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ω-3 Fatty-Acid Enriched Parenteral Nutrition in Hospitalized Patients: Systematic Review With Meta-Analysis and Trial Sequential Analysis

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Abstract

This systematic review and meta-analysis investigated ω-3 fatty-acid enriched parenteral nutrition (PN) vs standard (non-ω-3 fatty-acid enriched) PN in adult hospitalized patients (PROSPERO 2018 CRD42018110179). We included 49 randomized controlled trials (RCTs) with intervention and control groups given ω-3 fatty acids and standard lipid emulsions, respectively, as part of PN covering ≥70% energy provision. The relative risk (RR) of infection (primary outcome; 24 RCTs) was 40% lower with ω-3 fatty-acid enriched PN than standard PN (RR 0.60, 95% confidence interval [CI] 0.49-0.72; $P < 0.00001$). Patients given ω-3 fatty-acid enriched PN had reduced mean length of intensive care unit (ICU) stay (10 RCTs; 1.95 days, 95% CI 0.42-3.49; $P = 0.01$) and reduced length of hospital stay (26 RCTs; 2.14 days, 95% CI 1.36-2.93; $P < 0.00001$). Risk of sepsis (9 RCTs) was reduced by 56% in those given ω-3 fatty-acid enriched PN (RR 0.44, 95% CI 0.28-0.70; $P = 0.0004$). Mortality rate (co-primary outcome; 20 RCTs) showed a nonsignificant 16% reduction (RR 0.84, 95% CI 0.65-1.07; $P = 0.15$) for the ω-3 fatty-acid enriched group. In summary, ω-3 fatty-acid enriched PN is beneficial, reducing risk of infection and sepsis by 40% and 56%, respectively, and length of both ICU and hospital stay by about 2 days. Provision of ω-3-enriched lipid emulsions should be preferred over standard lipid emulsions in patients with an indication for PN. (*JPEN J Parenter Enteral Nutr.* 2020;44:44–57)

Keywords

fish oil; intensive care; lipid emulsion; meta-analysis; omega-3; parenteral nutrition; surgery; systematic review

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Introduction

Lipid emulsions are a key component of parenteral nutrition (PN) and are used as an energy-dense source of calories, reducing the glycemic load, supplying essential fatty acids, and lowering osmolarity.[1,2] The first generation of lipid emulsions was based on soybean oil or soybean/safflower oil and characterized by high concentrations of long-chain triglycerides providing high levels of ω-6 polyunsaturated fatty acids (PUFAs).[1,3] However, concerns arose that soybean oil lipid emulsions could promote inflammation and suppress immune function, thought to be related partly to an excess of ω-6 PUFAs and a low concentration of ω-3 PUFAs.[3-5]

The idea that ω-6 PUFAs might be "proinflammatory and immunosuppressive" led to the development of alternative lipid emulsions, including the partial replacement of soybean oil with medium-chain triglycerides, olive oil, and by the inclusion of fish oil.[3-5] Fish oil has been shown to have anti-inflammatory and immunomodulatory effects, most likely because of fish oil's ω-3 PUFA content, consisting of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) as they influence diverse inflammatory processes – from signal transduction to protein expression.[6] EPA and DHA are now known to be direct precursors of potent specialized proresolution mediators (ie, resolvins, protectins, and maresins) that improve outcomes in many animal disease models.[7] Fish oil may oppose the actions of ω-6 PUFAs, improve hepatic metabolism and liver function, and exert anticoagulatory and antiarrhythmic effects.[3] Thus, many trials have compared PN with or without fish oil to explore potential benefits for certain clinical conditions, in particular those characterized by an inflammatory over-response (eg, sepsis, pancreatitis, acute respiratory distress syndrome, and following major abdominal surgery).

The use of systematic reviews and meta-analyses is crucial to the formulation of guidelines, as they are the most powerful methods to inform healthcare decisions and form the highest level of the evidence-based medicine hierarchy,[8] summarizing evidence to allow judgement of risks and benefits.[9] In our previous meta-analysis we found significant clinical benefits for ω-3 fatty-acid enriched PN in hospitalized patients.[10] The rationale for an update is that many new clinical trials have been published, and though other recent meta-analyses have been performed, these do not have as broad a scope as our 2012 publication.[10] Furthermore, the update will adapt (1) the inclusion criteria to more closely match clinical practice and (2) the methodology to reflect the latest meta-analyses requirements. Thus, the objective for this new systematic review and meta-analysis was to investigate potential benefits of ω-3 fatty-acid enriched PN vs standard PN in adult hospitalized patients.

Methods

Registration and Overview

The protocol was published prospectively (PROSPERO 2018 CRD42018110179).[11] The systematic review and meta-analysis covered ω-3 fatty-acid enriched PN vs standard (non-ω-3 fatty-acid enriched) PN in adult hospitalized patients regarding clinical efficacy and laboratory parameter outcomes. The methods can be summarized as follows: (a) defining the eligibility criteria, (b) identification of databases and search strategy, (c) performing a structured literature search to identify publications followed by study selection based on title, abstract, and full text, progressively, and (d) data extraction and synthesis of the results.

Eligibility Criteria

Eligibility criteria for included studies are shown according to participants, interventions, comparisons, outcomes, and study designs (PICOS).[12,13]

Participants. Publications included human studies of adult hospitalized patients (later assigned as being within an intensive care unit [ICU] or non-ICU setting, as defined by the authors using the criteria that ICU studies should have a mean of at least 48 hours in an ICU) who were eligible to receive PN covering at least 70% of their total energy provision. This excluded nontarget populations (ie, pediatric or neonatal patients), or enteral nutrition studies.

Interventions and comparisons. Interventions and comparators included were ω-3 fatty-acid enriched PN and standard (non-ω-3 fatty-acid enriched) PN, respectively. This excluded "off-label" interventions (specifically in which fish oil was used as the sole source of parenteral lipids), and studies in which enteral nutrition accounted for >30% of the daily caloric provision.

Outcomes. Clinical outcomes were infection rate (primary outcome), mortality rate (co-primary outcome), length of hospital stay, length of ICU stay, sepsis rate, hospital readmissions, ICU-free days until day 30 or day 60, and ventilation-free days until day 30 (note: sepsis included events defined by publication authors as septic or systemic inflammatory response syndrome; see Table S1). Other outcomes were transfused blood units and oxygenation index, fatty-acid composition of plasma phospholipids and lipid profile (α-tocopherol, EPA, DHA, arachidonic acid, plasma triglycerides), markers of inflammation and antioxidant status (interleukin-6, leukotriene [LT] B5, LTB4, LTB5:LTB4 ratio, C-reactive protein, tumor necrosis factor [TNF]-α), and routine laboratory parameters (lactate; urea; serum creatinine; creatinine clearance; platelets; prothrombin time; partial thromboplastin time [PTT]; international

normalized ratio; bleeding time; liver enzymes aspartate [AST], alanine aminotransferase [ALT], and γ-glutamyl transferase [GGT]; and total bilirubin).

Study design. Randomized controlled trials (RCTs) published in English in peer-review journals containing at least 1 predefined outcome were included.

Information Sources and Search Methods

Keywords for the search were "parenteral nutrition," "fish oil," "omega-3," "lipids," "emulsion," and "randomized controlled trial." The search strategy was formulated *a priori* in a structured manner using the PICOS criteria.[11-13] No restrictions or filters were used, and exclusions were based on the selection process defined in the eligibility criteria. The time interval of inclusion was from any date to present (September 28, 2018). MEDLINE (PubMed interface), EMBASE (Elsevier interface), and the Cochrane Central Register of Controlled Trials (Wiley interface) were searched. The search string was modified according to each database's requirements.[11] Results were combined to eliminate duplicates using an Excel-based algorithm, constituting the core systematic review database. Manual searches were performed of reference lists of included studies, plus reviews and meta-analyses on the subject. Extra RCTs identified were integrated into the core database.

Study Selection, Data Collection, and Data Items

Two review authors independently screened titles and abstracts of all publications in the core database against the eligibility criteria. The full text of eligible papers was then checked against the inclusion criteria and to ensure no exclusion criteria were present. Conflicting opinions were discussed with a third review author, and original publication authors were consulted for clarification if necessary. Two authors independently extracted data from each trial using a predefined standardized collection grid. Disagreements were resolved in consultation with the principal investigator. If outcomes were only shown in a graphical format, then numerical values were extrapolated using Engauge digitizer software version 10.11.[14] Outcomes were reported as SI units or those prevalent in clinical practice. Standard error of the mean (SEM) values were transformed into standard deviations (SD) using standard formulas. Data reported as median and interquartile range were converted into estimated mean and SD using the formulas suggested in Wan et al.[15] When dispersion data (SD/SEM) were missing, the original authors of the study were contacted. If these data could not be obtained, an imputation based on the coefficient of variation (SD/mean) of all available data was performed.

Risk of Bias in Individual Studies

Included trials were assessed by 2 reviewers working independently using the Cochrane Collaboration tool for assessing the risk of bias.[12] If there was insufficient detail reported in the study, the risk of bias was judged as "unclear," and the original study investigators were contacted for more information.

Summary Measures

For continuous outcomes, the summary measure was the weighted mean difference (with 95% confidence interval [CI]), although standardized mean difference was used in the case of different measurement scales. For dichotomous outcomes, the summary measure was relative risk (RR) with 95% CI. The proportional odds ratio was used as a summary measure for categorical outcomes on an ordinal scale.

Synthesis of Results (Meta-Analysis) and Trial Sequential Analysis

Data from included studies was statistically combined through meta-analysis using Review Manager (RevMan5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). All methods applied are thoroughly detailed in the Cochrane Handbook.[12] As per Cochrane Handbook recommendations,[12] analyses were performed first via fixed effect models, based on which heterogeneity was analyzed. Trial sequential analyses were performed for all primary and secondary outcomes with a significant pooled effect using TSA 0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark, 2011) as detailed in the published protocol.[11] This explored whether the pooled analyses were adequately powered to evaluate treatment effect on outcomes.

Subgroup Analyses and Meta-Regression

For highly heterogeneous outcomes ($I^2 > 50\%$), data were included in random effects models. Any source of heterogeneity, or outcomes with $\geq$10 studies, underwent subgroup analyses and meta-regression, stratifying data by patient characteristics, intervention, study characteristics, and clinical setting. Mantel–Haenszel study weighting was performed for dichotomous outcomes, and inverse variance was used for continuous data. The DerSimonian and Laird inverse-variance approach was used for random effects meta-analysis, adjusting study weights by heterogeneity among intervention effects. The between-study variation was estimated by comparing each study's intervention effect with the pooled estimate of the corresponding fixed effects analysis. Note: a 0-cell correction was applied for meta-analyses of dichotomous and count of events data in studies

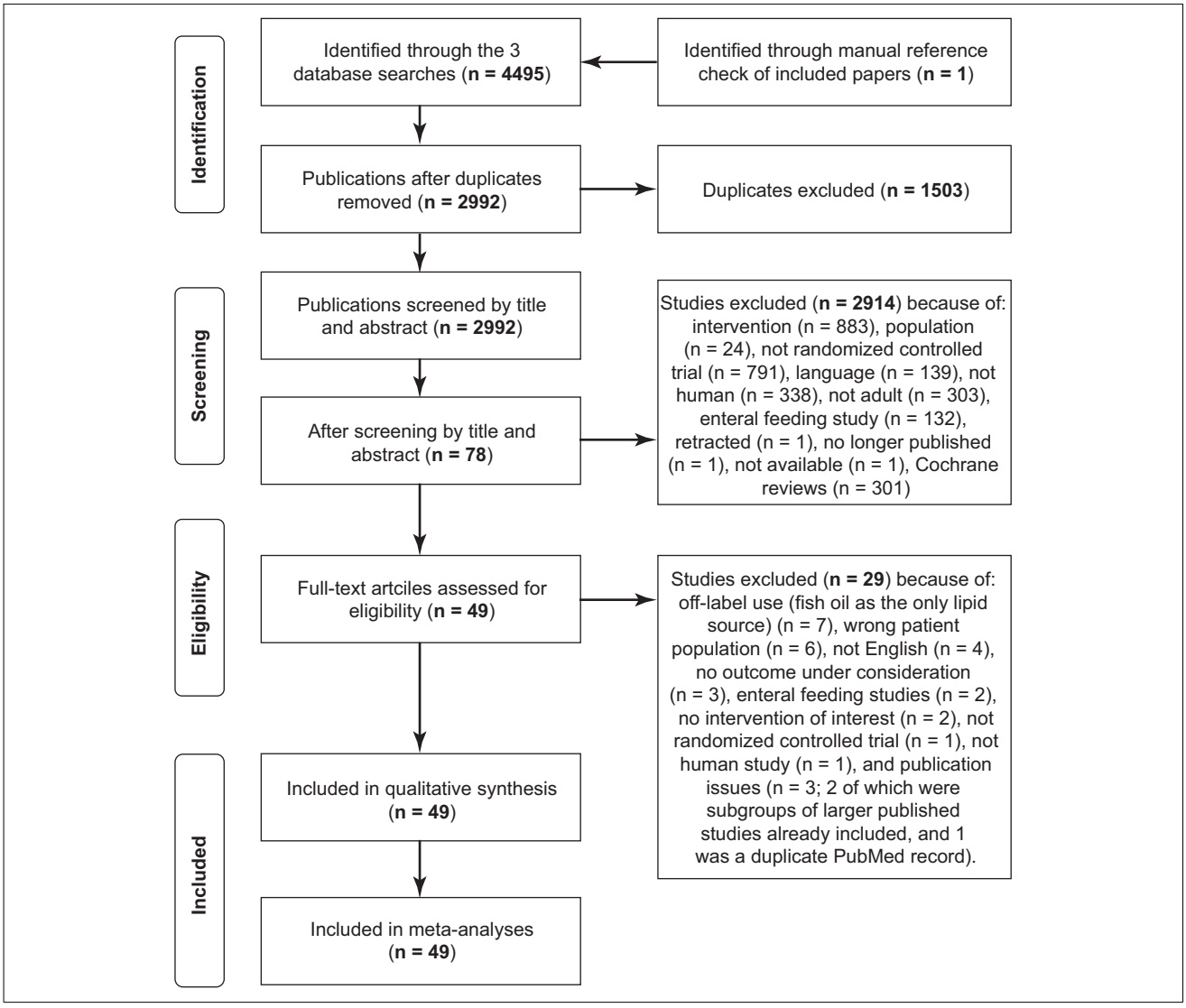

Figure 1. Study selection and screening.

in which there were no events in 1 or both groups, requiring STATA statistical software (STATA 14.2, StataCorp LLC, College Station, TX, USA).

Risk of Bias Across Studies (Meta Bias) and Confidence in Cumulative Estimate

Risk of bias that could affect the cumulative evidence (eg, publication bias, selective reporting within studies) was assessed by checking whether a protocol for each RCT was published before the RCT was conducted and by evaluating whether selective reporting of outcomes was present. Reporting bias was further explored by funnel plots if ≥10 studies were available. Confidence in cumulative estimates for all statistically significant outcomes was judged using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology using GRADEpro v.3.6.1 (GradePro.org).[16]

Results

Study Selection and Characteristics

A total of 49 studies with 3641 patients were included in the review and meta-analysis (Figure 1 and Table 1).[10,17-65]

Clinical Outcomes

For the primary outcome, infection rate, 24 studies (2154 patients) were included that reported any nosocomial infections: 7 studies for ICU patients and 17 for non-ICU patients. Compared with standard lipid emulsions, ω-3 fatty-acid enriched PN resulted in a significant 40%

Table 1. Characteristics of the Randomized Controlled Trials Included (n = 49), Showing Extracted Outcomes.

Randomized Control Trial	Patient Type (Number Randomized)[a]	ω-3-Enriched Lipid Emulsion	Standard Lipid Emulsion	Primary and Secondary Clinical Outcomes[b]	Laboratory Outcomes
ICU patients					
Antebi et al, 2004[17]	Major surgery (n = 20)	SO/MCT/OO/FO	SO		Alpha-T, ALT, AST, CRP, GGT, TG
Barbosa et al, 2010[18]	SIRS or sepsis (n = 23, received study treatments)	SO/MCT/FO	SO/MCT	Mortality, H LOS, ICU LOS	AA, ALT, AST, bilirubin, CRP, DHA, EPA, GGT, IL-6, Lac, LTB4, OI, PTT, Plt, TNF
Berger et al, 2008[19]	Abdominal aortic aneurism surgery (n = 24, completed trial)	SO/MCT/FO	SO/MCT	Mortality, H LOS, ICU LOS	AA, alpha-T, CRP, DHA, EPA, TG
Chen et al, 2017[20]	Severe sepsis with Grade III acute gastrointestinal injury (n = 78)	SO/FO	SO	Mortality	CRP
Chen et al, 2017[21]	Patients with septicaemia and intestinal dysfunction (n = 48)	Standard TPN/FO	Standard TPN	Mortality, ICU LOS	CRP
Friesecke et al, 2008[22]	Critically ill medical (n = 165)	SO/MCT/FO	SO/MCT	Mortality, infections, H LOS, ICU LOS, bleeding events	IL-6, TBU
Grau-Carmona et al, 2015[23]	Medical and surgical ICU patients (n = 175)	SO/MCT/FO	SO/MCT	Mortality, infections, H LOS, ICU LOS	
Gultekin et al, 2014[24]	ICU patients with sepsis (n = 32)	SO/OO/FO	SO/OO	Mortality, H LOS	CRP, IL-6, LTB4, TG, TNF
Han et al, 2012[25]	Major surgery (n = 38)	SO/MCT/FO	SO/MCT	Infections	IL-6, TNF
Heller et al, 2002[26]	Cancer, major abdominal surgery (n = 44)	SO/FO	SO		Plt, PT, PTT
Heller et al, 2004[27]	Cancer, major abdominal surgery (n = 44)	SO/FO	SO	H LOS, ICU LOS	ALT, AST, bilirubin, CRP
Morlion et al, 1996[28]	Major abdominal surgery (n = 20)	SO/FO	SO		AA, DHA, EPA, LTB4, LTB5
Piper et al, 2009[29]	Major abdominal or craniomaxillofacial surgery (n = 44)	SO/MCT/OO/FO	SO/OO		ALT, AST, Plt, TG
Roulet et al, 1997[30]	Cancer, esophagectomy (n = 19, completed trial)	SO/FO	SO		AA, DHA, EPA, BT
Sabater et al, 2011[31]	ARDS (n = 16)	SO/MCT/FO	SO	Mortality	LTB4
Stephenson et al, 2013[32]	Surgery for hepatic colorectal metastasis (n = 20)	SO/MCT/FO	SO/MCT		AA, DHA, EPA
Wachtler et al, 1997[33]	Cancer, major intestinal surgery (n = 40)	SO/MCT/FO	SO/MCT	Infections, H LOS, ICU LOS	IL-6, LTB4, LTB5, LTB ratio, TNF
Wang et al, 2008[34]	Severe acute pancreatitis (n = 40)	SO/FO	SO	Mortality, infections, H LOS, ICU LOS, sepsis	CRP, EPA, IL-6, OI

(*continued*)

Table 1. (continued)

Randomized Control Trial	Patient Type (Number Randomized)[a]	ω-3-Enriched Lipid Emulsion	Standard Lipid Emulsion	Primary and Secondary Clinical Outcomes[b]	Laboratory Outcomes
Wang et al, 2009[35]	Severe acute pancreatitis (n = 56)	SO/FO	SO	Mortality, infections	
Weiss et al, 2002[36]	Gastrointestinal surgery (n = 24)	SO/FO	SO	Mortality, infections, H LOS, ICU LOS	IL-6, TNF
Wendel et al, 2007[37]	Cancer, major abdominal surgery (n = 44)	SO/FO	SO		TG
Wichmann et al, 2007[38]	Major intestinal surgery (n = 256)	SO/MCT/FO	SO	Mortality, infections, H LOS, ICU LOS, sepsis	Alpha-T, AST, bilirubin, Cr, CRP, EPA, GGT, LTB5, LTB ratio, Plt, PT, TG
Surgical patients					
Aliyazicioglu et al, 2013[39]	Colorectal cancer surgery (n = 36)	Standard TPN/FO	Standard TPN	H LOS	
Badia-Tahull et al, 2010[40]	Major intestinal surgery (n = 29)	SO/FO	SO/OO	Mortality, infections, H LOS, sepsis	ALT, Cr, CRP, GGT, PU, TBU
Chen et al, 2017[41]	Gastric cancer surgery (n = 120)	SO/MCT/OO/FO	SO	Infections, H LOS	ALT, bilirubin, CRP, IL-6
Demirer et al, 2016[42]	Major abdominal surgery (n = 52)	SO/OO/FO	SO/OO or SO/MCT		CRP, IL-6, TNF
Grimm et al, 2006[43]	Major abdominal surgery (n = 33)	SO/MCT/OO/FO	SO	H LOS	AA, alpha-T, DHA, EPA, LTB4, LTB5, LTB ratio
Hallay et al, 2010[44]	Gastrointestinal surgery (n = 41)	SO/MCT/OO/FO	SO/MCT		ALT, AST, bilirubin, GGT
Jiang et al, 2010[45]	Gastrointestinal cancer surgery (n = 206)	SO/FO	SO	Infections, H LOS, sepsis	Cr, IL-6, TNF
Klek et al, 2005[46]	Gastric cancer surgery (n = 105, enrolled)	SO/MCT/FO	SO/MCT	Infections, H LOS	ALT, AST, Cr, PU
Klek et al, 2008[47]	Gastrectomy or pancreaticoduodenectomy (n = 205)	SO/MCT/FO (plus glutamine)	SO/MCT	Mortality, infections, H LOS, sepsis	
Klek et al, 2011[48]	Gastrectomy or pancreaticoduodenectomy (n = 167)	SO/MCT/FO (plus glutamine)	SO/MCT	Mortality, infections, sepsis	
Koller et al, 2003[49]	Major abdominal surgery (n = 30)	SO/MCT/FO	SO		LTB4, LTB5, LTB ratio
Liang et al, 2008[50]	Radical colorectal cancer resection (n = 41)	SO/FO	SO	Mortality, infection, H LOS	GGT, IL-6, Plt, TNF
Linseisen et al, 2000[51]	Major abdominal surgery (n = 33)	SO/MCT/FO	SO		AA, alpha-T, DHA, EPA
Ma et al, 2012[52]	Gastrointestinal tumor surgery (n = 40)	SO/MCT/OO/FO	SO/MCT	H LOS	ALT, AST, bilirubin, Cr, CRP, IL-6, PU, TG, TNF

(*continued*)

Table 1. (continued)

Randomized Control Trial	Patient Type (Number Randomized)[a]	ω-3-Enriched Lipid Emulsion	Standard Lipid Emulsion	Primary and Secondary Clinical Outcomes[b]	Laboratory Outcomes
Ma et al, 2015[53]	Gastric and colorectal cancer surgery (n = 99)	SO/MCT/FO	SO/MCT	Infections	ALT, AST, bilirubin, CRP, GGT, IL-6, TG, TNF
Makay et al, 2011[54]	Major gastric cancer surgery (n = 26)	SO/FO	SO	Mortality, infections, H LOS	ALT, AST, Cr, Lac, PU
Mertes et al, 2006[55]	Abdominal or thoracic surgery (n = 249)	SO/MCT/OO/FO	SO	Mortality, H LOS	ALT, AST, bilirubin, GGT, TG
Schauder et al, 2002[56]	Large bowel surgery (n = 60)	SO/FO	SO		TNF
Senkal et al, 2007[57]	Colorectal surgery (n = 40, received study treatments)	SO/MCT/FO	SO/MCT	Infections	AA, DHA, EPA
Wang et al, 2012[58]	Gastrointestinal surgery (n = 64)	SO/MCT/FO	SO/MCT	Infections, sepsis	ALT, AST, bilirubin, CRP, GGT, IL-6, LTB ratio, Plt, PT, PTT, TG, TNF
Wei et al, 2014[59]	Surgical resection of gastric tumors (n = 52)	SO/FO	SO	Infections	CRP, IL-6, TNF
Wu et al, 2014[60]	Gastrointestinal surgery (n = 40)	SO/MCT/OO/FO	SO/MCT	Infections, H LOS	ALT, AST, bilirubin, Cr, CRP, GGT, IL-6, PU, TG, TNF
Zhang et al, 2017[61]	Hepatectomy (n = 320)	SO/MCT/FO	SO/MCT	Mortality, infections, H LOS, sepsis	ALT, bilirubin, Cr, CRP, TG, Plt, PU, PTT
Zhixue et al, 2018[62]	Liver cancer surgery (n = 75)	SO/MCT/FO	SO/MCT		IL-6, TNF
Zhu et al, 2012[63]	Liver transplant (n = 66)	SO/MCT/FO	SO/MCT	Mortality, infection, H LOS	ALT, AST, bilirubin, PT
Zhu et al, 2012[64]	Colorectal cancer surgery (n = 57, completed trial)	SO/FO	SO	Infection, H LOS, sepsis	IL-6, TNF
Zhu et al, 2013[65]	Pancreaticoduodenectomy (n = 76)	SO/MCT/FO	SO/MCT	Mortality, infection, H LOS, hospital readmission	ALT, AST, bilirubin

AA, (%) content of arachidonic acid in serum/cellular membranes; alpha-T, alpha-tocopherol; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BT, bleeding time; Cr, serum creatinine; CRP, C-reactive protein; DHA, (%) docosahexaenoic acid content in serum/cellular membranes; EPA, (%) eicosapentaenoic acid content in serum/cellular membranes; FO, fish oil emulsion; Lac, lactate; GGT, γ-glutamyl transferase; (H) LOS, (hospital) length of stay; ICU, intensive care unit; LTB, leukotriene B; LTB5:LTB4, LTB ratio; MCT, medium-chain triglycerides; OI, oxygenation index; OO, olive oil emulsion; PU, plasma urea; Plt, Platelet; PT, prothrombin time; PTT, partial thromboplastin time; SIRS, systemic inflammatory response syndrome; SO, soybean oil emulsion; TBU, transfused blood unit; TGs, triglycerides; TNF, tumor necrosis factor.

[a]Number of patients randomized was listed if available, but if not available an alternative descriptor was used for the patient population/number.

[b]An outcome of sepsis included events defined by publication authors as septic or as systemic inflammatory response syndrome.

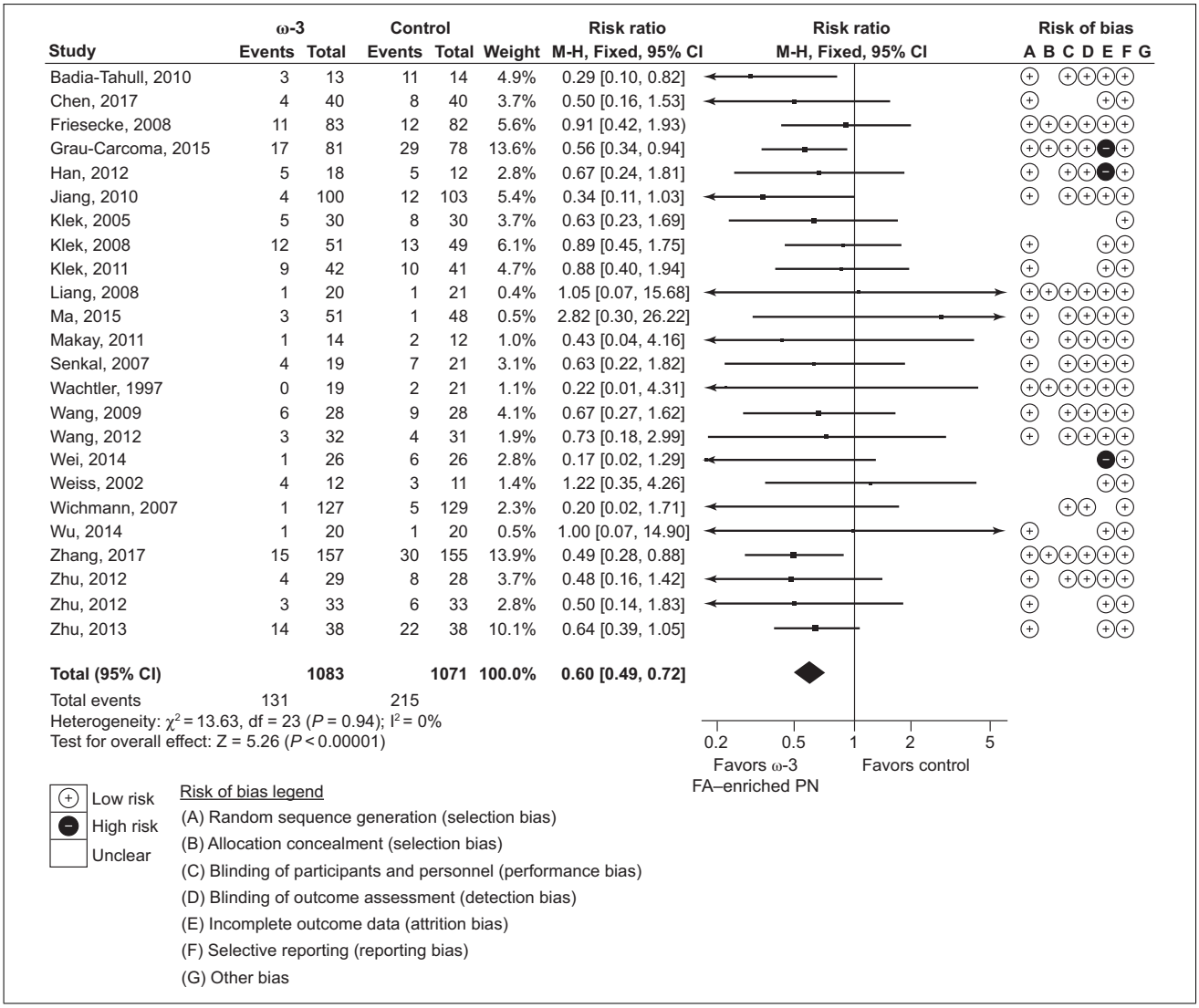

Figure 2. Infection rates. Forest plot of fixed effects meta-analysis showing individual study means, pooled estimates, and risk of bias for individual studies (Cochrane tool). CI, confidence interval; FA, fatty acid; PN, parenteral nutrition.

reduction of infection rates (RR 0.60, 95% CI 0.49-0.72; $P < 0.00001$) (Figure 2). No subgroup analysis was performed, as heterogeneity was low (I^2: 0%).

The 30-day mortality rate was reported by 20 studies (1839 patients): 9 studies of ICU patients and 11 for non-ICU patients (note: in this study, 30-day mortality was defined as any deaths occurring up to 30 days after receiving at least 1 dose of study treatment or prior to hospital discharge, whichever was reported). There was a nonsignificant 16% reduction in mortality rate (RR 0.84, 95% CI 0.65-1.07; $P = 0.15$) (Figure 3).

Length of hospital stay was reported by 26 studies (2182 patients), of which 10 were ICU studies and 16 non-ICU studies, and length of ICU stay was reported by 10 studies (822 patients). Results showed a reduction in ICU stay of 1.95 days (95% CI 0.42-3.49; $P = 0.01$) and reduction in length of hospital stay of 2.14 days (95% CI 1.36-2.93; $P < 0.00001$) (Figures 4 and 5, respectively). As data for both length of stay outcomes were classed as highly heterogeneous ($I^2 > 50\%$), subgroup analyses were considered. Although no subgroup analyses were performed for length of ICU stay (<10 studies were available for each subgroup analysis), length of hospital stay data were analyzed further. These subgroup analyses showed significantly greater effect with no heterogeneity ($I^2 = 0\%$) in total PN vs PN groups, and comparable but less heterogeneous effects in oncological studies vs non-oncological studies, and in non-ICU vs ICU studies. Thus, effects on length of stay were more consistent in more homogenous groups of patients such as these.

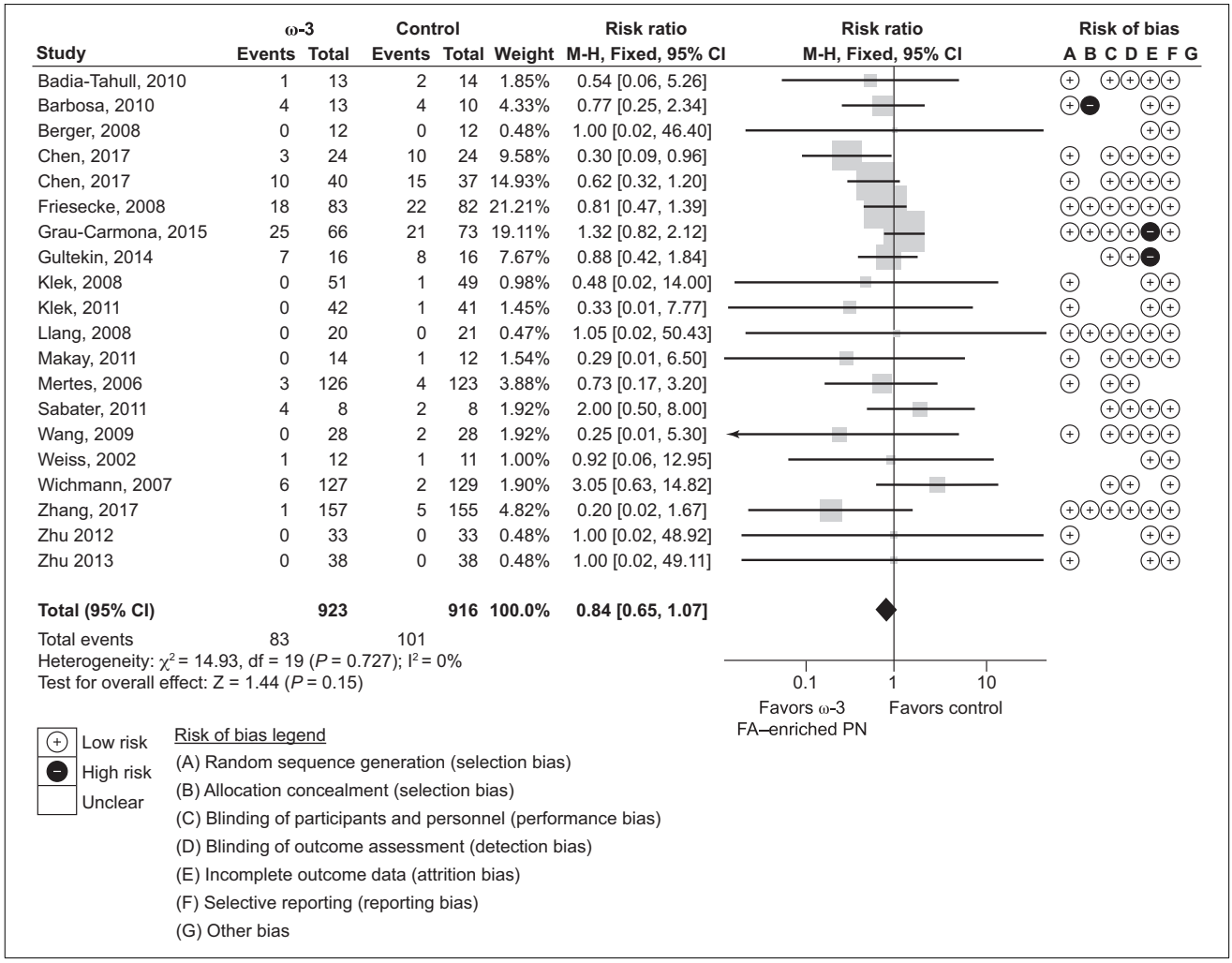

Figure 3. Thirty-day mortality rates. Forest plot of fixed effects meta-analysis showing individual study means, pooled estimates, and risk of bias for individual studies (Cochrane tool). Note: to correct for the 0 event studies as per the protocol (to add 0.5 events in both arms), this meta-analysis was performed using STATA software, as it is difficult to use RevMan for this correction. CI, confidence interval; FA, fatty acid; PN, parenteral nutrition.

Sepsis was reported in 9 studies (1141 patients), of which 2 were ICU studies and 7 non-ICU studies. Compared with standard lipid emulsions, ω-3 fatty-acid enriched PN resulted in a significant 56% reduction in the risk of sepsis (RR 0.44, 95% CI 0.28-0.70; $P = 0.0004$) (Figure 6). No meta-analyses were performed on hospital readmissions, ICU-free days, or ventilation-free days, as only 1 or no studies reported each of these outcomes.

Trial sequential analysis for all significant clinical outcomes (infection rate, length of hospital stay, length of ICU stay, and sepsis) showed adequate power (Figures S1–S4), and thus these estimates can be considered conclusive.

Nonclinical Outcomes

Significant benefits were found in 10 of the 24 laboratory parameters analyzed (Table S2). These were significant benefits in marker liver enzyme levels (AST, ALT, and GGT), higher levels of the antioxidant α-tocopherol, as well as lower levels for markers of inflammation such as TNF-α. A significant benefit was observed in fatty-acid profiles, with increases in levels of the ω-3 fatty acids, DHA, and EPA. A positive influence was also observed on LT levels, with a significant increase in LTB5 levels as well as on the LTB5:LTB4 ratio. PTT also increased significantly.

Confidence in Cumulative Estimate and Meta-Bias and Meta-Regression Results

Confidence in cumulative estimates for clinical outcomes was high for infection and sepsis rates and moderate for both length of hospital and ICU stays (Table S3). Confidence in cumulative estimates for laboratory parameters was either high or moderate, except TNF-α, which was judged as low.

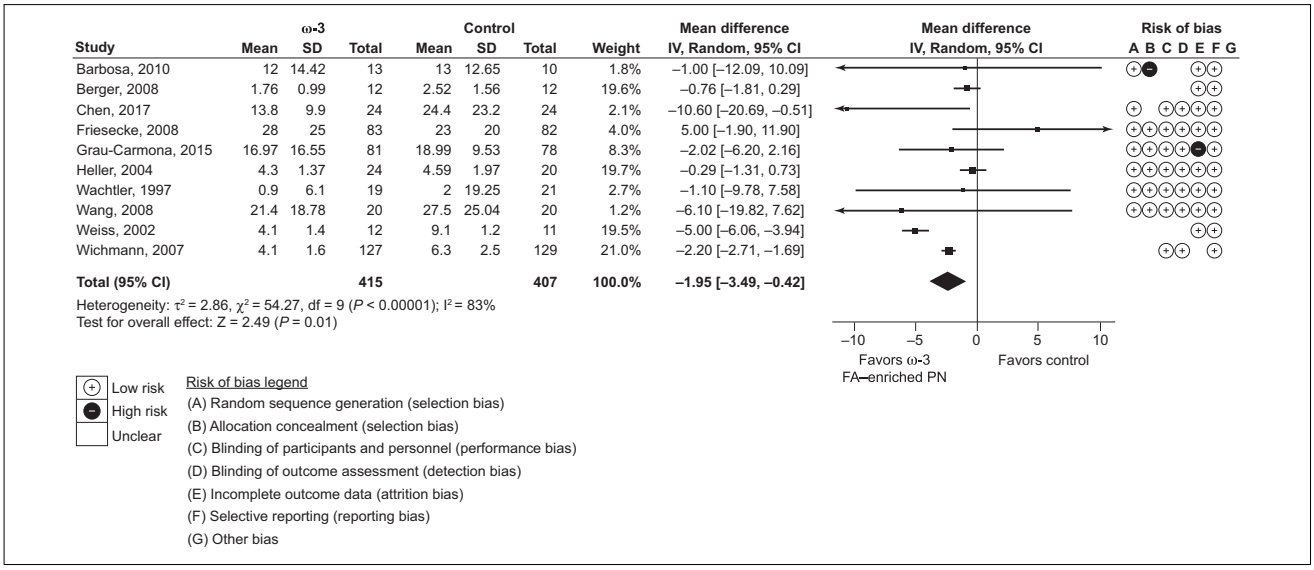

Figure 4. Length of intensive care unit stay. Forest plot of random effects meta-analysis showing individual study means, pooled estimates, and risk of bias for individual studies (Cochrane tool). CI, confidence interval; FA, fatty acid; IV, inverse variance; PN, parenteral nutrition; SD, standard deviation.

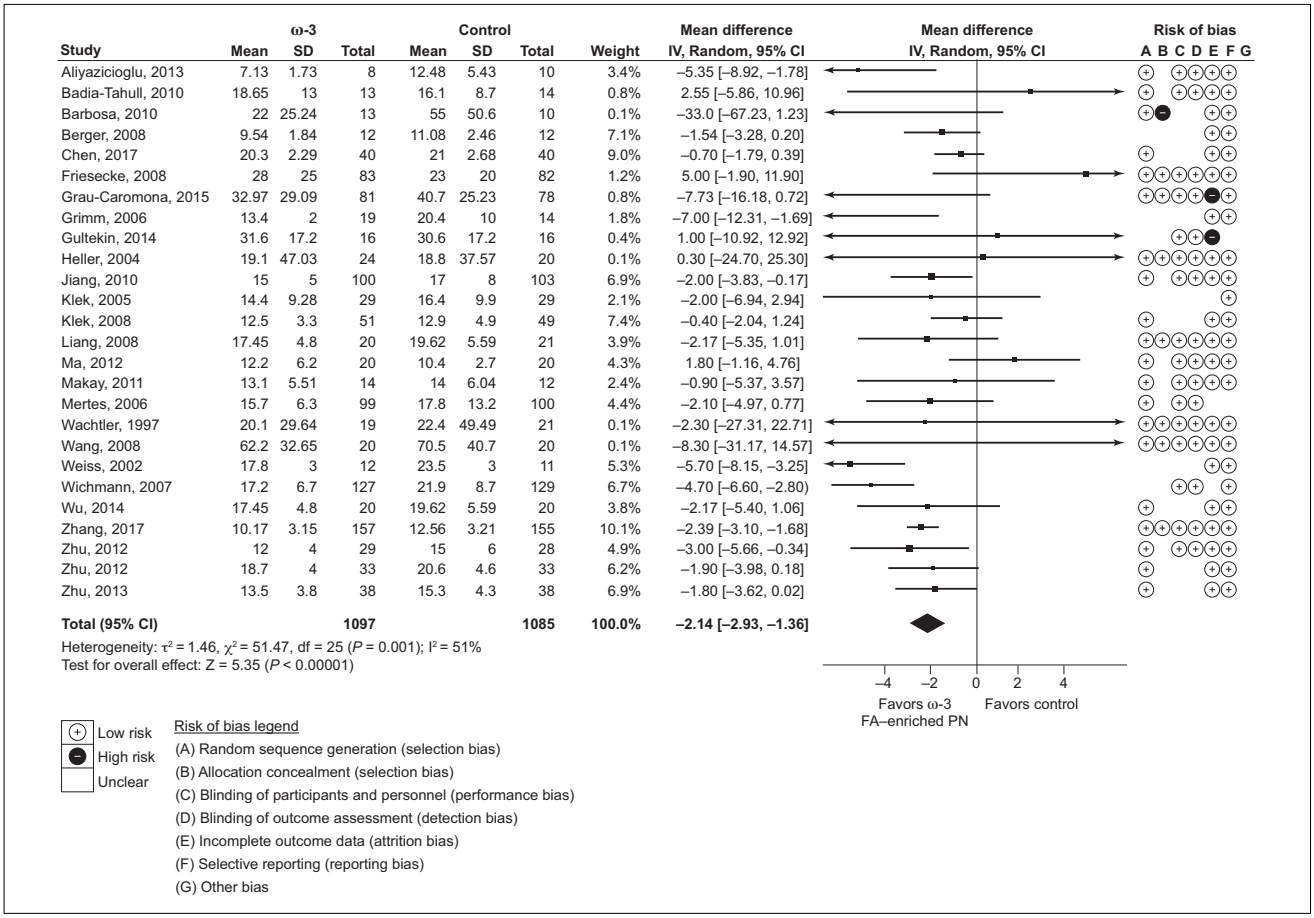

Figure 5. Length of hospital stay. Forest plot of random effects meta-analysis showing individual study means, pooled estimates, and risk of bias for individual studies (Cochrane tool). CI, confidence interval; FA, fatty acid; IV, inverse variance; PN, parenteral nutrition; SD, standard deviation.

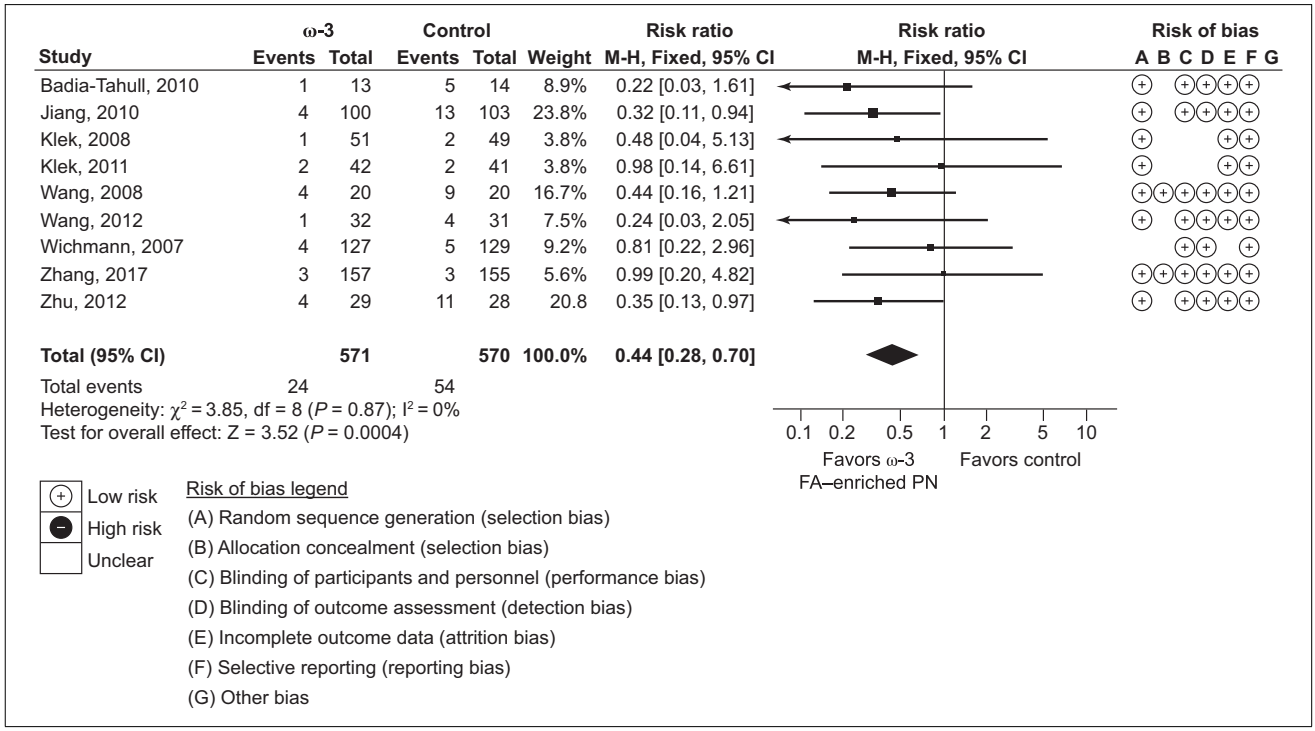

Figure 6. Sepsis. Forest plot of fixed effects meta-analysis showing individual study means, pooled estimates, and risk of bias for individual studies (Cochrane tool). CI, confidence interval; FA, fatty acid; PN, parenteral nutrition.

The potential for meta-bias (reporting bias) was explored by funnel plots for clinical outcomes. These appeared symmetrical, and there was no evidence of significant bias on the weighted regression using either Begg's or Egger's tests (Figure S5). Funnel plots were also performed for all other outcomes, and none showed evidence of bias.

Univariate and multivariate meta-regression were performed for length of hospital stay. Univariate meta-regression found no potential associations between length of hospital stay and the exclusiveness of parenteral administration ($P = 0.1868$), reason for PN ($P = 0.6406$), nutrition status of malnourished or non-malnourished ($P = 0.2281$), ICU or non-ICU setting ($P = 0.0956$), medical vs surgical ICU setting ($P = 0.8161$), or patients' oncological status ($P = 0.7452$), infection rate difference between the treatment and control groups ($P = 0.1485$), or mean age ($P = 0.3710$). However, univariate meta-regression found a significant association between treatment effect estimate and the mortality difference between the treatment and the control group ($P = 0.0255$). Nevertheless, there were more deaths in the control group, excluding any hypothesis that saved hospital days could be because of excess mortality in the fish-oil group. Multivariate regression results ($P = 0.0405$) were consistent with these, indicating a potential association between the mortality difference and treatment effect estimate on the length of hospital stay.

Discussion

ω-3 Fatty-acid enriched PN significantly reduces the risk of infections and length of both ICU and hospital stays compared with standard PN. Furthermore, ω-3 fatty-acid enriched PN had potentially beneficial effects on liver chemistry, antioxidant status, markers of inflammation, coagulation, and fatty-acid profile.

The validity and robustness of results from our previous publication that encompassed 23 RCTs[10] have been confirmed and extended by the present study using a much larger and current dataset and the addition of trial sequential analysis. Moreover, this update was needed, as the Cochrane Collaboration recommends that systematic reviews and meta-analyses are updated at least every 2 years, if possible.[12] When comparing the results of the previous meta-analysis[10] and this update, there is a great degree of similarity, but an increased number of patients have resulted in greater precision (narrower CIs) (Table S4). The current results also include sepsis, demonstrating a significant (approximately 56%) reduction in sepsis associated with the use of PN including fish oils ($P = 0.0004$). The only clinical outcome that was not statistically significant was mortality, as shown previously.

To the best of our knowledge, the current systematic review and meta-analysis is the largest conducted to date on this subject. A number of other meta-analyses have

compared clinical outcomes for PN enriched with ω-3 fatty acids vs standard PN in surgical patients,[66-70] ICU and/or critically ill patients,[71-73] ICU and non-ICU patients,[10,74] or patients with gastrointestinal cancer.[75] Only 2 of these 11 meta-analyses failed to find 1 or more significant clinical benefits in favor of ω-3 fatty-acid enriched PN,[68,72] though both were probably underpowered, as each only included 6 RCTs, 1 with a total of 306 patients[68] and the other 390 patients.[72] To our knowledge, no meta-analyses have found any significant clinical benefits in favor of standard PN.

There is considerable confidence in the effect estimates of the current study as assessed using GRADE and trial sequential analysis. This is necessary for the result to be relevant to clinical practice.[76] The quality of evidence for clinical outcomes and all laboratory parameters (except TNF-α) were rated as high or moderate. Moreover, there was no evidence of meta-bias (reporting bias) from funnel plots. Although we have a high level of confidence in the meta-analysis estimates, especially infection and sepsis reduction estimates, ideally it would be useful to confirm these evaluations by performing further large-scale RCTs. In particular, large, properly designed trials are required to prove or reject any effect on mortality rates. Finally, we adhered to best practices, such as prospective registration of methods and following the PRISMA statement for reporting systematic reviews and meta-analyses.

In summary, this meta-analysis confirms and extends previous results in greater numbers of patients and clinical trials, providing greater precision. It provides clear evidence that omega-3 fatty-acid enriched PN provides significant clinical and nonclinical benefits over standard non-ω-3 fatty-acid enriched PN in adult hospitalized patients.

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Statement of Authorship

L. Pradelli, K. Mayer, S. Klek, A. J. O. Alsaleh, M. D. Rosenthal, A. R. Heller, and M. Muscaritoli contributed to the conception and design of the research; L. Pradelli and A. J. O. Alsaleh contributed to the acquisition and analysis of the data; L. Pradelli, K. Mayer, S. Klek, A. J. O. Alsaleh, R. A. C. Clark, M. D. Rosenthal, A. R. Heller, and M. Muscaritoli contributed to the interpretation of the data; and R. A. C. Clark drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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