients with early sepsis	EN	A: High-dose omega-3 + antioxidants B: Low-dose omega-3 + antioxidants	Standard care	28 days
Burkhart et al., 2014 [24]	Switzerland	1 center, 50 patients with sepsis	PN	Omegaven	Nutritional therapy but without omega-3	Median follow-up 109 days
Gultekin et al., 2014 [25]	Turkey	1 center, 32 patients with severe sepsis or septic shock	PN	Omegaven + ClinOleic—Baxter olive oil emulsion	ClinOleic olive oil emulsion	NR
Hall et al., 2015 [26]	United Kingdom	1 center, 60 patients with sepsis	PN	Omegaven	Standard care	28 days
Shirai et al., 2015 [27]	Japan	1 center, 46 patients with sepsis-induced acute respiratory distress syndrome	EN	Oxepa	Ensure Liquid	60 days
Chen et al., 2017 [28]	China	1 center, 48 patients with sepsis-induced gastrointestinal dysfunction	PN	Standard TPNs with omega-3 fatty acids	Standard TPNs without omega-3 fatty acids	28 days
Chen et al., 2017 [29]	China	1 center, 78 patients with severe sepsis with gastrointestinal dysfunction	PN	Long chain fatty acid soybean oil and fish oil	Long chain fatty acid soybean oil without addition of fish oil	28 days
Ibrahim et al., 2018 [30]	Egypt	1 center, 110 patients with severe sepsis	EN	Omega-3 fatty acids	EN formula without omega-3 fatty acids	ICU

PN, parenteral nutrition; EN, enteral nutrition; NR, not reported; EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid; PUFAs, polyunsaturated fatty acids, LCTs, long-chain triglycerides; TPN, total parenteral nutrition.

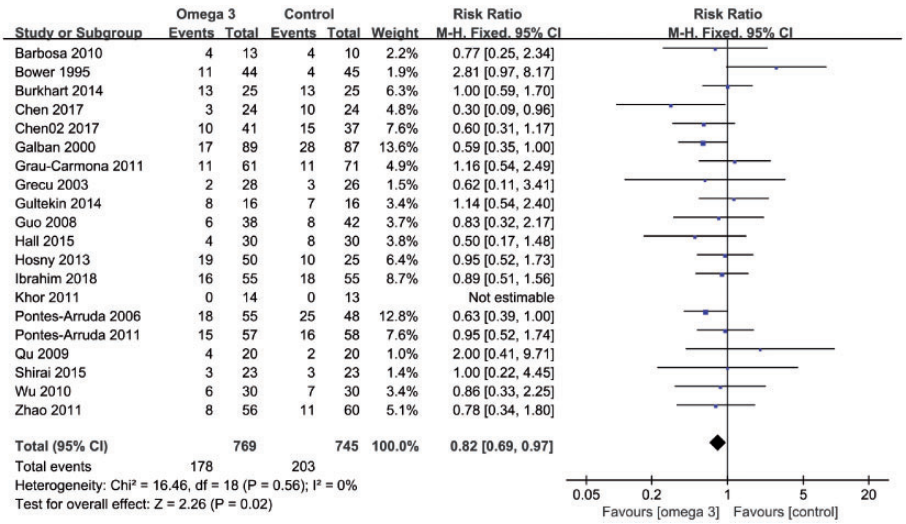

Figure 4. Forest plot of mortality.
CI, confidence interval; M-H, Mantel–Haenszel.

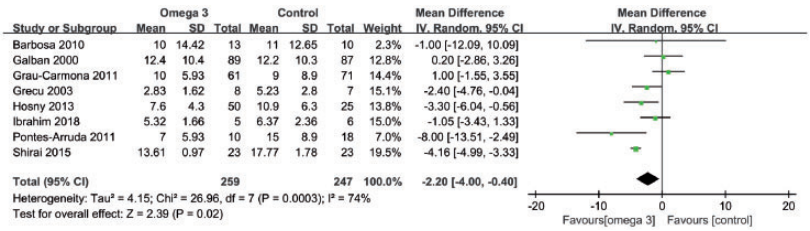

Figure 5. Forest plot of the duration of mechanical ventilation.
SD, standard deviation; CI, confidence interval; IV, inverse variance.

investigated the effects of omega-3 fatty acids on ICU LOS. Significant heterogeneity was found across the studies ($I^2 = 91\%$, $P < 0.00001$), and we used a random-effects model for the analysis. The results suggested that supplementation with omega-3 fatty acids decreased ICU LOS in patients with sepsis (WMD = −3.86, 95% CI = −5.72 to −2.0, $P < 0.0001$, Figure 6). Sensitivity analysis was performed to identify the possible sources of heterogeneity. After eliminating several studies,[13,15,18,20,21,27] heterogeneity decreased among the remaining studies ($I^2 = 40\%$, $P = 0.1$), and the conclusion was not altered (WMD = −2.63, 95% CI = −3.86 to −1.40, $P < 0.0001$, Appendix 5).

Subgroup analysis

We conducted a subgroup analysis to explore whether the stages of sepsis were associated with the effects of omega-3 fatty acid supplementation on mortality in various subgroups. In this study, nine trials[11,12,15–18,22,24,26] enrolled patients diagnosed with sepsis, two trials[21,23] enrolled patients diagnosed with early sepsis, four trials[14,21,25,30] involved patients diagnosed with severe sepsis or septic shock, two

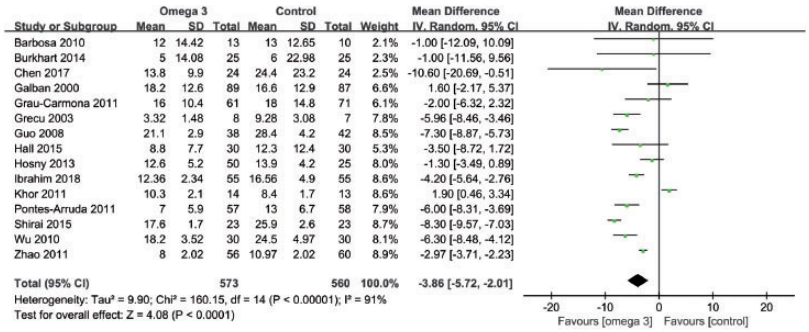

Figure 6. Forest plot of the intensive care unit length of stay.
SD, standard deviation; CI, confidence interval; IV, inverse variance.

trials[19,27] included patients diagnosed with sepsis and ALI or ARDS, and in three trials,[13,28,29] patients with sepsis also presented with gastrointestinal dysfunction. Mortality was significantly reduced in patients with sepsis and gastrointestinal dysfunction (RR = 0.5, 95% CI = 0.29 to 0.86, $P = 0.01$, $I^2 = 0$, Appendix 6). The result suggested that omega-3 fatty acid supplementation might benefit patients with sepsis and gastrointestinal dysfunction.

Publication bias

The funnel plots indicated that there was no conspicuous publication bias in the meta-analysis (Appendix 7).

Discussion

Twenty eligible RCTs involving 1514 patients were included in this meta-analysis. The results revealed that supplementation with omega-3 fatty acids might be associated with reduced mortality and shortened DMV and ICU LOS in patients with septic. Nonetheless, these results were impaired by heterogeneity. Caution should be exercised when interpreting our findings.

Concerning mortality, a previous meta-analysis[31] of 17 studies indicated that supplementation with omega-3 fatty acid did not reduce mortality in patients with sepsis. However, our meta-analysis suggested otherwise. An important difference was that three newly published studies were included in our meta-analysis. Additionally, two newly added studies enrolled patients with sepsis and gastrointestinal dysfunction. Furthermore, the studies in our meta-analysis included patients with various stages of sepsis. The subgroup analysis indicated that omega-3 fatty acids might act as positive modulators in patients with sepsis and gastrointestinal dysfunction. Hence, the effects of omega-3 fatty acid supplementation on mortality in patients with sepsis could vary by the stage of sepsis, and patients with sepsis tend to have several complications.

A previous meta-analysis[32] covering 12 RCTs indicated that parenteral supplementation with omega-3 fatty acids did not significantly shorten DMV in patients with sepsis. The discrepancy between their findings and our data might be ascribed to the exclusion of RCTs in which omega-3 fatty acids were supplied enterally. However, additional nutrients, such as anti-oxidant vitamins and amino acids (arginine or glutamine), were supplemented with omega-3 fatty acids via the enteral route, whereas concerning parenteral supplementation, only omega-3 fatty acids were given.

The addition of other nutrients may have affected the results.

Our meta-analysis, which included 15 RCTs, indicated that supplementation with omega-3 fatty acids could decrease ICU LOS in patients with sepsis, contradicting a previous meta-analysis[36] involving 11 studies. Because the heterogeneity was high among our included studies, more trials are needed to further support our findings.

Several mechanisms might explain the beneficial effects of omega-3 fatty acids on sepsis. Presumably, critical illness may well disturb the intestinal microenvironment, thereby upsetting the balance among intestinal flora and further leading to immunosuppression and other undesired consequences in patients with sepsis.[4] A recent study[37] demonstrated that the gut microbiome could alter the immunophenotype and survival rate of septic mice and might serve as a therapeutic target for sepsis. In addition, Watson et al.[6] demonstrated that omega-3 fatty acid supplementation could induce a reversible increase in the counts of bacteria that produce short-chain fatty acids, such as *Bifidobacterium*, *Lactobacillus*, and *Roseburia*. Additionally, an animal study by Kaliannan et al.[38] revealed that omega-3 fatty acid supplementation in mice could decrease the counts lipopolysaccharide-producing bacteria (enterobacteria) and increase those of lipopolysaccharide-suppressing bacteria (*Bifidobacterium*), thereby altering the gut microbiota and alleviating endotoxemia. Thus, omega-3 fatty acids might act as positive modulators in patients with sepsis by altering the gut microbiome and increasing the production of anti-inflammatory mediators, such as short-chain fatty acids. Moreover, omega-3 fatty acids could affect inflammation by increasing the production of anti-inflammatory factors and pro-resolving mediators as well as inhibiting the activation of NF-κB.[39,40]

In fact, the target organ of omega-3 fatty acid treatment remains unclear. Previous studies in schoolchildren with asthma revealed improved lung function after the administration of omega-3 fatty acids.[41,42] Another meta-analysis involving 17 trials indicated that omega-3 fatty acids reduced joint pain, the duration of morning stiffness, and the dosage of nonsteroidal anti-inflammatory drugs in patients with rheumatoid arthritis.[43] Additionally, several studies yielded inconsistent results regarding the role of omega-3 fatty acids in inflammatory bowel disease.[44,45] Our subgroup analysis demonstrated that omega-3 fatty acids might act as positive modulators in patients with sepsis and gastrointestinal dysfunction. Future efforts should be directed at identifying the target organs of omega-3 fatty acids.

Some factors such as the dose of omega-3 fatty acids, the proportions of n-3 and n-6 fatty acids, and the proportions of EPA and DHA might alter the effects of omega-3 fatty acids in patients with sepsis. The major studies included in the current meta-analysis used an omega-3 fatty acid dose of 0.2 g/kg/day, and previous studies illustrated that high-dose omega-3 fatty acids in patients with sepsis appear safe, and they may have a key role in treatment.[23] The proportions of EPA and DHA in the included studied ranged 0.86 to 2.3 g/day, and the different proportions may affect the evaluation of efficacy. Previous studies indicated that ratios of 1:2 to 1:4 might be optimal for n-3 and n-6 fatty acids to reduce inflammation.[46] Currently, high-quality trials with a large number of patients with sepsis are needed to further explore the optimal dosage and components of omega-3 fatty acids to improve patient outcomes.

Our meta-analysis had several limitations. First, the patients included in our meta-analysis had various stages of sepsis, and the patient background should be

considered when evaluating the efficacy of omega-3 fatty acids. Second, the high heterogeneity in the ICU LOS and DMV analyses could affect the interpretation of treatment efficacy. Third, although most RCTs administered a placebo solution to the control group, two RCTs[23,26] provided control groups with only standard sepsis care. One strength of this meta-analysis consisted was that it included more eligible studies than previous meta-analyses. To our knowledge, the present study is the largest meta-analysis to systemically examine the efficacy of omega-3 fatty acid supplementation in patients with sepsis. Additionally, no obvious publication bias was found in our analysis.

Conclusions

Omega-3 fatty acid supplementation might be associated with reduced mortality in patients with sepsis, especially those with gastrointestinal dysfunction. Furthermore, the administration of omega-3 fatty acids appeared to shorten DMV and ICU LOS. High-quality trials with a large number of patients with sepsis are needed to further support our findings. Future studies should further identify the organs targeted by omega-3 fatty acids.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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: 801–810.
2. Napolitano LM. Sepsis 2018: Definitions and Guideline Changes. *Surg Infect* 2018; 19: 117–125.
3. Fay KT, Ford ML and Coopersmith CM. The intestinal microenvironment in sepsis. *Biochim Biophys Acta* 2017; 1863: 2574–2583.
4. Haak BW and Wiersinga WJ. The role of the gut microbiota in sepsis. *Lancet Gastroenterol Hepatol* 2017; 2: 135–143.
5. Cabrera-Perez J, Badovinac VP and Griffith TS. Enteric immunity, the gut microbiome, and sepsis: Rethinking the germ theory of disease. *Exp Biol Med* 2017; 242: 127–139.
6. Watson H, Mitra S, Croden FC, et al. A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota. *Gut* 2018; 67: 1974.
7. Calder PC. Polyunsaturated fatty acids and inflammatory processes: New twists in an old tale. *Biochimie* 2009; 91: 791–795.
8. Serhan CN, Chiang N and Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* 2008; 8: 349–361.
9. Martin JM and Stapleton RD. Omega-3 fatty acids in critical illness. *Nutr Rev* 2010; 68: 531–541.
10. Novak TE, Babcock TA, Jho DH, et al. NF-kappa B inhibition by omega -3 fatty acids modulates LPS-stimulated macrophage TNF-alpha transcription. *Am J Physiol Lung Cell Mol Physiol* 2003; 284: 84–89.
11. Bower RH, Cerra FB, Bershadsky B, et al. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. *Crit Care Med* 1995; 23: 436–449.

12. Galbán C, Montejo JC, Mesejo A, et al. An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. *Crit Care Med* 2000; 28: 643–648.
13. Grecu I, Mirea L and Grintescu I. Parenteral fish oil supplementation in patients with abdominal sepsis. *Clin Nutr* 2003; 22: S23.
14. Pontes-Arruda A, Aragao AM and Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, γ-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. *Crit Care Med* 2006; 34: 2325–2333.
15. Guo Y. ω-3 duo bu baohe zhifangsuan dui nong du zheng huanzhe linchuang liaoxiao ji yuhou de yingxiang (Effect of omega-3 polyunsaturated fatty acids on clinical efficacy and prognosis in patients with sepsis). *Shanxi Med J* 2008; 37: 727–729.
16. Qu A and Xu L. Yuyou zhifang ru dui nong du zheng huanzhe mianyi gongneng de tiaojie zuoyong guancha (Regulation of fish oil fat emulsion on immune function in patients with sepsis). *Shandong Med J* 2009; 49: 13–15.
17. Barbosa VM, Miles EA, Calhau C, et al. Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: a randomized, controlled clinical trial. *Crit Care* 2010; 14: R5.
18. Wu YY. ω-3-duo bu baohe zhifangsuan dui nong du zheng huanzhe mianyi gongneng ji yuhou de yingxiang (Omega-3 polyunsaturated fatty acids on immune function and prognosis in patients with sepsis). Master's thesis, Hebei Medical University, 2010.
19. Grau-Carmona T, Morán-García V, García-de-Lorenzo A, et al. Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and anti-oxidants on the outcome of mechanically ventilated, critically ill, septic patients. *Clin Nutr* 2011; 30: 578–584.
20. Khor B, Liaw S, Shih H, et al. Randomized, Double Blind, Placebo-Controlled Trial of Fish-oil-based Lipid Emulsion Infusion for Treatment of Critically Ill Patients With Severe Sepsis. *Asian J Surg* 2011; 34: 1–10.
21. Pontes-Arruda A, Martins LF, De Lima SM, et al. Enteral nutrition with eicosapentaenoic acid, γ-linolenic acid and antioxidants in the early treatment of sepsis: results from a multicenter, prospective, randomized, double-blinded, controlled study: the INTERSEPT study. *Crit Care* 2011; 15: R144.
22. Zhao KF, Zhou WN and Bo CH. ω-3 yuyou zhifang ru dui nong du zheng huanzhe de linchuang liaoxiao (Clinical efficacy of omega-3 fish oil fat emulsion in patients with sepsis). *Shangdong Med J* 2011; 51: 102.
23. Hosny M, Nahas R, Ali S, et al. Impact of oral omega-3 fatty acids supplementation in early sepsis on clinical outcome and immunomodulation. *Egypt J Crit Care Med* 2013; 1: 119–126.
24. Burkhart CS, Dell-Kuster S, Siegemund M, et al. Effect of n-3 fatty acids on markers of brain injury and incidence of sepsis-associated delirium in septic patients. *Acta Anaesthesiol Scand* 2014; 58: 689–700.
25. Gultekin G, Sahin H, Inanc N, et al. Impact of Omega-3 and Omega-9 fatty acids enriched total parenteral nutrition on blood chemistry and inflammatory markers in septic patients. *Pak J Med Sci* 2014; 30: 299–304.
26. Hall TC, Bilku DK, Al-Leswas D, et al. A Randomized Controlled Trial Investigating the Effects of Parenteral Fish Oil on Survival Outcomes in Critically Ill Patients With Sepsis. *JPEN J Parenter Enteral Nutr* 2015; 39: 301–312.
27. Shirai K, Yoshida S, Matsumaru N, et al. Effect of enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with sepsis-induced acute respiratory distress syndrome. *J Intensive Care* 2015; 3: 24.
28. Chen HS, Wang W, Hong YC, et al. Single-blinded, randomized, and controlled clinical trial evaluating the effects of Omega-3 fatty acids among septic patients with intestinal dysfunction: A pilot study. *Exp Ther Med* 2017; 14: 1505–1511.
29. Chen HS, Wang W, Hong CY, et al. Omega-3 Fish Oil Reduces Mortality Due to Severe Sepsis with Acute Gastrointestinal Injury

Grade III. *Pharmacogn Mag* 2017; 13: 407–412.
30. Ibrahim ES. Enteral nutrition with omega-3 fatty acids in critically ill septic patients: A randomized double-blinded study. *Saudi J Anaesth* 2018; 12: 529–534.
31. Lu C, Sharma S, McIntyre L, et al. Omega-3 supplementation in patients with sepsis: a systematic review and meta-analysis of randomized trials. *Ann Intensive Care* 2017; 7: 58.
32. Mo YP, Hu XL, Chang LL, et al. The effect of omega-3 fatty acid supplementation in parenteral nutrition on the outcome of patients with sepsis: a systematic review and meta-analysis. *Chin Crit Care Med* 2014; 26: 142–147.
33. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
34. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Available from www.training.cochrane.org/handbook.
35. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560.
36. Tao W, Li PS, Shen Z, et al. Effects of omega-3 fatty acid nutrition on mortality in septic patients: a meta-analysis of randomized controlled trials. *BMC Anesthesiol* 2016; 16: 39.
37. Fay KT, Klingensmith NJ, Chen C, et al. The gut microbiome alters immunophenotype and survival from sepsis. *FASEB J* 2019; 33: 11258–11269.
38. Kaliannan K, Wang B, Li X, et al. A host-microbiome interaction mediates the opposing effects of omega-6 and omega-3 fatty acids on metabolic endotoxemia. *Sci Rep* 2015; 5: 11276.
39. Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochim Biophys Acta* 2015; 1851: 469–484.
40. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc Trans* 2017; 45: 1105–1115.
41. Brigham EP, Woo H, McCormack M, et al. Omega-3 and Omega-6 Intake Modifies Asthma Severity and Response to Indoor Air Pollution in Children. *Am J Respir Crit Care Med* 2019; 199: 1478–1486.
42. Hodge L, Salome CM, Hughes JM, et al. Effect of dietary intake of omega-3 and omega-6 fatty acids on severity of asthma in children. *Eur Respir J* 1998; 11: 361–365.
43. Goldberg RJ and Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. *Pain* 2007; 129: 210–223.
44. Belluzzi A, Brignola C, Campieri M, et al. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N Engl J Med* 1996; 334: 1557–1560.
45. Limketkai BN, Wolf A and Parian AM. Nutritional Interventions in the Patient with Inflammatory Bowel Disease. *Gastroenterol Clin North Am* 2018; 47: 155–177.
46. Mayer K and Seeger W. Fish oil in critical illness. *Curr Opin Clin Nutr* 2008; 11: 121–127.