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Meta-analysis

The efficacy of omega-3 fatty acids (O3FAs) as a complementary in colorectal cancer patients: A systematic review and meta-analysis

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SUMMARY

Background & aims: Colorectal cancer (CRC) is the third most common malignancy in developed countries. Therefore, omega-3 fatty acids (O3FAs) have been suggested as a beneficial complementary treatment due to their ability to regulate inflammatory responses and improve nutrition levels.This study aimed to evaluate the effects of O3FAs as a complementary treatment for inflammation, nutrition levels, post-operative infectious complications, and enhancement of recovery in CRC patients.

Methods: The literature search was carried out through three databases. The outcomes of interest were assessed by measuring pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and CRP levels, serum albumin levels for nutrition assessment, post-operative infectious complications, and length of stay for recovery evaluation. Quality appraisal and meta-analysis were performed using RoB 2.0 and RevMan 5.4, respectively.

Results: The result showed that O3FAs significantly reduced IL-6, CRP, and TNF-α, but did not affect IL-1β. Furthermore, the variable slightly increased serum albumin levels and the supplementation led to a decrease in post-operative infectious complications and shortened hospital stays.

Conclusion: O3FAs as a complementary treatment provided advantages for CRC patients, Further clinical trials and experiments should also be made emphasizing the impact and clinical implementation of O3FA in the nutritional status of CRC patients.

1. Introduction

Colorectal cancer (CRC) was responsible for an estimated 1.9 million incidence cases and 0.9 million deaths worldwide in 2020 as the third and second most common malignancy and deadly cancer [1]. For many years, the incidence has been higher in highly developed countries with a rising incidence of early-onset CRC [2]. However, recent reports showed an increasing incidence of CRC in middle- and low-income countries due to the Westernization of lifestyles [3]. There has been a rising trend for this disease across Asia with some regional geographic variations. In 2018, Asia contributed to the highest CRC disease burden with the highest proportions of both incident (51.8%) and mortality (52.4%) CRC cases per 100,000 population in the world [4].

The most typical treatments for CRC are surgical removal and chemotherapy, depending on the stage of the cancer [5–7]. However, colorectal cancer surgery is associated with a great number of complications, specifically post-operative infections, affecting the efficacy of the surgery, health, and survival of the patient [8,9]. Therefore, the prevention and treatment of severe postoperative infections of the abdominal and pelvic cavity in CRC patients have always been important issues.

Omega-3 polyunsaturated fatty acids (O3FAs) have become an essential part of immune nutrition for patients due to their anti-inflammatory properties, which improve body immunity [10–12]. Even though there is no significant association between O3FAs supplements and cancer-incidence reduction has been found, the positive roles on host immune function seem promising in the pre- or post-operative management of cancer patients [13–16]. Previous meta-analyses including all kinds of surgical patients indicated that O3FAs improved clinical outcomes, such as reduced infection incidence and hospital stay [17].

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Many studies have shown that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) exhibit anti-inflammatory and anti-CRC effects [10,17–20]. Therefore, O3FAs may have a potential role in multiple stages of CRC management, starting with the primary CRC prevention and continuing through the complementary prevention stage following the treatments until the advanced metastatic diseases. The results of several recent studies on the nutritional status, inflammation, and recovery after CRC chemotherapy are controversial. A study by Ma et al. (2016) found that O3FAs lowered C-reactive protein (CRP) levels and shortened the duration of systemic inflammatory response syndrome [21]. Furthermore, the co-supplementation of O3FA plus Vitamin D3 has beneficial impacts on inflammation and nutritional status markers in patients subjected to chemotherapy [22]. Results of a meta-analysis of the O3FA effects on inflammatory markers also suggested the benefits of n-3 PUFA supplementation on some inflammatory mediators. These benefits are specific to certain supplementation protocols involving duration, dose, and route of administration, as well as the concomitant anti-cancer treatment adopted [23]. An earlier meta-analysis of all surgical patients showed that O3FAs improved clinical outcomes, including infection rates and hospital stays [10]. According to Lam, O3FAs had no substantial effect on the nutritional improvement or inflammatory regulation of cancerous patients [24]. Even though O3FAs were safe and effective in lowering TNF-α and IL-6 levels as well as shortening the length of stay, patients failed to show improvements in CRP, IL- 1β, albumin, BMI, weight, infectious and non-infectious complication rates, or life quality [25]. The initial findings of studies exploring the effectiveness of omega-3 PUFA-enriched nutrition for CRC patients suggested that the immunological benefits of omega-3 PUFAs assisted in preventing post-operative infectious complications. However, the application of these findings to specific CRC patients in clinical practice was complex due to the diverse factors influenced by various diseases and surgical procedures [13,21,26–30].

Given the lack of complete consistency in both results and conclusions, attributed to constraints such as a limited sample size, divergent study designs, and potential biases, a comprehensive meta-analysis was undertaken. This analysis encompassed all pertinent randomized controlled trials (RCTs) and centered on assessing the impacts of O3FAs as a supplementary treatment. The focus was on areas such as inflammation, nutritional levels, post-operative infectious complications, and the facilitation of recovery in patients diagnosed with CRC.

Most EPA and DHA for human consumption are derived from small fatty fish, specifically Atlantic salmon (*Salmo salar*), caught in coastal waters. In depleting global salmon fish stocks, the EPA and DHA for human consumption have become very expensive. Consequently, efforts have been made to obtain local fish substitutes for salmon as a source of O3FAs, since Indonesia has been the second world producer of milkfish (*Chanos chanos*) after the Philippines and the second producer of Pangasius catfish (*Pangasius pangasius*) after Vietnam [31]. These species of fish contain considerable amounts of EPA and DHA used as a source of O3FAs instead of salmon widely available in Indonesia [32]. However, the nutritional and biochemical composition of fish varies widely and within the same species due to feeding habits, sex, and seasonal variations. Chakma et al. (2022) found that the percentage in the wild pangasius was significantly higher than the farmed pangasius. Therefore, it is imperative to comprehend the composition of a particular fish to ensure human nutritional requirements [33].

2. Methods

This meta-analysis was made based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. The literature search was carried out with keywords using boolean operators, namely: ("omega-3" OR "ω-3" OR "O3FAs") AND ("colorectal cancer" OR "CRC") AND ("efficacy" OR "safety" OR "complications" OR "recovery"). The literature search flow was structured like the flowchart in Fig. 1 (see Fig. 2).

2.1. Study eligibility criteria

Inclusion and exclusion criteria were determined before the literature search to make the results specific and homogenous. The inclusion criteria were 1) data available or accessible in English language form, 2) randomized-controlled trial (RCT), 3) studies that involve priorly diagnosed colorectal cancer patients, 4) studies using O3FAs through all routes of administration as the intervention of interest, and 5) studies including at least one parameter analyzed namely: IL-1β, IL-6, TNF-α, CRP, albumin, rate of infectious complications, or length of stay. The exclusion criteria were 1) non-human RCT studies and 2) journals not accessible online. The inclusion criteria of this meta-analysis refer to the PICO framework in Table 1.

2.2. Outcome of interest

The effect of O3FAs on inflammation evaluated through the measurements of the pro-inflammatory cytokines, includes the serum levels of IL-1β, IL-6, and TNF-α, and CRP as an acute-phase reactant protein generated by the stimulation of IL-6 on the gene responsible for CRP transcription during the acute phase of an inflammatory condition [34]. Albumin measurements indicated the effect of O3FAs on nutrition levels as the most abundant circulating protein found in plasma [35]. Therefore, the rapid decline of plasma levels of albumin indicates malnutrition in patients [36]. Infection is the most prominent complication of post-operative colorectal surgery, where infection occurs four times more than in any other abdominal surgery, contributing to morbidity and mortality [9]. Recovery is evaluated by the length of stay, which is influenced by a complex array of internal and external effects [26].

2.3. Data extraction and analysis

Literature search and data extraction were carried out independently from June 29th, 2023 to July 2nd, 2023 on three

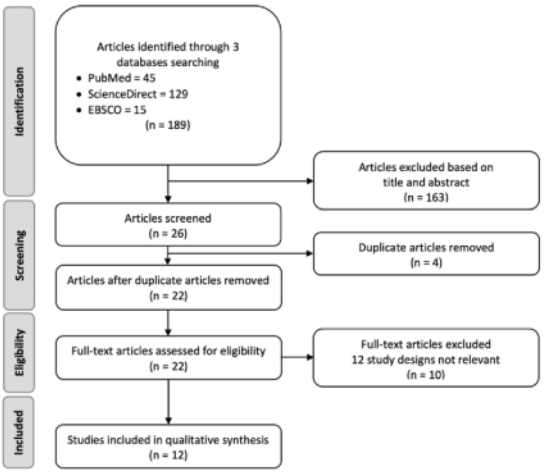


Fig. 1. PRISMA flowchart for literature search.

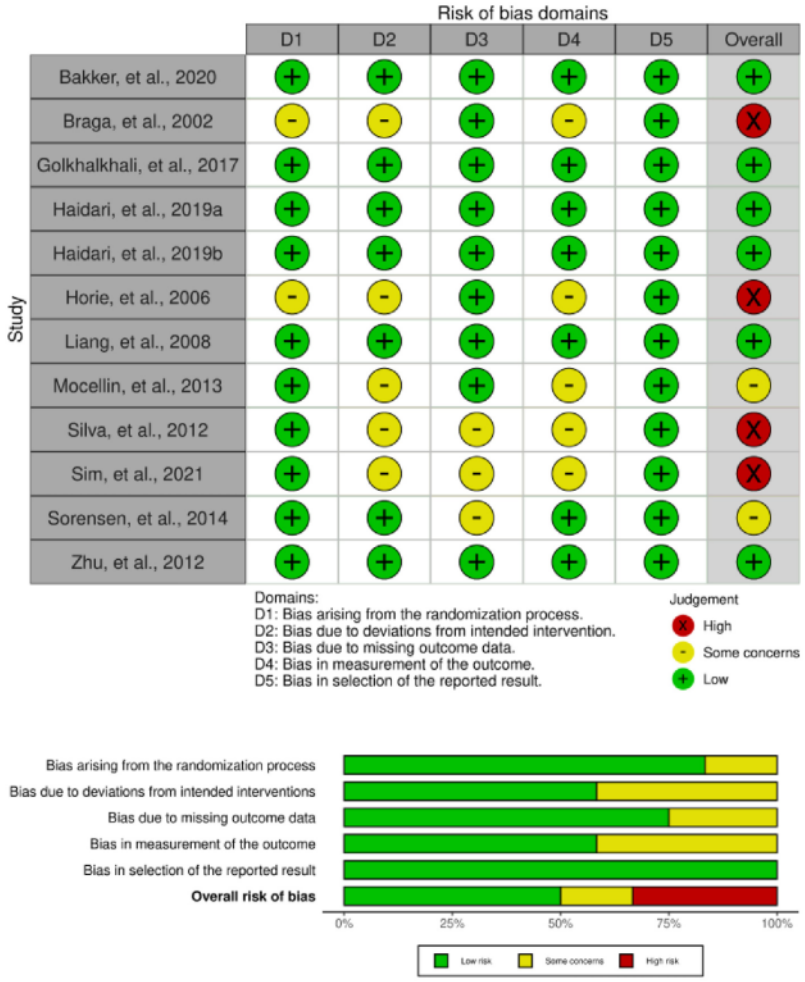


Fig. 2. Risk of Bias summary using the Cochrane Risk of Bias 2.0 tool for randomized-controlled trial studies.

Table 1
PICO framework.

Patient	Patients priorly diagnosed with colorectal cancer
Intervention	Omega 3 fatty acids administration through all routes
Control	Placebo using vitamin D, soybean oil, regular diet, normal saline infusion, or oral nutrition supplementation (ONS)
Outcome	Pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), CRP, albumin, rate of infectious complications, and length of stay

databases, namely PubMed, ScienceDirect, and EBSCO. The selected studies were extracted into a Google Sheet, which was then assessed for their eligibility and accuracy.

2.4. Risk of bias assessment (Qualitative synthesis)

The Revised Tool for Risk of Bias in Randomized Trials (RoB 2.0) was used to assess the potential for bias in the final studies included in the analysis. The Cochrane Collaboration's algorithm was used to assess the likelihood of bias and the findings were filled into the domain file bias on the spreadsheet. To provide the appropriate visualization of the results, the spreadsheet was uploaded to the ROBVIS website.

2.5. Quantitative data synthesis (Meta-analysis)

Meta-analysis was performed using Review Manager ver. 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen) and the data obtained were evaluated for IL-1β, IL-6, and TNF-α, CRP, albumin, and length of stay. Meanwhile, post-operative infectious complications were examined as dichotomous data with a 95% confidence interval (CI). Mean differences and odds ratios with a 95% confidence interval (CI) were extracted from studies for pre-post intervention and intervention versus control. The inverse variance model served as the statistical method, while the random and fixed effect models were used during analysis based on the heterogeneity of each outcome. The cutpoint for heterogeneity was I^2 >50%, indicating the use of the random effect model for statistical analysis.

3. Results

3.1. Study selection and identification

In the literature search, 189 studies published were obtained according to the inclusion and exclusion criteria from three databases. After screening for duplicates and abstracts, 22 articles were thoroughly assessed, and 12 studies were included in the quantitative synthesis.

3.2. Summaries of the included studies

The characteristics of each study were examined and listed in Table 2.

3.3. Risk of bias assessment

The quality of each study was assessed with the Cochrane Risk of Bias 2.0 tool for randomized-controlled trial studies. A total of six studies were conducted by Bakker et al., 2020; Golkhalkhali et al., 2017; Haidari et al., 2019a; Haidari et al., 2019b; Liang et al., 2008; and Zhu et al., 2012 on low risk of bias in the overall domain [22,26,27,37–39]. Studies from Braga et al., 2002 and Horie et al., 2006 did not provide a blinding process and a poor explanation of randomization. Therefore, these studies were classified as 'some concerns' of bias in D1, D3, and D4, hence being classified as having a high risk of bias in the overall domain [13,40]. A study by Mocellin et al., 2013 did not provide a clear blinding process and was classified as having 'some concerns' risk of bias [41]. Silva et al., 2012 and Sim et al., 2021 did not provide a clear blinding process and the missing outcome data was sufficient to impact the result [42,43]. A study by Sorensen et al., 2014 had 19 missing outcome data without including evidence that the result was not biased by missing outcome data, classified as having 'some concerns' risk of bias [28].

3.4. The efficacy of O3FAs on pro-inflammatory cytokines

3.4.1. The efficacy of O3FAs on IL-1β

A total of three eligible studies [39,41,42], which included 74 patients were analyzed to investigate IL-1β mean change level following O3FA supplementation for the experimental and control groups (Fig. 3). The heterogeneity test was $p = 0.05$ and $I^2 = 67\%$, and the meta-analysis showed that the IL-1β level was not affected by the supplementation of O3FAs (MD = −0.06, 95% CI: −0.20 to 0.07, $p = 0.36$).

3.4.2. The efficacy of O3FAs on IL-6

Approximately six eligible studies [22,26,27,38,42,43], which included 341 patients were conducted to investigate the IL-6 mean change level following O3FA supplementation for the experimental and control groups (Fig. 4). Furthermore, the results of the heterogeneity test were $p = 0.01$ and $I^2 = 66\%$. The meta-analysis showed that the IL-6 level was markedly lowered by the supplementation of O3FAs compared to the control (MD = −4.86, 95% CI: −7.75 to −1.98, $p = 0.009$).

3.4.3. The efficacy of O3FAs on TNF-α

A total of seven eligible studies [22,26,27,38,41–43], which included 352 patients was carried out to investigate TNF-α mean change level following O3FA supplementation for the experimental and control groups (Fig. 5). The meta-analysis reported that the TNF-α level was not affected by the supplementation of O3FAs compared to the control (MD = −0.00, 95% CI: −0.90 to 0.90, $p = 1.00$). However, there was considerable heterogeneity across the included trials ($p < 0.00001$ and $I^2 = 94\%$).

In the sensitivity analysis, three studies [27,41,43] were classified as outlier studies and not included in the meta-analysis. As a result of the remaining studies in 244 patients, the heterogeneity test was $p = 0.25$ and $I^2 = 27\%$. The meta-analysis showed that the TNF-α level was minimally lowered by the supplementation of O3FAs (MD = −0.55, 95% CI: −1.11 to 0.02, $p = 0.06$).

3.5. The efficacy of O3FAs on CRP

Approximately five eligible studies [22,38,41–43], which included 254 patients were performed to investigate the CRP mean change level following O3FA supplementation for the experimental and control groups (Fig. 6). The heterogeneity test was $p = 0.003$ and $I^2 = 75\%$, and the meta-analysis showed that the CRP level was lowered by the supplementation of O3FAs compared to the control (MD = −1.09, 95% CI: −3.03 to 0.85, $p = 0.27$).

Golkhalkhali et al., 2017 was classified as an outlier and was not included in the meta-analysis [38]. Due to the remaining studies in 114 patients, the heterogeneity test was $p = 0.09$ and $I^2 = 54\%$. The meta-analysis showed that the CRP level was lowered by the supplementation of O3FAs (MD = −1.87, 95% CI: −3.12 to −0.63, $p = 0.003$).

3.6. The efficacy of O3FAs on serum albumin level

Approximately four eligible studies [22,41,43], were analyzed which included 114 patients to investigate the serum albumin mean change level following O3FA supplementation for the experimental and control groups (Fig. 7). The meta-analysis showed that the serum albumin level was slightly increased compared to the control group (MD = 0.31, 95% CI: −0.12 to 0.74, $p = 0.16$). However, there was considerable heterogeneity across the included trials ($p < 0.00001$ and $I^2 = 97\%$).

Haidari et al., 2019a was classified as an outlier study and was not included in the meta-analysis [22]. As a result of the remaining studies in 74 patients, the heterogeneity test was $p = 0.05$ and $I^2 = 66\%$. The meta-analysis showed that the serum albumin level was slightly increased by the supplementation of O3FAs (MD = 0.13, 95% CI: −0.06 to 0.33, $p = 0.18$).

3.7. The efficacy of O3FAs on post-operative infectious complications

A total of six eligible studies [13,26–28,37,40], which included 454 patients were analyzed and the total event of postoperative infectious complications following O3FA supplementation was investigated for the experimental and control groups (Fig. 8). The results of the heterogeneity test were $p = 0.01$ and $I^2 = 66\%$. The meta-analysis showed that the total event of postoperative infectious complications was less frequent by the supplementation of O3FAs compared to the control group (OR = 0.68, 95% CI: 0.25 to 1.85, $p = 0.45$).

3.8. The efficacy of O3FAs on length of stay

Approximately four eligible studies [26,27,37,40], which included 239 patients were analyzed and the mean change in length of stay duration was investigated for the experimental and control groups (Fig. 9). The meta-analysis showed that the length of stay was slightly shortened by the supplementation of O3FAs compared to the control (MD = −1.42, 95% CI: −3.61 to 0.77, $p = 0.20$). However, there was considerable heterogeneity across the included trials ($p = 0.0007$ and $I^2 = 83\%$).

Bakker et al., 2020 was classified as an outlier study and was not included in the meta-analysis [37]. As a result of the remaining

Table 2
Baseline characteristics, type of intervention, and outcomes reported in each included studies.

No.	Author, Year	Study Design	Age, mean (SD)	Sample size (n)	Intervention	Control	Center	Country	Duration	Group	IL-6 (pg/ml)	TNF-α (pg/ml)	CRP (pg/ml)	IL-1β (pg/ml)	Albumin (g/L)	Rate of Infectious Complication	Length of Stay
1	Bakker, et al., 2020	Randomized-Controlled Trials (RCT)	67 (63-75)	Intervention: 18 Control: 23	n-3 PUFAs 2 ml/kg (0.2 g fish oil-kg-1 . D-1) infusion	NaCL 2ml/kg infusion	Single	Netherlands	21 months	Intervention	NI	NI	NI	NI	NI	8	4.4 ± 1.7
										Control	NI	NI	NI	NI	NI	3	3.5 ± 1.4
2	Mocellin, et al., 2013	Randomized-Controlled Trials (RCT)	54.5	Intervention: 6 Control: 5	2 g/day of fish oil	NI	Single	Brazil	8 months	Intervention	NI	Baseline: 2.49 ± 00.01 Post-intervention: 2.48 ± 0.01 Change: NI	Baseline: 3.39 Post-intervention: 1.46 Change: -8.8 ± 13.5	Baseline: 1.57 ± 0.01 Post-intervention: 1.57 ± 0.01 Change : NI	Baseline: 4.23 ± 0.25 Post-intervention: 4.27 ± 0.24 Change: NI	NI	NI
										Control	NI	Baseline: 2.49 ± 00.00 Post-intervention: 2.48 ± 0.01 Change: NI	Baseline: 4.85 Post-intervention: 18.14 Change: 27.4 ± 30.2	Baseline: 1.56 ± 0.00 Post-intervention: 1.57 ± 0.01 Change : NI	Baseline: 4.34 ± 0.29 Post-intervention: 4.02 ± 0.24 Change: -0.32 ± 0.26	NI	NI
3	Haidari et al., 2019a	Randomized-Controlled Trials (RCT)	Control: 59.90 ± 8.75 Omega-3 : 56.75 ± 10.60 Vitamin D: 56.90 ± 12.45 Vitamin D-Omega 3 Cosupplementation: 57.15 ± 10.17	Control: 20 Omega-3: 20 Vitamin D: 21 Vitamin D-Omega 3 Cosupplementation: 20	1. 2 omega-3 fatty acid capsules (each capsule containing 330 mg of omega-3 fatty acids) daily vitamin D placebo weekly 2. 50.000 iu vitamin D soft gel weekly b 2omega-3 fatty acid placebo capsule capsules daily 3. Supplementation group (n 1/4 20): receiving a 50.000 IU vitamin D soft gel weekly b 2 omega-3 fatty acids capsules (each capsule containing 330mg of omega-3 fatty acids) daily for 8 weeks	Placebo	Single	Iran	NI	Intervention 1	Baseline: 32.0 ± 34.0 Post-intervention: 29.9 ± 33.1 Change: -2.0 ± 2.7	Baseline: 5.9 ± 1.3 Post-intervention: 5.3 ± 1.4 Change: -0.6 ± 0.6	Baseline: 7.7 ± 6.8 Post-intervention: 6.5 ± 7.1 Change: -1.2 ± 2.1	NI	Baseline: 4.4 ± 0.4 Post-intervention: 4.4 ± 0.4 Change: 0.0 ± 0.1	NI	NI
										Intervention 2	Baseline: 38.8 ± 32.9 Post-intervention: 33.5 ± 28.8 Change: -5.2 ± 5.3	Baseline: 5.9 ± 2.6 Post-intervention: 4.9 ± 2.3 Change: -1.0 ± 0.7	Baseline: 18.6 ± 8.6 Post-intervention: 14.3 ± 8.0 Change: -4.2 ± 3.7	NI	Baseline: 3.7 ± 0.8 Post-intervention: 3.5 ± 0.8 Change: -0.1 ± 0.2	NI	NI
										Intervention 3	Baseline: 39.0 ± 44.0 Post-intervention: 34.5 ± 40.7 Change: -4.4 ± 4.4	Baseline: 6.1 ± 2.3 Post-intervention: 4.8 ± 2.1 Change: -1.2 ± 0.9	Baseline: 8.2 ± 4.5 Post-intervention: 5.4 ± 4.7 Change: -2.7 ± 3.5	NI	Baseline: 4.2 ± 0.4 Post-intervention: 4.2 ± 0.4 Change: 0.0 ± 0.1	NI	NI
										Control	Baseline: 41.9 ± 51.4 Post-intervention: 4.16 ± 51.2 Change: -0.3 ± 2.6	Baseline: 6.6 ± 2.8 Post-intervention: 6.7 ± 2.8 Change: 0.0 ± 0.6	Baseline: 14.0 ± 9.6 Post-intervention: 14.9 ± 9.7 Change: 0.9 ± 2.5	NI	Baseline: 4.1 ± 0.8 Post-intervention: 3.2 ± 1.0 Change: -0.8 ± 0.3	NI	NI
4	Sorensen et al, 2014	Randomized-Controlled Trials (RCT)	70	Intervention: 74 Control: 74	148 (54.1% male, 55.9% female), 74 control, 74 intervention	Control ONS	Single	Denmark	31 months	Intervention	NI	NI	NI	NI	NI	28	NI
										Control	NI	NI	NI	NI	NI	27	NI
5	Haidari et al., 2019b	Randomized-Controlled Trials (RCT)	Control: 59.90 ± 8.75 Omega-3 : 56.75 ± 10.60 Vitamin D: 56.90 ± 12.45 Vitamin D-Omega 3 Cosupplementation: 57.15 ± 10.17	Control: 20 Omega-3: 20 Vitamin D: 21 Vitamin D-Omega 3 Cosupplementation: 20	1. 2 omega-3 fatty acid capsules (each capsule containing 330 mg of omega-3 fatty acids) daily vitamin D placebo weekly 2. 50.000 iu vitamin D soft gel weekly b 2omega-3 fatty acid placebo capsule capsules daily 3. Supplementation group (n 1/4 20): receiving a 50.000 IU vitamin D soft gel weekly b 2 omega-3 fatty acids capsules (each capsule containing 330mg of omega-3 fatty acids) daily for 8 weeks	Placebo	Single	Iran	NI	Intervention 1	NI	NI	NI	Baseline: 2.42 ± 0.77 Post-intervention: 2.23 ± 0.76 Change : -0.18 ± 0.22	NI	NI	NI
										Intervention 2	NI	NI	NI	Baseline: 2.34 ± 0.65 Post-intervention: 2.26 ± 0.66 Change : -0.07 ± 0.11	NI	NI	NI
										Intervention 3	NI	NI	NI	Baseline: 2.31 ± 0.73 Post-intervention: 2.15 ± 0.69	NI	NI	NI
										Control	NI	NI	NI	Baseline: 2.53 ± 0.81 Post-intervention: 2.49 ± 0.80 Change: -0.03 ± 0.18	NI	NI	NI

6	Sim et al., 2021	Randomized-Controlled Trials (RCT)	Intervention: 63.64 ± 1.79 Control: 65.39 ± 2.44	Intervention: 22 Control: 18	Regular nutrition counseling and education, while only experimental group was asked to take ONS twice a day (400 ml, 400 kcal). ONS enriched with omega-3 fatty acids (70 mg/200 ml) and arginine (250mg/200ml)	Regular nutrition counseling and education	NI	Korea	8 months	Intervention	Intervention	Baseline: 6.53 ± 0.98 Week 4: 13.09 ± 4.68 Week 8: 9.26 ± 2.42	Baseline: 16.64 ± 1.63 Week 4: 23.79 ± 6.69 Week 8: 21.67 ± 2.84	Baseline: 10.05 ± 2.46 Week 4: 25.19 ± 15.28 Week 8: 14.99 ± 5.21		Baseline: 3.64 ± 0.11 Week 4: 3.76 ± 0.08 Week 8: 3.65 ± 0.11	NI	NI
										Control	Control	Baseline: 7.14 ± 1.99 Week 4: 10.41 ± 4.21 Week 8: 16.11 ± 6.60	Baseline: 18.70 ± 3.15 Week 4: 18.26 ± 2.95 Week 8: 20.29 ± 2.99	Baseline: 12.59 ± 3.91 Week 4: 11.79 ± 4.42 Week 8: 18.02 ± 8.71		Baseline: 3.91 ± 0.16 Week 4: 3.76 ± 0.16 Week 8: 3.86 ± 0.12	NI	NI
7	Braga, et al., 2002	Randomized-Controlled Trials (RCT)	62	Intervention: 50 Control: 50	1 L/day of a liquid diet supplemented with arginine (12.5 g/L) and n-3 fatty acids (3.3 g/L) for 5 days before surgery	1 L/day of an isonitrogenous, isoenergetic specially formulated liquid diet for 5 days before surgery 14	NI	Italy	NI	Intervention	Intervention	NI	NI	NI	NI	Baseline: 42.2 ± 4.8 Post-intervention: Change:	5	9.8 ± 3.1
										Control	Control	NI	NI	NI	NI	Baseline: 41.5 ± 4.1 Post-intervention: Change:	16	120 ± 4.5
8	*Silva et al.*, 2012	Randomized-Controlled Trials (RCT)	Intervention: 50.1 (8.2) Control: 54.3 (9.3)	Intervention: 11 Control: 12	4 capsules of fish oil supplement per day, totaling 660 mg of EPA, DHA, for 9 wk	Regular diet	Single	Korea	8 months	Intervention	Intervention	Post-intervention: 81.2 (68.5-96.4) Change: 1.3 (61.72)	Post-intervention: 61.1 (56.0-68.4) Change: 2.2 (17.05)	Baseline: 5.1 (4.1-12.3) Post-intervention: 3.4 (1.6-4.0) Change: -1.4 (9.13)	Post-intervention: 3.6 (1.2-4.2) Change: 2.3 (8.0)	Baseline: 4.2 (0.4) Post-intervention: 4.2 (0.4) Change: 0.1 (0.5)	NI	NI
										Control	Control	Post-intervention: 69.7 (61.9-144.3) Change: -1.9 (111.48)	Post-intervention: 69.7 (52.8-71.7) Change: 10.5 (23.36)	Baseline6.4 (1.or 23.7) Post-intervention: 13.0 (2.6-32.7) Change: 1.0 (2-56)	Post-intervention: 1.3 (1.0-1.2) Change: -1.2 (7.0)	Baseline: 4.2 (0.4) Post-intervention: 4.2 (0.4) Change: 0.1 (0.2)	NI	NI
9	Zhu et al., 2012	Randomized-Controlled Trials (RCT)	Intervention: 69.8 ± 10.5 Control: 70.48 ± 6.4	Intervention: 29 Control: 28	0.2 g/kg fish oil + 1.0 g/kg soy bean oil	1.2 g/kg soybean oil	Multi	China	21 months	Intervention	Intervention	Baseline: 13.9 ± 17.7 Day 1: 17.8 ± 12.3 Day 8: 18.26 ± 7.6	Baseline: 2.8 ± 3.3 Day 1: 4.6 ± 2.9 Day 8: 5.7 ± 2.8	NI	NI	NI	4	12 ± 4
										Control	Control	Baseline: 14.7 ± 16.8 Day 1: 18.7 ± 13.5 Day 8: 23.7 ± 8.2	Baseline: 2.7 ± 3.2 Day 1: 4.7 ± 2.7 Day 8: 7.8 ± 3.2	NI	NI	NI	8	15 ± 6
10	Liang, et al., 2008	Randomized-Controlled Trials (RCT)	Intervention: 55.89 ± 10.10 Control: 59.19 ± 10.61	Intervention: 20 Control: 21	Soybean oil + fish oil (SO + FO)	Soybean oil (SO)	Single	China	17 months	Intervention	Intervention	D-1: 9.02 ± 23.25 D+1: 59.66 ± 34.11 D+8: 34.21 ± 44.12 Change 1 (margin D-1 > D+1): 50.64 ± 32.21 Change 2 (margin D+1 > D+8): -44.43 ± 30.53	D-1: 2.7 ± 3.2 D+1: 3.31 ± 2.83 D+8: 2.49 ± 2.06 Change 1 (margin D-1 > D+1): 0.57 ± 3.46 Change 2 (margin D+1 > D+8): -0.82 ± 2.71	NI	NI	NI	1	17.45 ± 4.80
										Control	Control	D-1: 10.42 ± 10.75 D+1: 42.60 ± 50.12 D+8: 34.21 ± 44.12 Change 1 (margin D-1 > D+1): 32.18 ± 47.69 Change 2 (margin D+1 > D+8): -8.39 ± 69.08	D-1: 2.48 ± 3.73 D+1: 2.66 ± 2.76 D+8: 2.94 ± 3.12 Change 1 (margin D-1 > D+1): 0.18 ± 4.50 Change 2 (margin D+1 > D+8): 0.27 ± 1.67	NI	NI	NI	1	19.62 ± 5.59
11	Horie, et al., 2006	Randomized-Controlled Trials (RCT)	Intervention: 69 ± 9 Control: 63 ± 11	Intervention: 33 Control: 34	Japanese version contains 9.6g arginine, 2.49 g w-3 fatty acids	Placebo	Single	Japan	12 months	Intervention	Intervention	NI	NI	NI	NI	NI	0	NI
										Control	Control	NI	NI	NI	NI	NI	5	NI

(continued on next page)

Table 2 (*continued*)

12	Golkhalkhali et al., 2017	Randomized-Controlled Trials (RCT)	Intervention: <=56=20 (30.8) 57-66=22 (33.8 >=67=19 (35.4) Control: <=56=20 (342.4) 57-66=22 (28.8) >=67=19 (28.8)	Intervention: 70 Control: 70	Oxaliplatin 130 mg/m2 aza 120-min intravenous infusion on day 1 and oral capecitabine 1000 mg/m2 on days 1-14 every 3 weeks	Placebo	Single	Malaysia	6 months	Intervention	Baseline: 5.70 (15.27) Post-intervention: 3.50 (11.20) Post-chemotherapy: 4.50 (20.82)	Baseline: 2.40 (7.71) Post-intervention: 3.43 (6.81) Post-chemotherapy: 2.25 (0.83-4.80)	Baseline: 0.34 (1.79) Post-intervention: 0.45 (1.41) Post-chemotherapy: 0.40 (0.22-0.99)	NI	NI	NI	NI	NI	NI
										Control	Baseline: 3.88 (14.95) Post-intervention: 3.75 (4.34) Post-chemotherapy: 3.40	Baseline: 3.29 (11.85) Post-intervention: 3.39 (17.32) Post-chemotherapy: 4.13 (1.13-11.13)	Baseline: 0.28 (1.52) Post-intervention: 0.24 (0.88) Post-chemotherapy: 0.30 (0.88)						

studies in 198 patients, the heterogeneity test was $p = 0.87$ and $I^2 = 0\%$. The meta-analysis showed that the length of stay was remarkably shorter with the supplementation of O3FAs (MD = −2.36, 95% CI: −3.58 to −1.15, $p = 0.0001$).

4. Discussion

This meta-analysis of 12 RCTs assessed the effect of O3FAs as a complementary treatment for inflammation, nutrition level, post-operative infectious complications, and hospital length of stay in CRC patients.

4.1. The efficacy of O3FAs on inflammatory markers

The production of inflammatory cytokines indicates the rate of inflammation and its complication, systemic inflammatory response syndrome (SIRS). Examining the inflammatory response in patients with CRC is crucial due to the potential consequences of unregulated SIRS, such as organ dysfunction, unfavorable outcomes, and extended hospital stays for CRC patients [21]. The anti-inflammatory effects of O3FAs were attributed to their ability to decrease the duration of SIRS. This was achieved by competing with arachidonic acid for binding sites on cyclooxygenase and 5-lipoxygenase, reducing the production of pro-inflammatory eicosanoids derived from arachidonic acid [44]. The result reported that O3FAs significantly reduced the inflammatory markers in CRC patients, namely the IL-6, CRP, and TNF-α. However, IL-1β was not affected by the supplementation of O3Fas, which was effective in reducing the production of inflammatory mediators at the site of tissue injury [25,41,45].

4.2. The efficacy of O3FAs on the efficacy of O3FAs on nutrition levels through serum albumin levels

CRC patients are frequently malnourished as a response to depressed immune function and alterations in the inflammatory response [20]. The measurement of serum albumin is important to review the nutrition levels in response to the O3FAs supplementation [35]. The findings indicate that O3FAs resulted in a slight elevation of serum albumin levels. Therefore, the supplementation slightly increased the nutrition levels of CRC patients. Increased serum albumin levels also indicate better response in inflammatory management by increasing the negative acute-phase proteins [17]. However, this finding is contrary to Liu et al., 2023, where O3FAs did not increase the serum albumin levels [25].

4.3. The efficacy of O3FAs on post-operative infectious complications

Examining the impact of supplementing O3FAs on the incidence of infection, which is the most common complication following colorectal surgery is important [9]. This study showed that the number of patients experiencing post-operative infectious complications was less frequent after O3FAs supplementation. The finding is consistent with multiple studies that reported the effectiveness of O3FAs in reducing the incidence of post-operative infectious complications [17,21,46]. However, Liu et al., 2023 found that the supplementation was not effective in reducing the incidence of postoperative infectious complications [25].

4.4. The efficacy of O3FAs on length of hospital stay

Assessing the length of hospital stay provides insights into the efficacy of O3FAs supplementation on the recovery of CRC

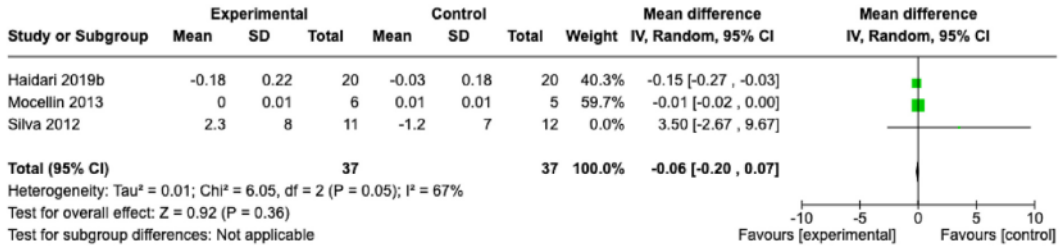


Fig. 3. Forest plot of O3FAs supplementation versus control for IL-1β mean change level.

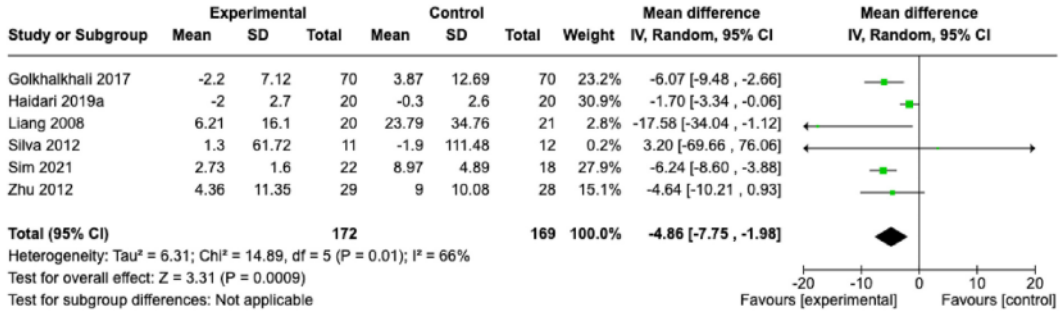
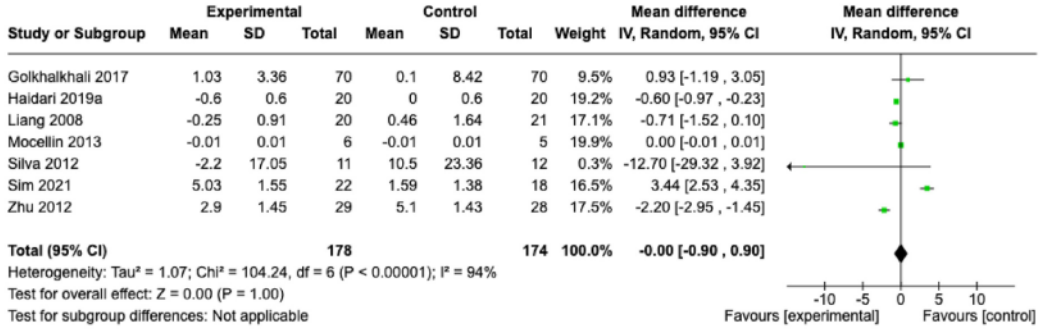


Fig. 4. Forest plot of O3FAs supplementation versus control for IL-6 mean change level.



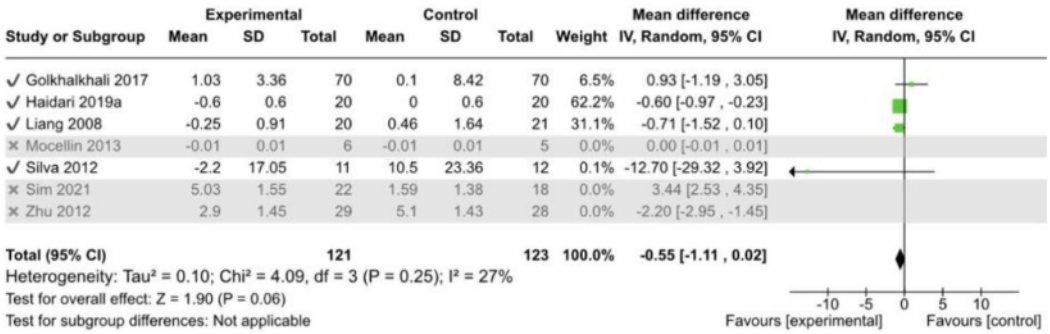


Fig. 5. Forest plot of O3FAs supplementation versus control for TNF-α mean change level.

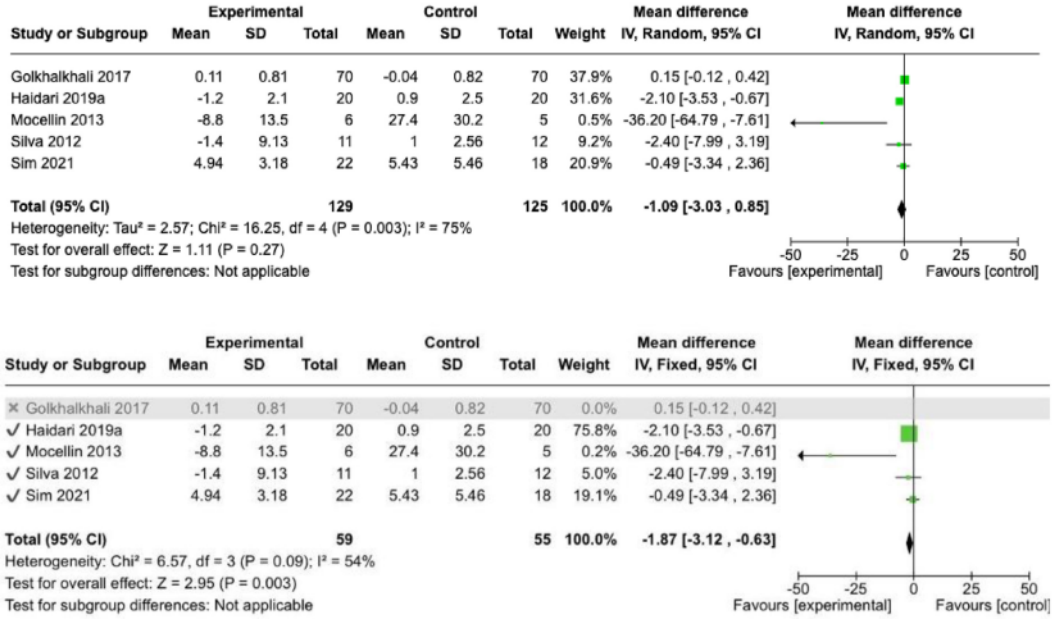


Fig. 6. Forest plot of O3FAs supplementation versus control for CRP mean change level.

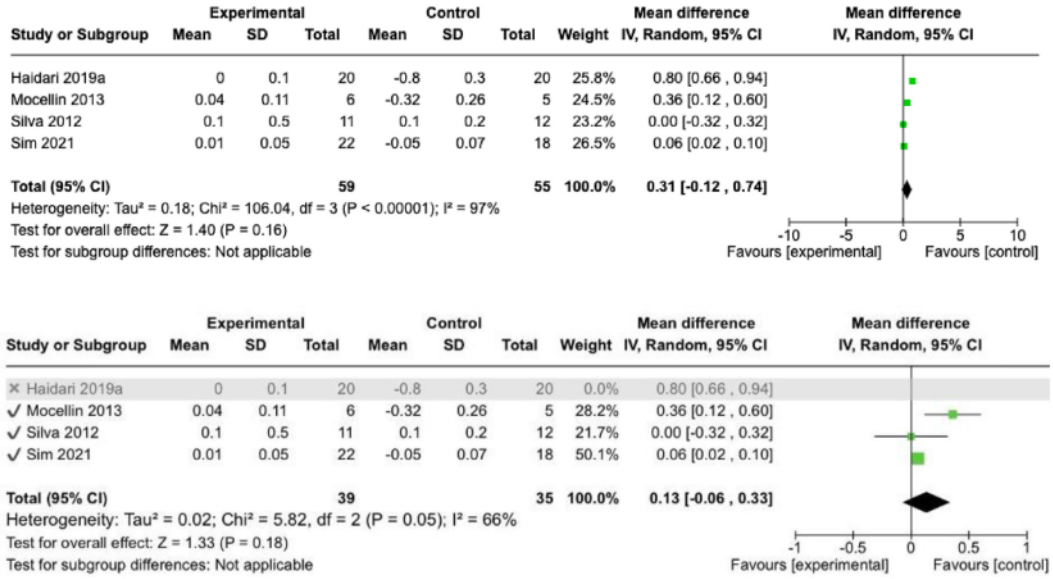


Fig. 7. Forest plot of O3FAs supplementation versus control for serum albumin mean change level.

patients. This stems from the ability to regulate proinflammatory cytokines, sustain adequate nutrition levels, and minimize the occurrence of postoperative complications [21]. This study showed that O3FAs supplementation was successful in shortening the length of hospital stay, favoring recovery among CRC patients. The outcome corroborated the findings from previous studies that showed the efficacy of O3FAs in reducing the duration of hospital stays [21,46].Sultan et al. (2012) stated that the supplementation did not influence the length of hospital stays, hence further investigation should be conducted to address the controversy [47].

4.5. Study limitations and advantages

This study serves as the latest meta-analysis on RCTs held until 2023 to provide consideration regarding the safety and efficacy of using O3FAs as a complementary treatment. Concerning the limitations, firstly, there was significant heterogeneity in the pooled

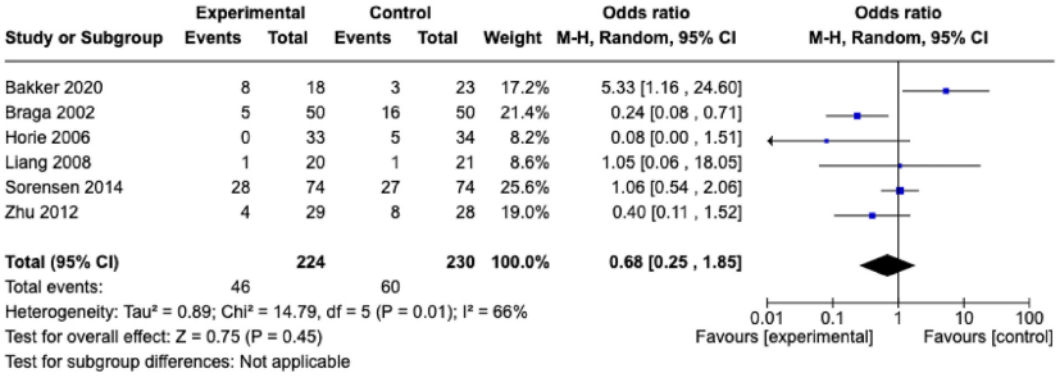


Fig. 8. Forest plot of O3FAs supplementation versus control for postoperative infectious complications.

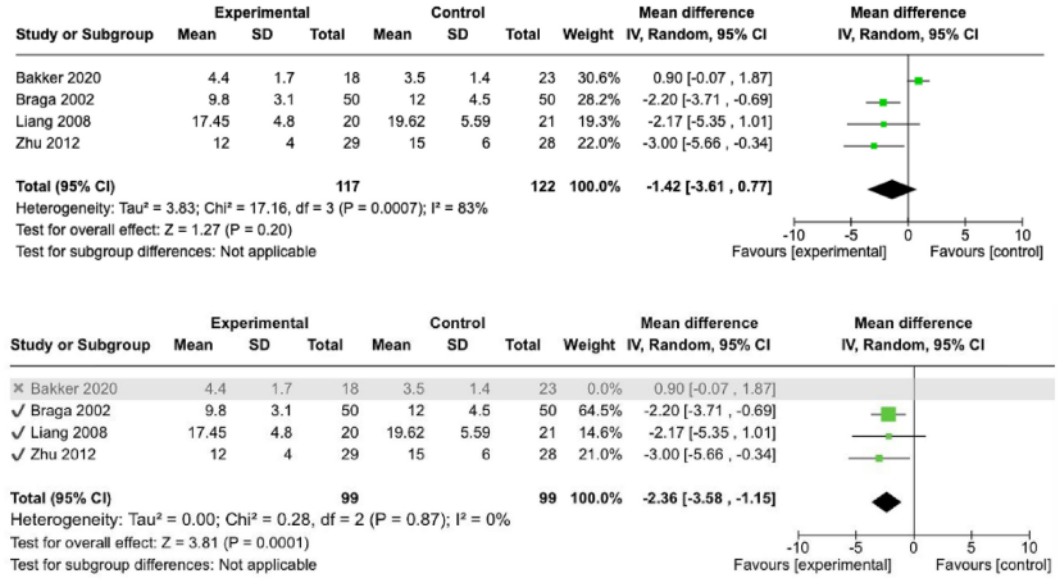


Fig. 9. Forest plot of O3FAs supplementation versus control for mean change in length of stay duration.

outcomes of TNF-α level ($I^2 = 94\%$), CRP level ($I^2 = 75\%$), serum albumin level ($I^2 = 97\%$), and length of hospital stay ($I^2 = 83\%$). The sources of heterogeneity identified are the differences in the method of the studies, the difference in participants, the type of intervention, the dose of the supplementation, the timing of the parameter examination, and the duration of the study. To minimize heterogeneity, sensitivity analysis was performed to remove several papers substantial in increasing the heterogeneity. Secondly, this study did not measure the combined effect of O3FAs in the presence of chemotherapy treatment, gut microbiota, or related enzymes such as CYP4A11 and CYP4F11. Thirdly, the number of randomized-controlled trial studies was limited, which necessitated up-to-date meta-analyses in the future.

5. Conclusion

In conclusion, a meta-analysis of randomized controlled trials indicated that O3FAs were helpful as an additional treatment to reduce inflammatory markers like IL-6, CRP, and TNF-α, increase albumin levels, and decrease postoperative infectious complications, as well as length of hospital stay. To strengthen the clinical implementation and advancement of nutritional therapies, as well as standardized nutritional preparations in CRC patients, future meta-analyses should be conducted with an updated pool of studies including a broader range of parameters. Further clinical trials and experiments should also be made emphasizing the impact and clinical implementation of O3FA in the nutritional status of CRC patients.

Author contributions

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Investigation: agung ary wibowo.
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Project administration: agung ary wibowo, Nathan Aditya Willyanto.

Resources: agung ary wibowo.
Software: agung ary wibowo.
Validation: agung ary wibowo.
Writing – review & editing: agung ary wibowo, Nathan Aditya Willyanto.

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