The role of omega-3 fatty acids in acute pancreatitis

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Abbreviations

MR	Mendelian randomization
SNPs	Single nucleotide polymorphisms
GWAS	Genome-wide association studies
CIs	Confidence intervals
OR	Odds ratio
MD	Mean difference
SD	Standard deviation
RCTs	Randomized controlled trials
IVW	Inverse variance weighted

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Abstract

Prior observational studies have reported the potential protective effect of omega-3 fatty acids on the prognosis of acute pancreatitis. However, the causal impact of omega-3 fatty acids on acute pancreatitis is unclear. We aimed to investigate further the association of omega-3 fatty acids with acute pancreatitis. We performed a meta-analysis and Mendelian randomization (MR) to explore the association between omega-3 fatty acids and the prognosis of acute pancreatitis from clinical observation and genetics perspectives, respectively. 9 randomized controlled trials were included in this study. The result meta-analysis showed that complementary therapy of omega-3 fatty acids significantly decreased mortality (RR: 0.30; 95% CI 0.14 to 0.65, P＜0.05) and infectious complications in acute pancreatitis (RR: 0.45; 95% CI 0.27 to 0.77, P＜0.05). Compared to the control groups, the hospital stays (MD: -1.02; 95% CI -1.85 to -0.20, P＜0.05) in acute pancreatitis patients with omega-3 fatty acids treatment were statistically reduced. However, the ICU stay (MD: -0.49; 95% CI -1.29 to -0.31, P＞0.05) between control groups and acute pancreatitis patients with omega-3 fatty acids treatment was insignificant. Utilizing genetic susceptibility analysis in the Mendelian randomization (MR) approach, the MR showed omega-3 fatty acids have a significant causal effect on the acute pancreatitis risk (OR, 0.887; 95% CI, 0.797-0.986, P = 0.027, fixed-effect; OR, 0.887; 95% CI, 0.792-0.993, P = 0.037, random-effect). Omega-3 fatty acids complementary therapy may improve the prognosis of acute pancreatitis. Furthermore, genetically predicted serum levels of omega-3 fatty acids can significantly lower acute pancreatitis risk.

Keywords: meta-analysis, Mendelian randomization, omega-3 fatty acids, acute pancreatitis, metabolomics, genetic evidence.

Introduction

Most gastrointestinal disease-related hospital admissions are due to pancreatitis, which has a significant risk of morbidity, death, and socioeconomic hardship[1]. Acute pancreatitis (AP) is an unpredictable and potentially lethal disease. The critical determinants of prognosis are the development of organ failure and subsequent infection of pancreatic or peripancreatic necrosis[2]. The incidence and mortality rates for acute pancreatitis were estimated to be 33.74 cases (95% CI 23.33-48.81) per 100,000 person-years and 1.60 fatalities (95% CI 0.85-1.58) per 100,000 person-years globally[3]. The last ten years have seen a shift in the management of acute pancreatitis toward a multidisciplinary, individualized, and minimally invasive strategy. Despite advances in therapy and critical care, severe acute pancreatitis still has a significant death rate.

In up to 20% of patients, severe acute pancreatitis (SAP) may develop[4-5]. In the early phase of SAP, a pro-inflammatory response develops that is characterized by the release of large quantities of cytokines. This cytokine storm may trigger a systemic inflammatory response syndrome (SIRS) and often leads to organ failure. Organ failure is associated with a mortality of up to 35% in AP[6-7].

Omega-3 fatty acids (FA) are found in fish oil and contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)[8]. Multiple clinical studies have found that omega-3 fatty acids may improve the prognosis of acute pancreatitis and reduce in-hospital deaths and ICU admissions[9-16]. However, the specific role of omega-3 fatty acids in acute pancreatitis is not well understood. The pieces of evidence for these studies are derived from clinical observational studies. Unmeasured confounding factors or reverse causality are continuously interfered with conventional observational findings. Considering the vulnerability of observational studies to confounding and reverse causality, it is still uncertain the causal impact of circulating omega-3 fatty acid levels on the elevated risk of acute pancreatitis.

Genome-wide association studies (GWAS) involve testing genetic variants across the genomes of many individuals to identify genotype-phenotype associations. GWAS have revolutionized the field of complex disease genetics over the past decade, providing numerous compelling associations for complex human traits and diseases. Genetic tools are

used as instrumental variables (IVs) in the Mendelian randomization (MR) design to distinguish between correlation and causality in observed data. It accomplishes causality exploration by decreasing the possibility of reverse causality and minimizing residual confusion. Individual qualities are often unrelated because genetic variation is randomly distributed after conception. This procedure is comparable to a randomized controlled trial, randomly assigning individuals to experimental and control groups. It ensures that those with genetic variations linked to higher risk factors are distributed equally among the groups, minimizing the possibility that these risk factors would have confusing effects. Since alleles are fixed and unaffected by the beginning or progression of the disease, MR analysis also helps to avoid the problem of reverse causality[16]. Even though Mendelian randomization (MR) has been used in pancreatitis[17–19], the exposure factors currently being studied are only traditional risk factors. It is still very encouraging to use Mendelian randomization to further investigate the function and value of metabolomics in pancreatitis at the gene level.

Therefore, in order to further explore the role of omega-3 fatty acids in acute pancreatitis and whether there is a causal effect on the pathogenesis of acute pancreatitis, we conducted a systematic review and meta-analysis of randomized controlled trials of omega-3 fatty acids in the treatment of acute pancreatitis. Furthermore, we investigated the causal effect of omega-3 fat on acute pancreatitis based on MR analysis.

Materials and methods

Study design

This work developed primary analyses to research the effects of omega-3 fatty acids complementary therapy on acute pancreatitis based on system review and meta-analysis. We performed a meta-analysis of randomized controlled trial studies involving omega-3 fatty acids in the treatment of acute pancreatitis. The evaluation indicators included mortality, infectious complications, length of hospital stay, and length of ICU stay. Furthermore, to further investigate the causal effect of omega-3 fatty acids on the onset of acute pancreatitis, we performed a Mendelian randomization analysis. The instrumental variables of omega-3 fatty acids came from one metabolomics quantitative trait loci study on circulating

metabolites. The studies used the 249 circulating metabolites linked to human genetic variations through genome-wide association scans and high-throughput metabolic profiling. We achieved these circulating metabolites from the UK Biobank (unpublished, accessible via the MRC IEU OpenGWAS database). To strengthen the validity of our conclusions, we developed two-sample MR analyses. We used publicly available summary statistics. Therefore, it is unnecessary to obtain new ethical approval.

The search strategy of meta-analysis

Keywords, including “omega-3 fatty acids”, “omega-3 FA”, “acute pancreatitis”, were searched in the PubMed, Embase, and Cochrane Library databases up to January 31, 2024. We screened studies according to the following inclusion and exclusion criteria (see below). This study followed the guidelines of the Cochrane Collaboration Handbook, observational studies in epidemiology statement[20], Meta-Analysis and Systemic Reviews of Observational Studies (MOOSE), and Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)[21]. This systematic review and meta-analysis protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO Number: CRD42022353127).

Inclusion and exclusion criteria

The inclusion criteria are as follows: 1) Reported the definition of omega-3 fatty acids intervention duration, 2) Available outcome events (mortality, infectious complications, length of hospital stay, length of ICU stay) or data for meta-analysis, 3) Randomized controlled trials (RCTs); The exclusion criteria are as follows: 1) If the report is duplicated, only the most recent report is included, 2) The whole research process is not reported in detail (Conference paper without full text).

Study selection, data extraction, and quality assessment

Studies were independently selected and assessed by three reviewers (TBB, GAJ, and YG). Duplicated articles were excluded by reviewing the title and abstract. The three reviewers independently assessed these studies for eligibility. Then, data including author, study type, region, study size (patients/controls), duration of intervention, mean age, dose, route of nutrition, severity criteria of use, and the interest outcomes (e.g., mortality, infectious

complications, length of hospital stay, length of ICU stay) in each study, and baseline characteristics in each study were extracted by the reviewers. The Cochrane risk-of-bias tool was used to evaluate the quality of the included RCTs. This tool assessed bias across the following seven domains: (i) random-sequence generation, (ii) allocation concealment, (iii) blinding of participants and personnel, (iv) blinding of outcome assessment, (v) incomplete outcome data, (vi) selective reporting, and (vii) other bias. Each domain was determined as low risk, unclear risk, or high risk.

Data sources

Metabolic profile for analyses

Summary-level datasets on 249 circulating metabolites used in primary analysis were obtained from Nightingale Health Metabolic Biomarkers Phase 1 release study in UK Biobank (June 2019–April 2020). This study included 115,078 randomly selected participants. Metabolic biomarkers were measured with non-fasting baseline EDTA plasma samples by high-throughput nuclear magnetic resonance (NMR) (https://biobank.ndph.ox.ac.uk/ukb/label.cgi?id=220). The biomarkers include 168 absolute metabolites (unit, mmol/L) and 81 metabolite ratios spanning multiple metabolic pathways such as lipoproteins, fatty acids, amino acids, and ketone bodies. The details of sample collection and NMR profiling have been depicted in previous publications[22-24].

IV selection

We screened SNPs relevant to metabolite biomarkers by a traditional genome-wide association significance criterion ($p < 5 \times 10^{-8}$). We excluded SNPs that were in linkage disequilibrium (LD) (R^2 > 0.001 or within ±10,000 kb of the 1000 Genomes European-ancestry Reference Panel). The F statistics were applied to measure the strength of IVs. We computed mean F-statistics to test for weak instruments. Calculation of the F statistic (β^2/SE^2) to assess weak IV bias. An F value below 10 indicates a weak IV bias, which might lead to an underestimation of statistical power.

GWAS summary data for acute pancreatitis

GWAS refer to multi-centre, large sample, and repeatedly validated studies on the association between genes and diseases at the whole genome level. It is a research method

that uses high-density genetic markers (such as SNPs) to genotype large-scale population DNA samples in order to identify genetic factors associated with complex diseases and comprehensively reveal genetic genes related to disease occurrence, development, and treatment. We searched GWAS summary data for acute pancreatitis from the GWAS Catalog accession. The GWASID is finn-b-K11_ACUTPANC (https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_ACUTPANC/). In particular, the GWAS data with 16,380,428 SNPs were obtained from the Finland Biobank-related acute pancreatitis, with a total sample size of 198,166 Europeans, 3,022 cases, and 195,144 controls.

Mendelian randomization

This study used ten MR analytic tools. They are MR Egger and MR Egger (bootstrap), the Wald ratio, inverse-variance weighted (fixed-effect and random-effect), simple mode, simple median, weighted mode, and penalized weighted median.

The inverse-variance weighted (IVW) method was utilized as the primary method for causal estimation in that it provides a valid causal estimate despite heterogeneity. Wald ratios of the impacts of each SNP on the outcome were coupled with either a fixed-effect IVW for IVs ≤ 3 or a random-effect IVW for IVs > 3. Cochran's Q values, I^2, and the H-statistics were used to estimate the heterogeneities of the IVW studies[25]. $P < 0.05$ from the Cochran Q test was seen as a sign of outcome heterogeneity[25]. Further sensitivity studies used weighted mode, weighted median, and MR-Egger[26–27]. Due to its ability to identify and correct horizontal pleiotropy, the MR-Egger technique may provide reliable causal estimates even when pleiotropy is present (p for intercept < 0.05)[27]. When up to 50% of the weight in the MR analyses originated from unreliable instrument variables, the weighted median is a strategy that can be utilized to reinforce the causal estimations[26]. The effect estimate supported by the most significant number of genetic instruments is reported using the weighted mode technique[27]. In R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria), all statistical analyses were performed using the "TwoSampleMR" and "Mendelian randomization"[28] packages. Statistical significance was determined to have a two-tailed p-value of less than 0.05.

Results

Inclusion of studies

Based on the search strategy, 235 studies were screened out. After removing unrelated ones, 9 RCTs were finally included in our study. The screening strategy is shown in Fig. 1. The general information of these studies is shown in Table 1. The risk bias score for the study is presented in Supplementary Fig.1. Among the included 408 individuals, 305 (74.75%) individuals have come from China. 203 patients were randomized to omega-3 fatty acids treatment, and 205 patients were placed in the control group. Seven studies administered parenteral nutrition, while two studies used enteral nutrition. The subjects were middle-aged and elderly patients. The duration of the intervention was over 5 days. The intervention dose was a standard dose of 0.15–0.20 g/kg/day.

Search findings

Of these studies, 8 studies reported the mortality, and the results of the meta-analysis showed that complementary therapy of omega-3 fatty acids significantly reduced mortality (RR: 0.30; 95% CI 0.14 to 0.65, $P < 0.05$; Figure 2). 7 studies reported the infectious complications, the results of meta-analysis showed that complementary therapy of omega-3 fatty acids significantly reduced infectious complications in acute pancreatitis (RR: 0.45; 95% CI 0.27 to 0.77, $P < 0.05$; Figure 3). 6 studies reported the length of hospital stay, the results of meta-analysis showed that complementary therapy of omega-3 fatty acids significantly reduced length of hospital stay in acute pancreatitis (MD: -1.02; 95% CI -1.85 to -0.20, $P < 0.05$; Figure 4). 4 studies reported the length of ICU stay, the results of meta-analysis showed that complementary therapy of omega-3 fatty acids also reduced length of ICU stay in acute pancreatitis (MD: -0.49; 95% CI -1.29 to -0.31, $P < 0.05$; Figure 5) but without significant difference.

Mendelian randomization study

Based on previous studies, we comprehensively reviewed the risk factors for acute pancreatitis and found 75 genome-wide SNPs were significantly associated with omega-3 fatty acids. Checking these 75 SNPs in the PhenoScanner V2 web[29], we discovered that one SNP was associated with the risk of acute pancreatitis, and it was removed from the raw data.

Ultimately, 75 SNPs were included in the two-sample MR analysis. The characteristics of these 75 SNPs are listed in Supplementary Table 1. The results derived from nine MR analysis methods are shown in Fig. 6 (A). Nine MR analysis approaches include fixed-effect, random-effect IVM, simple mode, weighted mode, simple median, weighted median, penalized weighted median, and MR-Egger (bootstrap). The fixed-effect and random-effect IVW models (OR, 0.887; 95% CI, 0.797-0.986, P = 0.027; OR, 0.887; 95% CI, 0.792-0.993, P = 0.037, respectively, Fig. 5) all showed omega-3 fatty acids has a significant causal effect on the acute pancreatitis risk. Other MR methods such as simple mode (OR, 0.821; 95% CI, 0.575-1.172, P = 0.280), weighted method (OR, 0.806; 95% CI, 0.694-0.937, P = 0.006), simple median (OR, 0.853; 95% CI, 0.686-1.060, P = 0.151), weighted median (OR, 0.803; 95% CI, 0.683-0.944, P = 0.008), penalized weighted median (OR, 0.799; 95% CI, 0.676-0.944, P = 0.008), MR-Egger (OR, 0.901; 95% CI, 0.760-1.068, P = 0.233) and MR Egger (bootstrap) (OR, 0.833; 95% CI, 0.721-0.964, P = 0.003) method were also showed a causal relationship between omega-3 fatty acids and risk of developing acute pancreatitis (Supplementary Table 2). There was no heterogeneity in the MR-Egger analysis (Q = 82.184, P = 0.193) and the IVW analysis analysis (Q = 82.256, P = 0.215), as shown in Supplementary Table 3. Moreover, MR-Egger regression analysis demonstrated no directional pleiotropic effect across the genetic variants (intercept, -0.002; P = 0.803), as shown in Supplementary Table 4. The leave-one-out sensitivity analysis indicated that no single SNP significantly contributed to the association between omega-3 fatty acids and the high risk of developing acute pancreatitis (Fig. 6 C).

Discussion

To the best of our knowledge, this is the first research integrated into a meta-analysis of clinical observational RCTs and Mendelian randomization analysis of genetic evidence to investigate the role of omega-3 fatty acids in acute pancreatitis. The results of our study found that omega-3 fatty acids complementary therapy can significantly reduce in-hospital deaths and improve infectious complications of acute pancreatitis. Furthermore, genetically predicted serum levels of omega-3 fatty acids significantly reduced the risk of acute pancreatitis.

Omega-3 fatty acids were classified as essential because the organism cannot synthesize them; hence, the consumption of food rich in omega-3, such as fish from cold waters, nuts, and seed oils, is mandatory[30]. Previous studies have confirmed the critical role of omega-3 fatty acids in autoimmune diseases, heart failure, and lung function[31-33]. Our study found that omega-3 fatty acids were also an excellent complementary therapy for acute pancreatitis. Treatment with omega-3 fatty acids for more than 5 days significantly reduced in-hospital mortality (70% mortality) and infectious complications (55% mortality) of acute pancreatitis and substantially reduced hospital stay (1.1 days). Several previous meta-analyses reported the effect of omega-3 fatty acids on acute pancreatitis. Consistently published meta-analyses[34-36], the results of this study also supported that supplementary omega-3 fatty acids significantly reduce infection complications, mortality, and length of hospital stay. In addition to these outcomes, previous authors discovered a noticeable reduction in organ failure in patients with omega-3 fatty acids[35,37]. In a network meta-analysis comparing different immune nutrients in acute pancreatitis patients, omega-3 polyunsaturated performed the best efficacy in decreasing mortality, length of hospital stay and intensive care unit stay, and CRP[38].

The mechanism by which omega-3 fatty acids improve hospitalization outcomes in acute pancreatitis and reduce infectious complications may be related to the anti-inflammatory effects of omega-3 fatty acids. Inflammation is an essential part of host defence, firstly by creating a hostile environment for microbes and later by initiating tissue repair, recovery, and maintenance of homeostasis. However, prolonged (unresolved) inflammation and continuous release of pro-inflammatory mediators can cause tissue damage, metabolic changes, and loss of function[39-41]. In acute pancreatitis, a large number of inflammatory cytokines were released, leaving the whole body in a state of “hyperinflammation”. The increased serum levels of omega-3 fatty acids are linked with decreased levels of other inflammatory markers, including various cytokines and chemokines, acute-phase proteins, and adhesion molecules[42-45]. Additionally, omega-3 fatty acids decreased the production of arachidonic acid-derived eicosanoids. They do this partly by competing with arachidonic acid for incorporation into cell membrane phospholipids, partly

by reducing the release of arachidonic acid from membranes, partly by inhibiting the action of the enzymes COX-2 and 5-LOX on arachidonic acid, and partly by competing with arachidonic acid for metabolism by COX and LOX enzymes[46]. Innate antioxidant defense mechanisms, production of anti-inflammatory mediators (e.g. IL-10), and intracellular signaling pathways are promoted by omega-3 fatty acids. The anti-inflammatory effects of omega-3 fatty acids were often reported to involve decreased activation of the pro-inflammatory transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) in response to inflammatory stimuli as a result of the inhibition of phosphorylation of the inhibitory subunit of NFκB, IκB[47-48]. Therefore, early intervention with omega-3 fatty acids is an appropriate treatment strategy for severe acute pancreatitis.

Omega-3 in the diet experiences enzymatic changes to generate EPA and DHA molecules, which then become components of the phospholipid structure of cell membranes and affect inflammation[49]. The EPA&DHA have been intensively researched in terms of their capacity to regulate inflammation. They are able to lessen the generation of reactive oxygen species and pro-inflammatory cytokines, which helps to improve oxidative damage and inflammation in a variety of tissues, including the lungs. The underlying mechanisms entail the activation of critical signalling pathways, including the nuclear factor erythroid 2-related factor 2 pathway, which is involved in the expression of pro-inflammatory genes and plays an essential role in the cellular antioxidant response. This effect reduces the production of inflammatory cytokines, including TNF-x, IL-1β, and IL-6[50,51]. The impact of EPA&DHA on inflammation has been applied to several inflammatory diseases, such as lung disease, inflammatory bowel disease, and so on. Numerous studies have shown the positive effects of omega-3 fatty acids in the setting of lung disorders. In models of acute respiratory distress syndrome, asthma, and chronic obstructive pulmonary disease, for example, dietary fish oil has been demonstrated to reduce symptoms and enhance lung function. The above effect of omega-3 fatty acids on lessening the respiratory system's oxidative stress and inflammation is attributed to EPA&DHA[52-54]. Previous studies demonstrated the association between EPA&DHA and inflammatory bowel diseases, as shown by the National Health and Nutrition Examination Survey. They recommended that the consumption of EPA

(0.0045-0.01g) and DHA (>0.073g) every day effectively prevent the development of inflammatory bowel disease[55]. In addition, researchers discovered Ulcerative Colitis patients taking EPA (3.2g) and DHA (2.16g) every day had notablely lower colonoscopic scores[56]. A meta-analysis concluded that DHA and EPA can relieve body burden due to inflammatory factors[57].

In the present study, we also confirmed that omega-3 fatty acids have a causal effect on reduced risk of acute pancreatitis. Globally, the distribution of etiologies of acute pancreatitis differs by region, with gallstones and alcohol as the leading causes in the United States and a predominance of gallstones in southern Europe. The increasing trend of hypertriglyceridemia in China has been postulated to be related to the changing lifestyle and behaviors of the Chinese population, as well as the increasing prevalence of metabolic syndrome and increasing caloric intake[58]. However, an etiology is not established in approximately 10%–30% of acute pancreatitis cases, which can classified as idiopathic acute pancreatitis[59]. One recent study indicated that combined intake of omega-3 fatty acids near linearly lowers triglyceride and non-high-density lipoprotein cholesterol[60]. Lowering triglyceride and non-high-density lipoprotein cholesterol may be an important mechanism by which omega-3 fatty acids reduce the risk of acute pancreatitis. Furthermore, omega-3 fatty acids have strong antioxidant stress and anti-inflammatory effects[61]. Dietary supplementation of omega-3 fatty acids can down regulated serum IL-1β, IL-6, IL-8, TNF-α, and caspase-1[62]. Oxidative stress and inflammatory response are the key pathological bases of acute pancreatitis. Therefore, early intervention of omega-3 fatty acids can significantly improve the hospitalization prognosis of patients with acute pancreatitis, and daily supplementation of appropriate omega-3 fatty acids dose may effectively prevent the occurrence of acute pancreatitis.

A strength of our study was that it integrated meta-analysis and MR design. Meta-analysis based on RCT studies can provide evidence with sufficient confidence. However, in order to overcome the interference of confounding factors as much as possible, we can use MR to provide genetic evidence. MR studies that leverage genetic variants in genomic regions (e.g., omega-3 fatty acids) with a biological link to the metabolism of the

exposure of interest (e.g., omega-3 fatty acids) are less likely to be affected by confounding compared to traditional observational studies. The observed consistency in a meta-analysis of RCTs and genetic evidence of MR studies strengthens the proof of causality. This research methodology is groundbreaking and can provide a reference for the subsequent research. A potential limitation of our work is that the results of genetic evidence might only be generalizable to European populations. In addition, with only two genetic instruments and summary-level data, we could not use statistical methods to investigate possible pleiotropy biasing the MR estimates or non-linear relationships between plasma omega-3 fatty acids and acute pancreatitis risk. We, therefore, cannot rule out a threshold effect, with a protective effect only seen, for example, with very high plasma levels of omega-3 fatty acids. This study provided evidence to support the protective effect of omega-3 fatty acids on acute pancreatitis by meta-analysis and MR analysis. This suggestion supplies a potential adjuvant intervention for clinicians to prevent and treat acute pancreatitis. Patients also attach importance to the dietary intake of omega-3 fatty acids.

Conclusions

Omega-3 fatty acids complementary therapy may improve the prognosis of acute pancreatitis. Specifically, early intervention with omega-3 fatty acids can significantly reduce in-hospital mortality and infectious complications in acute pancreatitis patients. Furthermore, genetically predicted serum levels of omega-3 fatty acids can substantially reduce the risk of acute pancreatitis. Therefore, early intervention of Omega-3 fatty acids is an essential strategy for the treatment of acute pancreatitis.

Limitation

This study reported a genetic association between Omega-3 fatty acids and acute pancreatitis in MR analysis. However, Several host factors may influence serum levels of Omega-3 fatty acids, such as metabolites, exercise, lifestyle, diet, and so on. MR analysis can not establish causality for these factors. Further investigations are required to explore more factors influencing the association between Omega-3 fatty acids and acute pancreatitis.

Declarations

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Conflict of Interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authorship:

TBB developed the main research plan. MYD, GAJ, and TBB analyzed the data, generated charts, and MYD wrote the manuscript. YG collected the data and assemble references. All authors contributed to the article and approved the submitted version.

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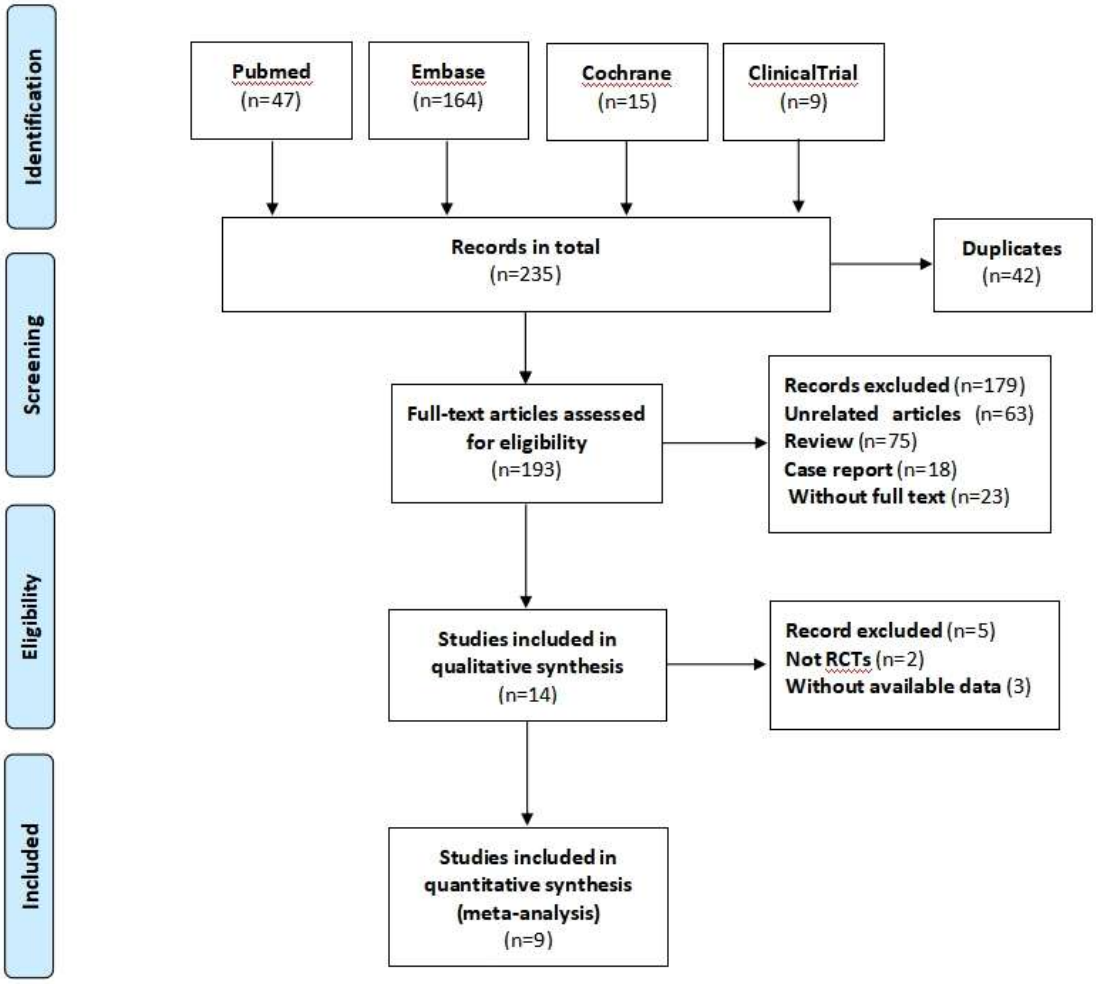

Figure 1. Flow chart illustrating the study selection process.

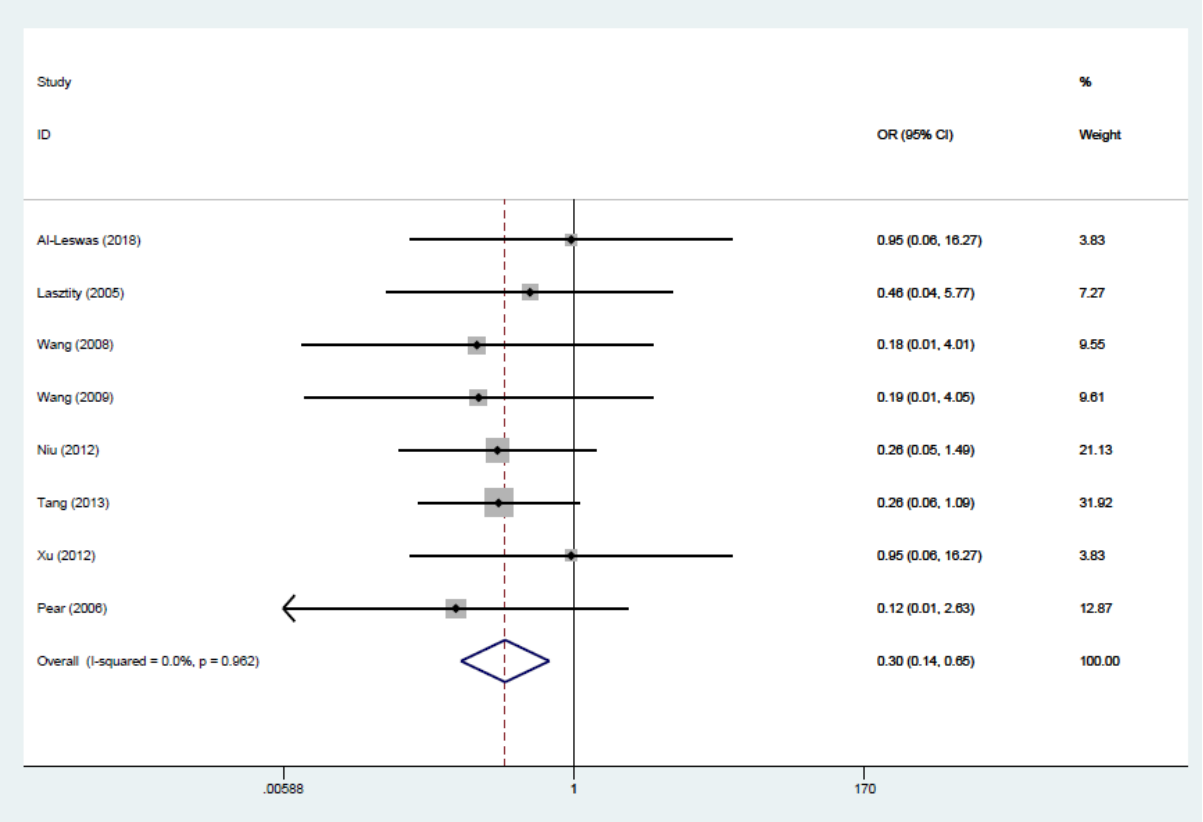

Figure 2. Forest plot of the effect of omega-3 fatty acids on mortality in acute pancreatitis. CI, confidence interval; df, degrees of freedom; IV, inverse variance (statistical method).

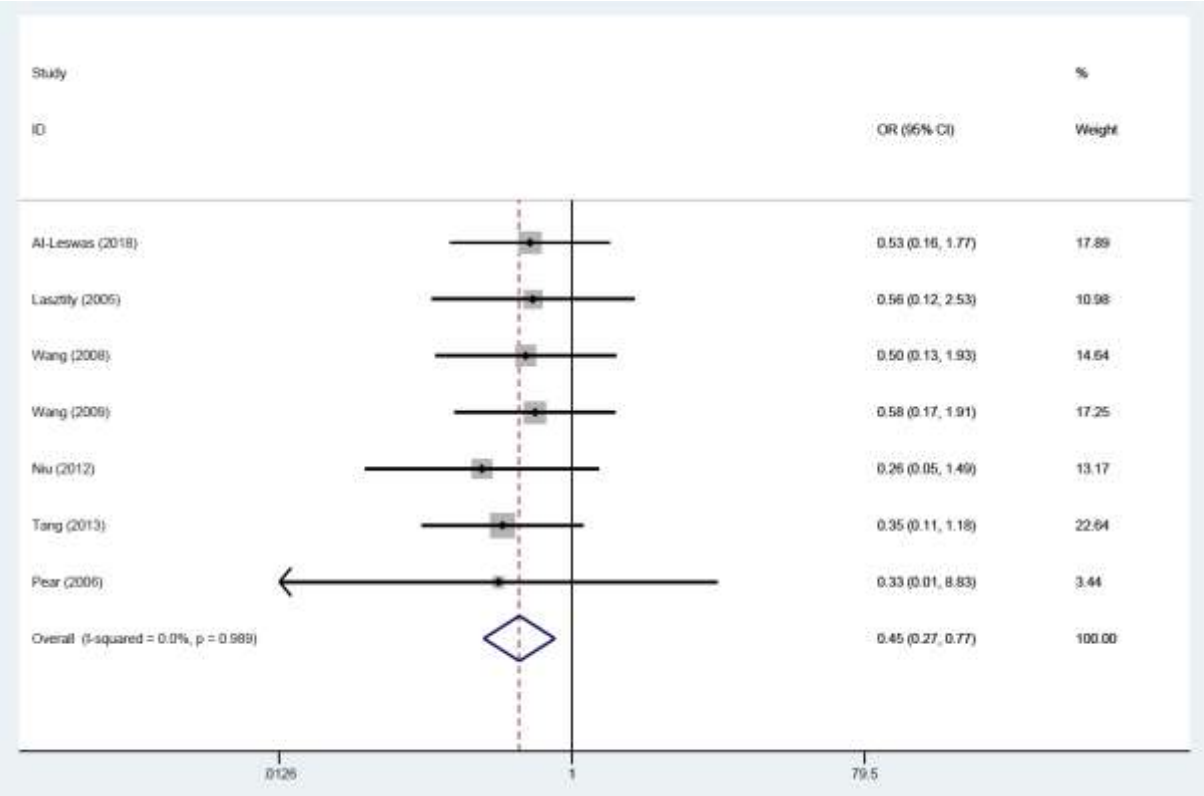

Figure 3. Forest plot of pooled estimates of omega-3 fatty acid supplementation on infectious complications in acute pancreatitis. CI, confidence interval; df, degrees of freedom; IV, inverse variance (statistical method).

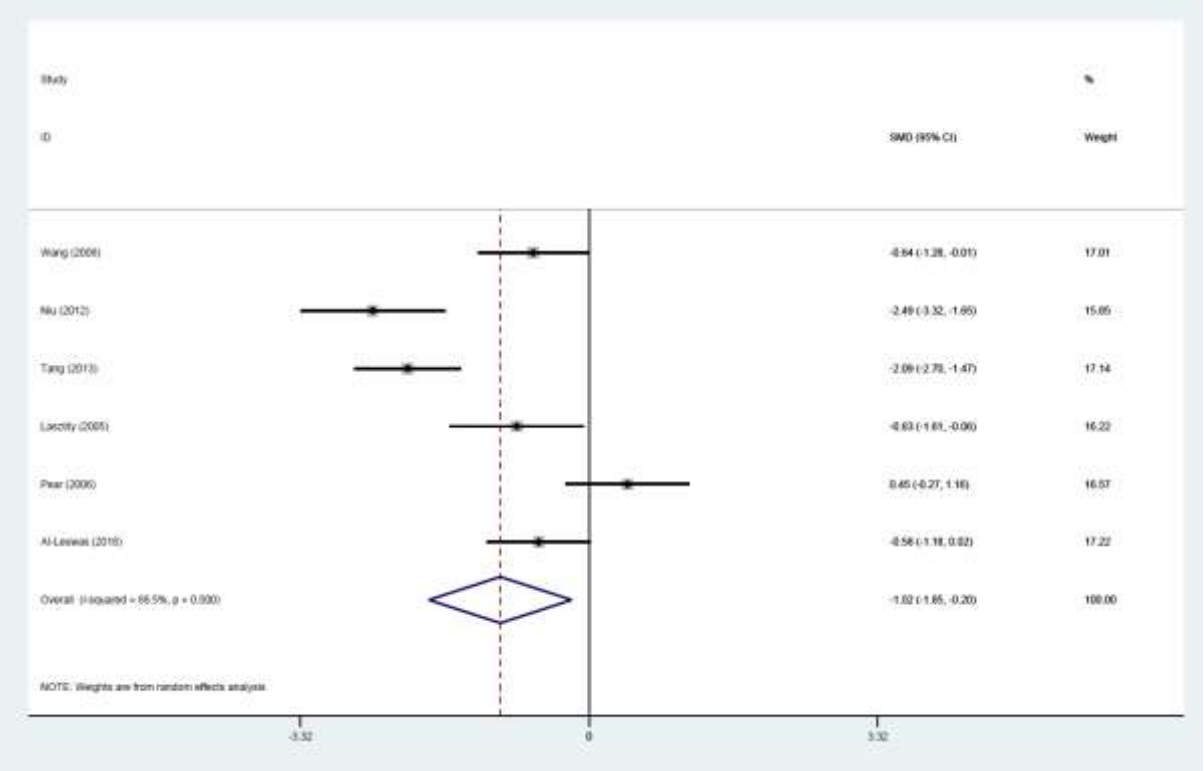

Figure 4. Forest plot of pooled estimates of omega-3 fatty acid supplementation on length of hospital stay in acute pancreatitis. CI, confidence interval; df, degrees of freedom; IV, inverse variance (statistical method).

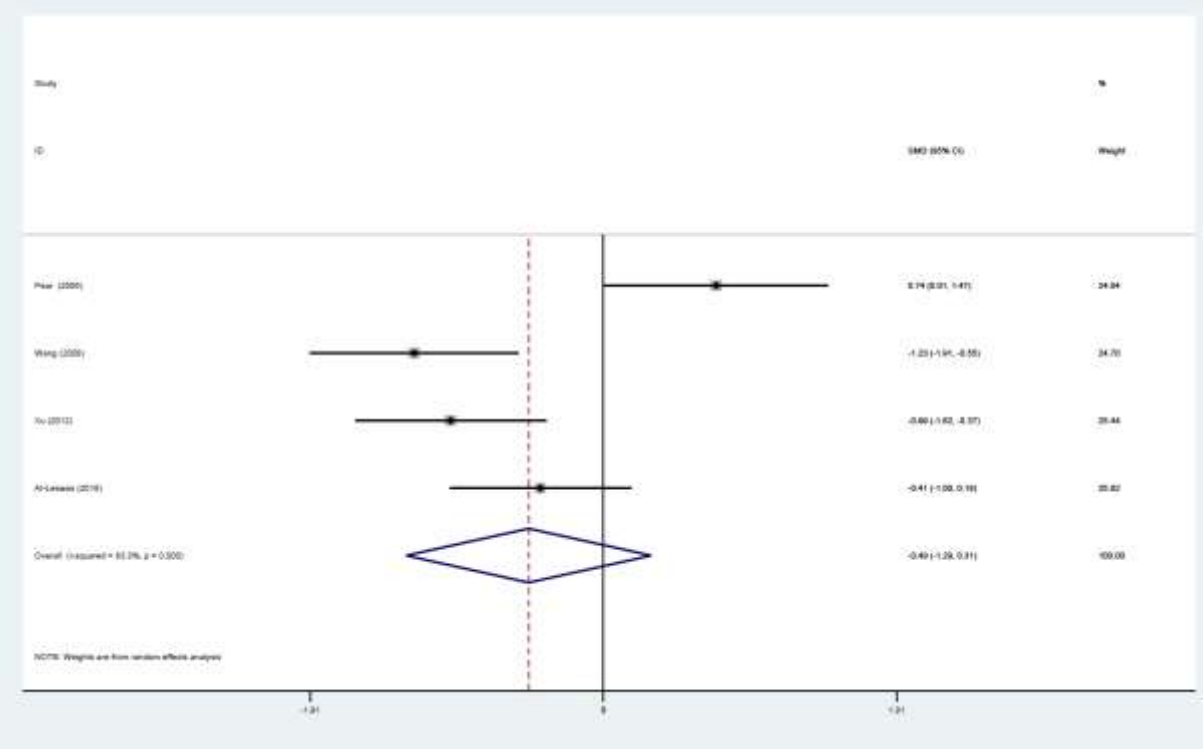

Figure 5. Forest plot of pooled estimates of omega-3 fatty acid supplementation on length of ICU stay in acute pancreatitis. CI, confidence interval; df, degrees of freedom; IV, inverse variance (statistical method).

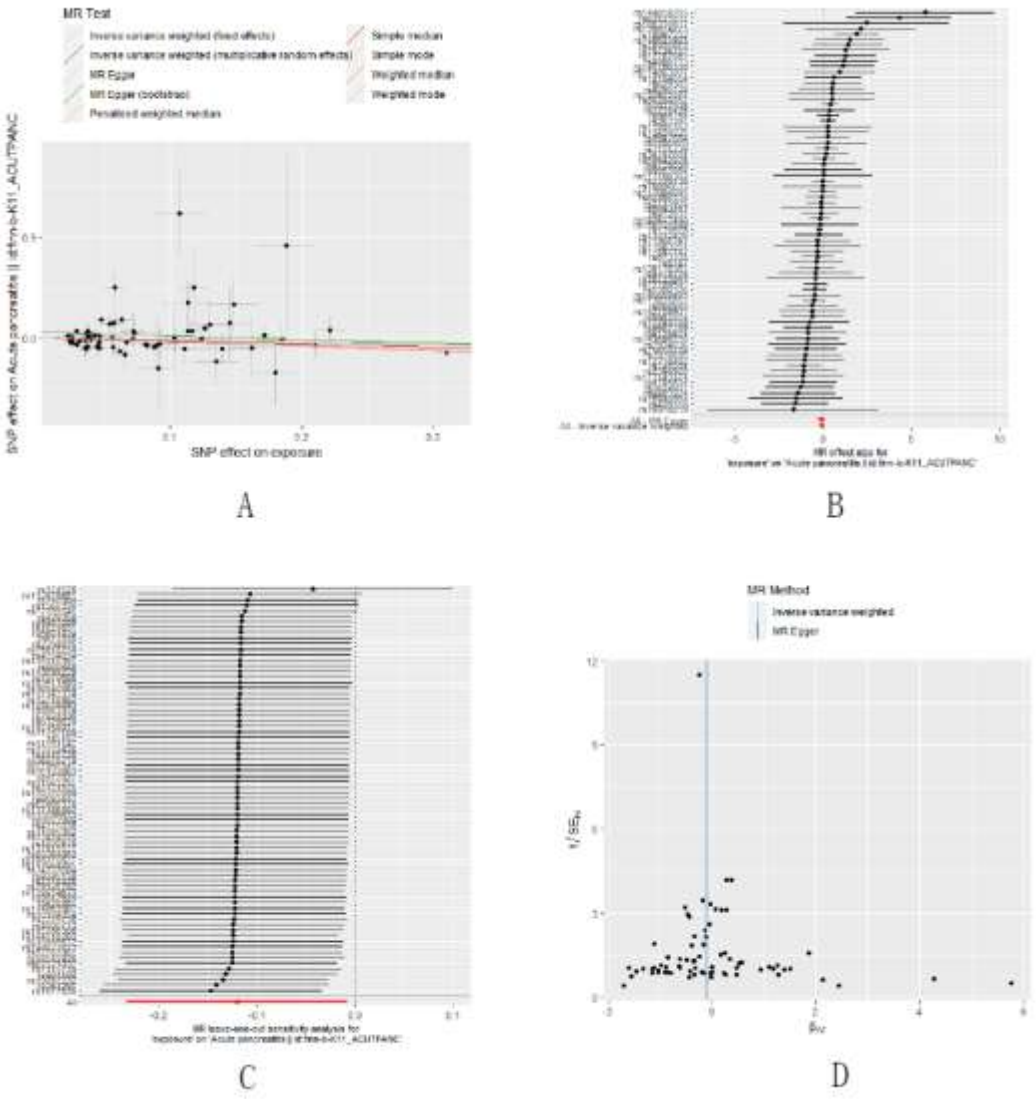

Figure 6. A. Scatter plot to visualize causal effect of omega-3 fatty acid on acute pancreatitis. The slope of the straight line indicates the magnitude of the causal association; Figure B. Fixed-effect IVW analysis of the causal association of omega-3 fatty acid with acute pancreatitis. The black dots and bars indicated the causal estimate and 95% CI using each SNP. The red dot and bar indicated the overall estimate and 95% CI meta-analyzed by MR-Egger and fixed-effect inverse variance weighted method. Figure C. MR leave-one-out sensitivity analysis for omega-3 fatty acid on acute pancreatitis. Circles indicate MR estimates for omega-3 fatty acid on acute pancreatitis using inverse-variance weighted fixed-effect method if each SNP was omitted in turn. Figure D. MR funnel plot for omega-3 fatty acid on acute pancreatitis.

Table 1: Characteristics of included studies

Author /year	region	Size	Patients (ω-3/con)	Mean age (ω-3/con)	Study type	Duration of Intervention	Dose	Intervention	Route of Nutrition	Severity Criteria of Used
Lasztity2005	Hungary	28	14/14	56.1/55.9	RCT	5–7 days	2.84 g/kg/day	omega-3 fatty acids alone	enteral nutrition	APACHE II score ≥ 5
Pearce/2006	UK	31	15/16	63.2/73.2	RCT	3–15 days	not reported	omega-3 fatty acids composite	enteral nutrition	APACHE II score ≥ 8
Wang/2008	China	40	20/20	37/40	RCT	5 days	0.15–0.20 g/kg/day	omega-3 fatty acids alone	parenteral nutrition	Mean APACHE II score = 12.5
Wang/2009	China	56	28/28	40/42	RCT	5 days	0.15–0.20 g/kg/day	omega-3 fatty acids alone	parenteral nutrition	Mean APACHE II score = 14
Xiong/2009	China	60	30/30	41.2/42.7	RCT	2 weeks	0.20 g/kg/day	omega-3 fatty acids alone	parenteral nutrition	APACHE-II ≥ 8; Ranson's score ≥ 3; Balthazar CT severity score > 6

Xu/2012	China	54	22/23	50.5/51.7	CT	RCT	2 weeks	0.20 g/kg/day	omega-3 fatty acids alone	parenteral nutrition	APACHE II score > 8; Ranson score > 3
Niu/2012	China	40	20/20	Mean 50	CT	RCT	5 days	not reported	omega-3 fatty acids alone	parenteral nutrition	APACHE II score ≥ 8
Tang/2013	China	64	32/32	Mean 37.5	CT	RCT	5 days	not reported	omega-3 fatty acids alone	parenteral nutrition	APACHE II score ≥ 8; Ranson's score ≥ 3
Al-Leswas/2018	UK	44	22/22	8-18 years	CT	RCT	7 days	0.20 g/kg/day	omega-3 fatty acids alone	parenteral nutrition	Glasgow (Imrie) score ≥ 3

RCT—randomized controlled trial; APACHE—Acute Physiology and Chronic Health Evaluation