Effects of fish oil-containing nutrition supplementation in adult sepsis patients: a systematic review and meta-analysis

Hongyu Wang1,3, Sen Su1, Chao Wang2, Jianhong Hu2, Wu Dan1 and Xi Peng1,2,*

1Clinical Medical Research Center, Southwest Hospital, The Third Military Medical University, Chongqing 400000, China; 2Institute of Burn Research, Southwest Hospital, State Key Laboratory of Trauma, Burns and Combined Injury, The Third Military Medical University, Chongqing, China; and 3Department of Burns and Plastic, PLA No.983 Hospital, Tianjin 300000, China

*Correspondence. Email: pxlrm@163.com

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Abstract

Background: Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Although fish oil has been used as an immunonutritional preparations for the treatment of sepsis patients, there is still controversy as to whether it is beneficial to them. We systematically reviewed published clinical trial data to evaluate the effectiveness of fish oil-containing nutrition supplementation in sepsis patients.

Methods: A systematic search was undertaken in PubMed, Embase, Chinese Biomedicine Database, the Cochrane Library and the China Knowledge Resource Integrated Database to obtain clinical controlled trails. RCTs on nutrition therapy containing fish oil among adult sepsis patients were selected for analysis in comparison with routine therapy.

Results: Twenty-five published trials were included in the meta-analysis. Fish oil-containing nutrition supplementation reduced the mortality compared with the control group (relative risk (RR) 0.74, I² = 0%). Fish oil also shortened the ICU stay (MD −3.57 days; 95% CI −4.54, −2.59; p<0.00001; I² = 76%), hospital stay (MD −9.92 days; 95% CI −15.37, −4.46; p = 0.0004; I² = 91%) and the duration of mechanical ventilation support (MD −2.26; 95% CI −4.27, −0.26; p = 0.03; I² = 83%). A subgroup analysis based on the route of administration revealed that parenteral administration of fish oil could reduce mortality in septic patients (RR =0.68, I² = 0%), but no significant difference in mortality was observed in the fish oil group administered by enteral route (RR = 0.80, I² = 0%). No statistically significant publication biases were detected for the above clinical endpoints (p>0.05).

Conclusions: Parenteral nutrition containing fish oil could significantly decrease mortality in sepsis patients while enteral administration could not. Fish oil-containing nutrition supplementation.

Key words: Sepsis, Fish oil, Meta-analysis, Nutrition therapy, Omega-3 fatty acids

Highlights

• We carried out a systematic review and meta-analysis of RCTs to evaluate the effect of fish oil-containing nutrition provision on patients with sepsis compared with standard nutrition supplementation.
• The potential outcomes that might be related to the different routes for nutrition supplementation (parenteral and enteral nutrition) were analyzed.
• Parenteral nutrition containing fish oil could significantly decrease mortality in sepsis patients while enteral administration could not.
• Fish oil-containing nutrition supplementation decreased the duration of ICU stay, hospital stay and mechanical ventilation.

Background
Sepsis is life-threatening organ dysfunction resulting from dysregulated host responses to infection [1]. This syndrome is a complex disorder that develops as a dysregulated host response to an infection, and is associated with acute organ dysfunction and a high risk of death [2,3]. Sepsis is an important public health issue with considerable economic consequences over the past 30 years [4]. Despite the development of pharmacology, life support and intensive care technology, the morbidity and mortality for patients with sepsis, particularly those with shock, remain high [5,6]. Nutritional support is one of the indispensable therapeutic strategies for patients with sepsis, which is a condition of high catabolism in need of ramped-up energy provision [7]. Hypercatabolism in septic patients can lead to dramatic loss of lean body mass, myophagism, weakness, organ dysfunction, etc. if not corrected in time [8].

On the one hand, conventional nutrition therapy provides the body with the necessary energy and metabolic substrates [9]. On the other hand, the addition of pharmaco-nutrients such as glutamine, arginine, omega-3 (ω-3) fatty acids, vitamin C and selenium can invigorate systemic immune defense. Among these special nutrients, omega-3 fatty acids are increasingly valued and widely used in clinical practice. Fish oil contains rich omega-3 polyunsaturated fatty acids (PUFA), particularly, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Administration of fish oil nutrition support has been found to be beneficial for a multitude of diseases, such as diabetes [10], cancer, asthma [11], cardiovascular diseases [12], obesity [13], HIV [14,15] and organ transplant [16], etc.

Fish oil may modulate the inflammatory response and uncontrolled cytokines cascade in sepsis. Therefore, clinical trials have been conducted to evaluate the potential benefit of fish oil-containing nutritional support in patients with sepsis. Nevertheless, the efficacy of fish oil-containing nutrition therapy for patients with sepsis is controversial. A study by Chen et al. reported that omega-3 fatty acid supplementation could reduce the mortality rate of sepsis and sepsis-induced acute respiratory distress syndrome [17]. A meta-analysis by Mo et al. showed that fish oil supplementation by parenteral nutrition (PN) delivery decreased mortality and the length of intensive care unit (ICU) stay and hospitalization among patients with sepsis [18]. However, Tao et al. concluded the opposite result via meta-analysis on some previous randomized controlled trials (RCTs), which revealed that fish oil provision did not improve mortality but did reduce the duration of mechanical ventilation [19]. Similarly, another earlier meta-analysis showed that PN enriched with fish oil did not reduce the mortality of patients with sepsis, although it could reduce the overall length of hospitalization [20].

To date, a few RCTs have investigated the effect of fish oil-containing nutrition supplementation in adults with sepsis, although their results are inconsistent. Causal inferences from RCTs can, however, be undermined by flaws in design, conduct, analyses and reporting. Systematic reviews and meta-analyses aim to collate and synthesize all studies that meet pre-specified eligibility criteria using methods that attempt to minimize bias [21]. Thus, in this paper, we carried out a systematic review and meta-analysis of RCTs to evaluate the effect of fish oil-containing nutrition provision on patients with sepsis compared with standard nutrition therapy and, furthermore, we analyzed the potential outcomes that might be related to the different routes for nutrition supplementation [PN and enteral nutrition (EN)].

Methods
Inclusion criteria
A total of 25 RCTs involving fish oil-containing nutrition supplementation for adult patients with sepsis were included. Mortality was the primary outcome and durations of ICU stay, hospital stay and mechanical ventilation were secondary outcomes. Only RCTs designed with parallel control groups were selected, with self-control and crossover trials excluded. The control groups were provided the same nutrition except for fish oil supplementation. As long as the primary endpoint was described, the research could be included in the meta-analysis. The following criteria were applied in selecting the studies: (1) research design: RCT; (2) demographic: adult patients with sepsis; (3) intervention: fish oil-containing nutrition supplementation vs the therapy without fish oil; (4) primary endpoint: mortality; (5) secondary endpoint: duration of ICU stay, hospital stay and mechanical ventilation.

Exclusion criteria
Publications in the form of reviews, letters to the editor, animal or cellular studies were excluded. In addition retrospective studies and studies that were not original, papers reporting the same RCTs, RCTs that included children and papers in which the control group was set as healthy people were all excluded.

Search strategy
An overall literature search was conducted online, using a combination incorporating the population (sepsis or septic patient) and the intervention (fish oil, omega-3 fatty acid, EPA or DHA) through to 1 June 2021. Relevant papers and reports were reviewed and screened with no language preferences in PUBMED, EMBASE, Chinese Biomedicine Database (CBM)
and China Knowledge Resource Integrated Database (CNKI), all from 1990, and the Cochrane Library from 2000 to 2021. To acquire sufficient relevant materials, the limits put on human studies and clinical trials were removed and the built-in sensitive strategies were taken in search of the studies. [22,23].

The following keywords were used: ‘fish oil’, ‘ω-3’, ‘eicosapentaenoic acid’, ‘docosahexaenoic acid’ or ‘yu you (fish oil)’ and ‘sepsis’, ‘septic patient’ or ‘nong du zheng (sepsis)’, ‘bai xue zheng (sepsis)’ in English and Chinese. In addition, the following journals were searched: Annals of Surgery, The Journal of Parenteral and Enteral Nutrition, Nutrition and Clinical Nutrition (all four from January 1990 to 1 June 2021), and the Chinese Journal of Clinical Nutrition (from January 1993 to 1 June 2021). After viewing and screening the potentially relevant papers, the final included studies were selected for further analysis (Figure 1).

**Study selection**

Two reviewers (HW and SS) independently viewed titles, abstracts and then full manuscripts progressively according to the inclusion criteria. Discrepancies were settled through discussion involving a third reviewer.

**Data extraction and management**

Two investigators (HW and CW) independently extracted the following data: study characteristics, methodology of the RCT (design, setting, enrolment date, sample size, eligibility criteria, quality, funding, ethics), demographics data (baseline characteristics), intervention regimen (e.g. duration, intensity, comparison of intakes) and control regimen. Divergences were resolved through discussion by reference to the source study. Of the papers where the data was insufficient in its published form, we requested the data that we needed from the source authors through communication by email.

**Assessment of risk of bias**

Two investigators (HW and XP) assessed the methodological quality in all selected articles independently, following the Cochrane Handbook 6.2 (www.training.cochrane.org/handbook). Funnel plots were used to analyze publication bias.

**Data analysis**

All results were analyzed using Review Manager (version 5.3) and R (version 4.03).
The common risk ratio (RR) was reported for binary outcomes with 95% confidence intervals (CIs). We estimated mean differences with 95% CIs for the ICU stays, hospital stays and duration of mechanical ventilation. Heterogeneity was evaluated using both the I² test and the Mantel Haenszel $\chi^2$ method and either $I^2 \geq 50\%$ or $p < 0.05$ indicates statistical heterogeneity. We reported the results from the included trials with no significant heterogeneity. Meta regression was performed when $I^2 \geq 50\%$.

**Results**

A total of 537 potentially relevant publications were identified. After strict screening, 79 RCT papers were further considered, among which, 25 RCTs [24–48] met the inclusion criteria. Apart from the data and results accessed online, we contacted the researchers who performed the RCTs included in this meta-analysis for further supportive data.

**Study characteristics**

Table 1 shows the key characteristics of the included studies. Seven articles were published in Chinese and the others were published in English. Of the 25 RCTs, 7 were conducted in Europe, 14 in East Asia, 2 in Africa and 2 in South America. All of them are RCTs and placebo-controlled trials. A total of 1903 patients were included in this study. Sample sizes ranged from 23 to 181 participants. The control groups were given standard nutrition in 16 RCTs, medium-chain triglycerides/long-chain triglycerides in 2 RCTs, 0.9% normal saline in 1 RCT and other nutritional therapy without fish oil in 6 RCTs. Six RCTs involved the EN route, the others involved the PN route. The fish oil dosages given to the patients are listed in Table 1. Total calorie intake was reported in 7 RCTs [24–27, 37, 43, 48].

After evaluating the risk of bias in the included RCTs by using the Cochrane collaboration’s tool, it turned out that there was no significant risk of bias nor publication bias according to the funnel plots (Figure 2).

**Primary outcome**

The meta-analysis included 25 RCTs with 1903 participants, of whom 959 received fish oil-containing nutrition (fish oil group) and 944 received nutrition without fish oil or omega-3 (control group). With no significant heterogeneity among all trials ($p = 0.94, I^2 = 0\%$), the fixed-effects model was adopted for further analysis between the fish oil group and control for RR (Figure 3). Forest plots showed that in general, additional intake of fish oil was closely correlated to lower mortality in the experimental groups compared with the control groups (95% CI, RR = 0.74 (0.63–0.86); $p < 0.0001$, Figure 3).

According to the different routes of nutrition support, subgroups PN and EN were further analyzed. Interestingly, lower mortality was found in the PN subgroup (95% CI, RR = 0.68 (0.56–0.84); $p = 0.0004; I^2 = 0\%$, Figure 3). However, in the EN subgroup, the addition of fish oil did not make a significant difference in mortality among patients (RR = 0.80; 95% CI 0.64–1.01; $p = 0.06; I^2 = 0\%$, Figure 3).

**Secondary outcomes**

The fish oil-containing nutrition intake among patients impacted on their ICU stay, hospital stay and duration of mechanical ventilation as shown in the forest plots (Figure 4).

In detail, a significant reduction in ICU stay was observed in the fish oil group [Figure 4a, mean difference (MD): $−3.57$ days; 95% CI ($−4.54, −2.59$); $p < 0.00001$; $I^2 = 76\%$].

Fish oil-containing nutrition supplementation also helped to shorten hospital stay (Figure 4b, MD: $−9.92$ days; 95% CI ($−15.37, −4.46$); $p = 0.0004$; $I^2 = 91\%$). In the meta-analysis of three studies including 328 participants, the duration of mechanical ventilation was shorter in patients receiving fish oil (Figure 4c, MD $−2.84$ days; 95% CI ($−5.24, −0.44$); $p = 0.02; I^2 = 67\%$).

**Heterogeneity and meta-regression**

Considering the high heterogeneity, the random effect model was used to evaluate the secondary outcomes. The causes for heterogeneity in ICU stay were examined by meta-regression. Age, area (regional differences), severity of sepsis and route of administration were selected as covariates based on the available data and clinical analysis. The results of univariate meta-regression indicated that area ($p = 0.0122$), severity ($p = 0.0015$) and route of administration ($p = 0.001$) collectively contributed to the heterogeneity (Figure 5). Due to the lack of sufficient data for hospital stay and mechanical ventilation, we failed to perform meta-regression related to those two factors.

**Discussion**

This meta-analysis was conducted to evaluate the efficacy of fish oil among patients with sepsis. The primary outcome of our meta-analysis suggested that PN containing fish oil decreased mortality in septic patients. We found no statistically significant results with respect to mortality in the fish oil group administered by the EN route. The secondary outcomes suggested that fish oil-containing nutrition supplementation decreased the duration of ICU stay, hospital stay and mechanical ventilation.

Sepsis is a time-dependent syndrome, initiating from systemic and hypermetabolic inflammation to an imbalanced state of the immune system. The imbalanced state includes immunosuppression and cytokine storm. The fish oil should be given at the initial hyperinflammatory stage or early stage of sepsis. Pathophysiological, endotoxins and exotoxins secreted from pathogens, activate the innate immune response, resultantly mediating the production of inflammatory cytokines, like TNF-α, IL-1β, IL-6, IL-10, interferon regulatory factor 3/7 (IRF3, IRF7), etc. [49, 50]. This further disturbs endothelium functions, microcirculation, glucose and protein metabolism, impairs mitochondrial functions and
| Study          | Region     | Patient Description                                                                 | Route    | Critical score in FO groups | Critical score in control groups | Nutrition in FO groups                                      | Nutrition in control groups | Clinical outcomes                                                                 |
|---------------|------------|--------------------------------------------------------------------------------------|----------|----------------------------|----------------------------------|------------------------------------------------------------|----------------------------|----------------------------------------------------------------------------------|
| Barbosa et al. 2010 [25] | Portugal   | 23 Patients in ICU, sepsis, severe sepsis, sepsis shock                              | PN       | APACHE II 26 ± 9           | APACHE II 26 ± 11                | Fish oil emulsion 100 mL/d, 7 d                            | Standard treatment          | Shorter hospital stay in FO group, mortality, days of ventilation and ICU stay were not different between groups |
| Burkhart et al. 2014 [30] | Switzerland | 50 Patients with sepsis in ICU                                                      | PN       | APACHE II 22.60 ± 3.40     | APACHE II 20.67 ± 2.69           | Fish oil emulsion 100 mL/d, 7 d                            | Standard treatment          | Shorter ICU stay in FO group, mortality was similar in both groups               |
| Chen et al. 2011 [39]  | China      | 30 Patients in ICU, sepsis with organ failure                                        | PN       | APACHE II 25.6 ± 5.2       | APACHE II 23.4 ± 5.1             | Fish oil emulsion 10 g/d for at least 7 d                 | Standard treatment          | Days of ventilation and ICU stay were different between groups                   |
| Chen et al. 2011 [41]  | China      | 48 Patients in ICU, sepsis, severe sepsis, sepsis shock                              | PN       | APACHE II 32.0 ± 6.7       | APACHE II 30.5 ± 6.2             | Fish oil emulsion 10 g/d for at least 7 d                 | Standard treatment          | Lower mortality and ICU stay in FO group                                         |
| Chen et al. 2017 [40]  | China      | 78 Patients in ICU, sepsis with acute gastrointestinal injury                       | PN       | APACHE II 32.0 ± 6.7       | APACHE II 30.5 ± 6.2             | Fish oil emulsion 10 g/d for at least 7 d                 | Standard treatment          | Mortality was significantly improved in FO group, the length of stay in the ICU and the days of mechanical ventilation were not different between groups |
| Chen et al. 2014 [42]  | China      | 53 Patients in ICU, sepsis resulting from serious abdominal infection                | PN       | APACHE II 18.4 ± 5.6       | APACHE II 17.9 ± 5.2             | Arginine, mRNA, and fish oil                              | Standard treatment          | Shorter ICU stay in FO group, mortality was not different between groups         |
| Gallán et al. 2000 [43] | Spain      | 181 Patients in ICU, sepsis with APACHE II ≥ 10                                     | EN       | APACHE II 18.4 ± 5.6       | APACHE II 17.9 ± 5.2             | High protein control feed                                 | Standard treatment          | Significant reduction in the mortality rate, days of ventilation and ICU stay were not different between groups |
| Grau-Carmona et al. 2011 [24] | Spain      | 132 Patients in ICU, sepsis receiving mechanical ventilation                       | EN       | APACHE II 19 (IQ range 16–24) | APACHE II 19 (IQ range 16–23)   | EPA/GLA diet n-6:n-3 ratio 1.5:1                           | Control diet n-6:n-3 ratio 5.8:1 | Shorter ICU stay in FO group, days of ventilation and mortality were not different between groups |
| Grecu et al. 2003 [31] | Romania    | 54 Patients in ICU, sepsis from abdominal source                                    | PN       | APACHE II 19.1 ± 6.7       | APACHE II 17.9 ± 6.2             | Omegaven 1.5 mL/kg/day, 5 postoperative days              | Same lipid calorie intake and duration                       | Shorter ICU stay and hospital stay in FO group, no effect on mortality          |
| Hall et al. 2015 [33]  | UK         | 60 Patients in ICU or HDU, sepsis                                                  | PN       | APACHE II 19.1 ± 6.7       | APACHE II 17.9 ± 6.2             | Omegaven 0.2 g/kg/d, 14 days or until discharge from the ICU | Standard treatment          | No significant reduction in the length of ICU, hospital stay and mortality       |
| He 2018 [44]          | China      | 80 Patients in ICU, sepsis, APACHE II (12 ~ 30)                                   | PN       | APACHE II 14.5 ± 2.3       | APACHE II 15.3 ± 2.1             | Fish oil emulsion 0.2 g/kg/d, 6 d                         | Standard treatment          | Shorter hospital stay in FO group, mortality was not different between groups |
| Hosny et al. 2013 [34] | Egypt      | 75 Patients with early sepsis (high doses group 25, low doses group 25, control group 25) | PN       | SOFA 3.7 ± 0.96            | SOFA 3.6 ± 0.87                  | FO 9 g/day, ascorbic acid 1000 mg/day, alpha-tocopherol 400 IU/12 h and selenium 100 μg/day, 7 d | Standard treatment          | Shorter ICU stay and days of ventilation in FO group, mortality was not different between groups |

(Continued)
promotes gut permeability, which subsequently leads to organ dysfunction [5,51,52]. Therefore, it is of vital importance to keep the inflammatory cytokines in check.

Fish oil, as the major source of omega-3 fatty acids, EPA and DHA, has been widely reported for its inflammatory mediation in cells, animal models and humans by curbing...
the production of the pro-inflammatory regulators, IL-6, IL-1β, TNF-α, IL-2, LTB4, PGE2, etc. [53,54]. EPA and DHA produce resolvins and DHA also gives rise to maresins and neuroprotectins through cyclooxygenase/LOX pathways [55]. Previous human studies based on healthy volunteers showed that increased intake of fish oil promoted the blood concentration of the anti-inflammatory resolvins, resolin D1 and D2 [56]. Resolin D1 is also increased after 8 weeks of n-3 fatty acid supplementation in patients with chronic kidney disease [57]. Resolvins regulate the active process of resolving inflammation [58].

Nevertheless, the efficacy of fish oil-containing nutrition therapy for patients with sepsis is controversial [59]. For example, some clinical studies reported that administration of fish oil could decrease the mortality and other clinical outcomes of patients with sepsis [26,30,40]. However, a few RCTs concluded the opposite [24,37,47]. Similar contradictions also existed in the parenteral nutrition groups. The reasons for these differences may include different pathogenetic condition, administration route, administration time, etc.

Our primary outcome supported that fish oil use contributed to lower mortality in patients with sepsis. Previously, Chen et al. reported that fish oil-containing nutrition supplementation could reduce the mortality rate of sepsis [17]. However, it was claimed by Lu et al. that fish oil-containing nutrition supplementation may reduce ICU stay and duration of mechanical ventilation without significantly affecting mortality among critically ill septic patients [60]. However, no subgroup analyses were performed by Lu et al. In interventional studies of critically ill patients, many negative outcomes were due to heterogeneity. Therefore subgroup analysis was performed to reduce heterogeneity in our study.

Compared to the previous meta-analysis on the role of fish oil in septic patients, our subgroup analysis came to the conclusion that it was parenteral fish oil supplementation that could lower the mortality rate among septic patients and the enteral route seemingly did not have a similar effect.

There may be several reasons for the opposite clinical outcomes of different administration routes. Firstly, the severity of the patients included in the study was a very important
Figure 3. The effect of fish oil-containing nutrition supplementation on mortality. CI confidence interval, RR risk ratio, PN parenteral nutrition, EN enteral nutrition

indicator. Patients who received PN were generally sicker than those who received EN and had a more severe inflammatory response. For patients with severe inflammatory response, early administration of fish oil could effectively inhibit excessive inflammatory response and improved organ function. As a result, mortality was improved. However, in patients who could tolerate EN, the inflammatory response is relatively mild. The advantage of fish oil was not easy to show. Secondly, metabolic abnormalities and impaired gastrointestinal tract absorption common in critically ill patients also cannot be ignored. Fish oils are metabolized rapidly in patients with sepsis and the absorption of enteral medications and pharmaco-nutrients may be impaired in such patients. If enteral absorption is impaired, doses of enteral medications administered to critically ill patients may be suboptimal [61]. Thirdly, timing of administration and pharmacokinetics are also important to consider. Chen et al. pointed out that there was no significant difference in mortality after PN and EN provisions of fish oil in septic patients [17]. The dispute on this issue may result from the complexity of sepsis syndrome, the dynamic alterations in immune response and unpredictable individual variations among septic patients. Fish oil-containing nutrition makes sense at the initial hyper-inflammatory stage, but may be harmful during the hypo-inflammatory phase [62]. Therefore, apart from the administration route, timing is a key point, when to start, by which route and for how long [7,9]. Parenteral provision of nutrition shows its advantageous efficacy in patients if the prepared PN is well-indicated and provided for patients with the assistance of a professional nutrition team, which is, however, more challenging and expensive than EN [63]. Therefore, we need to identify the inflammatory status based on medical history, clinical manifestation and laboratory results (IL-6, CRP, neutrophil percentage, RCT, etc.). Then, fish oil should be administrated by the parenteral route during periods of hyper-inflammatory reaction.
The secondary outcomes based on our study indicated that fish oil-containing nutrition supplementation decreased the duration of ICU stay, hospital stay and mechanical ventilation support. Lu et al.'s research came to the same conclusion as ours [60]. Wei et al. found that patients treated with a lipid emulsion containing fish oil experienced fewer infectious complications and significantly shortened hospital stays [64]. Pradelli et al. found that n-3 PUFAs-enriched PN is safe and effective in reducing the infection rate and hospital/ICU stay in surgical and ICU patients [65]. Manzanares et al. found that fish oil may be able to decrease mortality and ventilation days in the critically ill based on a small set of clinical data [66,67]. Of course, there are other researchers who take a different view.

A high rate of lipid infusion led to lipid overload, aggravating lung injury [68]. Therefore, differences in lipid load may alter the immune responses and impact on clinical outcomes among patients as well [33]. This may account for the difference in results.

Meanwhile, the high heterogeneity for ICU stay impaired the statistical power. Therefore further meta-regression was performed (Figure 5). It suggested that the high heterogeneity for ICU stay mainly comes from regional differences, severity of sepsis and routes of administration in the selected RCTs.
Severity of sepsis and routes of administration were discussed before. The regional differences made it important for us to pay attention to genetic polymorphism.

This meta-analysis also has some limitations. The sample size was not large enough, which could weaken the statistical power. The energy intake of the patients was not strictly controlled, which might influence the analysis outcomes. Energy intake is an important confounder for nutritional treatment trials. However, only seven RCTs reported total calorie intake [24–27,37,43,48]. We suggest that the researchers should report and analyze energy intake in future studies. The duration, dosage and timing of administration were diverse in different included studies. Enteral feeding was also given in different ways. This could have an impact on the results. The specific treatment of the experimental group was not completely consistent in different studies. Meanwhile, the
treatment of the control group was not reported in detail. These may affect the evaluation of fish oil. The criteria for sepsis used in the included studies were not identical. Most of the research was based on criteria from a study by Bone et al. [69]. However, some studies were based on different clinical criteria. This may also have affected the results. Moreover, high heterogeneity for the duration of ICU stay, hospital stay and mechanical ventilation support, weighs against the reliability of the findings in this research.

Conclusions
In this meta-analysis, we have demonstrated that PN with fish oil could significantly decrease mortality in septic patients while enteral administration could not. Fish oil also decreased the duration of ICU stay, hospital stay and mechanical ventilation support. However, the evidence provided by this meta-analysis is not enough. Therefore, these conclusions should be treated with caution. More high-quality RCTs need to be carried out to further validate the conclusions. Moreover, pharmacokinetics, gene polymorphism and lipid load are all important issues that deserve attention.

Abbreviations
CI: Confidence interval; DHA: docosahexaenoic acid; EN: Enteral nutrition; EPA: Eicosapentaenoic acid; ICU: Intensive care unit; MD: Mean difference; PN: Parenteral nutrition; PUFAs: Polyunsaturated fatty acids; RCT: Randomized controlled trials; RR: Risk ratio; TNF: Tumor necrosis factor; IL: interleukin; PGE2: prostaglandin E2; LOX: lipoxigenase; LTB4: leukotriene B4; CRP: c-reactive protein.

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Authors’ contributions
All authors read and approved the final manuscript. HW and SS were responsible for writing the manuscript. HW, XP and CW were responsible for the statistics. JH, HW, CW and DW were responsible for data collection.

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Conflicts of interest
The authors declare that they have no competing interests.

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