

Systematic review

Effects of omega-3 supplementation on gastrointestinal cancers and treatment-related complications: an umbrella review of meta-analyses

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Abstract

Background: Many meta-analyses and systematic reviews have explored the impact of omega-3 supplementation on clinical outcomes in individuals with gastrointestinal (GI) cancers. Thus, this study aimed to capture the effects of omega-3 supplementation on GI cancers and associated complications.

Methods: This umbrella study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive advanced search was executed across Scopus, PubMed, and Web of Science until 25 January 2025. Data were pooled by using random-effects models based on heterogeneity. The entire statistical analysis was performed via RStudio and R. The statistical analysis results are presented as the mean difference (MD), standard mean difference (SMD), and relative risk (RR) in conjunction with their 95% confidence intervals (CIs).

Results: Eight meta-analysis papers were included in our umbrella review. Omega-3 fatty acid supplementation improved the serum concentrations of tumor necrosis factor alpha (TNF- α) (SMD: -0.34; 95% CI: -0.56, -0.11), interleukin-6 (IL-6) (SMD: -0.30; 95% CI: -0.49, -0.12; MD: -4.96; 95% CI: -6.62, -3.30), and C-reactive protein (CRP) (MD: -5.46; 95% CI: -10.06, -0.87). Omega-3 supplementation improved the CD4⁺/CD8⁺ ratio (SMD: 0.48; 95% CI: 0.26, 0.71) and reduced the length of hospitalization (MD: -2.45 d; 95% CI: -3.11, -1.80). Omega-3 supplementation was associated with a 24% significant reduction in the risk of overall complications (RR: 0.76; 95% CI: 0.67, 0.86).

Conclusion: Omega-3 supplementation may reduce the risk of overall complications and length of hospitalization in individuals suffering from GI cancers. Additionally, supplementation with omega-3 may alleviate the levels of pro-inflammatory cytokines such as TNF- α and IL-6, and acute-phase proteins such as CRP.

Keywords: gastrointestinal cancer; omega-3 fatty acid; inflammation; cancer complications

Received: 08 October 2024. Revised: 15 August 2025. Accepted: 12 September 2025

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Introduction

Cancers of the gastrointestinal (GI) tract, such as those of the stomach, liver, esophagus, pancreas, and colon, account for more than a quarter of all cancers, and their prevalence is increasing steadily [1, 2]. Pre-pandemic data suggest that there were >5 million new cases of gastrointestinal cancer (GC) in 2018, associated with >3 million related deaths [3]. In Iran, 49.8% of fatal malignancies are GCs, including those of the stomach, colon, liver, pancreas, and esophagus [4].

The symptoms of GI cancers can range from asymptomatic to symptoms such as swallowing difficulties, abdominal pain, and bleeding, depending on the location within the gastrointestinal system [5]. The affected area determines the diagnosis of these tumors, which can be made via techniques such as endoscopy, colonoscopy, and endoscopic retrograde cholangiopancreatography [6]. Depending on the patient's condition and disease stage, treatment for these malignancies may involve medication, chemotherapy, surgery, and alternative therapies [7, 8]. Radiotherapy is a crucial component of comprehensive cancer treatment strategies [9], but it often leads to adverse effects that can significantly impact patients' overall well-being and quality of life (QOL) [10]. In an effort to better manage adverse effects and enhance patient outcomes, there has been a recent surge in interest in investigating alternative medicines. The use of dietary supplements that include omega-3 polyunsaturated fatty acids (PUFAs), which are known for their anti-inflammatory qualities and possible protective effects against oxidative stress, is an intriguing strategy [11]. Omega-3 PUFAs, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have demonstrated beneficial effects across various clinical contexts, including the prevention and management of cardiovascular disease, inflammation reduction, and mood regulation [12]. In patients with cancer, the anti-inflammatory properties of omega-3 PUFAs may offer protection against radiation-induced tissue damage and facilitate recovery post radiotherapy [13]. Omega-3 PUFAs may help reduce inflammation, which is often exacerbated by radiation exposure [14]. Furthermore, previous research has suggested that omega-3 PUFA supplementation could alleviate symptoms associated with chemoradiotherapy, such as fatigue, nausea, and cognitive dysfunction. However, more extensive investigations, particularly those focused on radiotherapy patients, are needed to draw definitive conclusions about the efficacy of omega-3 PUFA supplementation for improving QOL [15].

Therefore, this umbrella review aimed to synthesize evidence from existing meta-analyses on the effects of omega-3 fatty acid supplementation on clinical outcomes—including inflammatory markers, immune parameters, hospitalization duration, and complications—in patients with GCs.

Methods

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria, an umbrella review employing all related meta-analyses and systematic reviews was carried out [16].

Search strategy

A comprehensive advanced search was executed across three databases, namely Scopus, PubMed, and Web of Science, to identify meta-analyses concentrating on omega-3 supplementation in individuals diagnosed with GI cancer published from inception to 15 February 2025. The search methodology involved the utilization

of specific Medical Subject Heading (MeSH) terms and keywords to expand an effective search strategy: (((("Fatty Acids, Omega-3" [Mesh] OR "Eicosapentaenoic Acid" [Mesh]) OR "Docosahexaenoic Acids" [Mesh]) OR ((((((("omega 3" [Title/Abstract]) OR ("ω-3" [Title/Abstract]) OR ("eicosapentaenoic acid" [Title/Abstract]) OR ("EPA" [Title/Abstract]) OR ("Docosahexaenoic acid" [Title/Abstract]) OR ("DHA" [Title/Abstract])) AND (((((((("cancer" [Title/Abstract]) OR ("carcinoma" [Title/Abstract]) OR ("Radiotherapy" [Title/Abstract]) OR ("chemotherapy" [Title/Abstract]) OR ("neoplasm" [Title/Abstract]) OR ("adenoma" [Title/Abstract]) OR ("malignan" [Title/Abstract]) OR ("sarcoma" [Title/Abstract]) OR ("metastas" [Title/Abstract]) OR ("leukemia" [Title/Abstract]) OR ("Lymphoma" [Title/Abstract]) OR ("glioma" [Title/Abstract]) OR ("Neoplasms" [MeSH]) OR "Carcinoma" [MeSH])) AND (((("Systematic Review" [Publication Type]) OR "Meta-Analysis" [Publication Type]) OR ("meta-analysis" [Title/Abstract]) OR ("systematic review" [Title/Abstract]))). Additionally, to increase the sensitivity of the search strategies, the wild-card "*" was utilized. The PubMed alert was activated by the first author (H.A.) to ensure the article's retrieval and prevent its omission. Moreover, an exhaustive review of the citations within the qualifying papers was carried out to minimize the likelihood of missing critical research.

Eligibility criteria

In this umbrella review, only studies meeting the following conditions were considered: (i) systematic reviews and meta-analyses; and (ii) papers investigating the impact of omega-3 supplementation on individuals with GI cancer. Papers of an observational nature, quasi-experimental designs, case reports, animal studies, letters, reviews, and commentaries were excluded from our umbrella review. The PICO structure used in this study was as follows: population/patients (P: individuals with GI cancer); intervention (I: omega-3 fatty acid supplementation); comparison (C: placebo or standard treatment); and outcome (O: inflammatory markers, immune system, serum concentrations of albumin, length of hospitalization, and total complication risk).

Study selection

Using EndNote software, duplicate papers were excluded by an investigator (H.A.). Following the PICO structure and eligibility criteria, the titles/abstracts and full texts of the remaining publications were separately reviewed by the authors (S.N., Z.R.J., and A.P.). The papers were subsequently assessed by the first and corresponding authors (H.A. and S.D.).

Methodological quality assessment

One of the researchers (H.A.) carried out an entire evaluation of the meta-analyses and systematic analyses that were entered into this paper, which was subsequently inspected by the corresponding author (S.D.). Quality assessment of the methodology of the selected papers was conducted via the Assessment of Multiple Systematic Reviews (AMSTAR)-2 tool. The aforementioned tool is particularly designed for evaluating the quality of meta-analyses and systematic reviews, comprising 7 critical domains with 16 questions. The responses to these questions in the AMSTAR-2 tool are classified as "No meta-analysis," "No," "Partial Yes," or "Yes," and the overall quality of the selected papers is classified as "High," "Low," "Moderate," or "Critically low" [17].

Data extraction

One researcher (Z.M.) collected vital details, which were then inspected by another researcher (H.A.). Information such as country, publication year, study duration, outcomes, quality assessment

scales, first author of the selected papers, and basic characteristics of participants (including sample size, age, ranges for duration and dose of omega-3 supplementation, mean dosage, and duration of omega-3 supplementation) were written in a predesigned table.

Data synthesis and statistical analysis

For the statistical analysis, the mean difference (MD), standard mean difference (SMD), and relative risk (RR) were used in conjunction with their 95% confidence intervals (CIs). Relying on the I^2 and Q statistics, either a fixed-effect model or a random-effect model was selected. High and low heterogeneity were defined as $I^2 > 75\%$ and $I^2 \leq 40\%$, respectively [18]. Subgroup analysis of the included papers was conducted to explore sources of heterogeneity according to the following factors: age, AMSTAR score, number of included studies, and participants. Graphical funnel plots and trim-and-fill methods were drawn to assess the publication bias of the included papers. The entire statistical analysis was performed via RStudio version 2023.03.1 and R version 4.3.2 simultaneously, with a significance threshold set at $P \leq 0.05$.

Results

Study selection

In accordance with the PRISMA guidelines, a total of 1,347 records were initially identified through the mentioned

databases, of which 166 duplicates were removed. Among the 1,181 studies whose titles and abstracts were screened, 1,167 were excluded. Of the remaining 14 studies, 6 were removed because they did not explicitly mention GCs, leaving 8 studies that were eligible for assessment in the current umbrella review (Figure 1). Table 1 provides detailed information about the studies included in the umbrella review.

Methodological quality assessment

In accordance with the AMSTAR-2 tool, the methodological quality results of the meta-analyses are summarized in Table 2. In this umbrella review, five included meta-analyses were rated as high and the three remaining meta-analyses were rated as moderate.

Impact of omega-3 supplementation on inflammatory markers in papers reporting SMD

The selected papers that used SMD [19–22] were included in our umbrella analysis. Omega-3 fatty acid supplementation significantly alleviated tumor necrosis factor alpha (TNF- α) (SMD: -0.34 ; 95% CI: -0.56 , -0.11 ; Figure 2A) and interleukin-6 (IL-6) (SMD: -0.30 ; 95% CI: -0.49 , -0.12 ; Figure 2B) levels, with moderately significant and slightly insignificant heterogeneity, respectively ($I^2 = 63\%$, $P = 0.05$; $I^2 = 6\%$, $P = 0.38$). On the other hand, the C-reactive protein (CRP) concentration did not significantly

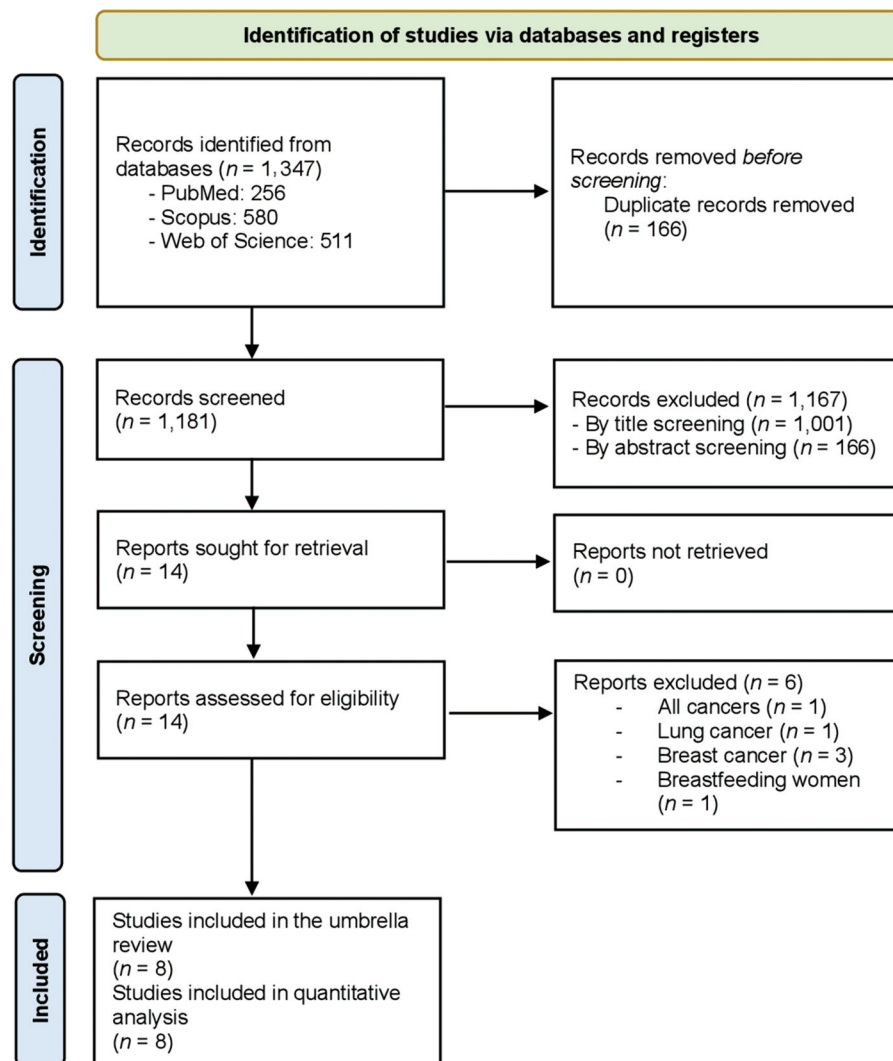


Figure 1. Study-selection process for the umbrella review on omega-3 supplementation and GCs.

Table 1. Detailed information about the studies included in the umbrella review

Study, date, reference number	Number of included studies	Location, duration	Number of participants	Age (years)	Intervention (range and mean of dose and duration)	Quality assessment scale	Outcomes
Yan et al., 2019 [19]	11	China, 2008–2017	755	I: 58.3 C: 60	0.04–2.03 g/d (0.83 g/d) 3 d–9 wk (5.3 wk)	Cochrane 5.3/7	IL-6 ^{NS} CRP ^{NS} TNF- α ^S IL-6 ^S CRP ^S TNF- α ^S Infection complications ^{NS} Pre-albumin ^{NS} Albumin ^{NS} Retinol-bind- ing protein ^{NS} TNF- α ^S IL-6 ^{NS} LOS ^S CRP ^{NS} IL-1 β ^{NS} Albumin ^{NS} Infectious and nonin- fectious complications ^{NS}
Lu et al., 2022 [23]	10	China, 2012–2015	663	I: 59.55 C: 62.34	0.2–2.26 g/d (1.47 g/d) 5 d–2 wk (1.14 wk)	Cochrane 6/7	IL-6 ^S CRP ^S TNF- α ^S Infection complications ^{NS} Pre-albumin ^{NS} Albumin ^{NS} Retinol-bind- ing protein ^{NS} TNF- α ^S IL-6 ^{NS} LOS ^S CRP ^{NS} IL-1 β ^{NS} Albumin ^{NS} Infectious and nonin- fectious complications ^{NS}
Liu et al., 2023 [24]	19	China, 2002–2020	179	I: 62.57 C: 64.93	0.108–4 g/d 2 d–12wk	Cochrane 6/7	IL-6 ^S CRP ^S TNF- α ^S Infection complications ^{NS} Pre-albumin ^{NS} Albumin ^{NS} Retinol-bind- ing protein ^{NS} TNF- α ^S IL-6 ^{NS} LOS ^S CRP ^{NS} IL-1 β ^{NS} Albumin ^{NS} Infectious and nonin- fectious complications ^{NS}
Yue et al., 2022 [26]	20	China, 2002–2021	1,761	I: 59.75 C: 59.64	0.2–10 g/d 3 d–24 wk (22.55 wk)	Cochrane 6/7	IgA ^S IgM ^S IgG ^S CD3 ⁺ CD4 ⁺ CD4 ⁺ /CD8 ⁺ IL-6 ^{NS} CRP ^{NS} Albumin ^{NS} Infectious complications ^S TNF- α ^S IL-6 ^S LOS ^S Total complications ^{NS} Surgical site infection ^{NS} CD4 ⁺ /CD8 ⁺ SIRS ^S LOS ^S CRP ^S Incidence of postopera- tive infectious complication ^S TNF- α ^S CRP ^{NS} IL-6 ^S
De Castro et al., 2022 [22]	6	Brazil, 2008–2018	278	I: 58.41 C: 59.71	2–7.1 g/d (4.4 g/d) 4–8 wk (5.33 wk)	Cochrane 5.7–7	IL-6 ^{NS} CRP ^{NS} Albumin ^{NS} Infectious complications ^S TNF- α ^S IL-6 ^S LOS ^S Total complications ^{NS} Surgical site infection ^{NS} CD4 ⁺ /CD8 ⁺ SIRS ^S LOS ^S CRP ^S Incidence of postopera- tive infectious complication ^S TNF- α ^S CRP ^{NS} IL-6 ^S
Xie et al., 2016 [21]	11	China, 1966–2016	694	Range: 50–71 years (60.5)	0.05–3.3 g/d (2.06 g/d) 5 d–2 wk (1.1 wk)	Cochrane 5.7/7	IL-6 ^{NS} CRP ^{NS} Albumin ^{NS} Infectious complications ^S TNF- α ^S IL-6 ^S LOS ^S Total complications ^{NS} Surgical site infection ^{NS} CD4 ⁺ /CD8 ⁺ SIRS ^S LOS ^S CRP ^S Incidence of postopera- tive infectious complication ^S TNF- α ^S CRP ^{NS} IL-6 ^S
Ma et al., 2015 [25]	15	China, 1995–2014	1,297	I: 62.86 C: 63.68	0.4–3.5 g/d (2.32 g/d) 1–2 wk (0.9 wk)	Cochrane 5.5/7	IL-6 ^{NS} CRP ^{NS} Albumin ^{NS} Infectious complications ^S TNF- α ^S IL-6 ^S LOS ^S Total complications ^{NS} Surgical site infection ^{NS} CD4 ⁺ /CD8 ⁺ SIRS ^S LOS ^S CRP ^S Incidence of postopera- tive infectious complication ^S TNF- α ^S CRP ^{NS} IL-6 ^S
Jamali et al., 2024 [20]	28	Iran, 1999–2022	1,561	I: 57.49 C: 59.06	0.3–12.85 g/d (3.352 g/d) 1–12 wk (4.84 wk)	Cochrane 17 studies: low risk of bias 7 studies: moderate risk of bias	IL-6 ^{NS} CRP ^{NS} Albumin ^{NS} Infectious complications ^S TNF- α ^S CRP ^{NS} IL-6 ^S

CD: cluster of differentiation, CRP: C-reactive protein, IG: immunoglobulin, IL: interleukin, LOS: length of hospital stay, SIRS: systemic inflammatory response syndrome, TNF- α : tumor necrosis factor α , CRP = C-reactive protein, I = intervention, C = control, wk = week, NS = non-significant, S = significant.

Table 2. Results of the selected papers according to AMSTAR-2

Study, date, reference number	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall
Yan et al., 2019 [19]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	PY	Y	Moderate
Lu et al., 2022 [23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	PY	Y	High
Liu et al., 2023 [24]	Y	Y	Y	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	PY	PY	Y	Moderate
Yue et al., 2022 [26]	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	PY	Y	High
De Castro et al., 2022 [22]	Y	PY	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	High
Xie et al., 2016 [21]	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	PY	Y	Moderate
Ma et al., 2016 [25]	Y	PY	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	PY	Y	High
Jamali et al., 2024 [20]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High

Y = Yes, PY = Partially Yes, N = No. Questions: Q1: Did the research questions and inclusion criteria for the review include the components of PICO? Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review, and did the report justify any significant deviations from the protocol? Q3: Did the review authors explain their selection of the study designs for inclusion in the review? Q4: Did the review authors use a comprehensive literature search strategy? Q5: Did the review authors perform study selection in duplicate? Q6: Did the review authors perform data extraction in duplicate? Q7: Did the review authors provide a list of excluded studies and justify the exclusions? Q8: Did the review authors describe the included studies in adequate detail? Q9: Did the review authors use a satisfactory technique for assessing risk of bias (RoB) in individual studies that were included in the review? Q10: Did the review authors report on the sources of funding for the studies included in the review? Q11: If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results? Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Q13: Did the review authors account for RoB in individual studies when interpreting/discussing the review results? Q14: Did the review authors provide a satisfactory explanation for and discussion of any heterogeneity observed in the review results? Q15: If they performed quantitative synthesis, did the review authors conduct an adequate investigation of publication bias (small-study bias) and discuss its likely impact on the review results? Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

change after omega-3 supplementation (SMD: -0.08 ; 95% CI: $-0.24, 0.09$; Figure 2C), with low heterogeneity ($I^2 = 0\%$, $P = 0.69$). With respect to subgroup analysis, in papers on colorectal cancer (CC), the impact of omega-3 supplementation on serum TNF- α and IL-6 concentrations was significant in those with a study duration of >7 years and in studies with durations of both <5 years and >5 years (Table 3). Despite the serum concentrations of TNF- α and IL-6, the combined SMD for the serum CRP concentration did not change even after subgroup analysis. Graphical inspection of the funnel plots for those inflammatory markers revealed the presence of publication bias (Figure 2D–F). Trim-and-fill analysis for TNF- α , IL-6, and CRP was applied, and the results showed no small-studies effect.

Impact of omega-3 supplementation on inflammatory markers in papers reporting MD

Three selected papers [23–25] explored the positive influence of omega-3 supplementation on the serum concentrations of CRP (MD: -5.46 ; 95% CI: $-10.06, -0.87$; Figure 3A) and TNF- α (MD: -0.43 ; 95% CI: $-0.71, -0.16$; Figure 3B). Moreover, highly significant heterogeneity was detected ($I^2 = 13\%$, $P = 0.28$). Furthermore, a significant reduction in the serum IL-6 concentration was detected in two studies (MD: -4.96 ; 95% CI: $-6.62, -3.30$; Figure 3C). Subgroup analysis of CRP revealed that omega-3 supplementation significantly decreased CRP concentrations in meta-analyses of patients with gastric cancer and those with fewer than six included studies (Table 4). In contrast, the CRP levels did not change after subgroup analysis. Visual inspection of the funnel plots for the CRP, TNF- α , and IL-6 levels confirmed their asymmetric shapes (Figure 3D–F, respectively). To evaluate the impact of small papers, a trim-and-fill analysis for CRP was performed and the results showed no small-studies effect.

Impact of omega-3 supplementation on the immune system

In the three selected papers that evaluated the effect of omega-3 supplementation on the CD4 $^+$ /CD8 $^+$ ratio, a significant increase (SMD: 0.48 ; 95% CI: $0.26, 0.71$; Figure 4A) was found, with insignificant heterogeneity ($I^2 = 28\%$, $P = 0.25$). Subgroup analysis revealed that a significant increase in the CD4 $^+$ /CD8 $^+$ ratio was detected in those papers that were on CC and had a duration of >6 years and <9 years (Table 3). The funnel plot was

asymmetrical (Figure 4B). After the trim-and-fill method was applied, the results remained similar, confirming the robustness of the findings.

Impact of omega-3 supplementation on the serum ALB concentration

Impact of omega-3 supplementation on the serum albumin concentration in papers reporting SMD

Two studies [22, 26] that investigated the effect of omega-3 supplementation on the level of albumin included in the umbrella analysis revealed an insignificant increase in the albumin level (SMD: 0.16 ; 95% CI: $-0.38, 0.71$; Figure 5A), with highly significant heterogeneity among the papers ($I^2 = 83\%$, $P = 0.02$). The obtained funnel plot did not reject the absence of publication bias (Figure 5B).

Impact of omega-3 supplementation on the serum albumin concentration in papers reporting MD

In two meta-analyses [23, 24], serum albumin concentrations were reported to have an insignificant impact on omega-3 supplementation (SMD: 0.36 ; 95% CI: $-0.02, 0.74$; Figure 6A), with low, meaningless between-paper heterogeneity ($I^2 = 0\%$, $P = 0.50$). The absence of publication bias was not confirmed due to the asymmetric shape of the funnel plot (Figure 6B).

Impact of omega-3 supplementation on the length of hospital stay

On the basis of four meta-analyses [21, 23–25], omega-3 supplementation eventually led to a significant reduction in the length of hospital stay (MD: -2.45 ; 95% CI: $-3.11, -1.80$; Figure 7A). However, moderate between-paper heterogeneity was observed ($I^2 = 72\%$, $P = 0.01$). Subgroup analysis revealed a significant reduction in papers that involved patients with GC and those with more than six included studies (Table 4). Visual inspection of the funnel plot revealed asymmetry (Figure 7B). After small papers were omitted, a trim-and-fill analysis indicated no change in the pooled MD.

Impact of omega-3 supplementation on total complication risk

In three meta-analyses [21, 24, 25], the effect of omega-3 supplementation on the risk of total complications was explored and

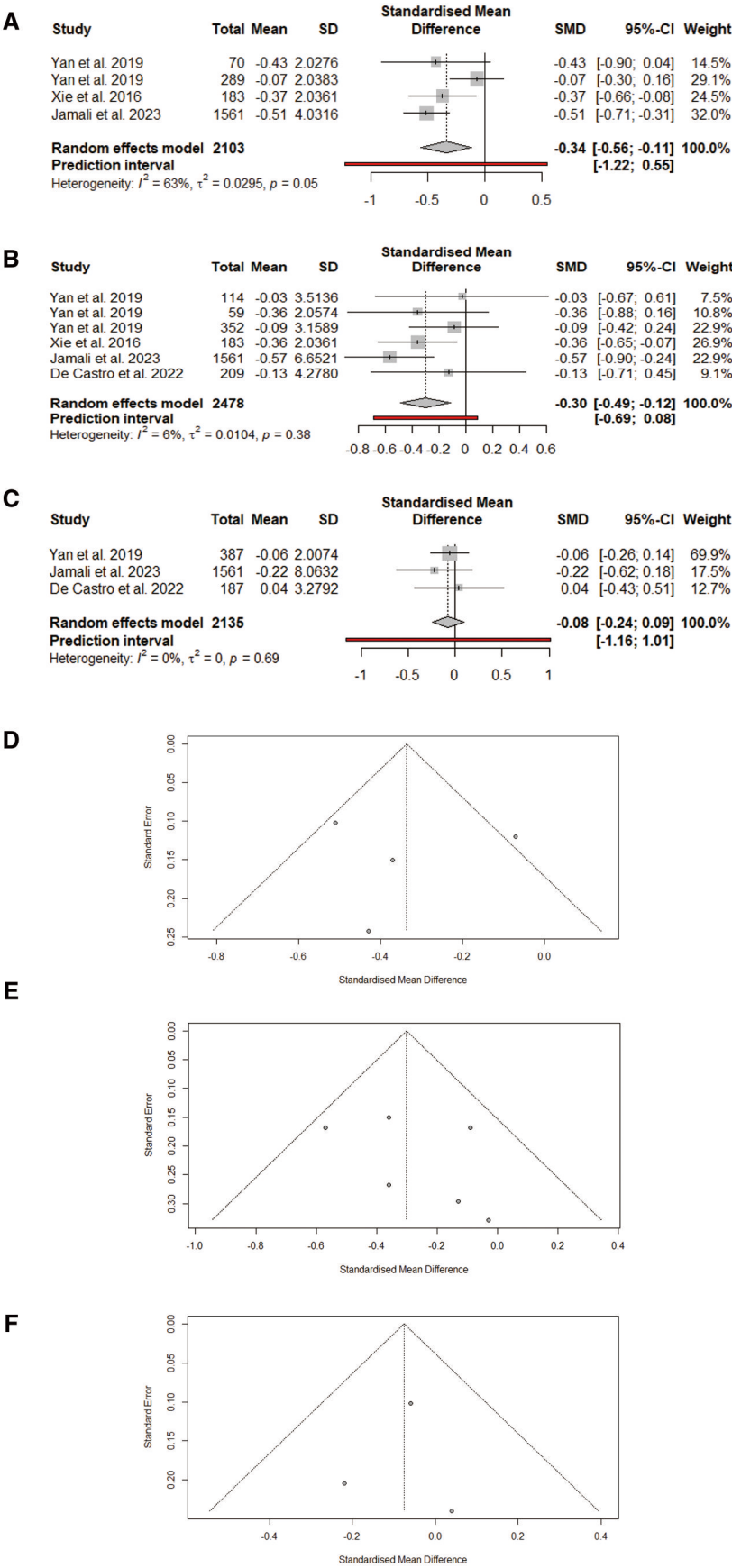


Figure 2. Impact of omega-3 supplementation on inflammatory markers in patients with GCs. Meta-analysis of randomized-controlled trials that evaluated the effect of omega-3 supplementation on serum levels of TNF- α , IL-6, and CRP using SMD with 95% CI. (A) Forest plot showing the pooled SMD in TNF- α levels across four studies. (B) Forest plot showing the pooled SMD in IL-6 levels across the same six studies. (C) Forest plot showing the pooled SMD in CRP levels across the same three studies. (D–F) Funnel plots corresponding to (A–C), respectively, assessing potential publication bias. Egger's test results were non-significant, indicating no major publication bias. IL-6 = interleukin-6, CRP = C-reactive protein, SD = standard deviation, I^2 = I-squared statistic for heterogeneity, τ^2 = tau-squared, between-study variance, P = statistical significance.

Table 3. Subgroup analysis of the impact of omega-3 supplementation on inflammatory markers (TNF- α , IL-6, and CRP) and CD4⁺/CD8⁺ ratio in studies reporting SMD

Subgroup variable	Effect size (N)	SMD (95% CI)	I ² (%)	P-heterogeneity
TNF-α				
Overall	4	-0.34 (-0.56, -0.11)	63	0.05
Type				
CC	2	-0.39 (-0.64, -0.14)	0	0.83
Other GCs	2	-0.29 (-0.73, 0.14)	87	<0.01
Duration (years)				
≥7	2	-0.47 (-0.63, -0.11)	0	0.44
<7	2	-0.19 (-0.52, 0.14)	44	0.18
IL-6				
Overall	6	-0.30 (-0.49, -0.12)	6	0.38
Type				
CC	2	-0.36 (-0.62, -0.10)	0	1.00
GC	3	-0.29 (-0.62, 0.05)	55	0.11
EC	1	-0.03 (-0.67, 0.61)		
Duration (years)				
≥7	3	-0.41 (-0.62, -0.21)	0	0.39
<7	3	-0.14 (-0.40, 0.11)	0	0.65
Included studies				
≥5	2	-0.42 (-0.83, -0.12)	40	0.20
<5	4	-0.24 (-0.43, -0.04)	0	0.56
CRP				
Overall	3	-0.08 (-0.24, 0.09)	0	0.69
Type				
DC	1	-0.06 (-0.26, 0.14)		
GC	2	-0.11 (-0.42, 0.19)	0	0.41
Duration (years)				
≥16	2	-0.11 (-0.42, 0.19)	0	0.41
<16	1	-0.06 (-0.26, 0.14)		
Included studies				
≥7	2	-0.09 (-0.27, 0.09)	0	0.48
<7	1	0.04 (-0.43, 0.51)		
CD4⁺/CD8⁺ ratio				
Overall	3	0.48 (0.26, 0.71)	28	0.25
Type				
CC	2	0.55 (0.27, 0.83)	33	0.22
GC	1	0.35 (0.04, 0.66)		
Duration (years)				
≥6	2	0.52 (0.21, 0.71)	55	0.14
<6	1	0.36 (-0.04, 0.76)		
Included studies				
≥9	1	0.66 (0.40, 0.92)		
<9	2	0.35 (0.11, 0.60)	0	0.97

N represents the number of included studies in each subgroup analysis.

the results revealed a 24% significant reduction (RR: 0.76; 95% CI: 0.67, 0.86; **Figure 8A**), with low, insignificant between-paper heterogeneity ($I^2 = 0\%$, $P=0.48$). Apart from CC, other subgroup analyses demonstrated a significant reduction in the total complication risk (**Table 5**). Graphical inspection revealed an asymmetric funnel plot (**Figure 8B**). The results of the trim-and-fill analysis did not change, even after the omission of small papers.

Discussion

It is crucial to optimize the intake of key nutrients in a way that greatly inhibits carcinogenesis and improves the treatment response to achieve the most effective and efficient nutritional intervention in cancer treatment. Over the past few decades, the results of clinical studies on omega-3 supplementation among GI cancer patients undergoing radiotherapy have been ambiguous. As an umbrella review study, we have therefore compiled the findings of excellent systematic reviews and meta-analyses. In the present study, supplementation with omega-3 fatty acids was associated with improvements in TNF- α and IL-6 levels. IL-6 is one of the most sensitive and critical inflammatory agents.

During surgery, IL-6 drives the liver to generate the acute-phase protein CRP, which increases the phagocytic activity of neutrophils and macrophages [27]. The release of IL-6 and the presence of CRP in the body can reflect the body's stress status. Recent research has demonstrated that omega-3 PUFAs can lower the levels of IL-6 and TNF- α in cancer patients following surgery, shorten the duration of ventilator use and hospital stay in patients undergoing major abdominal surgery, and enhance immune function [28]. These findings are consistent with the results of our umbrella review. Studies have shown that the dietary support of omega-3 PUFAs reduces inflammatory situations in cancer patients in the digestive system. Many preclinical studies indicate that inflammation is a key step in the initiation and progression of cancer [29, 30]. Omega-3 PUFAs play a critical role in lowering inflammation and facilitating tissue homeostasis recovery in various diseases, including certain gastrointestinal ailments [31]. This is likely attributed to their strong anti-inflammatory and antioxidant properties, as well as their ability to promote the early epithelialization of ulcers. However, other studies reported no associations between the levels of inflammatory factors, such as IL-6, IL-10, and CRP, and the intake of

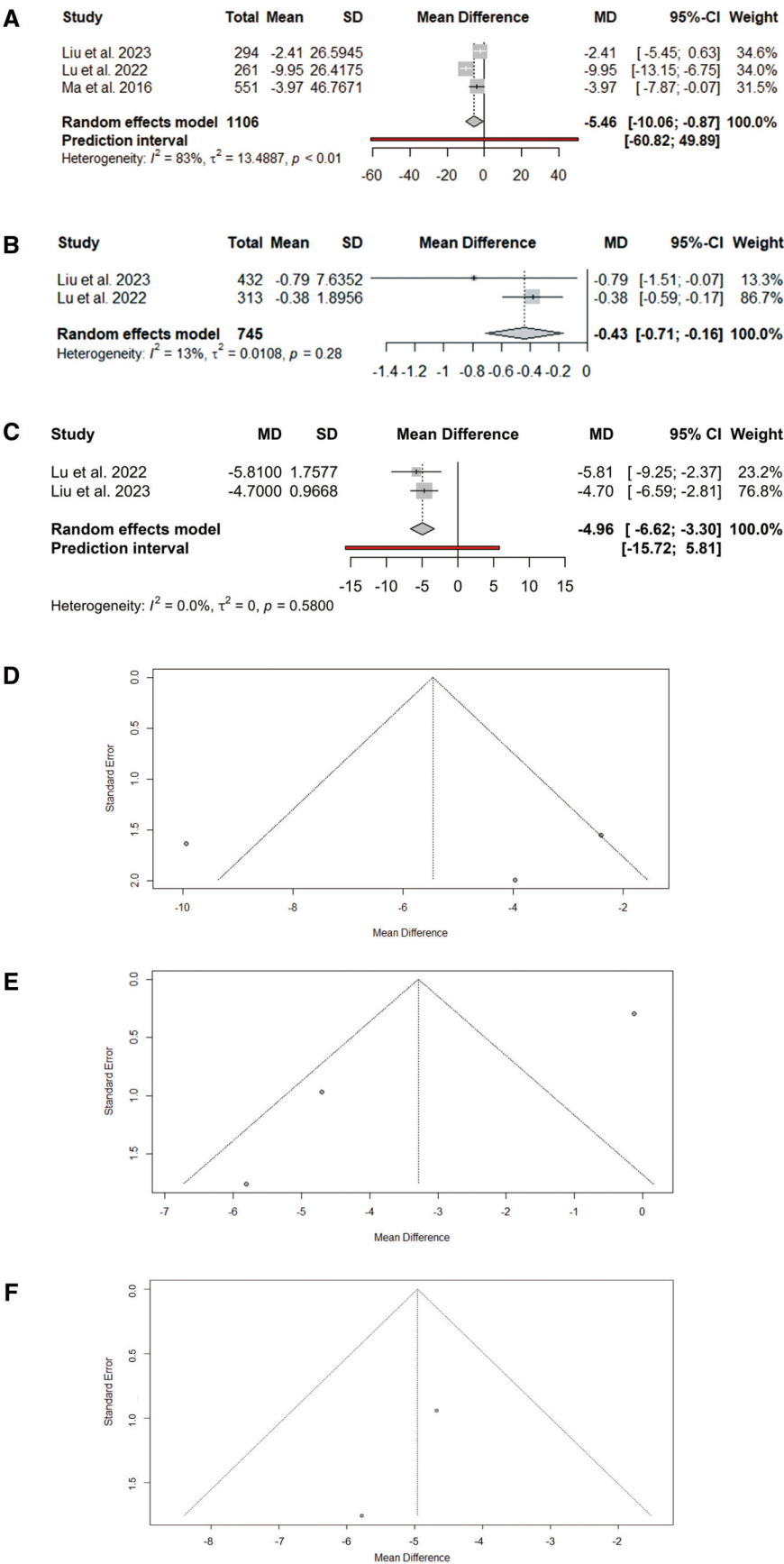
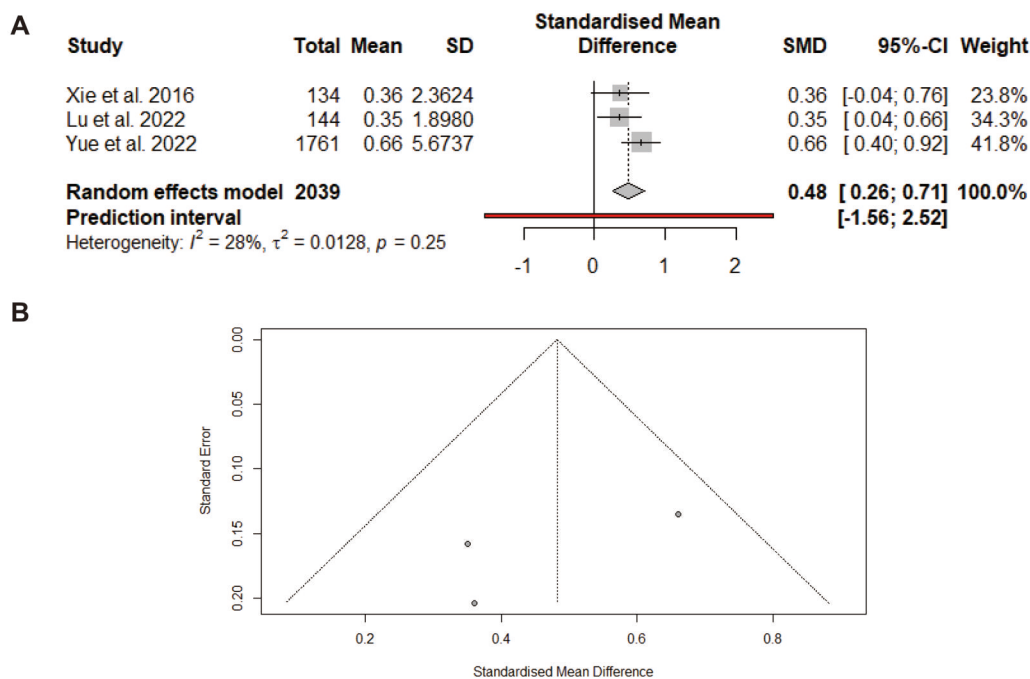


Figure 3. Impact of omega-3 supplementation on inflammatory markers in patients with GCs. Meta-analysis of randomized-controlled trials assessed the effect of omega-3 supplementation on serum levels of CRP, TNF- α , and IL-6 using MD with 95% CI. (A) Forest plot showing the pooled MD in CRP levels across three studies. (B) Forest plot showing the pooled MD in TNF- α levels across two studies. (C) Forest plot showing the pooled MD in IL-6 levels across two studies. (D–F) Funnel plots corresponding to (A–C), respectively, assessing potential publication bias. SD = standard deviation, I^2 = I-squared statistic for heterogeneity, τ^2 = tau-squared, between-study variance, P = statistical significance.

Table 4. Subgroup analysis of the impact of omega-3 supplementation on inflammatory markers (TNF- α , IL-6, and CRP) and length of hospital stay in studies reporting MD

Subgroup variable	Effect size (N)	MD (95% CI)	I ² (%)	P-heterogeneity
LOS				
Overall	4	-2.45 (-3.11, -1.80)	72	0.01
Type				
CC	2	2.71 (-9.26, 14.68)	91	<0.01
Other GCs	2	-2.48 (-3.20, -1.76)	0	0.95
Duration (years)				
≥12	3	0.51 (-6.43, 7.46)	81	<0.01
<12	1	-2.54 (-4.39, -0.69)		
Included studies				
≥6	2	-2.55 (-3.25, -1.85)	0	0.64
<6	2	2.88 (-8.74, 14.50)	90	<0.01
CRP				
Overall	3	-5.46 (-10.06, -0.87)	83	<0.01
Type				
CC	1	-2.41 (-5.45, 0.63)		
GC	2	-7.07 (-12.92, -1.21)	81	0.02
Duration (years)				
≥18	2	-6.16 (-13.55, 1.23)	91	<0.01
<18	1	-3.97 (-7.87, -0.07)		
Included studies				
≥6	1	-2.41 (-5.45, 0.63)		
<6	2	-7.07 (-12.92, -1.21)	81	0.02

LOS = length of hospital stay. N represents the number of included studies in each subgroup analysis.

**Figure 4.** Effect of omega-3 supplementation on CD4⁺/CD8⁺ T-cell ratio in patients with GCs. Meta-analysis of randomized-controlled trials evaluated the impact of omega-3 supplementation on immune function, specifically the CD4⁺/CD8⁺ ratio, using SMD with 95% CI. (A) Forest plot showing the pooled SMD for the CD4⁺/CD8⁺ ratio across included studies. Heterogeneity and prediction interval values are reported to assess consistency across studies. (B) Funnel plot corresponding to (A), used to evaluate potential publication bias. SD = standard deviation, I² = I-squared statistic for heterogeneity, τ^2 = tau-squared, between-study variance, P = statistical significance.

omega-3 supplements [32]. The anti-inflammatory effect may be dose- and duration-dependent in terms of supplement intake.

Moreover, the improvement in the CD4⁺/CD8⁺ ratio in individuals receiving radiation therapy for gastrointestinal malignancies was another finding of the study. Studies have demonstrated increases in immune function in GC patients taking omega-3 supplements [26]. The majority of GCs are in an immune-suppressive state, which further lowers immunity as a result of

decreased appetite, digestive and absorptive abnormalities, tumor self-suppression, and the decreased generation of immune-suppressive substances. By increasing the total number of T cells and CD4⁺ T cells in the peripheral blood, omega-3 PUFAs increase the immunological response [33]. A small number of studies on postoperative complications of gastrointestinal surgeries have reported no significant correlation between omega-3 supplementation and decreased infection rates. The type of study,

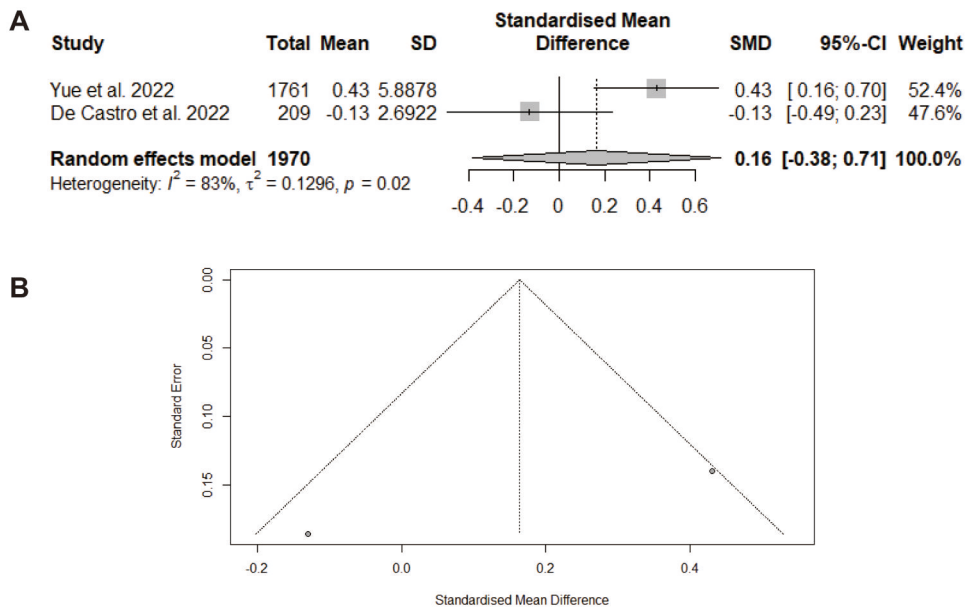


Figure 5. Effect of omega-3 supplementation on serum albumin concentration in patients with GCs. Meta-analysis of randomized-controlled trials evaluated the impact of omega-3 supplementation on serum albumin using SMD with 95% CI. (A) Forest plot showing the pooled SMD for the serum albumin across the included studies. Heterogeneity and prediction interval values are reported to assess consistency across studies. (B) Funnel plot corresponding to (A), used to evaluate potential publication bias. SD = standard deviation, I^2 = I-squared statistic for heterogeneity, τ^2 = tau-squared, between-study variance, P = statistical significance.

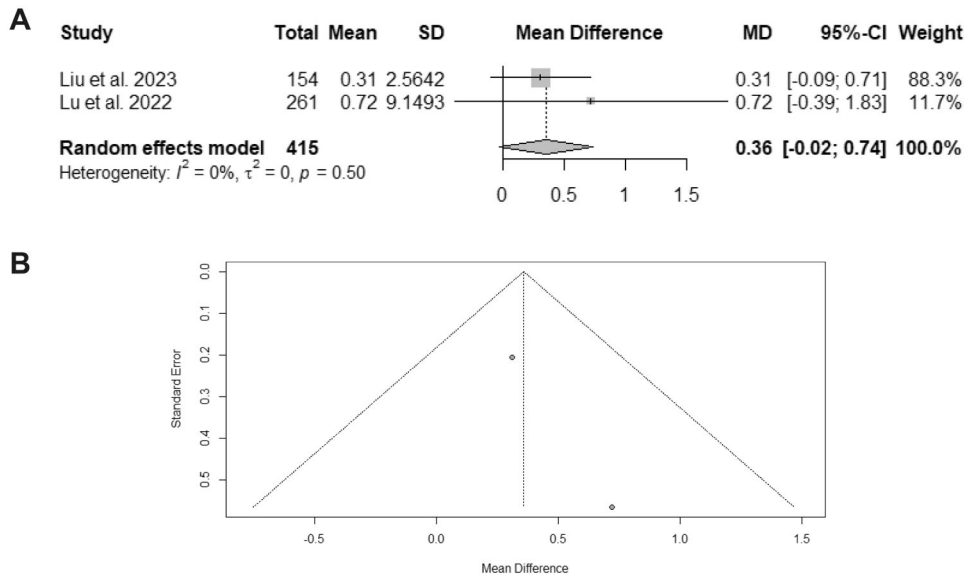


Figure 6. Effect of omega-3 supplementation on serum albumin concentration in patients with GCs. Meta-analysis of randomized-controlled trials evaluated the impact of omega-3 supplementation on serum albumin using MD with 95% CI. (A) Forest plot showing the pooled MD for the serum albumin across the included studies. Heterogeneity and prediction interval values are reported to assess consistency across studies. (B) Funnel plot corresponding to (A), used to evaluate potential publication bias. SD = standard deviation, I^2 = I-squared statistic for heterogeneity, τ^2 = tau-squared, between-study variance, P = statistical significance.

sample size, mode of supplement delivery, and length of supplementation can all significantly affect the outcome [34]. Another significant finding of this study was the association between omega-3 supplement use and reduced hospitalization duration in patients with GCs receiving chemotherapy. Studies by Tsekos et al. [35] in 2004 and Lu et al. [23] in 2022 also obtained similar results. Pre-albumin, albumin, and retinol-binding protein are protein components of total plasma protein and are significant

markers for evaluating patients' nutritional health. Under stressful and critical conditions following surgery, a decrease in plasma proteins is typically observed [36]. In the present study, supplementation with omega-3 support was associated with improvements in albumin levels in patients receiving radiotherapy for GCs. However, a study by Lu et al. [23] in 2022 did not draw such a conclusion. The heterogeneity and small size of that study may be potential biases in the interpretation of the results.

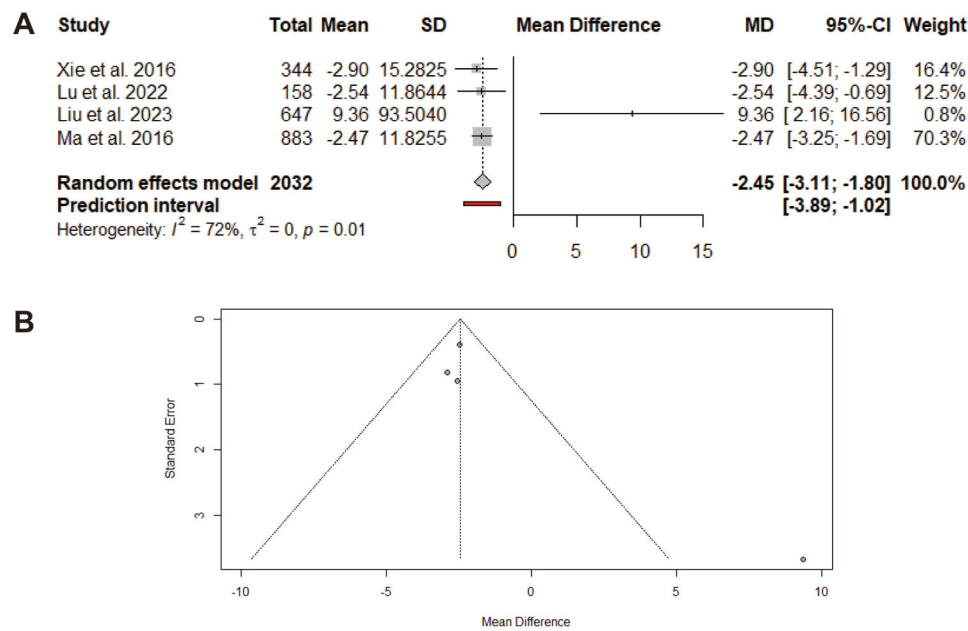


Figure 7. Effect of omega-3 supplementation on length of hospital stay in patients with GCs. Meta-analysis of randomized-controlled trials evaluated the impact of omega-3 supplementation on length of hospital stay using MD with 95% CI. (A) Forest plot showing the pooled MD for the length of hospital stay across the included studies. Heterogeneity and prediction interval values are reported to assess consistency across studies. (B) Funnel plot corresponding to (A), used to evaluate potential publication bias. SD = standard deviation, I^2 = I-squared statistic for heterogeneity, τ^2 = tau-squared, between-study variance, P = statistical significance.

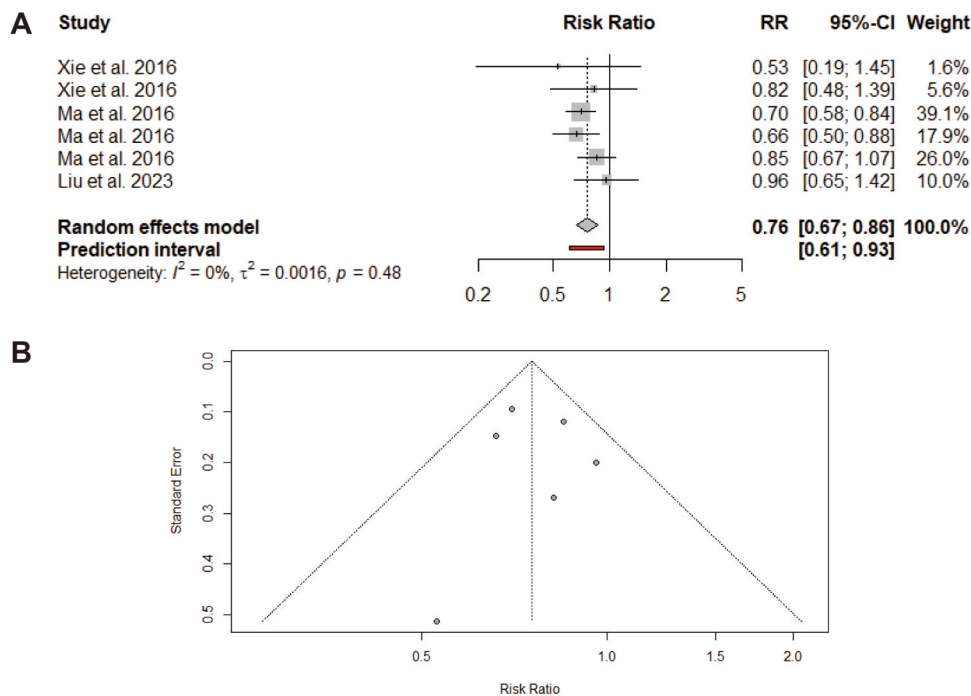


Figure 8. Effect of omega-3 supplementation on total complication risk in patients with GCs. Meta-analysis of randomized-controlled trials evaluated the impact of omega-3 supplementation on total complication risk using RR with 95% CI. (A) Forest plot showing the pooled RR for the total complication risk across the included studies. Heterogeneity and prediction interval values are reported to assess consistency across studies. (B) Funnel plot corresponding to (A), used to evaluate potential publication bias. SD = standard deviation, I^2 = I-squared statistic for heterogeneity, τ^2 = tau-squared, between-study variance, P = statistical significance.

Strengths and limitations

The current umbrella review has several strengths, including the use of comprehensive search strategies with various publications and databases, rigorous quality assessment (risk of bias assessment), and precise statistical analysis. As meta-analyses were pooled in the current studies, they can provide promising and

robust evidence on this issue. Moreover, publication-bias assessment and different subgroup analyses contributed to the reliability of the findings. However, there were several limitations, such as the small number of studies, which could have affected the generalizability of the findings. This umbrella review of meta-analyses faced the following limitations: (i) the low number of

Table 5. Subgroup analysis of the impact of omega-3 supplementation on total complication risk

Subgroup variable	Effect size (N)	RR (95% CI)	I ² (%)	P-heterogeneity
Total complications				
Overall	6	0.76 (0.67, 0.86)	0	0.48
Type				
CC	3	0.87 (0.64, 1.17)	0	0.54
Other GCs	3	0.73 (0.64, 0.84)	13	0.32
Duration (years)				
≥13	3	0.71 (0.59, 0.84)	0	0.73
<13	3	0.80 (0.66, 0.98)	29	0.24
Included studies				
≥8	4	0.76 (0.60, 0.96)	0	0.41
<8	2	0.76 (0.63, 0.92)	38	0.20

N represents the number of included studies in each subgroup analysis.

meta-analyses included in this study affects generalizability to patients struggling with GCs. Also, although funnel plots were presented, the limited number of included studies restricts their interpretability regarding publication bias; (ii) the selected meta-analyses did not separate the various types of omega-3 fatty acids, such as EPA and DHA; (ii) few included studies mentioned the type of omega-3 fatty acids used for patients with GCs; (iv) most of the selected meta-analyses did not designate which omega-3 fatty acids used in their studies are for which stage of cancer treatment, encompassing radiation therapy, chemotherapy, and surgery; and (v) serum proteins, which are used in the present study, are not reliable markers of nutritional status, as inflammation usually affects their levels.

Conclusions

The current umbrella review highlights the potential benefits of omega-3 supplementation for individuals with different GCs. Our findings indicated that omega-3 supplementation is associated with improvements in inflammatory markers (TNF- α , IL-6, and CRP) and immune function (increased CD4⁺/CD8⁺ ratio), a reduced hospital length of stay, and a decreased risk of complications.

While these findings are promising, more longitudinal studies are warranted to identify the optimal dosage and proper duration of omega-3 supplementation in GC patients. Moreover, more comprehensive, long-term trials are necessary to validate the accurate benefits and potential associated risks. Overall, omega-3 supplementation can enhance the QOL of individuals with GCs, provided that future studies validate our conclusions.

Data availability

The datasets used and/or examined in the present investigation may be obtained from the corresponding author upon reasonable request.

Authors' contributions

H.A. was responsible for the study's design, collection and analysis of data, data curation, and drafting of the manuscript. M.K., A.E., M.H.N., Z.R., A.P., F.T., M.A., M.G.H., and S.D. were responsible for the study's design. Z.M., F.B., B.A., A.S.H.K., and S.D. contributed to the study's design and provided a critical review of the manuscript. The final manuscript was reviewed and approved by all the authors.

Funding

This study was derived from a project approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ethics code: IR.SBMU.CRC.REC.1403.020). Shahid Beheshti University of Medical Sciences, Tehran, Iran, provided financial support for the investigation [Code 43011537].

Acknowledgements

We thank the participants and our colleagues at Shahid Beheshti Medical Science University for their cooperation.

Conflicts of interest

The authors affirm that they do not possess any conflicting interests.

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