

Perioperative omega-3 fatty acids for liver surgery

A meta-analysis of randomized controlled trials

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Abstract

Introduction: The effect of perioperative omega-3 fatty acids for liver surgery remained controversial. We conducted a systematic review and meta-analysis to explore the influence of omega-3 fatty acids versus placebo in patients undergoing liver surgery.

Methods: We have searched PubMed, EMBASE, Web of Science, EBSCO, and Cochrane library databases through May 2020, and included randomized controlled trials (RCTs) assessing the effect of omega-3 fatty acids versus placebo for liver surgery. This meta-analysis was performed using the random-effect model.

Results: Five RCTs were included in the meta-analysis. Overall, compared with control group for liver surgery, omega-3 fatty acids were associated with substantially reduced incidence of infection (odds ratio [OR]=0.56; 95% confidence interval [CI]=0.34–0.91; $P=.02$), but revealed no remarkable influence on complications (OR=0.60; 95% CI=0.29–1.24; $P=.17$), mortality (OR=0.76; 95% CI=0.06–9.37; $P=.83$), liver failure (OR=0.72; 95% CI=0.10 to 5.00; $P=0.74$), biliary leakage (OR=1.24; 95% CI=0.41 to 3.76; $P=.70$), bleeding (OR=1.76; 95% CI=0.63–4.95; $P=.28$), or ileus (OR=0.39; 95% CI=0.07–2.05; $P=.27$).

Conclusion: Perioperative omega-3 fatty acids may be beneficial to reduce the incidence of infection after liver surgery.

Abbreviations: CI = confidence interval, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, SMD = standard mean difference.

Keywords: liver surgery, omega-3 fatty acids, randomized controlled trials

1. Introduction

Omega-3 fatty acids are the essential nutritional components in the human body,^[1–4] and are associated with extraordinarily low incidence of coronary heart disease.^[5] The liver is known as a central metabolic target of omega-3 fatty acids, and there is growing evidence showing the beneficial effects of omega-3 fatty acids on fatty liver and metabolic syndrome.^[6] Omega-3 fatty acids were documented to lower intrahepatic lipid contents and mitigate inflammatory responses in the liver.^[7–9]

Liver surgery may result in an amplified ischemia-reperfusion injury and impaired regeneration.^[10] Significant liver protection

of ischemia-reperfusion injury and improved regeneration was observed after the treatment with omega-3 fatty acids in the animal models of hepatic surgery.^[11,12] For instance, intravenous administration of single dose of omega-3 fatty acids before liver ischemia could mitigate the production of reactive oxygen species (ROS), which was mediated via the GPR120 receptor located on hepatic Kupffer cells.^[13] The protective effect of omega-3 fatty acids on liver function was associated with the enhancement of hepatic beta oxidation, significant reduction of endogenous lipid production and pro-inflammatory molecules.^[14]

The efficacy of omega-3 fatty acids for liver surgery remained not fully established, and several studies reported the conflicting results.^[5,15–17] With accumulating evidence, we therefore performed this meta-analysis of randomized controlled trials (RCTs) to explore the efficacy of omega-3 fatty acids for liver surgery.

2. Materials and methods

Ethical approval and patient consent were not required because this was a meta-analysis of previously published studies. This meta-analysis is conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).^[18,19]

2.1. Search strategy and study selection

Two investigators have independently searched the following databases (inception to May 2020): PubMed, EMBASE, Web of Science, EBSCO, and Cochrane library databases. The electronic search strategy was conducted using the following keywords: “omega-3 fatty acids,” and “liver” or “hepatic,” and “surgery” or “operation,” and “cancer” or “tumor.” We also checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria were as follows: study design was RCT; patients underwent the surgery due to liver tumor;

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Consent for publication: is not applicable.

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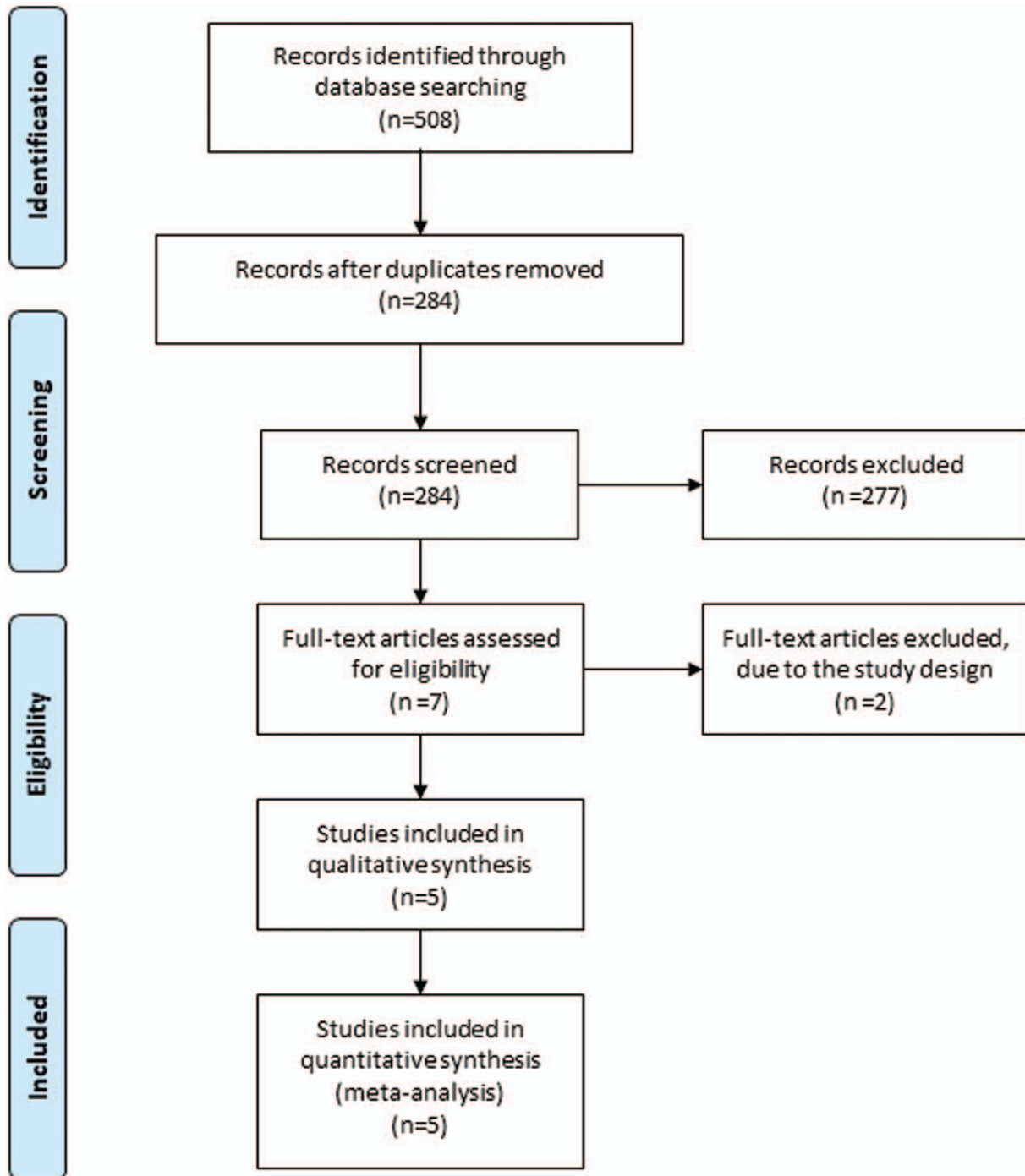


Figure 1. Flow diagram of study searching and selection process.

intervention treatments were perioperative omega-3 fatty acids versus placebo.

2.2. Data extraction and outcome measures

We extracted the following information: author, number of patients, age, male, body mass index, and detail methods in each group, and so on. Data were extracted independently by 2 investigators, and discrepancies were resolved by consensus. We also contacted the corresponding author to obtain the data when

necessary. The primary outcomes were infection and complications. Secondary outcomes included mortality, liver failure, biliary leakage, bleeding, and ileus.

2.3. Assessment for risk of bias

The risk of bias tool was used to assess the quality of individual studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*,^[20] and the following sources of bias were considered: selection bias, performance

Table 1
Characteristics of included studies.

No.	Author	Omega-3 fatty acids group					Control group				
		No.	Age, y	Male (n)	Body mass index, kg/cm ²	Methods	No.	Age, y	Male (n)	Body mass index, kg/cm ²	Methods
1	Linecker 2020	132	59 (44–68)	62	24 (22–27)	One dose of Omegaven (100 mL) contains 10 g of highly refined fish oil mainly containing eicosapentaenoic and docosahexaenoic acid before liver surgery	129	60 (50–68)	67	25 (23–28)	Placebo
2	Zhang et al, 2017 ^[15]	157	—	—	—	10% n-3 Fatty acid for 5 consecutive days postoperatively	155	—	—	—	Placebo
3	Watson et al, 2016 ^[16]	43	—	—	—	Eicosapentaenoic acid 2 g taken as 2 gastroresistant capsules twice daily after the surgery	45	—	—	—	Placebo
4	Seguin et al, 2016 ^[17]	18	65±8	17	26.9±4.5	Oral impact 3 times daily for 7 days before and 3 days after surgery	17	68±6	14	28.0±4.6	Placebo
5	Kazuhiro 2011	13	67.5±11.3	10	23.6±3.8	750 mL for n-3 fatty acid, arginine, and nucleic acid per day for 5 days before the hepatectomy	13	61.5±10.2	8	21.5±4.4	Placebo

Data are presented as mean ± standard deviation (SD) or median (IQR).

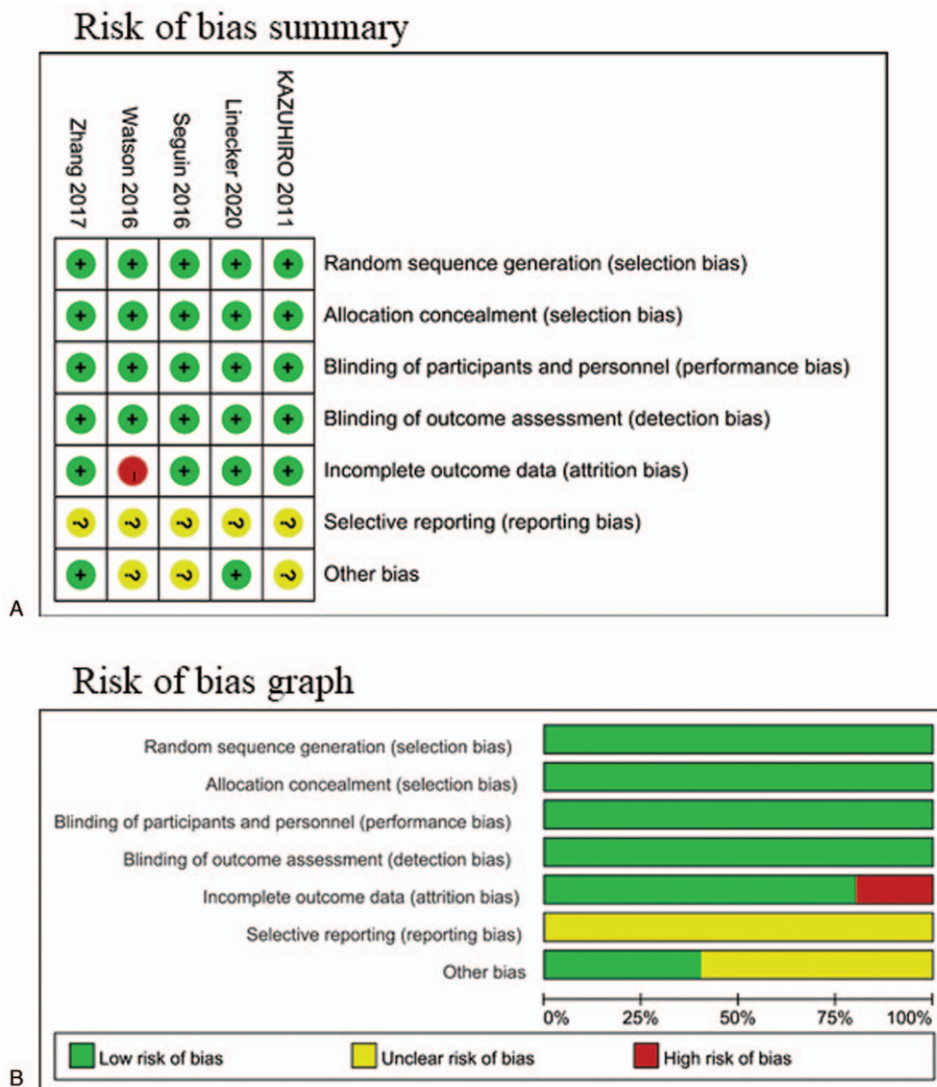


Figure 2. Risk of bias assessment. (A) Authors’ judgments about each risk of bias item for each included study. (B) Authors’ judgments about each risk of bias item presented as percentages across all included studies.

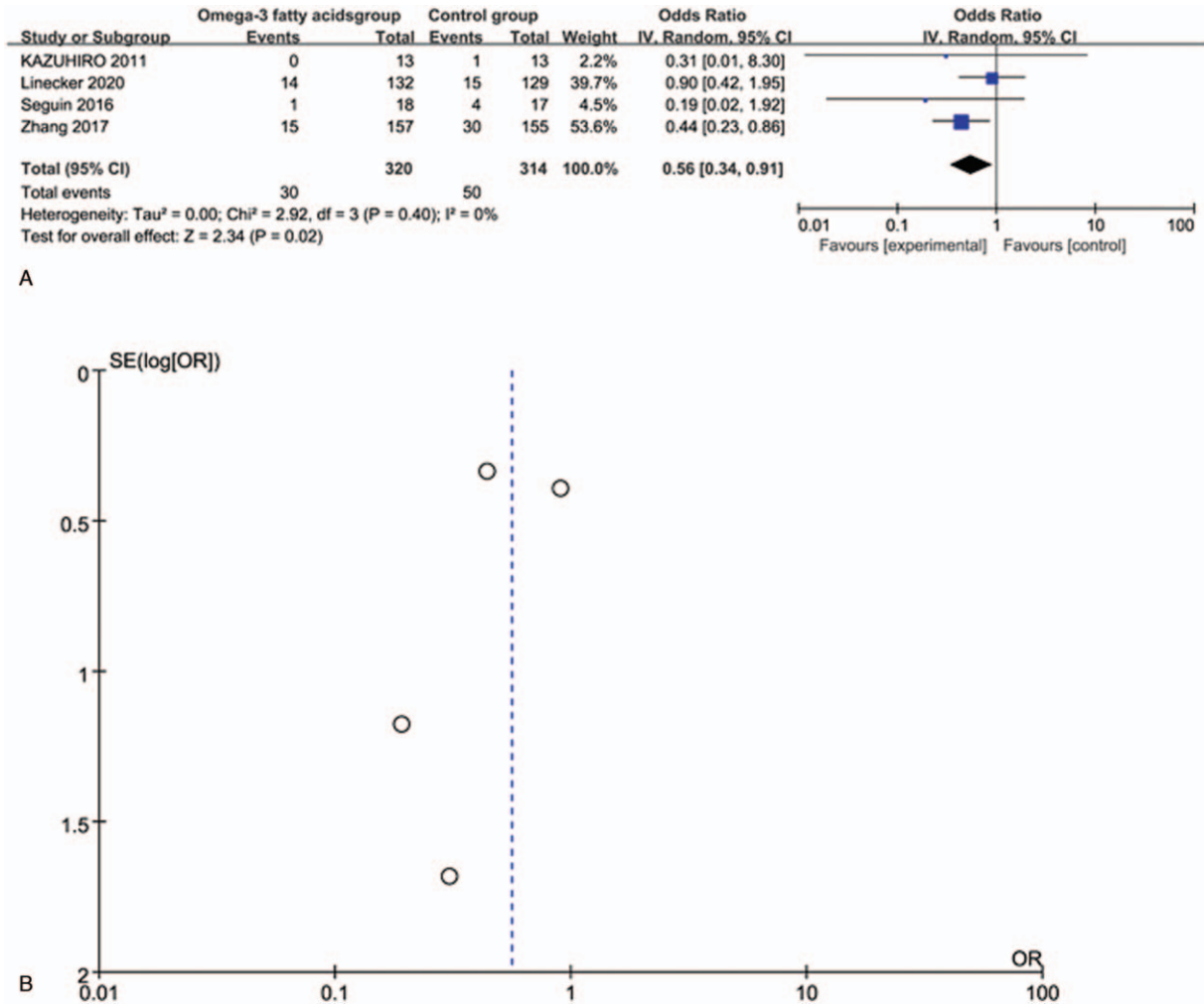


Figure 3. (A) Forest plot and (B) funnel plot for the meta-analysis of infection.

bias, attrition bias, detection bias, reporting bias, and other potential sources of bias. The overall risk of bias for each study was evaluated and rated: low, unclear, and high.^[21] Two investigators assessed the quality of included studies. Any discrepancy was solved by consensus.

2.4. Statistical analysis

We estimated the odd ratio (OR) with 95% confidence interval (CI) for dichotomous outcomes. The random-effects model was used regardless of heterogeneity. Heterogeneity was reported using the I² statistic, and I² > 50% indicated significant heterogeneity.^[19,22] Whenever significant heterogeneity was present, we searched for potential sources of heterogeneity via omitting one study in turn or performing the subgroup analysis. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

3. Results

3.1. Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results was shown in Figure 1. A total number of 508 potentially relevant articles

were identified initially and 5 RCTs were finally included in the meta-analysis.^[5,15–17,23]

The baseline characteristics of the five eligible RCTs were summarized in Table 1. The 5 studies were published between 2011 and 2020, and total sample size is 722. Among the 5 studies included here, 4 studies reported infection and complications,^[5,15,17,23] as well as 2 studies reported mortality, liver failure, biliary leakage, bleeding, and ileus.^[5,15]

3.2. Assessment of risk of bias

Risk of bias analysis (Fig. 2) showed that 1 study had high risk of attrition bias,^[16] but all RCTs generally had high quality.

3.3. Primary outcomes: infection and complications

These outcome data were analyzed with the random-effects model, and compared to control group for liver surgery, omega-3 fatty acids substantially reduced the incidence of infection (OR = 0.56; 95% CI = 0.34–0.91; P = .02) with no heterogeneity among the studies (I² = 0%, heterogeneity P = .40) (Fig. 3A), but showed no obvious impact on complications (OR = 0.60; 95% CI = 0.29–1.24; P = .17) with significant heterogeneity among the studies (I² = 67%, heterogeneity P = .03) (Fig. 4A).

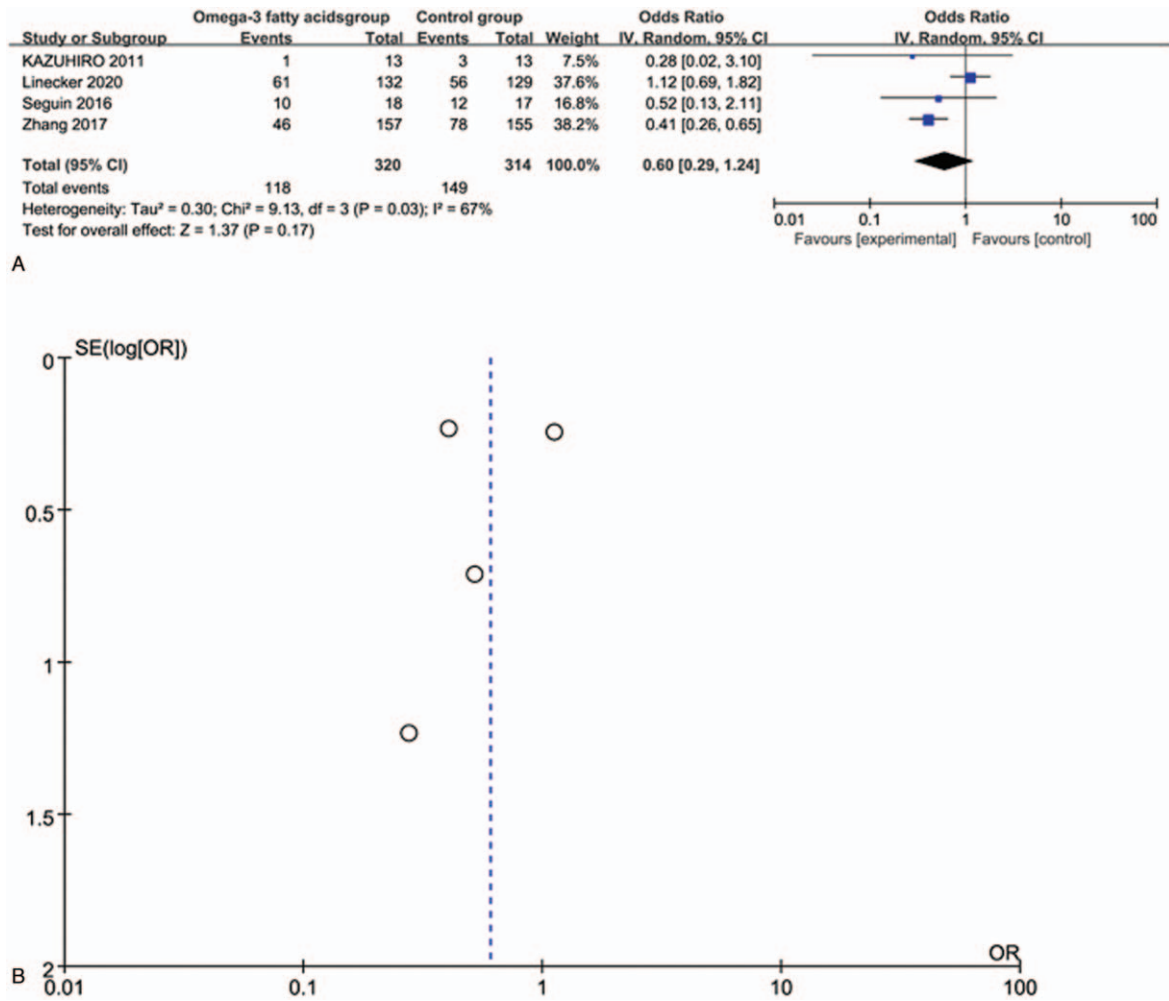


Figure 4. (A) Forest plot and (B) funnel plot for the meta-analysis of complications.

3.4. Sensitivity analysis

Figure 3B and 4B showed the funnel plots for studies reporting infection and complications, separately. These were not symmetrical, indicating significant heterogeneity. Significant heterogeneity remained for complications. After excluding the study conducted by Linecker et al,^[5] omega-3 fatty acids were associated with significantly reduced complications than placebo after liver surgery (OR=0.41; 95% CI=0.27–0.64; P < .0001), and no heterogeneity remained (I²=0%, heterogeneity P=.90).

3.5. Secondary outcomes

In comparison with control group for liver surgery, omega-3 fatty acids had no notable effect on mortality (OR=0.76; 95% CI=0.06–9.37; P=.83; Fig. 5), liver failure (OR=0.72; 95% CI=0.10–5.00; P=.74; Fig. 6), biliary leakage (OR=1.24; 95% CI=0.41 to 3.76; P=.70; Fig. 7), bleeding (OR=1.76; 95% CI=0.63–4.95; P=.28; Fig. 8), or ileus (OR=0.39; 95% CI=0.07–2.05; P=.27; Fig. 9).

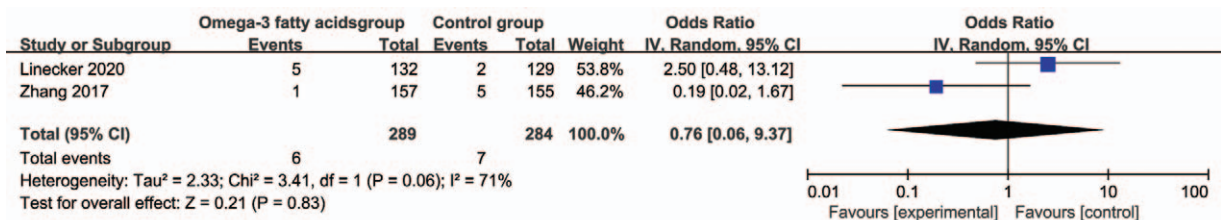


Figure 5. Forest plot for the meta-analysis of mortality.

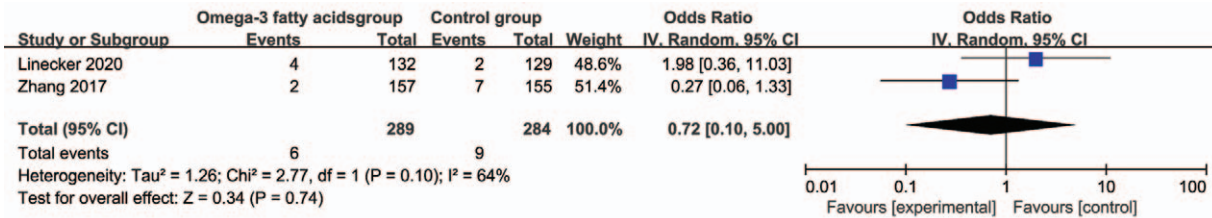


Figure 6. Forest plot for the meta-analysis of liver failure.

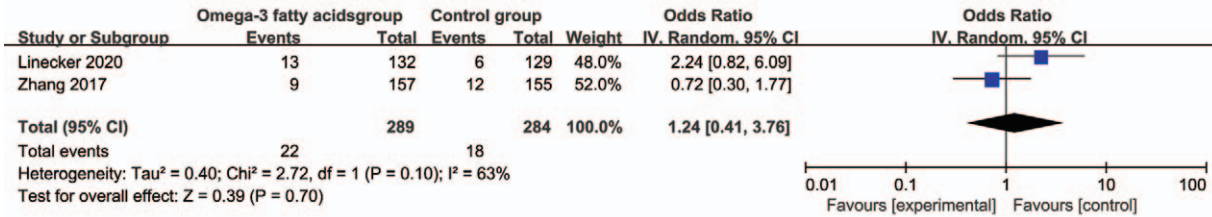


Figure 7. Forest plot for the meta-analysis of biliary leakage.

4. Discussion

In various animal studies, the beneficial effects of omega-3 fatty acids were observed to alleviate ischemia-reperfusion injury and promote liver regeneration.^[11,13,24] Previous studies also revealed the anti-cancer effects of omega-3 fatty acids.^[12,25,26] However, in this meta-analysis, we included 5 RCTs involving 722 patients and found that perioperative omega-3 fatty acids was only associated with substantially reduced incidence of infection after the liver surgery, but had no obvious impact on the total complications, mortality, liver failure, biliary leakage, bleeding, or ileus.

Regarding the sensitivity analysis, there was significant heterogeneity for the complications. Among the 4 included RCTs, only the study conducted by Linecker et al reported the 1 dose of omega-3 fatty acids before the surgery, whereas other studies reported the continuous use of omega-3 fatty acids for several days before and/or after the surgery. After excluding the study conducted by Linecker et al,^[5] omega-3 fatty acids could significantly reduce complications than placebo after liver surgery (OR=0.41; 95% CI=0.27–0.64; P<.0001), and no heterogeneity was observed among the remaining studies (I²=0%, heterogeneity P=.90). These indicated that continuous use of

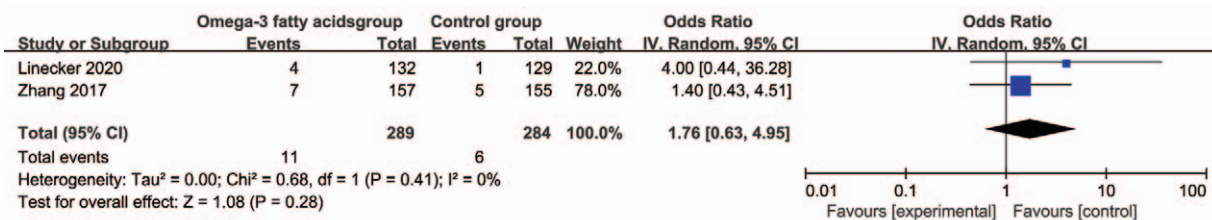


Figure 8. Forest plot for the meta-analysis of bleeding.

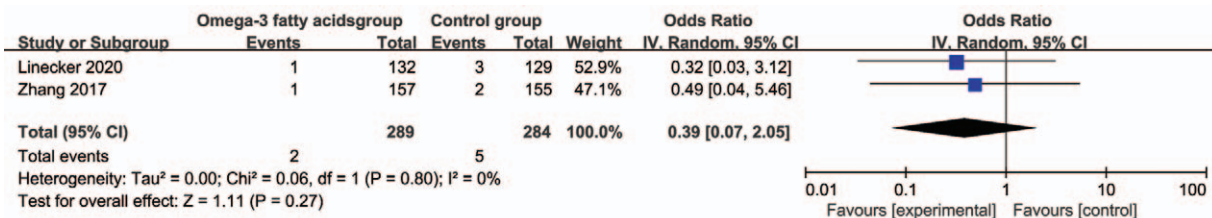


Figure 9. Forest plot for the meta-analysis of ileus.

omega-3 fatty acids for several days before and/or after the surgery had significantly better efficacy to reduce the rate of complications than only 1 dose.

Oral supplementation of omega-3 fatty acids for 4 weeks was documented to reduce intrahepatic lipid content in preparation for bariatric surgery and living donor liver transplantation.^[27,28] Parenteral use of omega-3 fatty acids supplementation for 7 consecutive days was associated with the reduction in infectious complications and hospitalization time after liver transplantation.^[29] Another 3 studies also demonstrated the positive effects of omega-3 fatty acids on liver regeneration, mortality and length of hospital stay after liver surgery.^[15,30,31] A 5-day course of postoperative intravenous supplementation of omega-3 fatty acids resulted in a reduction of total postoperative complications and length of hospital stay after hepatectomy.^[30] These suggested that the protective effect of omega-3 fatty acids for liver surgery was affected by the forms, doses, and duration of omega-3 fatty acids.

Omega-3 fatty acid, a fish oil, was enriched in eicosapentaenoic acid and docosahexaenoic acid. It showed the anti-inflammatory effect through regulating the arachidonic acid pathway and producing 3-series prostaglandins, thromboxanes, and 5-series leukotrienes.^[32] These subsequently reduced the proinflammatory cytokines including interleukin (IL)-6, IL-8, and tumor necrosis factor- α .^[33] In addition, omega-3 fatty acid was documented to change membrane fluidity through the regulation of gene transcription such as sterol regulatory element-binding protein-1, protein acylation, and calcium release.^[34]

This meta-analysis had several potential limitations. First, our analysis was based on 5 RCTs, and all of them had a relatively small sample size ($n < 100$). Overestimation of the treatment effect was more likely in smaller trials compared with larger samples. Next, there was significant heterogeneity, which may be caused by different doses, forms, and duration of omega-3 fatty acids. Finally, it was not feasible to perform the subgroup analysis based on different dosages and treatment time for drug administration.

5. Conclusions

Omega-3 fatty acids may benefit to reduce the incidence of infection after liver surgery.

Author contributions

FB.X and W.H were involved in the acquisition of data. Q.Y and JJ.K analyzed and interpreted the data. BX.J drafted the article. XJ.F designed the paper and approved the version to be published. All authors approved this version for publication.

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