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Research Article

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

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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, $I^2 = 0\%$). Fish oil also shortened the ICU stay (MD −3.57 days; 95% CI −4.54, −2.59; $p<0.00001$; $I^2 = 76\%$), hospital stay (MD −9.92 days; 95% CI −15.37, −4.46; $p = 0.0004$; $I^2 = 91\%$) and the duration of mechanical ventilation support (MD −2.26; 95% CI −4.27, −0.26; $p = 0.03$; $I^2 = 83\%$). 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, $I^2 = 0\%$), but no significant difference in mortality was observed in the fish oil group administered by enteral route (RR = 0.80, $I^2 = 0\%$). 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.

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- 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)

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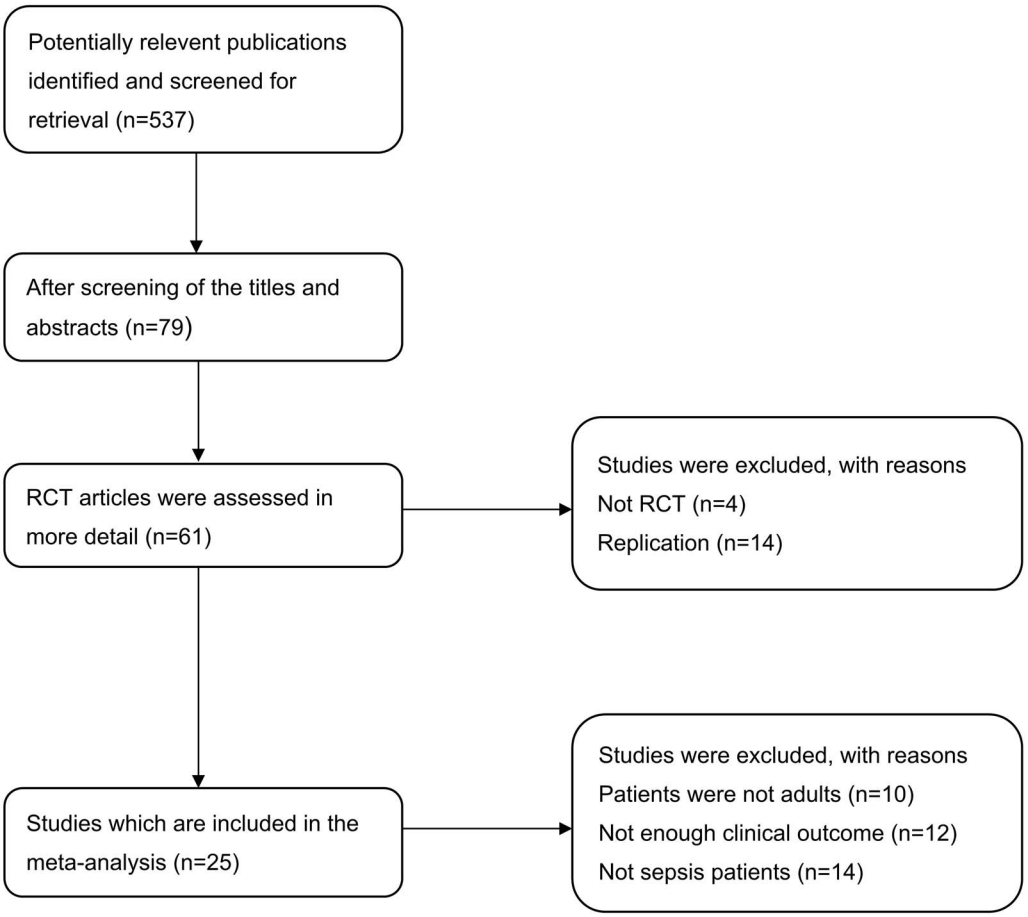

Figure 1. Strategy used for each database. *RCT* randomized-control trial

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).

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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 I^2 test and the Mantel Haenszel χ^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. Pathophysiologically, 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

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Table 1. Key characteristics of the included studies

Study	Region	Patient	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	SOFA 9.5 ± 0.9	SOFA 8.9 ± 1.2	50:40:10 MCT/LCT/FO, Lipoplus 250 mL/d, 5 d	50:50 MCT/LCT	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	APACHEII 26 ± 9	APACHEII 26 ± 11	Omegaven 2 mL/kg/d, 2–7 d	Standard treatment	Mortality was similar in both groups
Chen et al. 2011 [39]	China	30 Patients in ICU, sepsis with organ failure	PN	APACHEII 22.60 ± 3.40	APACHEII 20.67 ± 2.69	Fish oil emulsion 100 mL/d,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	APACHEII 25.6 ± 5.2	APACHEII 23.4 ± 5.1	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, severe sepsis with acute gastrointestinal injury	PN	APACHEII 32.0 ± 6.7	APACHEII 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	_	_	Fish oil emulsion 0.2 g/kg/d, 5 d	Standard treatment	Shorter ICU stay in FO group, mortality was not different between groups
Galbán et al. 2000 [43]	Spain	181 Patients in ICU, sepsis with APACHEII≥10	EN	APACHEII 18.4 ± 5.6	APACHEII 17.9 ± 5.2	Arginine, mRNA, and fish oil	High protein control feed	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	Mean APACHE II 19 (IQ range 16–24)	Mean 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	_	_	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	APACHEII 19.1 ± 6.7	APACHEII 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, APACHEII (12 ~ 30)	PN	APACHEII 14.5 ± 2.3	APACHEII 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*)

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Table 1. Continued

Study	Region	Patient	Route	Critical score in FO groups	Critical score in control groups	Nutrition in FO groups	Nutrition in control groups	Clinical outcomes
Ibrahim 2018 [47]	Egypt	110 Critically ill septic patients in ICU	EN	APACHEII 15.45 ± 3.13	APACHEII 15.24 ± 3.96	3 g omega-3 in three divided daily doses until the patients were discharged from ICU	Standard treatment	Decreased ICU stay in FO groups, no effect on mortality
Khor et al. 2011 [29]	Taiwan	27 Patients in ICU, severe sepsis	PN	APACHE II 19.3 ± 7.8	APACHE II 16.3 ± 7.2	Omegaven 100 ml/d for 5 d, lasted for 6 h	0.9% Normal saline	No significant differences in the ICU stay or length of hospitalization
Leiderman IMO et al. 2010 [35]	Russia	27 Abdominal sepsis patients	PN	APACHEII 17.1 ± 4.3	APACHEII 19.6 ± 3.6	MCT\LCT \omega3	MCT\LCT	No effect on mortality
Liang X et al. 2009 [36]	China	32 Patients in ICU, severe sepsis	PN	APACHEII 24.5 ± 3.2	APACHEII 24.9 ± 3.3	Fish oil emulsion 100 ml/d	Standard treatment	Lower mortality and shorter hospital stay in FO group
Liu 2011 [32]	China	54 Patients in ICU, sepsis,	PN	APACHEII 17.4 ± 6.3	APACHEII 17.7 ± 8.3	Omegaven 0.15–0.2 g/kg/d, 5 d	Standard treatment	Shorter ICU stay and hospital stay in FO group, no effect on mortality
Pontes-Arruda et al. 2006 [26]	Brazil	103 Mechanically ventilated patients, severe sepsis and septic shock in ICU	EN	SOFA 8.6 ± 0.8	SOFA 8.8 ± 0.9	EPA, GLA and anti-oxidant	High-fat, low-carbohydrate	Lower mortality in FO group, shorter ICU stay and hospital stay in FO group
Pontes-Arruda A et al. 2011 [27]	Brazil	115 Patients in the early stages of sepsis in ICU	EN	Mean APACHE II 19.5 (IQ range 17–25)	Mean APACHE II 20 (IQ range 16–23)	EPA, GLA and anti-oxidant	High-carbohydrate	No effect on mortality Shorter ICU stay, hospital stay and days of ventilation in FO group
Qu et al. 2009 [28]	China	40 Patients in ICU, sepsis, APACHEII (10 ~ 25)	PN	APACHEII	17.7 ± 1.6*	Fish oil emulsion 2 ml/kg/d, 5 d	Standard treatment	No effect on mortality
Shirai et al. 2015 [37]	Japan	46 Patients in ICU. Sepsis-induced ARDS	EN	Mean APACHE II 24 (IQ range 21–28)	Mean APACHE II 23 (IQ range 21–26)	Oxepa™ (EPA, GLA and antioxidants)	Standard treatment	Did not improve duration of mechanical ventilation, mortality, shorter duration of ICU stay
Wu et al. [48]	China	72 Patients in ICU, sepsis, APACHEII (10 ~ 25)	PN	APACHEII 17.6 ± 2.2	APACHEII 18.1 ± 2.5	Fish oil emulsion 1-2 ml/kg/d, 5 d	Standard treatment	No effect on mortality
Wu et al. 2011 [38]	China	60 Patients in ICU, sepsis	PN	APACHEII 20.73 ± 4.13	APACHEII 21.37 ± 4.08	Fish oil emulsion 0.2 g/kg/d, 5 d	MCT\LCT emulsion	Decreased ICU stay in FO groups, no effect on mortality.
Zhao et al. 2011 [45]	China	102 Patients in ICU, sepsis with ARDS	PN	-	-	Fish oil emulsion 100 ml/d, 5–7 d	Standard treatment	Lower mortality in FO group, shorter ICU stay and days of ventilation in FO group
Zhao et al. 2012 [46]	China	126 Patients in ICU, sepsis	PN	APACHEII 21.1 ± 3.8	APACHEII 19.6 ± 4.4	Fish oil emulsion 100 ml/d, 5–7 d	Standard treatment	Decreased ICU stay in FO groups, no effect on mortality

*This value represents the overall outcome for all patients in the FO group and control group. Results for the two groups were not presented separately in the literature. *FO* group of fish oil-containing nutrition supplementation, *MCT/LCT* medium-chain triglycerides/long-chain triglycerides, *ARDS* acute respiratory distress syndrome, *HDU* high-dependency unit, *APACHE* acute physiologic and chronic health evaluation score, *SOFA* sequential organ failure assessment, *IQ* interquartile, *EPA* eicosapentaenoic acid, *GLA* γ-linolenic acid, *PN* parenteral nutrition, *EN* enteral nutrition

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

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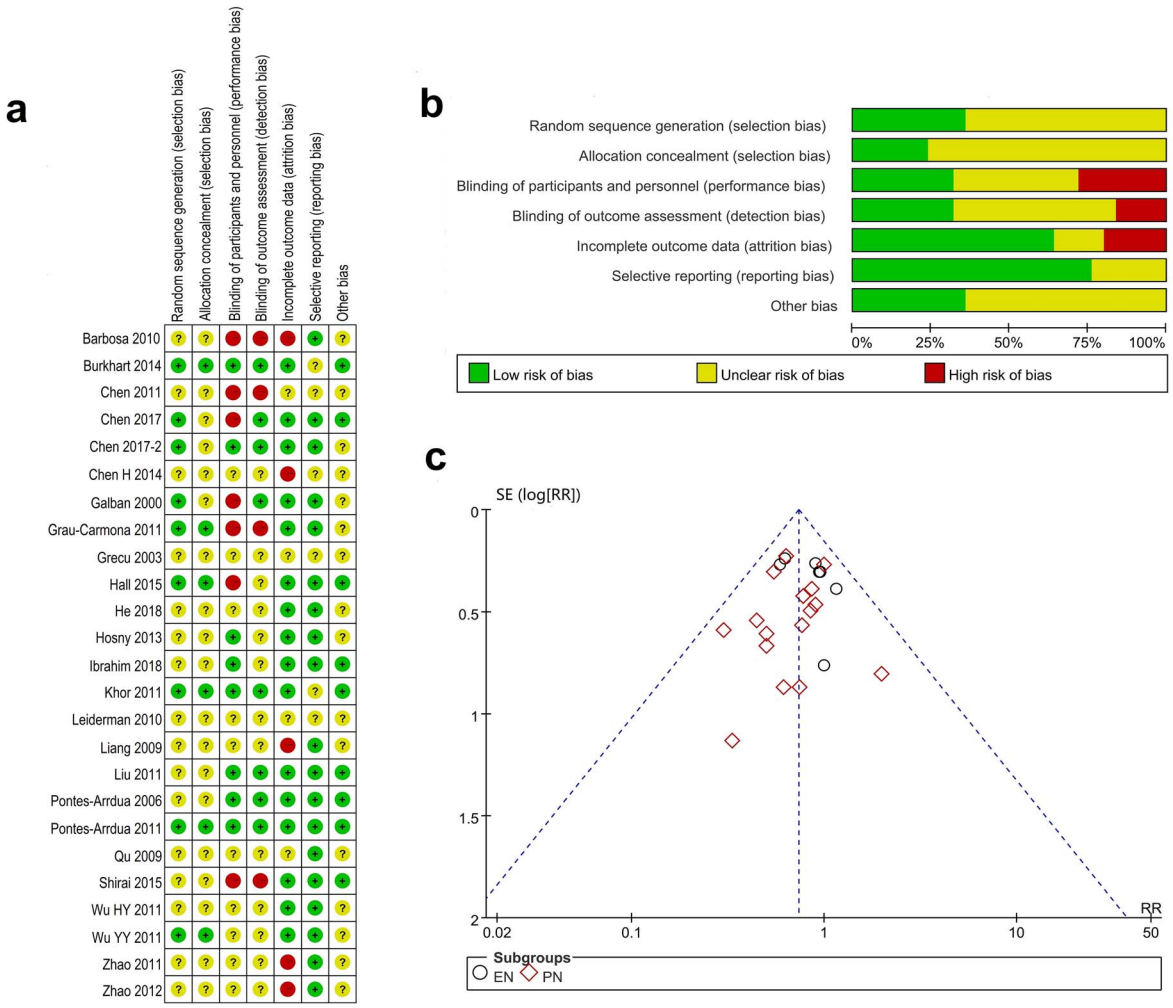

Figure 2. Risk of bias of the studies. *RR* risk ratio, *PN* parenteral nutrition, *EN* enteral nutrition

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, resolvin D_1 and D_2 [56]. Resolvin D_1 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 subgroups 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

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Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 EN						
Galban 2000	17	89	28	87	10.4%	0.59 [0.35, 1.00]
Grau-Carmona 2011	11	61	11	71	3.7%	1.16 [0.54, 2.49]
Hosny 2013	19	50	10	25	4.9%	0.95 [0.52, 1.73]
Ibrahim 2018	18	55	20	55	7.3%	0.90 [0.54, 1.51]
Pontes-Arrdua 2006	18	55	25	48	9.8%	0.63 [0.39, 1.00]
Pontes-Arruda 2011	15	57	16	58	5.8%	0.95 [0.52, 1.74]
Shirai 2015	3	23	3	23	1.1%	1.00 [0.22, 4.45]
Subtotal (95% CI)		**390**		**367**	**43.0%**	**0.80 [0.64, 1.01]**
Total events	101		113			
Heterogeneity: Chi² = 4.14, df = 6 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.91 (P = 0.06)						
1.4.2 PN						
Barbosa 2010	4	13	4	10	1.7%	0.77 [0.25, 2.34]
Burkhart 2014	13	25	13	25	4.8%	1.00 [0.59, 1.70]
Chen 2011	3	15	6	15	2.2%	0.50 [0.15, 1.64]
Chen 2017	3	24	10	24	3.7%	0.30 [0.09, 0.96]
Chen 2017-2	11	41	18	37	6.9%	0.55 [0.30, 1.01]
Chen H 2014	2	25	3	28	1.0%	0.75 [0.14, 4.11]
Grecu 2003	2	28	3	26	1.1%	0.62 [0.11, 3.41]
Hall 2015	4	30	9	30	3.3%	0.44 [0.15, 1.29]
He 2018	1	40	3	40	1.1%	0.33 [0.04, 3.07]
Khor 2011	0	14	0	13		Not estimable
Leiderman 2010	5	13	6	14	2.1%	0.90 [0.36, 2.24]
Liang 2009	20	70	35	78	12.1%	0.64 [0.41, 0.99]
Liu 2011	7	27	9	27	3.3%	0.78 [0.34, 1.79]
Qu 2009	4	20	2	20	0.7%	2.00 [0.41, 9.71]
WU HY 2011	3	36	6	36	2.2%	0.50 [0.14, 1.85]
WU YY 2011	6	30	7	30	2.6%	0.86 [0.33, 2.25]
Zhao 2011	8	56	11	60	3.9%	0.78 [0.34, 1.80]
Zhao 2012	10	62	12	64	4.3%	0.86 [0.40, 1.85]
Subtotal (95% CI)		**569**		**577**	**57.0%**	**0.68 [0.56, 0.84]**
Total events	106		157			
Heterogeneity: Chi² = 8.91, df = 16 (P = 0.92); I² = 0%						
Test for overall effect: Z = 3.55 (P = 0.0004)						
Total (95% CI)		**959**		**944**	**100.0%**	**0.74 [0.63, 0.86]**
Total events	207		270			
Heterogeneity: Chi² = 13.65, df = 23 (P = 0.94); I² = 0%						
Test for overall effect: Z = 3.93 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.02, df = 1 (P = 0.31), I² = 2.3%						

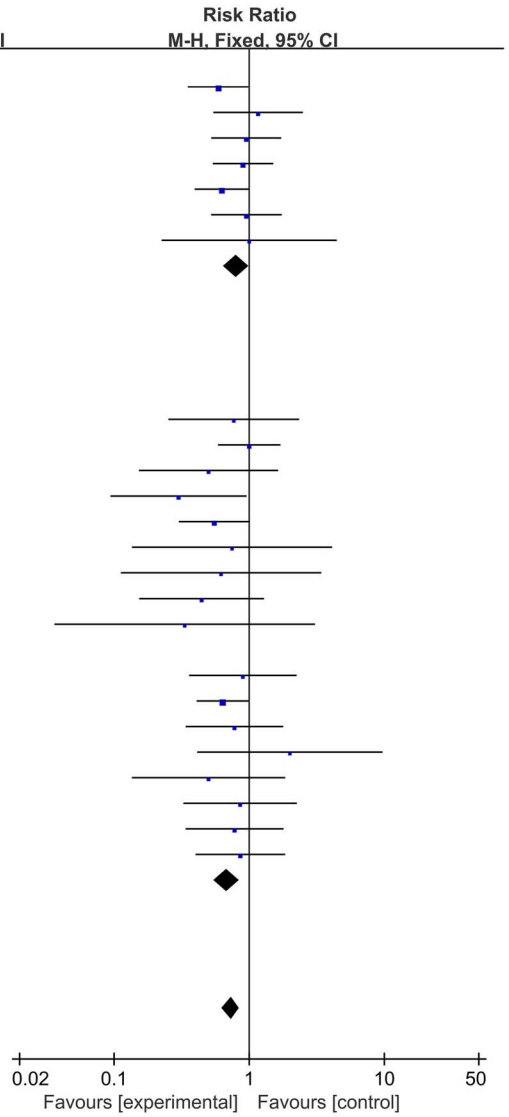

Figure 3. The effect of fish oil-containing nutrition supplementation on mortality. *CI* confidence interval, *RR* risk ratio, *PN* parenteral nutrition, *EN* enteral nutrition

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 pharmaconutrients 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 hyperinflammatory stage, but may be harmful during the hypoinflammatory 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 first (IL-6, CRP, neutrophil percentage, RCT, etc.). Then, fish oil should be administrated by the parenteral route during periods of hyperinflammatory reaction.

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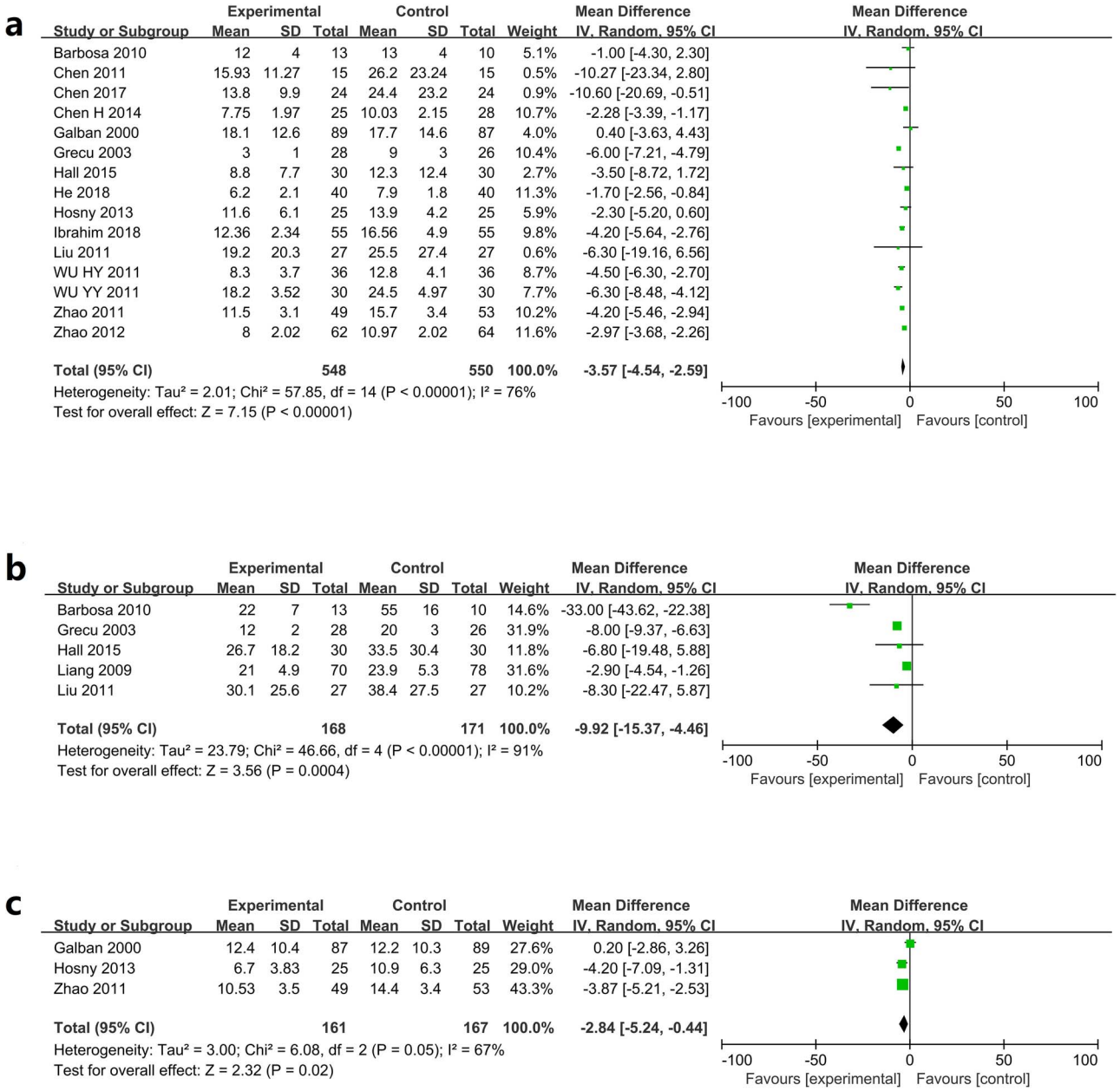

Figure 4. The effect of fish oil-containing nutrition supplementation on the duration of (**a**) ICU stay, (**b**) hospital stay and (**c**) mechanical ventilation support. *CI* confidence interval, *RR* risk ratio, *PN* parenteral nutrition, *EN* enteral nutrition

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.

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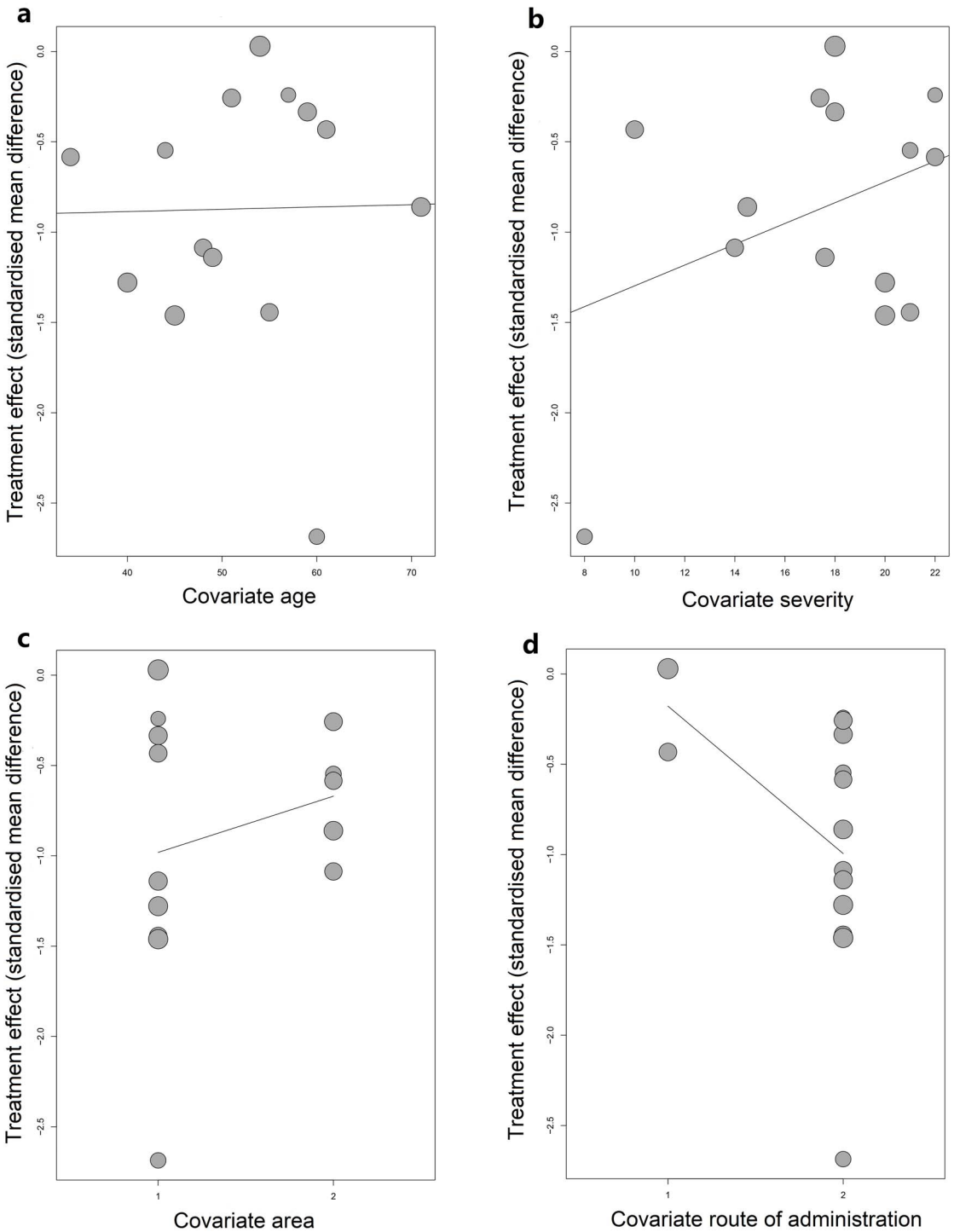

Figure 5. Meta-regression for ICU-stay. (**a**) Age, (**b**) severity, (**c**) area and (**d**) route of administration. *ICU* intensive care unit

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

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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; PUFA: Polyunsaturated fatty acid; RCT: Randomized controlled trials; RR: Risk ratio; TNF: tumor necrosis factor; IL: interleukin; PGE2: prostaglandin E2; LOX: lipoxygenase; 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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