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Associations between omega-3 polyunsaturated fatty acids supplementation and surgical prognosis in patients with gastrointestinal cancer: A systematic review and meta-analysis

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ABSTRACT

Background: Surgical resection remains the primary treatment for gastrointestinal (GI) cancer, omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been reported to improve the prognosis of patients undergoing gastrointestinal tumor surgery. This meta-analysis aims to explore the efficacy of n-3 PUFAs on GI cancer patients undergoing surgery.
Methods: A systematic search of PubMed, Cochrane Library databases, EMBASE (until December 2021) was conducted. PRISMA checklist was followed. The data were analyzed by RevMan v5.3.0.
Results: A total of ten RCTs articles including 663 patients were studied. The analysis demonstrated that the n-3 PUFAs group significantly reduced levels of interleukin-6 (IL-6) (P = 0.001), C-reactive protein (CRP) (P < 0.00001), tumor necrosis factor-α (TNF-α) (P = 0.0003) compared with the control group. and higher levels of CD4$^+$T cells (P = 0.03), CD8$^+$T cells (P = 0.02) and CD4$^+$/CD8$^+$ratio (P = 0.03) compared with the control group. but there was no significant difference in infection complications rate (P = 0.50) and the level of pre-albumin (P = 0.80), albumin (P = 0.21), retinol-binding protein(P = 0.80) between the two groups. In addition, the n-3 PUFAs group significantly reduced the length of hospital stay (P = 0.007).
Conclusion: Our meta-analysis shows that n-3 PUFAs can effectively improve the immune function of patients undergoing gastrointestinal cancer surgery, reduce inflammatory response and reduce the length of hospital stay, But it has no significant impact on the incidence of infectious-related complications and the level of nutrient protein.

1. Introduction

GI cancers are the most common group of malignancies and it has become the leading cause of cancer deaths worldwide (Qu, Bi, & Qu, 2016; Song, Zhu, & Lu, 2016). Surgery is the primary treatment for patients with early-stage GI cancer. However, patients undergoing selective GI cancer.

surgery will face the risk of developing various postoperative complications due to negative impact factors, such as malnutrition, tumor-

induced immune suppression, surgical stress, and inflammation, resulting in prolonged hospital-stay and increased costs, which brings huge chalenges to the rehabilitation of patients after GI cancer surgery (Horgan, 2014).

As an important essential fatty acid, n-3 PUFAs have received increasing attention from researchers.The research on n-3 PUFAs mainly focuses on the prevention and treatment of cardiovascular and cerebrovascular diseases, n-3 PUFAs plays an active role in nutritional support for cardiovascular and cerebrovascular diseases through anti-

thrombosis and vasodilation mechanisms (Pisaniello, Psaltis, & King, 2021). It has been reported in the literature that n-3 PUFAs has a positive effect on improving the nutritional status of tumor patients, reducing inflammation, and enhancing immune function (Cheng, Zhang, Ning, & Huo, 2021). However, other studies have shown that n-3 PUFAs cannot improve the nutritional status and clinical outcomes of cancer patients (Giger-Pabst, Lange, & Maurer, 2013), the impact of n-3 PUFAs on disease inflammation and nutritional status remains controversial. Considering the results and conclusions in these studies were not completely consistent because of limited sample size, different study designs, and potential bias, we conducted a meta-analysis of all relevant randomized controlled trials (RCTs), focusing on the effects of n-3 PUFAs on the nutritional status, inflammation and immune function of patients after gastrointestinal tumor surgery, provide a theoretical basis for the clinical standardized application of n-3 PUFAs in GI cancer patients.

2. Materials and methods

2.1. Search strategy

We searched the PubMed, EMBASE, and Cochrane library databases for articles published before December 2021 to collect randomized controlled trials of GI cancer surgery patients receiving n-3 PUFAs treatment and any control intervention. using various combinations of keywords including fatty acids, omega-3,gastrointestinal neoplasms and operation. The study was limited to published articles with no restrictions on language. The references of related articles were also searched. Two authors independently performed the study selection (LS and ZY).Full-text review was required where titles and abstracts were insufficient to determine if the study met the inclusion criteria. When there was any controversy, articles would be sent to the third author (TH) for assessment. If necessary, authors would be contacted to provide more accurate data from their researches.

2.2. Inclusion and exclusion criteria

The studies were included in our analysis if they met the following criteria: (1) research design: randomized controlled trials; (2) participants: the patients with gastrointestinal cancer; (3) intervention measures: n-3 fatty acid supplementation during perioperative period; (4) outcomes: postoperative infectious complications, length of hospital stay, immune indicators: CD4(%), CD8(%), CD4/CD8; Inflammation indicators: Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α), C-reactive protein (CRP); nutritional indicators: Prealbumin (PAB), Albumin (ALB),Retinol-binding protein (RBP).

Exclusion criteria: (1) animal studies, in vitro studies, review, case report, conference summary and other non-clinical research literature; (2) incorrect or incomplete data could not be extracted; (3) The intervention group contains other immunonutritions such as glutamine or arginine; Two authors (LS and ZY) independently reviewed the literature and extracted all potentially eligible studies; the inconsistencies were discussed until a consensus was reached (Fig. 1).

2.3. Quality assessment

Quality assessment was performed by using the Cochrane bias-risk tool, which includes six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias.The risk of each included study was rated as"high bias risk","unclear biasrisk"or"low bias risk"according to the information extracted. The graphical results of methodological quality are shown in Fig. 2.

2.4. Data extraction

The following data were extracted independently by 2 authors (LS and ZY) from the included studies: name of first author, publication year, cancer types, number of participants, age and gender of the participant, body mass index (BMI), intervention measures, intervention time, and reported outcomes. Any disagreements in the results of data
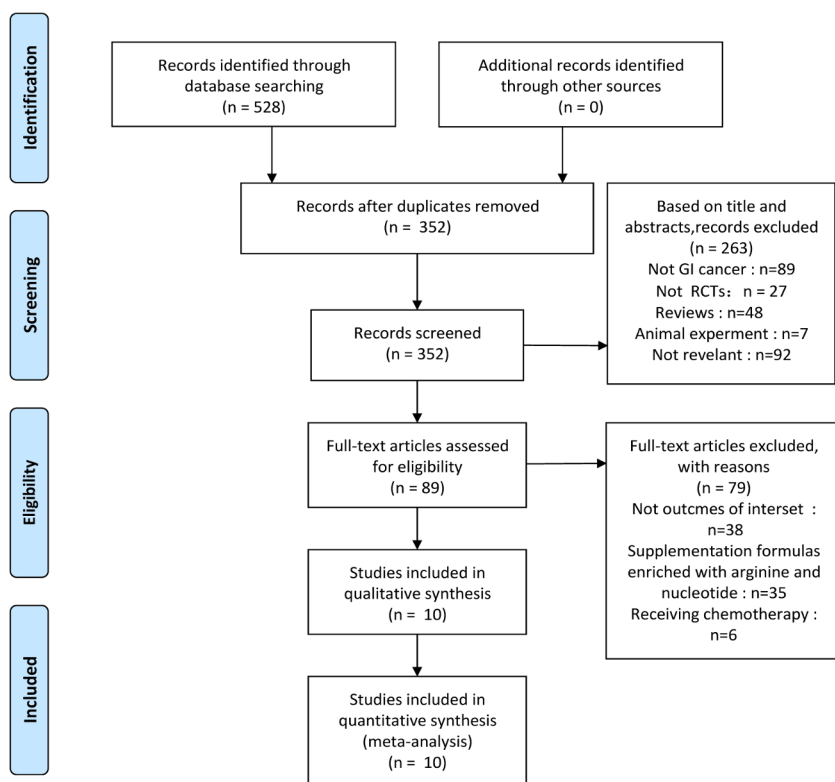

Fig. 1. The process of study selection according to Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) guidelines. Our search strategy found 528 articles, 176 of which were deleted as duplicate documents retrieved from two or more databases. After carefully examining their abstracts and titles, we excluded 263 articles. Among the remaining 89 articles, 79 articles were excluded due to lack of valid data. Finally, 10 RCTs articles involving a total of 663 subjects (330 in the n-3 PUFAs group and 333 in the control group) were selected for this meta-analysis.

Fig. 2. Summary of the quality assessment of the included studies. All of the selected studies were RCTs. Among the included studies, four studies (Liang B, Zhu M W, Ma C J, Nathalie B) generated the random sequence by computer and two studies(Sorensen L S, Wei Z) generated from sealed opaque envelopes containing randomized numbers, one study (Zhang C H) generated from random number method and one study (Liu Y M) carried out the randomisation by medical record number, seven studies (Liang B, Liu Y M, Ma C J, Nathalie B, Sorensen L S, Zhang C H, Zhu M W) described their blind-ing method. Four studies (Liang B, Liu Y M, Nathalie B, Wei Z) had no follow-up bias, five studies (Kiek S,Sorensen L, Zhang C H, Zhang Y, Zhu M W) might have follow-up bias, and one study (Ma C J) had follow-up bias. Six studies (Liang B, Liu Y M, Ma C J, Wei Z, Zhang C H, Zhu M W) had no reporting bias and Four studies had reporting bias(Kiek S, Nathalie B, Sorensen L S, Zhang Y). Nine studies with no other bias and one study(Wei Z) may have other biases.

extraction were resolved through discussion with a third author (TH). If useful data were presented indirectly by figures and graphs or through different metrics, they were translated into correlative patterns by using get-data software or relevant formulae. If mean values or standard deviation (SD) for analysis were unavailable, they were calculated from medians and ranges using relevant formulae.

2.5. Statistical analysis

The analysis of comparable data was conducted by Review Manager 5.3 (Cochrane Collaboration). We assessed the continuous outcomes using mean difference (MD) and dichotomous outcomes using the odds ratio (OR).We estimated the comparable data using 95% confidence interval (CI). The I^2 test would be accounted to evaluate statistical heterogeneity. A random-effects model would be adopted for the result if the $I^2 > 50\%$; otherwise, a fixed-effects model was chosen. $p < 0.05$would be considered statistically significant.

3. Results

3.1. Search results and study characteristics

The process of study selection according to Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) guidelines is shown in Fig. 1,

Our search strategy found 528 articles, 176 of which were deleted as duplicate documents retrieved from two or more databases. After checking their abstracts and titles carefully, we excluded 263 articles. Among the remaining 89 articles, 79 articles were excluded due to lack of valid data. Finally, 10 RCTs (Bakker, van den Helder, Stoutjesdijk, van Pelt, & Houdijk, 2020; Cheng-Jen & Jin-Ming, 2015; Kłek, Kulig, & Szczepanik, 2005; Liang, Wang, & Ye, 2008; Liu, Zhang, & Liu, 2020; Sorensen, Thorlacius-Ussing, & Schmidt, 2014; Wei et al., 2014; Zhang et al., 2012; 2014; Zhu, Tang, & Hou, 2012) articles involving a total of 663 subjects (330 in the n-3 PUFAs group and 333 in the control group) were selected for this meta-analysis. The baseline characteristics of 10 studies are summarized in Table 1.

3.2. Quality of the individual studies

All of the selected studies were RCTs. Among all the literature studies, four generated the random sequence by computer and two generated from sealed opaque envelopes containing randomized numbers. One generated from random number method and one study carried out the randomisation by medical record number. Seven studies described their blind-ing method, The quality assessment is summarised in Fig. 2. Publication bias was assessed using a funnel plot regarding postoperative infectious complications, which contained the largest number of trials. The funnel plot of infectious complications was symmetrical based on visual inspection suggesting no evidence of publication bias Fig. 3.

3.3. Effect of n-3 PUFAs on postoperative infectious complications

Eight RCTs with a total of 560 patients (282 in the n-3 PUFAs group and 278 in the control group) evaluated the incidence of infectious complications, The results of heterogeneity test were P = 0.05 and I^2 = 49%. The forest plot indicated that there was no statistical significance in incidence of infectious complications between the n-3 PUFAs group and the control group (OR = 0.86, 95% CI 0.55–1.34, P = 0.50) (Fig. 4).

3.4. Effect of n-3 PUFAs on postoperative level of inflammatory factor

3.4.1. Il-6
Five RCTs enrolling 295 patients (151 in the n-3 PUFAs group and 144 in the control group) reported the level of serum IL-6. The results of heterogeneity test were P = 0.32 and I^2 = 15%. The pooled results showed that the n-3 PUFAs group had a statistically lower than control group (MD = -5.81; 95%CI, −9.25 - −2.36; P = 0.0010) (Fig. 5A).

3.4.2. Crp
Four RCTs enrolling 261 patients (134 in the n-3 PUFAs group and 127 in the control group) reported the level of serum C-reactive protein (CRP).The results of heterogeneity test were P = 0.18 and I^2 = 39%. The pooled results showed that the n-3 PUFAs group had a statistically lower than control group (MD = -9.95; 95%CI, −13.16 - −6.75; P < 0.00001) (Fig. 5B).

3.4.3. Tnf-α
Five RCTs enrolling 313 patients (157 in the n-3 PUFAs group and 156 in the control group) reported the level of serum tumor necrosis factor-α (TNF-α).The results of heterogeneity test were P = 0.11 and I^2 = 46%. The pooled results showed that the n-3 PUFAs group had a statistically lower than control group (MD = -0.38; 95%CI, −0.59 - −0.17;

Table 1
Characteristics of included randomized trials.

Study	Cancer types	Sample size		Mean age, years (SD or range)		Gender (Male/Female)		BMI		Treatment protocol	
		Exp	Con	Exp	Con	Exp	Con	Exp	Con	Exp	Con
Kiek S	GC	30	30	NA	NA	NA	NA	NA	NA	Standard PN + ω-3 PUFA after operation; (1-9d);	Standard PN 9 days after operation;(1-9d);
Liang B	CRC	20	21	55.80 ± 10.10	59.19 ± 10.61	10/10	15/6	23.38 ± 2.38	23.92 ± 2.84	SO + FO after operation; (1-7d);	SO after operation; (1-7d)
Zhang C H	GIC	32	32	56.6 ± 11.9	56.8 ± 12.6	20/12	24/8	23.1 ± 2.4	23.5 ± 2.6	Lipoplus(MCT + LCT + ω-3 PUFA) after operation; (1-5d);	Lipofund (MCT + LCT) after operation; (1-5d);
Zhu M W	CRC	29	28	69.8 ± 10.5	70.8 ± 6.4	17/11	16/13	22.9 ± 3.1	23.2 ± 3.6	1.2 g/kg SO per day after operation; (1-7d);	0.2 g/kg FO and 1.0 g/kg SO per day after operation; (1-7d);
Sorensen L S	CRC	74	74	64 ± 11	71 ± 10	44/30	36/38	26 ± 5	26 ± 5	ω-3PUFA enriched(ONS) (Supportan, 200 ml twice daily) providing 2 g EPA and 1 g DHA; (7 days before and 7 days after operation);	Standard isocaloric and isonitrogenous ONS; (7 days before and 7 days after operation);
Zhang Y	GIC	32	32	58.13 ± 11.32	56.40 ± 11.57	17/15	16/16	22.26 ± 2.27	23.88 ± 2.63	LCT:MCT = 5:5 after operation; (1-5d);	LCT:MCT:ω-3PUFA = 5:4:1 after operation; (1-5d);
Wei Z	GC	26	25	50.5 (29–75)	59 (36–74)	15/11	11/9	22.2 (15.–28.1)	22.5 (17–29.7)	The fat emulsion used was omega-6 lipid (20% Intralipid) after operation; (≧6d);	The omega-6 lipid content of TPN was partially replaced by ω-3PUFA(10%Omegave) up to 0.2 g/kg body weight daily after surgery; (≧6d);
Ma C J	GIC	44	41	61.55 ± 9.78	62.85 ± 10.12	29/22	27/21	23.45 ± 3.44	23.91 ± 3.79	ω-3PUFA enriched intravenous fat emulsion (IVFE) after operation; (1-7d);	lipid emulsion comprised of soybean oil and MCTs after operation; (1-7d);
Nathalie B	CRC	18	23	65 (64–75)	69 (63–74)	13/5	15/8	26.9 (25.1–27.8)	25.7 (23.5–29.4)	2 intravenous ω-3PUFA infusions the night before and the morning after operation;	2 intravenous saline control infusions the night before and the morning after operation;
Liu Y M	GC	25	27	54.6 ± 10.3	56.1 ± 9.8	18/7	19/8	NA	NA	Enteral nutrition preparations twice a day after operation, 500 ml each time, including 1.5 g ω-3PUFA;(1–3 months)	Routine enteral nutrition after surgery; (1–3 months)

BMI,body mass index;CRC, colorectal cancer; GC, gastric cancer; GIC, gastrointestinal cancer; PUFA,polyunsaturated fatty acids;SO,soybean oil;FO, fish oil;DHA, docosahexaenoic acid;EPA,eicosapentaenoic acid; LCT,long-chain triglycerides;MCT,mediumchain triglycerides, Exp, experimental;Con, control; NA, no available.
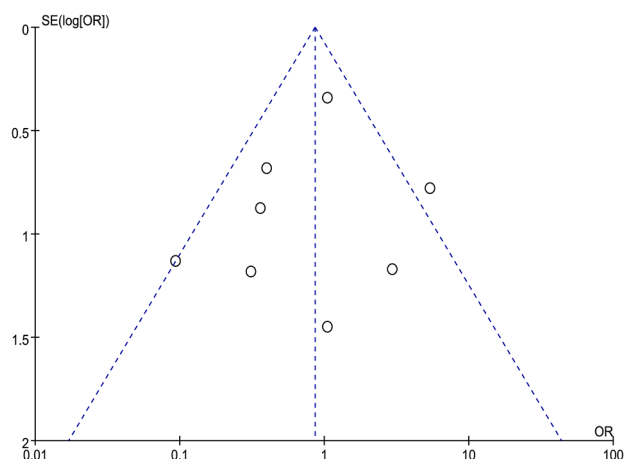

Fig. 3. Funnel plot of the studies included in our meta-analysis. Publication bias was assessed using a funnel plot regarding postoperative infectious complications, which contained the largest number of studies. The funnel plot of infectious complications was symmetrical based on visual inspection suggesting no evidence of publication bias.

P = 0.0003) (Fig. 5C).

4. Effect of n-3 PUFAs on postoperative immune function

4.1. CD4$^+$T cells

Three RCTs enrolling 144 patients (75 in the n-3 PUFAs group and 69 in the control group) reported the level of CD4$^+$T cells.The results of heterogeneity test were P = 0.3 and I^2 = 16%. The pooled results showed that the n-3 PUFAs group had a statistically higher than control group (MD = 3.40; 95%CI, 0.31–6.50; P = 0.03) (Fig. 6A).

4.2. CD8$^+$T cells

Three RCTs enrolling 144 patients (75 in the n-3 PUFAs group and 69 in the control group) reported the level of CD8$^+$T cells.The results of heterogeneity test were P = 0.27 and I^2 = 24%. The pooled results showed that the n-3 PUFAs group had a statistically lower than control group (MD = -2.95; 95%CI, −5.36 - −0.53; P = 0.02) (Fig. 6B).

4.3. CD4$^+$/CD8$^+$T cells

Three RCTs enrolling 144 patients (75 in the n-3 PUFAs group and 69 in the control group) reported the level of CD4$^+$/CD8$^+$T cells.The results of heterogeneity test were P = 0.90 and I^2 = 0%. The pooled results

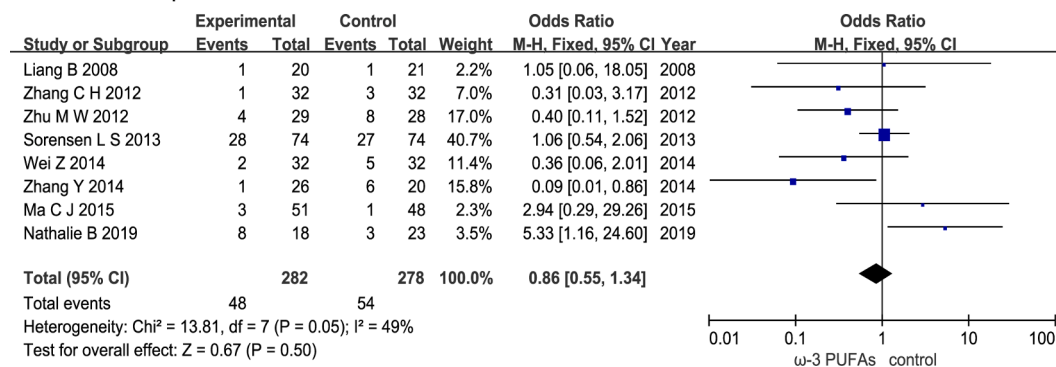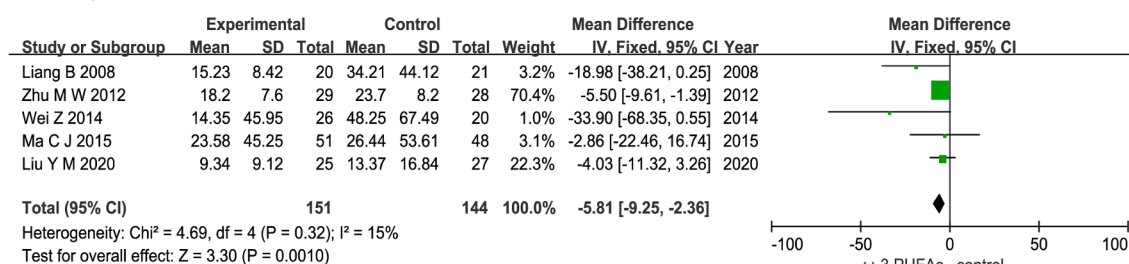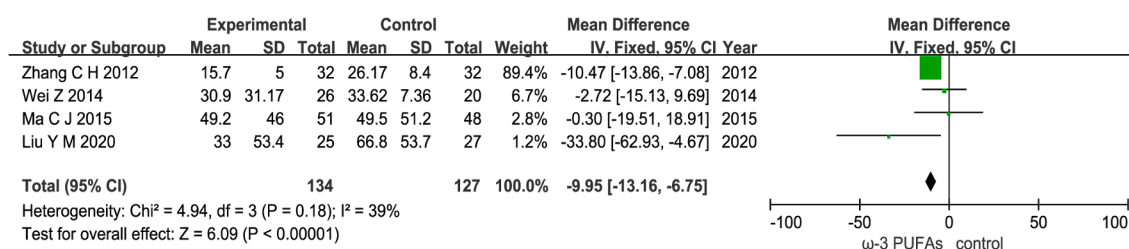## Infectious complications

Fig. 4. Effect of n-3 PUFAs on postoperative infectious complications Eight RCTs with a total of 560 patients evaluated the incidence of infectious complications. The forest plot indicated that there was no statistical significance in incidence of infectious complications between the n-3 PUFAs group and the control group.
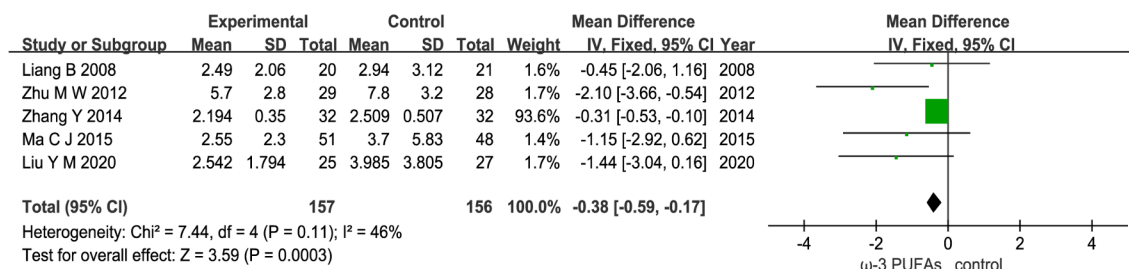

Fig. 5. Effect of n-3 PUFAs on postoperative level of inflammatory factor Five RCTs enrolling 295 patients reported the level of serum IL-6. The pooled results showed that the n-3 PUFAs group was statistically lower than the control group. Four RCTs enrolling 261 patients reported the level of serum C-reactive protein (CRP). The pooled results showed that the n-3 PUFAs group had a statistically lower than control group. Five RCTs enrolling 313 patients reported the level of serum TNF-α. The pooled results showed that the n-3 PUFAs group had a statistically lower than control group.

showed that the n-3 PUFAs group had a statistically higher than control group (MD = 0.35; 95%CI, 0.04–0.66; P = 0.03) (Fig. 6C).

5. Effect of n-3 PUFAs on postoperative nutritional status

5.1. Prealbumin

Four RCTs enrolling 222 patients (113 in the n-3 PUFAs group and 109 in the control group) reported the level of prealbumin. The results of heterogeneity test were P = 0.04 and I^2 = 65%. The forest plot indicated

that there was no statistical significance in the level of prealbumin between the n-3 PUFAs group and the control group (MD = 2.89; 95%CI, −19.28–25.07; P = 0.80) (Fig. 7A).
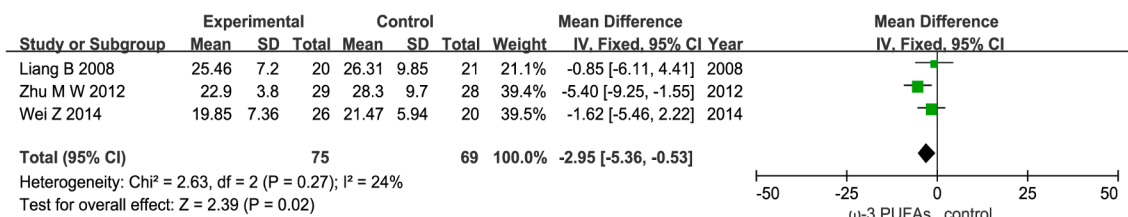
5.2. Albumin

Three RCTs enrolling 158 patients (81 in the n-3 PUFAs group and 77 in the control group) reported the level of albumin. The results of heterogeneity test were P = 0.96 and I^2 = 0%. The forest plot indicated that there was no statistical significance in the level of albumin between the
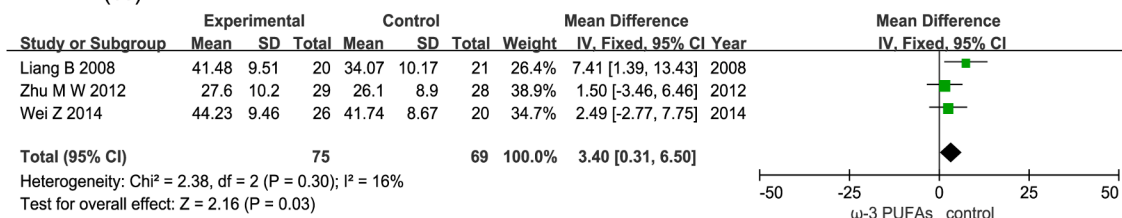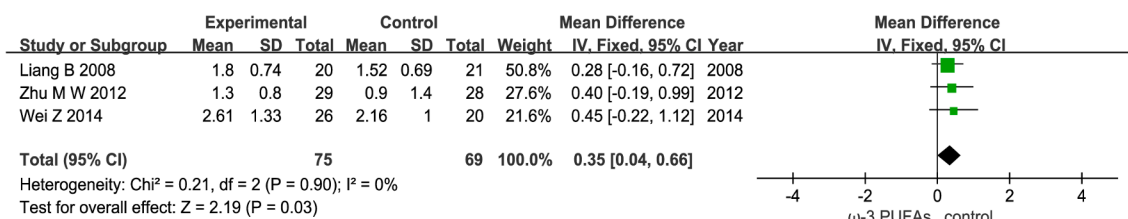
Fig. 6. Effect of n-3 PUFAs on postoperative immune function Three RCTs enrolling 144 patients reported the level of CD4$^+$T cells. The pooled results showed that the n-3 PUFAs group had a statistically higher than control group. Three RCTs enrolling 144 patients reported the level of CD8$^+$T cells. The pooled results showed that the n-3 PUFAs group had a statistically lower than control group. Three RCTs enrolling 144 patients reported the level of CD4$^+$/CD8$^+$T cells. The pooled results showed that the n-3 PUFAs group had a statistically higher than control group.

n-3 PUFAs group and the control group (MD = 0.72; 95%CI, −0.39–1.83; P = 0.21) (Fig. 7B).

5.3. Retinol-binding protein

Two RCTs enrolling 110 patients (58 in the n-3 PUFAs group and 52 in the control group) reported the level of retinol-binding protein. The results of heterogeneity test were P = 0.05 and I^2 = 75%. The forest plot indicated that there was no statistical significance in the level of retinol-binding protein between the n-3 PUFAs group and the control group (MD = 2.46; 95%CI, −19.91–24.83; P = 0.83) (Fig. 7C).

5.4. Effect of n-3 PUFAs on length of hospital stay

Three RCTs enrolling 158 patients (79 in the n-3 PUFAs group and 79 in the control group) reported the length of hospital stay. The results of heterogeneity test were P = 0.89 and I^2 = 0%. The pooled results showed that the n-3 PUFAs group had a statistically lower than control group (MD = -2.54; 95%CI, −4.391 - −0.69; P = 0.007) (Fig. 8).

6. Discussion

n-3 PUFAs are essential fatty acids for the human body, which can not only oxidize and supply energy in the body, but also participate in changes in cell structure and metabolites, thereby affecting cell functions. Studies have shown that n-3 PUFAs play an important role in the host immune response and inflammatory response of gastrointestinal tumors, so compared with isocaloric nutrition, n-3 PUFAs are the best choice for postoperative treatment (Kew, Mesa, & Tricon, 2004; Wallace, Miles, & Evans, 2001; Yaqoob & Calder, 1995). Our meta-analysis evaluated 10 RCTs to assess the impact of n-3 PUFA nutritional support on postoperative infectious complications, levels of inflammatory

cytokines, immune cells and nutrient proteins, and length of stay in patients with gastrointestinal cancer. The main result of this study is that n-3 PUFAs nutritional support effectively reduces the levels of serum IL-6, TNF-α, CRP, and CD8 + T lymphocytes and improved the number of CD4 + T lymphocytes and the ratio of CD4+/CD8 + in patients undergoing gastrointestinal cancer surgery. n-3 PUFAs reduce the patient's hospital stay by enhancing the body's immune function and reducing the body's inflammatory response.

Due to poor appetite, digestion and absorption disorders, tumor self-depletion and the production of immunosuppressive factors, most gastrointestinal tumor microenvironments are in an immunosuppressive state, and radical surgical resection further reduces the body's immune function. n-3 PUFAs improve the immune response by increasing the total number of peripheral blood lymphocytes (including T lymphocytes and CD4 + T cells) (Marano, Porfidia, & Pezzella, 2013). Different subsets of mature T cells carry out the functions of cell-mediated immunity, including killing virally infected cells and tumor cells (CD8 + Tcells) and providing help for and regulating components of the immune system (CD4 + T cells). Turbitt showed that n-3 PUFAs may induce an increase in the production of IL-2 and IFN-g in T cells, thereby driving the Th1 response and enhancing the anti-tumor immune function (Turbitt, Black, & Collins, 2015). By regulating Th1/Th2 differentiation and Th17 response, n-3 PUFAs play an important role in alleviating stress-induced immunosuppression after surgical resection (Suzuki, Furukawa, & Kimura, 2010).

IL-6 is one of the most sensitive and important inflammatory factors. During surgery, IL-6 induces the liver to synthesize the acute phase reactive protein-C reactive protein that promotes the phagocytic activity of neutrophils and macrophages, the release level of IL-6 and C-reactive protein in the body can reflect the body's stress situation. The platelet activating factor PAF has a powerful inflammatory effect by inducing the massive production of inflammatory factors to cause the cascade

A   Prealbumin
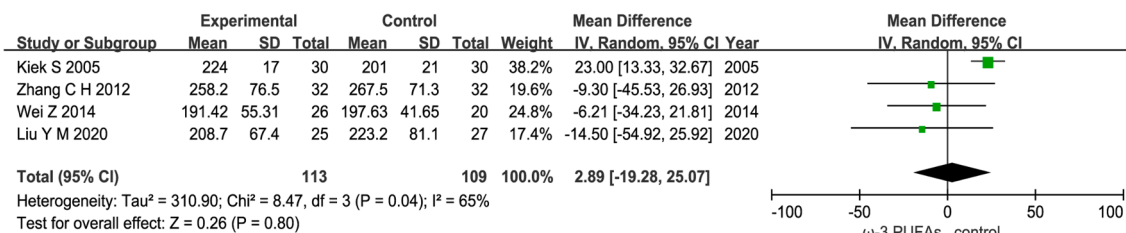
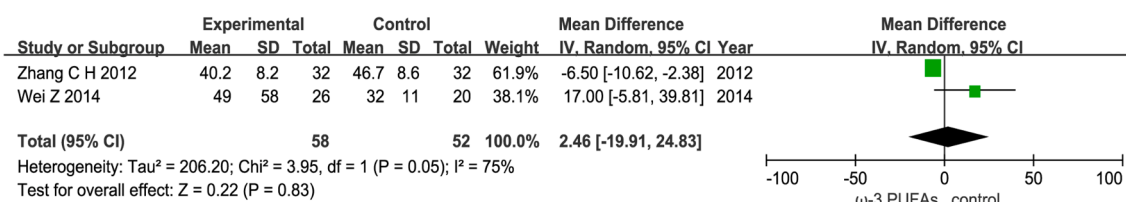
B   Albumin
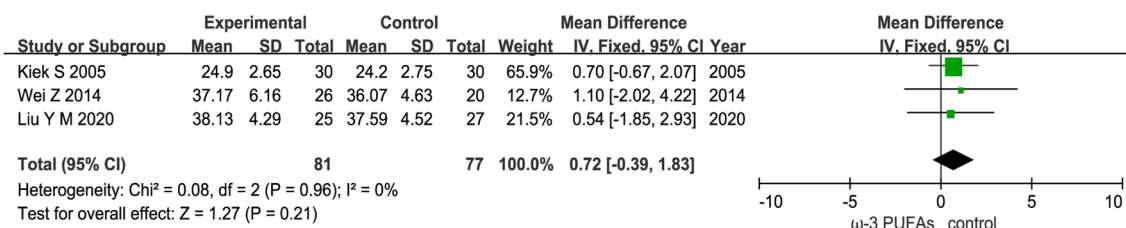
C   Retinol-binding protein

Fig. 7. Effect of n-3 PUFAs on postoperative nutritional status Four RCTs enrolling 222 patients reported the level of prealbumin. The forest plot indicated that there was no statistical significance in the level of prealbumin between the n-3 PUFAs group and the control group. Three RCTs enrolling 158 patients reported the level of albumin. The forest plot indicated that there was no statistical significance in the level of albumin between the n-3 PUFAs group and the control group. Two RCTs enrolling 110 patients reported the level of retinol-binding protein. The forest plot indicated that there was no statistical significance in the level of retinol-binding protein between the n-3 PUFAs group and the control group.
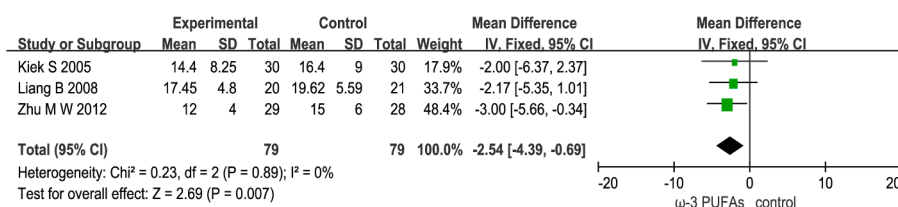
Length of hospital stay

Fig. 8. Effect of n-3 PUFAs on length of hospital stay Three RCTs enrolling 158 patients reported the length of hospital stay. The pooled results showed that the n-3 PUFAs group had a statistically lower than control group.

effect of inflammatory factors release. n-3 PUFAs can inhibit the release of IL-6, reduce the production of CRP and PAF, reduce the degree of inflammatory response, and enhance the immune function of the body (Koch & Heller, 2005; Liang, Shan, & Ye, 2008; Matos, Santana, & Garcia, 2013). A number of previous studies have shown that n-3 PUFAs can down-regulate the levels of IL-6 and TNF-α in cancer patients after surgery (Ancrile, Lim, & Counter, 2007; Don & Kaysen, 2004; Ghavami et al., 2009; Knüpfer & Preiss, 2010; Schneider et al., 2000), and shorten the use of ventilator and hospital stay in patients with major abdominal surgery (Tsekos, Reuter, & Stehle, 2004), this conclusion is consistent with the results of our meta-analysis. However, we did not observe the effect of n-3 PUFAs on the incidence of infectious complications in our analysis. Compared with Ma's study, taking supplements containing n-3 PUFAs, glutamine, arginine and nucleotides reduced the incidence of postoperative infection-related complications (Ma, Liu, Xiao, & Cao, 2016), the methods of nutritional intervention can partly explain these

differences.

Prealbumin, albumin, and retinol-binding protein are important components of plasma total protein and are important indicators for nutritional evaluation. Patients in stress and critical conditions after surgery basically have a decrease in plasma protein (Wu, Ho, Lai, Chen, & Lin, 2021). Studies have shown that n-3 PUFAs can improve the quality of life, functional status and nutritional status of patients (van der Meij et al., 2010; van der Meij et al., 2012). n-3 PUFAs are also recommended as fatty acid supplements in the nutritional treatment of many diseases (Lemoine et al., 2019; Pappalardo & AlmeidaA, 2015). However, a study of 137 patients with advanced non-small cell lung showed no effect of taking n-3 PUFAs on patients' nutritional status (Lu, Chen, Wei, Hu, & Sun, 2018). The results of our meta-analysis showed that taking n-3 PUFAs did not increase the levels of prealbumin, albumin and retinol binding protein. Regarding the analysis results of the three proteins in the nutritional indicators, because the number of trials we

included is small and heterogeneous, there may be potential bias in the interpretation of the results.

Our meta-analysis has several limitations. First of all, Although all the included studies were randomized controlled trials, most of them were single-center trials with small sample sizes. Second, there was moderate heterogeneity in the pooled outcome of the level of pre-albumin and significant heterogeneity in the pooled outcome of the level of retinol-binding protein. Patients characteristics and the type, duration, timing of n-3 PUFAs interventions, as well as patient nutritional status across the trials, could be the source of heterogeneity. Finally, due to the limitation of the number of existing studies, our research results should be confirmed by long-term follow-up randomized controlled trials, which require sufficient sample size and fixed-dose data.

7. Conclusions

As a basic nutritional supplement, n-3 PUFAs can effectively enhance the immune function of patients with gastrointestinal cancer and reduce the level of inflammatory cytokines, and shortening the length of hospital stay, but it has no significant impact on the incidence of infectious-related complications and the level of nutrient protein. The results of this study can provide a basis for the clinical application of n-3 PUFAs. However, due to the limitations of the included studies and the potential risk of bias, it is necessary to conduct a large-scale, randomized, prospective trial to further evaluate the impact of n-3 PUFAs supplementation on patients with gastrointestinal tumors after surgery.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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