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Omega-3 fatty acids in parenteral nutrition – A Systematic Review with Network Meta-Analysis on clinical outcomes

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ABSTRACT

Background & Aims: Accumulating scientific evidence supports the benefits of parenteral nutrition (PN) with fish oil (FO) containing intravenous lipid emulsions (ILEs) on clinical outcomes. Yet, the question of the most effective ILE remains controversial. We conducted a network meta-analysis (NMA) to compare and rank different types of ILEs in terms of their effects on infections, sepsis, ICU and hospital length of stay, and in-hospital mortality in adult patients.

Methods: MEDLINE, EMBASE, and Web of Science databases were searched for randomized controlled trials (RCTs) published up to May 2022, investigating ILEs as a part of part of PN covering at least 70% of total energy provision. Lipid emulsions were classified in four categories: FO-ILEs, olive oil (OO)-ILEs, medium-chain triglyceride (MCT)/soybean oil (SO)-ILEs, and pure SO-ILEs. Data were statistically combined through Bayesian NMA and the Surface Under the Cumulative RAnking (SUCRA) was calculated for all outcomes.

Results: 1651 publications were retrieved in the original search, 47 RCTs were included in the NMA. For FO-ILEs, very highly credible reductions in infection risk versus SO-ILEs [odds ratio (OR)=0.43 90% credibility interval (CrI) (0.29-0.63)], MCT/soybean oil-ILEs [0.59 (0.43-0.82)], and OO-ILEs [0.56 (0.33-0.91)], and in sepsis risk versus SO-ILEs [0.22 (0.08-0.59)], as well as substantial reductions in hospital length of stay versus SO-ILEs [mean difference (MD)= -2.31 (-3.14 to -1.59) days] and MCT/SO-ILEs (-2.01 (-2.82 to -1.22 days) were shown. According to SUCRA score, FO-ILEs were ranked first for all five outcomes.

Conclusions: In hospitalized patients, FO-ILEs provide significant clinical benefits over all other types of ILEs, ranking first for all outcomes investigated.

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KEYWORDS

Omega 3 fatty acids, fish oil, parenteral nutrition, lipid emulsion, network meta-analysis

INTRODUCTION

As an integral part of parenteral nutrition (PN), intravenous lipid emulsions (ILEs) provide an energy-dense source of calories that helps reduce glucose load, contribute to the supply of essential fatty acids (EFAs) and lipid-soluble vitamins, and modulate inflammatory and immune responses, coagulation, and cell signalling (1, 2). The earliest ILEs, subsequently referred to as "first generation", were derived from pure soybean oil (SO). Subsequent generations contain mixtures of SO with alternative oil sources such as medium-chain triglycerides (MCT), olive oil (OO) and/or fish oil (FO) (1, 2). In particular FO as a source of omega-3 polyunsaturated fatty acids (PUFAs) has become an important component of modern, composite ILEs (2, 3).

There is a growing body of evidence from a number of meta-analyses (4-8) showing the beneficial impact of PN with FO on clinical outcomes when compared to PN without FO. In our own meta-analysis (7), including 49 randomized controlled trials (RCTs) and 3641 patients, we showed that their use was associated with fewer infections and sepsis, and shorter duration of hospital and ICU stay. The RCTs included in these meta-analyses compared FO-containing ILEs (FO-ILEs) to several different interventions, such as pure SO-ILE and mixtures of soybean oil with other oils.

While, for some of these comparisons, ample data are available, for others, data are scarce. Where data from direct comparisons are lacking, a technique allowing an indirect comparison may still be possible if comparative studies with a third intervention are available. Altogether, the studies comparing different types of ILEs form a network of interventions, and this is where network meta-analysis (NMA) comes in, a technique developed as an extension of conventional, pairwise meta-analysis. The NMA combines both direct and indirect evidence across a network of three or more interventions to produce estimates of the relative effects of every intervention compared with each other, also for comparisons that have not been evaluated directly in RCTs (9, 10). Moreover, it allows for relative rankings of the competing interventions for a particular outcome and may increase the precision of effect estimates by combining both direct and indirect evidence (10). Thus, NMAs offer

added value, as they have the potential to give insights that complement individual trials or conventional pairwise meta-analysis. NMAs are widely used in the medical field and are increasingly recognized as a valid method by reimbursement bodies or health technology appraisal agencies (11). A broader use of this technique has also been suggested for nutrition research (12, 13).

The aim of the present NMA was to compare and rank the different types and generations of ILEs - with and without FO - in terms of their effectiveness in improving clinical outcomes in adult hospitalized patients. ILEs with FO could be any combination of FO with one or more other oils.

METHODS

The protocol was registered prospectively (PROSPERO 2022 CRD42022328660) (14).

Eligibility criteria

To be included in the analysis, articles retrieved had to be RCTs, published in English in peer-reviewed journals, and contain original data from at least one clinical outcome of interest. According to participants, interventions, comparisons, and outcomes (PICO) criteria (15, 16), studies had to meet the following characteristics to be eligible:

Participants: Adult (≥ 18 years of age) hospitalized patients. Studies in paediatric or neonatal patients were excluded.

Interventions: ILEs as a part of PN covering at least 70% of total energy provision. For studies with FO-ILEs, the mean daily FO daily dose had to be in the range of 0.1 to 0.2 g/kg body weight according to ESPEN recommendation (17), allowing for a deviation of ±20% to account for natural fluctuations in the omega-3 content of FO. Studies investigating off-label use of ILEs, e.g., FO as a sole source of parenteral lipids, where enteral nutrition (EN) accounted for more than 30% of daily caloric intake, or comparing interventions that were not isocaloric, isolipidic, isoproteic, or isoglucidic, were excluded.

Comparisons: PN with different types/generations of ILEs grouped by dominant oil, with FO leading the aggregation. This classification resulted in 4 categories of ILEs: (1) FO-ILEs, the combinations of FO with one or more of the other oils (FO/SO, FO/MCT/SO, FO/SO/OO, FO/MCT/SO/OO) (2) OO-ILEs, the combination of OO and SO (3) MCT/SO-ILEs, the combination of MCT and SO and (4) pure SO (SO-ILEs).

Outcomes: Infections, sepsis, ICU length of stay (LOS), hospital LOS, and in-hospital mortality.

Information sources and search strategy

We searched MEDLINE (PubMed interface), EMBASE (Elsevier interface), and the Web of Science (Clarivate Analytics interface) for RCTs published from any date up to May 2022 (last date searched). As suggested by the Cochrane recommendations on Systematic Reviews (15), there were no limits on the search and exclusion/inclusion criteria were checked manually for the hits. Keywords for the search were “parenteral nutrition”, “fish oil”, “soybean oil”, “olive oil”, and “randomized controlled trial”. The search string was adjusted according to the requirements of the databases. The full search strategies for each database are given in the Supporting Information (Supplementary files).

Results were combined and duplicate records were eliminated by using the Web App Rayyan (18) or by manual check, forming the core database for the systematic review. Additionally, manual searches of reference lists of included studies, as well as of previous reviews and meta-analyses on the subject were performed and extra RCTs identified integrated into the core database.

Study selection

Two independent reviewers screened titles and abstracts of all publications in the core database against the eligibility criteria. For matching papers, the full text was then checked against the inclusion and exclusion criteria. Conflicting opinions were discussed with a third reviewer and, if necessary, the original publication authors were consulted for clarification. Reasons for exclusion were documented at the end of each phase of the selection.

Data collection and extraction

Two reviewers independently extracted data on the study population, sample size, interventions, comparators, potential bias in trial conduct, and outcomes from each trial using a predefined standardized collection grid. Any disagreement was resolved through discussion and in consultation with the principal investigator. Where necessary, the authors of the studies were contacted for further information. For outcomes shown in graphical format only, numerical values were extrapolated using Engauge® digitizer software version 11.3. Missing mean and standard deviation (SD) data were either obtained from the authors of the studies or, otherwise, estimated from median and interquartile (IQR) according to the formula by Wan et al. 2014 (19). Standard error of the mean (SEM) values were transformed into SD values using standard formulas.

Assessment of risk of bias

Included trials were assessed for risk of bias by two independent reviewers using the revised Cochrane tool for randomized trials (20), covering five domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result) plus an overall risk-of-bias judgment for the results. Risk of bias was also assessed for each of the 5 outcomes of interest using the same Cochrane tool. If there was insufficient detail reported in the study, the original study investigators were contacted for more information. If data were still lacking thereafter, the risk of bias was judged as "unclear".

Summary statistics and synthesis of results

Data were statistically combined through Bayesian NMA conducted for each of the five outcome variables, producing estimates of the relative effects between any pair of interventions, direct or indirect, in the network. The model is based on the hierarchical random-effect model as described in Dias et al. (2013) (21) with correction for inconsistency networks (22). The relative treatment effects were expressed in terms of mean difference (MD) for continuous variables, i.e., ICU and hospital LOS, and in terms of natural logarithm of the odds ratio (OR) for dichotomous variables i.e.,

mortality, infection and sepsis rate. For both types of variables, 90% credibility intervals (CrI) are reported, indicating the interval in which the values of OR/MD lie with a probability of 90% (9). All analyses were performed by using the statistical software WinBugs 1.4.3 (23). The credibility of estimates was measured by reporting the posterior probability that the treatment effect was lower than 1 (for OR) or lower than 0 (for MD). Specifically, when comparing A vs. B, posterior probability higher than 90% was assumed to indicate very high credibility of the superiority of A with respect to B.

For the published direct comparisons, when at least two papers compared the same interventions, Bayesian pair-wise meta-analyses were performed in order to compare direct estimates with those obtained with the Bayesian NMA. In all cases, a random-effects model was specified except for the comparisons involving only two studies, where a fixed-effects model was used due to a limited information on the heterogeneity variance.

Heterogeneity between studies was calculated across each network. The level of heterogeneity was quantified via the magnitude of the between-study variance τ^2 (24, 25) and the additional variance τ_w^2 representing the network inconsistency (26), i.e. discrepancies between direct and indirect effect estimates. Variability due to the between-trial heterogeneity and due to the inconsistency over the total variance, I^2 and I_w^2, respectively, were calculated according to Roos et al. (27). I^2 ranges from 0% to 100% with low percentages corresponding to a low level of inconsistency.

In addition, cumulative rank curves (rankograms) were generated for all outcomes, showing the distribution of ranking probabilities for each intervention (10). The Surface Under the Cumulative RAnking (SUCRA) which transforms the cumulative probabilities into a single value was calculated according to Salanti et al. (2011) (28) and expressed as percentage. The SUCRA score allows for a ranking of the analysed interventions according to the probability of being the most effective intervention on a scale from 0% (certainly the least effective) to 100% (certainly the most effective).

RESULTS

Study selection and characteristics

A total of 1651 publications were retrieved in the original search. Following the removal of duplicates and the manual screening process, 47 studies remained and were included in the NMA (see Figure 1**Error! Reference source not found.**). Characteristics of the included studies are shown in Table 1 (extracted data for each outcome are detailed in the Supporting Information Table S1). The majority of the included studies had a low/moderate risk of bias, regardless of whether risk of bias was assessed at study or outcome level (see Figure 2).

Synthesis of results

The competing interventions and the direct comparisons investigated for each of the 5 outcomes of interest in the selected studies are shown in the network diagrams in Figure 3. For each outcome, the relative treatment effects estimated for the 6 possible direct and indirect comparisons and results of independent meta-analysis (for the available comparisons) are given in Table 2.

Infection risk was reported in 28 studies with a total of 3081 participants. The NMA showed a very highly credible reduction in infection risk with FO-ILEs versus SO-ILEs (OR=0.43, 90% CrI 0.29 to 0.63), MCT/SO-ILEs (OR=0.59, 90% CrI 0.43 to 0.82), and OO-ILEs (OR=0.56, 90% CrI 0.33 to 0.91). None of the other comparisons showed any highly credible treatment effects. Between-trial heterogeneity and network inconsistency were low (I^2=21.5% and I^2_w=20.9%, respectively).

Sepsis risk was reported in 10 studies with a total of 1627 participants. The NMA showed a very highly credible reduction in sepsis risk with FO-ILEs versus SO-ILEs (OR=0.22, 90% CrI 0.08 to 0.59) and OO-ILEs vs SO-ILEs (OR=0.32, 95% CrI 0.08 to 1). None of the other comparisons showed a substantial treatment effect. Between-trial heterogeneity was low (I^2=11.3%). Yet, network inconsistency was substantial (I^2_w=63.6%), indicating a contrast between direct and indirect evidence.

ICU-LOS was reported in 12 studies with a total of 1163 participants and *hospital LOS* in 28 studies with 3343 participants. There were no considerable treatment effects on ICU-LOS, with moderate heterogeneity between trials (I^2=47.8%). Between-trial heterogeneity was moderate to substantial also for *hospital LOS* (I^2=58.1%), however a substantial reduction was observed with FO-ILEs versus SO-ILEs (MD= -2.31 days, 90% CrI -3.14 to -1.59 days) and MCT/SO-ILEs (MD= -2.01 days, 90% CrI -2.82 to -1.22 days), and with OO-ILEs versus SO-ILEs (MD= -1.46 days, 90% CrI -3.2 to 0.16 days). Network inconsistency was moderate for ICU-LOS (I^2_w=37.8%) and low for hospital LOS (I^2_w=15.2%).

In-hospital mortality was reported in 31 studies with a total of 2828 participants. The NMA showed a very highly credible reduction in mortality with FO-ILEs vs SO-ILEs (OR=0.67, 90% CrI 0.42 to 1.06). None of the other comparisons showed a substantial treatment effect for any of the ILE categories. Both between-trial heterogeneity and network inconsistency were low (I^2=12.1% and I^2_w=9.1%, respectively).

The results from the NMA qualitatively agreed with those from the Bayesian pair-wise meta-analyses and, moreover, the variability was generally lower or comparable (Table S2).

According to the SUCRA score, FO-ILEs were consistently ranked first for all 5 outcomes investigated (see Table 3), with a particularly high probability for being the most effective intervention in terms of reducing infection risk (99.0%) and shortening hospital LOS (93.2%). OO-ILEs were ranked second for reducing sepsis risk and shortening ICU- and hospital LOS, and third for reducing infection and in-hospital mortality. SO-ILEs were ranked last for reducing in-hospital mortality, infection and sepsis risk, and for shortening hospital LOS, with the lowest probabilities of being the most effective intervention. For shortening ICU-LOS, SO/MCT-ILE was ranked last. The corresponding rankograms are shown in the Supporting Information (Figures S1 to S5).

DISCUSSION

In the present NMA, we found that, among the four categories of ILEs studied, FO-ILEs, providing FO at a mean daily dose between 0.1 and 0.2 g/kg body weight in accordance with ESPEN recommendation (17), represented the most effective intervention in improving clinical outcomes in adult hospitalized patients. Highly credible effects of FO-ILEs in the pairwise comparisons included a considerably reduced infection risk compared to all other categories of ILEs, a considerably reduced sepsis risk compared to SO-ILEs, and a considerably reduced hospital LOS compared to SO-ILEs and MCT/SO-ILEs. For these outcomes, results of our previous meta-analysis (7) have been confirmed, with new insights gained from the comparisons between the different types of ILEs and the rankings of ILEs for each outcome. Moreover, the Bayesian approach revealed a highly credible reduction in mortality with FO-ILEs versus SO-ILEs that was detected but not completely confirmed in our previous meta-analysis (7). Merely for ICU-LOS, no credible treatment effects with FO-ILEs compared to any other category of ILE studied could be shown in the pairwise comparisons. This is in contrast to the findings from out previous meta-analysis (7) and probably due to the heterogeneity between trials and included patients.

Overall, results underpin previous evidence (4-8) showing that FO-ILEs have the potential to confer meaningful clinical benefits for hospitalized patients receiving PN and should be standard of care, particularly in situations associated with a hypermetabolic and/or hyperinflammatory state e.g., in critical illness or post surgery (1). This can mainly be attributed to the anti-inflammatory, inflammation-resolution and immune-modulating, properties of the omega-3 PUFAs from FO, especially EPA and DHA (3). EPA and DHA serve as precursors for specialized pro-resolution mediators (SPMs) which have distinct roles in promoting the resolution of inflammation, in facilitating restoration of homeostasis, and in supporting tissue repair (3). These properties may be the main factor distinguishing FO-ILEs from other combinations of oils with reduced content of n-6 PUFAs, such as MCT/SO-ILEs and OO-ILEs.

Both the European Society for Clinical Nutrition and Metabolism (ESPEN) (29) and the Canadian Critical Care Nutrition Organization (30) acknowledge the benefits of FO-ILEs. In contrast, the recent 2022 update of the ASPEN ICU guidelines merely gave a weak recommendation suggesting that either mixed-oil ILEs or 100% SO-ILEs be provided to critically ill patients (31). The absence of a more specific recommendation is justified by the results of a meta-analysis of 7 RCTs comparing PN with FO-ILEs versus SO-ILEs. The authors found no significant differences between interventions with regard to the clinical outcomes investigated, with the exception of pneumonia (31). The guideline update has proved controversial, with many clinicians and experts within the field pointing to weaknesses in the guideline methodology and disagreeing with some conclusions, particularly the lack of guidance concerning lipid emulsion choice for clinicians (32, 33).

In light of this controversy and the call for action to further elucidate the role of FO-ILEs (31), the present NMA was conducted to add an additional level of detail to the insights gained from the previously conducted conventional pairwise meta-analyses. This established statistical technique was chosen, because it enables a more efficient use of the available study data by taking into account all relevant evidence, direct and indirect, which can increase the accuracy and robustness of the estimates (9) and potentially allows to compare interventions that have never been evaluated within individual randomized trials (10). Briefly, while conventional pairwise meta-analyses are only suitable to compare the value of two interventions (A vs. B), the NMA allows to gauge the value of more than two interventions, especially in situations when direct comparison data are lacking or scarce (13, 34). This is basically the situation for ILEs since, in adults, mixed-oil ILEs with FO have typically been compared to pure SO and MCT/SO-ILEs, but rarely to OO-ILEs. It should be noted that the NMA model can also be extended to multi-arm trials (22) even if only two armed studies met the inclusion criteria of the present systematic review.

Our systematic review has a number of strengths. We adhered to best practices, such as prospective registration of the protocol and following the PRISMA statement for reporting systematic reviews

and meta-analyses. Heterogeneity between studies for all dichotomous outcomes was very low, inconsistency was low for mortality, infection risk and hospital LOS; moreover, both heterogeneity and inconsistency were low for mortality and infection risk.

Nevertheless, our approach also has several limitations. Our findings for sepsis and ICU-LOS are associated with some degree of uncertainty with regard to substantial inconsistency (63.6% and 37.8%, respectively) and, for ICU- and hospital LOS, to high heterogeneity (47.8% and 58.1%, respectively). Specifically for sepsis, the comparisons between SO-ILEs, OO-ILEs and FO-ILEs could be unreliable due to the high inconsistency between direct and indirect treatment effects. Moreover, a NMA cannot replace properly conducted direct comparison studies, so it would be useful to perform further large-scale RCTs, in particular to prove or reject any effect on mortality. Yet, in this context it should be mentioned that in studies evaluation nutritional interventions in critically ill patients, mortality may not be a very meaningful outcome, due to the wide variations between patients and their predicted mortality rates. Indeed, morbidity and patient-centred outcomes, such as quality of life may allow for a much accurate estimate of treatments benefits (35).

CONCLUSION

Our findings confirm and expand the insights gained from previous conventional pairwise meta-analyses, corroborating existing evidence that FO-ILEs provide significant clinical benefits over all other types of ILEs, with FO-ILEs ranking first for all outcomes investigated. The results of this systematic review and NMA may contribute to the identification of the most effective ILE to improve clinical outcomes in hospitalized patients receiving PN.

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Conflict of interest

L. Pradelli is a director and employee of AdRes, which has received project funding from Fresenius Kabi. K. Mayer has received fees from Abbott, AstraZeneca, Baxter, BBraun, Fresenius Kabi, MSD, Nestlé, Novartis, and Pfizer. S. Klek has received speaker's honoraria from Baxter, Braun, Fresenius Kabi, Nestlé, Nutricia, Shire, and Vipharm and acted as an advisory board member for Fresenius Kabi, Shire, and Tracheron. M. Rosenthal has received fees from Fresenius, Nestle, and Abbott. M. Povero is an employee of AdRes, which has received project funding from Fresenius Kabi. A. R. Heller has received project funding from Fresenius Kabi. M. Muscaritoli has received speaker's fees from Fresenius Kabi.

Author contributions

L. Pradelli: *Conceptualization; Investigation; Methodology; Supervision; Writing - review & editing.*

K. Mayer: *Investigation; Supervision; Validation; Writing - review & editing.*

S. Klek: *Investigation; Supervision; Validation; Writing - review & editing*

M.D. Rosenthal: *Investigation; Supervision; Validation; Writing - review & editing*

M. Povero: *Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Validation; Visualization; Roles/Writing - original draft*

A.R. Heller: *Investigation; Supervision; Validation; Writing - review & editing*

M. Muscaritoli: *Investigation; Supervision; Validation; Writing - review & editing*

Table 1: Characteristics of the Randomized Controlled Trials included (n = 47)

Study	Patient population	ILE 1	ILE 2	N 1	N 2	PN duration (days)	Daily FO dose (g/kg)	% FO on total DLD	Clinical outcomes extracted
Aliyazicioglu 2013 (36)	Colorectal cancer surgery	SO	FO/SO	10	8	6	0.10-0.20	NA	Hospital LOS
Badia-Tahull 2010 (37)	Major GI surgery	SO/OO	FO/OO	14	13	Median 7	0.12 -0.17	16.6%	Infections, sepsis, hospital LOS, mortality*
Ball 1993 (38)	Critically ill	SO	MCT/SO	10	10	≥6	-	-	Mortality
Barbosa 2010 (39)	SIRS or Sepsis	MCT/SO	FO/MCT/SO	10	13	5	0.10	10%	ICU LOS, hospital LOS, mortality
Bellantone 1999 (40)	Colorectal surgery	SO	MCT/SO	10	9	5	-	-	Hospital LOS
Berger 2008 (41)	Abdominal aortic aneurism surgery	MCT/SO	FO/MCT/SO	12	12	Median 2.7	0.15	10%	ICU LOS, hospital LOS, mortality
Chen 2005 (42)	GI cancer surgery	SO	MCT/SO	15	15	7	-	-	Mortality
Chen 2017a (43)	Severe sepsis with Grade III acute GI injury	SO	FO/SO	37	41	7	0.14-0.20	20%	Mortality
Chen 2017b (44)	Gastric cancer surgery	SO	FO/MCT/SO/OO	40	40	7	0.15[1]	15%	Infections, hospital LOS
Demirer 2000 (45)	Hematologic malignancy	SO	MCT/SO	18	18	Median 8	-	-	Mortality
Donoghue 2019 (46)	Critically ill	SO	FO/MCT/SO/OO	33	35	≥5	0.10-0.20	10-20%	ICU-LOS
Friesecke 2008 (47)	Critically ill medical patients	MCT/SO	FO/MCT/SO	82	83	7	0.15	16.7%	Infections, ICU LOS hospital LOS, mortality
Garcia de Lorenzo 2005 (48)	Burn patients	MCT/SO	SO/OO	11	11	6	-	-	ICU LOS, hospital LOS. mortality

Study	Patient population	ILE 1	ILE 2	N 1	N 2	PN duration (days)	Daily FO dose (g/kg)	% FO on total DLD	Clinical outcomes extracted
Garnacho-Montero 2002 (49)	Sepsis	SO	MCT/SO	37	35	10	-	-	ICU LOS, mortality
Gong 2016 (50)	Hepatectomy	SO	FO/SO	60	59	5	0.14-0.20	10%	Mortality, infections, sepsis
Grau-Carmona 2015 (51)	Medical and surgical ICU	MCT/SO	FO/MCT/SO	78	81	≥5	0.12	10%	Infections, ICU LOS, hospital LOS, mortality
Grimm 2006 (52)	Major abdominal surgery	SO	FO/MCT/SO/OO	14	19	5	0.20	15%	Hospital LOS
Gultekin 2014 (53)	ICU patients with sepsis	SO/OO	FO/SO/OO	16	16	≥5	0.13-0.17	10%	Hospital LOS, mortality
Han 2012 (54)	Major surgery	MCT/SO	FO/MCT/SO	12	18	7	0.20	20%	Infections
Heller 2004 (55)	Major abdominal cancer surgery	SO	FO/SO	24	20	5	0.19	20%	ICU LOS, Hospital LOS,
Iovinelli 2007 (56)	Acute respiratory failure	SO	MCT/SO	13	12	≤15	-	-	Mortality
Jia 2015 (57)	Major surgery	SO	SO/OO	231	222	5-14	-	-	Infections, sepsis, hospital LOS
Jiang 2010 (58)	GI cancer surgery	SO	FO/SO	103	100	7	0.20	16.7%	Infections, sepsis, hospital LOS
Klek 2005 (59)	Gastric cancer surgery	MCT/SO	FO/MCT/SO	30	30	Mean 9	0.10	NA	Infections, hospital LOS
Klek 2008 (60)	Gastrectomy or pancreaticodudenectomy	MCT/SO	FO/MCT/SO	49	51	7	0.10	NA	Infections, sepsis, hospital LOS, mortality
Klek 2011 (61)	GI surgery	MCT/SO	FO/MCT/SO	41	42	G1: 7-15 G2: 7-14	0.10	NA	Infections, sepsis, mortality
Liang 2008 (62)	Colorectal cancer surgery	SO	FO/SO	21	20	7	0.20	16.7%	Infections

Study	Patient population	ILE 1	ILE 2	N 1	N 2	PN duration (days)	Daily FO dose (g/kg)	% FO on total DLD	Clinical outcomes extracted
Lindgren 2001 (63)	Critically ill	SO	MCT/SO	11	9	5	-	-	Infections, hospital LOS, mortality
Ma 2015 (64)	Gastric and colorectal cancer surgery	MCT/SO	FO/MCT/SO	48	51	8	0.10-0.15	10%	ICU-LOS, mortality
Makay 2011 (65)	Major gastric cancer surgery	SO	FO/SO	12	14	5	0.20	25%	Infections
Mertes 2006 (66)	Abdominal or thoracic surgery	SO	FO/MCT/SO/OO	123	126	5	0.20	15%	Infections, mortality
Onar 2011 (67)	Abdominal cancer surgery	SO	SO/OO	10	10	7	-	-	Hospital LOS, mortality
Sabater 2011 (68)	ARDS /respiratory failure	SO	FO/MCT/SO	8	8	12 hours	0.14	10%	Infections
Salazar 2021 (69)	General hospital population	SO	SO/OO	102	108	Mean 23	-	-	Infections, sepsis, ICU LOS, hospital LOS, mortality
Senkal 2007 (70)	Colorectal surgery	MCT/SO	FO/MCT/SO	21	19	5	0.10-0.14	10%	Infections
Umpierrez 2012 (71)	Medical/surgical ICU	SO	SO/OO	49	51	≤28	-	-	Infections, ICU LOS, hospital LOS, mortality
Wang 2009 (72)	Severe acute pancreatitis	SO	FO/SO	28	28	5	0.15-0.2	10-20%	Infections, mortality
Wang 2012 (73)	GI surgery	MCT/SO	FO/MCT/SO	31	32	5	0.10	10%	Infections, sepsis
Wang 2013 (74)	Oesophageal cancer surgery	MCT/SO	SO/OO	48	46	>7	-		Infections, mortality
Wei 2014 (75)	Gastric cancer surgery	SO	FO/SO	20	26	≥6	0.16[2]	20%	Infections
Wichmann 2007 (76)	Major GI surgery	SO	FO/MCT/SO	129	127	5	0.11	10%	Infections, ICU LOS, hospital LOS, mortality
Wu 2014 (77)	GI surgery	MCT/SO	FO/MCT/SO/OO	20	20	5	0.13	15%	Infections, hospital LOS, mortality

Study	Patient population	ILE 1	ILE 2	N 1	N 2	PN duration (days)	Daily FO dose (g/kg)	% FO on total DLD	Clinical outcomes extracted
Yu 2017 (78)	Abdominal surgery	SO	MCT/SO	118	121	6	-	-	Hospital LOS, mortality
Zhang 2017 (79)	Hepatectomy	MCT/SO	FO/MCT/SO	155	157	5	0.16[3]	33%	Infections, sepsis, hospital LOS, mortality
Zhu 2012a (80)	Liver transplantation	MCT/SO	FO/MCT/SO	33	33	7	0.20	20%	Hospital LOS, mortality
Zhu 2012b (81)	Colorectal cancer surgery	SO	FO/SO	28	29	8	0.20	16.7%	Infections, sepsis, hospital LOS
Zhu 2013 (82)	Pancreaticodudenectomy	MCT/SO	FO/MCT/SO	38	38	6	0.20	18.2%	Infections, hospital LOS, mortality

DLD: daily lipid dosage ILE: intravenous lipid emulsion SO: soybean oil OO: olive oil MCT: medium-chain triglyceride FO: fish oil N: number of patients receiving intervention GI: gastrointestinal LOS: length of stay * Mortality refers to in-hospital mortality throughout the table

[1]Total daily energy from fat is 42 kJ/kg corresponding to 0.5% of a 1000 ml bag of SMOFlipid that contains 30 g of FO (daily FO dose was 0.5% x 30 g=0.15 g/kg)

[2]The daily dose was calculated considering 10 g of FO (as Omegaven) and mean weight of 62 kg as reported in the paper (0.16 g/kg=10 g/62 kg)

[3]The daily dose was calculated considering 10 g of FO (as Omegaven) and mean weight of 63 kg as reported in the paper (0.16 g/kg=10 g/63 kg)

Table 2: Relative treatment effects estimated for the 6 possible direct and indirect comparisons for each outcome

	Infection OR (90% CrI)	**Sepsis OR (90% CrI)**	**ICU LOS MD (90% CrI)**	**Hospital LOS MD (90% CrI)**	**In-hospital mortality OR (90% CrI)**
FO-ILEs vs SO-ILEs	0.43 (0.29 to 0.63)*	0.22 (0.08 to 0.59)*	-0.97 (-2.5 to 0.87)	-2.31 (-3.14 to -1.59)*	0.67 (0.42 to 1.06)*
OO-ILEs vs SO-ILEs	0.77 (0.52 to 1.16)	0.32 (0.08 to 1)*	-0.35 (-3.77 to 3.06)	-1.46 (-3.2 to 0.16)*	0.82 (0.46 to 1.46)
MCT/SO-ILEs vs SO-ILEs	0.73 (0.45 to 1.16)	0.4 (0.09 to 1.73)	0.52 (-1.95 to 3.27)	-0.3 (-1.28 to 0.49)	0.78 (0.5 to 1.23)
FO-ILEs vs MCT/SO-ILEs	0.59 (0.43 to 0.82)*	0.57 (0.19 to 1.63)	-1.49 (-4.22 to 1)	-2.01 (-2.82 to -1.22)*	0.86 (0.52 to 1.37)
OO-ILEs vs MCT/SO-ILEs	1.06 (0.63 to 1.84)	0.82 (0.11 to 4.98)	-0.87 (-5.09 to 3.2)	-1.16 (-2.98 to 0.73)	1.05 (0.55 to 2.01)
FO-ILEs vs OO-ILEs	0.56 (0.33 to 0.91)*	0.69 (0.16 to 3.47)	-0.62 (-4.33 to 3.24)	-0.86 (-2.67 to 0.92)	0.82 (0.42 to 1.6)
I^2	21.5%	11.3%	47.8%	58.1%	12.1%
I^2_w	20.9%	63.6%	37.8%	15.2%	9.1%

ILE: intravenous lipid emulsion SO: soybean oil OO: olive oil MCT: medium-chain triglyceride FO: fish oil OR: odds ratio MD: mean difference CrI: credibility interval I^2 : Variability due to the between-trial heterogeneity I^2_w: Variability due to the inconsistency over the total variance * very high credibility of difference between interventions (posterior probability of OR<1 or MD<0 greater than 90%

Table 3: Probabilities of being the best intervention for each outcome according to the Surface Under the Cumulative RAnking (SUCRA) and median ranks with (90%) credibility intervals (CrI)

Infection risk	**SUCRA**	**Median rank (90% CrI)**
FO-ILEs	99.0%	1 (1 to 1)
MCT/SO-ILEs	47.6%	2 (2 to 4)
OO-ILEs	44.4%	3 (2 to 4)
SO-ILEs	9.1%	4 (3 to 4)
Sepsis risk	SUCRA	**Median rank (90% CrI)**
FO-ILEs	83.2%	1 (1 to 3)
OO-ILEs	60.8%	2 (1 to 3)
MCT/SO -ILEs	49.3%	3 (1 to 4)
SO-ILEs	6.7%	4 (3 to 4)
ICU LOS	**SUCRA**	**Median rank (90% CrI)**
FO-ILEs	77.2%	1 (1 to 3)
OO-ILEs	52.7%	2 (1 to 4)
SO-ILEs	39.9%	3 (1 to 4)
MCT/SO -ILEs	30.2%	3 (1 to 4)
Hospital LOS	**SUCRA**	**Median rank (90% CrI)**
FO-ILEs	93.2%	1 (1 to 2)
OO-ILEs	66.5%	2 (1 to 4)
MCT/SO -ILEs	27.6%	3 (2 to 4)
SO-ILEs	12.7%	4 (3 to 4)
In-hospital mortality	**SUCRA**	**Median rank (90% CrI)**
FO-ILEs	76.7%	1 (1 to 3)
MCT/SO-ILEs	55.8%	2 (1 to 4)
OO-ILEs	49.4%	3 (1 to 4)
SO-ILEs	18.1%	4 (2 to 4)

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Figure 1. Flow chart of literature search and study selection.

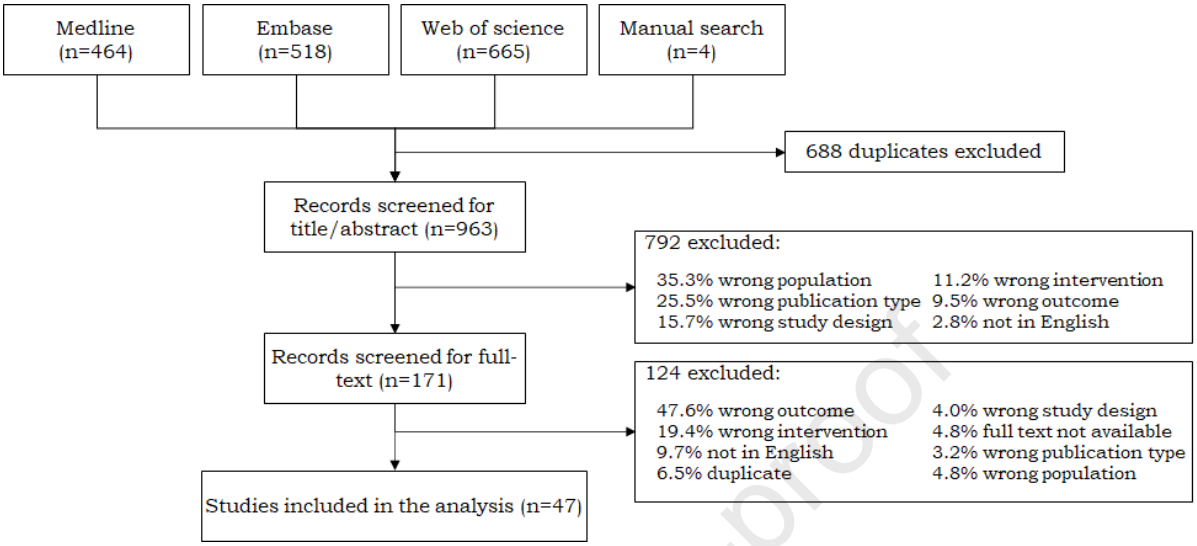


Figure 2: Assessment of the risk of bias for the included studies

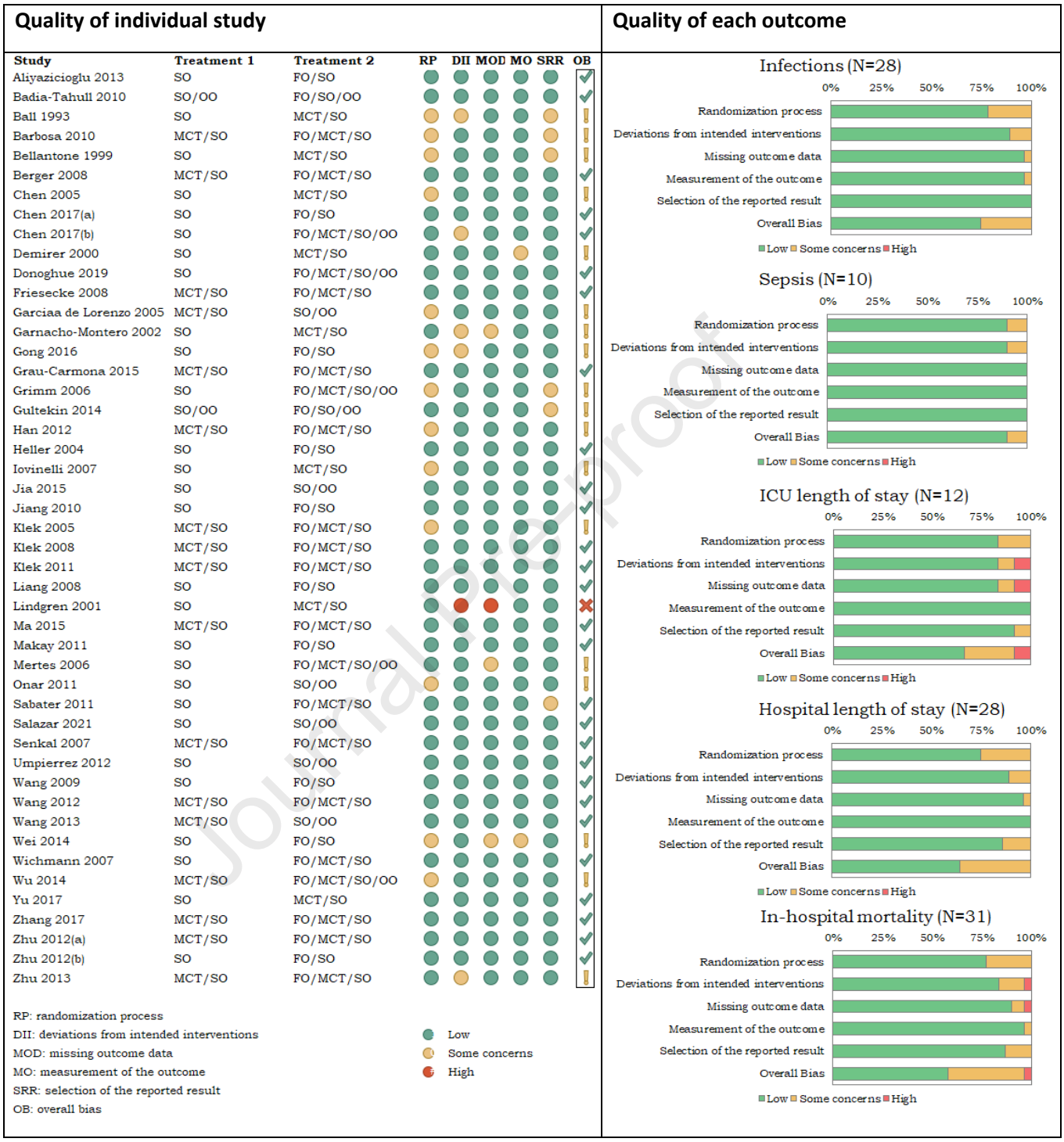
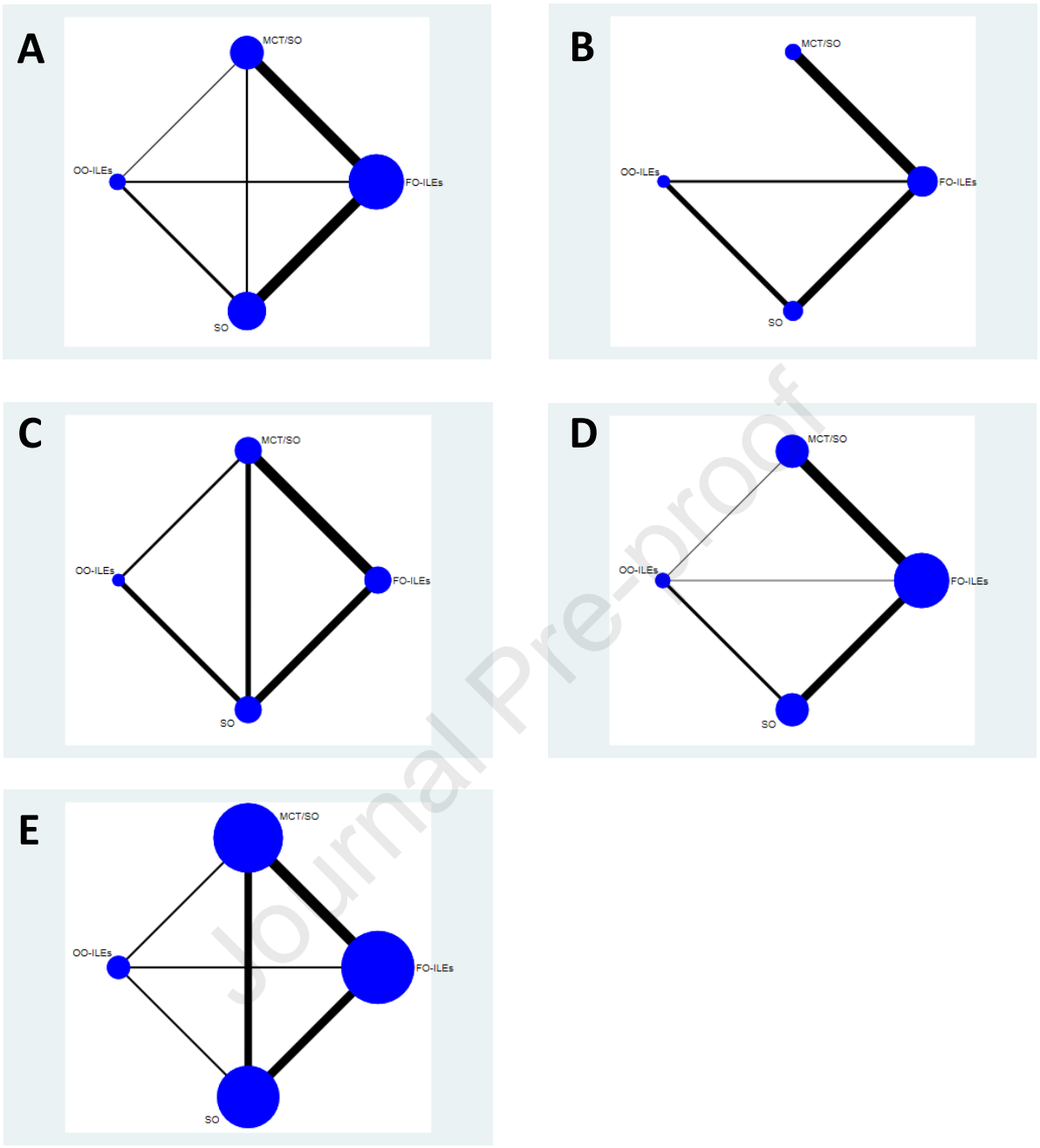


Figure 3: Network diagrams showing the competing interventions investigated in the selected studies for each clinical outcome



A: Infections, **B**: Sepsis, **C**: ICU length of stay, **D**: hospital length of stay; **E**: In-hospital mortality

Missing lines indicate the absence of RCTs with direct comparisons. The diameter of the nodes increases with the number of participants assigned to the intervention and the thickness of the lines reflects the number of RCTs for the respective direct comparison.