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RAPID COMMUNICATION

Impact of postoperative omega-3 fatty acid-supplemented parenteral nutrition on clinical outcomes and immunomodulations in colorectal cancer patients

Bin Liang, Shan Wang, Ying-Jiang Ye, Xiao-Dong Yang, You-Li Wang, Jun Qu, Qi-Wei Xie, Mu-Jun Yin

Bin Liang, Shan Wang, Ying-Jiang Ye, Xiao-Dong Yang, You-Li Wang, Jun Qu, Qi-Wei Xie, Mu-Jun Yin, Division of Surgical Oncology and Division of Gastroenterological Surgery, Peking University People's Hospital, Beijing 100044, China
Author contributions: Liang B and Wang S contributed equally to this work; Liang B and Wang S designed the research; Liang B, Ye YJ, Yang XD, Wang YL, Qu J, Xie QW, Yin MJ performed the research and collected the data; Wang S and Ye YJ supervised the research; Liang B and Ye YJ analyzed the data; Liang B wrote the paper and revised the manuscript.
Correspondence to: Shan Wang, Professor, Division of Gastroenterological Surgery, Peking University People's Hospital, Beijing 100044, China. dr.wangshan@yahoo.com.cn
Telephone: +86-10-88326806 Fax: +86-10-88326808
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Abstract

AIM: To investigate the effect of omega-3 fatty acid parenteral supplementation postoperatively on clinical outcomes and immunomodulation in colorectal cancer patients.

METHODS: Forty-two patients undergoing radical colorectal cancer resection with an indication for total parenteral nutrition postoperatively were enrolled in this prospective, double-blind, randomized, controlled study. Patients received total parenteral nutrition supplemented with either soybean oil (LCT; Intralipid®, Fresenius-Kabi, SO group, n = 21) or a combination of omega-3 fish oil and soybean oil (LCT:fish oil = 5:1, fish oil; Omegaven®, Fresenius-Kabi, FO group, n = 21), up to a total of 1.2 g lipid/kg per day for 7 d postoperatively. A same volume calorie and nitrogen was administrated. Routine blood test, biochemistry, systemic levels of IL-6 and TNF-α, percentage of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes were evaluated preoperatively and on postoperative d 1 and 8. Patient outcome was evaluated considering mortality during the hospital stay, length of postoperative hospital stay, and occurrence of infectious complications.

RESULTS: Both lipid regimens were well tolerated. No differences between the two groups were noticed in demographics, baseline blood test, biochemistry, serum levels of IL-6 and TNF-α, percentage of $CD4^+$, $CD8^+$ lymphocytes, and ratios of $CD4^+/CD8^+$. Compared with those on postoperative d 1, serum IL-6 levels on postoperative d 8 were significantly depressed in the FO group than in the reference group (-44.43 ± 30.53 *vs* -8.39 ± 69.08, P = 0.039). Simultaneously, the ratios of $CD4^+/CD8^+$ were significantly increased in the FO group (0.92 ± 0.62 *vs* 0.25 ± 1.22, P = 0.035). In addition, depression of serum TNF-α levels (-0.82 ± 2.71 *vs* 0.27 ± 1.67, P = 0.125) and elevation of $CD3^+$ and $CD4^+$ lymphocyte percentage (12.85 ± 11.61 *vs* 3.84 ± 19.62, P = 0.081, 17.80 ± 10.86 *vs* 9.66 ± 17.55, P = 0.084, respectively) were higher in the FO group than in the reference group. Patients in the FO group trended to need a shorter postoperative hospital stay (17.45 ± 4.80 d *vs* 19.62 ± 5.59 d, P = 0.19). No statistically significant difference was found when stratified to mortality and occurrence of infectious complications.

CONCLUSION: Postoperative supplementation of omega-3 fatty acids may have a favorable effect on the outcomes in colorectal cancer patients undergoing radical resection by lowering the magnitude of inflammatory responses and modulating the immune response.

Key words: Colorectal cancer; Parenteral nutrition; Omega-3 fatty acids; Immunomodulation; Abdominal surgery

Peer reviewer: Reinhold W Stockbrugger, Professor, Department of Gastroenterology and Hepatology, University Hospital Maastricht, Debyelaan 25, Maastricht NL-6206 AZ, The Netherlands

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INTRODUCTION

Lipid emulsions are regularly used postoperatively to supply energy and essential fatty acids[1]. Recently, the pharmacological role of fatty acid and omega-3

polyunsaturated fatty acid (PUFA) deficiency in colorectal cancer patients has been appreciated[2]. Conventional lipid soybean oil emulsions contain a very large amount of linoleic acid (LA; 18: 2n-6) and a relatively low amount of α-linolenic acid (LNA; 18: 3n-3). Arachidonic acid (AA, C20: 4n-6), derived from linoleic acid, is metabolized by cyclo-oxygenase and lipo-oxygenase pathway to pro-inflammatory mediators, such as prostaglandin, thromboxane, and leukotriene. Omega-3 long-chain polyunsaturated fatty acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which can compete with AA for the production of less inflammatory active eicosanoid, are absent in these vegetable oils[3,4]. Therefore, omega-3 fatty acids should be added directly into lipid emulsions to suppress the system inflammatory response and to decrease the risk of postoperative thrombosis. Recently, supplementation with fish oil is supposed to improve standard clinical therapy for chronic hyper-inflammatory diseases such as Crohn' disease[1,5], rheumatoid arthritis[6], cancer cachexia[7,8], and as an adjunct therapeutic measure for trauma, injure, and sepsis[2,9-12]. Although several studies have demonstrated the beneficial effects of omega-3 fatty acid supplementation on patient outcome or immune competence, randomized controlled clinical trials focusing on the use of parenteral fish oil are scarce[13-17]. The aim of this study was to assess whether parenteral supplementation of omega-3 fatty acid postoperatively improves the inflammatory and immunological function of colorectal cancer patients and their clinical outcomes.

MATERIALS AND METHODS

Patients

Forty-two patients with colon or rectal cancer staging TNM Ⅰ-Ⅲ undergoing radical resection, who gave their written, informed consent to participate in the study, were prospectively enrolled consecutively from May 2002 to October 2003. After operation, 41 patients were randomly assigned to receive total parenteral nutrition (TPN) supplemented with either soybean oil (SO) or SO + fish oil (FO) emulsion, one patient withdrew because of the unresectable disease. The clinical characteristics of the two groups of patients are summarized in Table 1.

Exclusion criteria

Exclusion criteria were: (1) age < 18 or > 70 years; (2) body mass index (BMI) < 16 or > 30; (3) diabetes mellitus; (4) hypertriglyceridemia (> 200 mg/dL) or hypercholesteremia (> 240 mg/dL); (5) abnormal liver function (ALT>60 IU/L or total bilirubin > 1.2 mg/dL); (6) abnormal renal function (serum creatinine > 1.6 mg/dL or BUN > 30 mg/dL); (7) post-splenectomy; (8) endocrine diseases, such as hyperthyroidism, hyperadrenocorticism, or medication with thyroxine, corticoids or other immunomodulators; (9) pregnancy or breast-feeding; (10) early chemotherapy or radiotherapy before postoperative d 8.

Interventions

Patients were assigned to respective groups by computer-derived block randomization. The pharmacist was the only person who was aware of the randomization list. Both the patients and the investigators were, thus, unaware of the infused drug. Postoperatively, all patients received TPN for consecutive 7 d, as shown in Table 2, through an indwelling central venous catheter or peripheral catheter. Glucose, amino acids, SO emulsion, fat- and water- soluble vitamins as well as trace elements were provided to both groups by infusion pumps for 16-20 h daily in an "All-In-One" manner. In the FO group, the omega-6 lipid content of TPN was partially replaced by omega-3 PUFA (Omegaven, Fresenius-Kabi) up to 0.2 g/kg body weight daily. Thus, in the FO group, the omega-3/omega-6 ratio was 1:3. Calculated on body mass, the nutrition in both groups was isonitrogenous and isocaloric.

Table 1 Demographic characteristics of the patients at entry (mean ± SD)

Group	Group FO (n = 20)	Group SO (n = 21)	t or χ^2	P
Age (yr)	55.80 ± 10.10	59.19 ± 10.61	1.047	0.3
Weight (kg)	63.50 ± 8.86	65.40 ± 9.20	0.675	0.5
Height (cm)	164.55 ± 6.68	165.29 ± 7.60	0.329	0.74
BMI	23.38 ± 2.38	23.92 ± 2.84	0.655	0.52
Gender (male/female)	10/10	15/6	1.977	0.16
Diagnosis (colon cancer/rectal cancer)	11/9	12/9	0.019	0.89
TNM stage				
Stage Ⅰ	0	3	3.2	0.21
Stage Ⅱ	10	10		
Stage Ⅲ	10	8		

Table 2 Regimen of daily TPN in the FO and SO groups/kg body weight (g)

Day	Both groups		SO + FO lipids	SO lipids
	Glucose	Nitrogen		
POD+1	3.0	0.18	0.5 SO + 0.1 FO	0.6 SO
POD+2-POD+7	3.0	0.18	1.0 SO + 0.2 FO	1.2 SO

Blood samples and analytical methods

For laboratory measurements, 12 mL of whole blood (8 mL serum, 4 mL EDTA) was withdrawn before breakfast in the morning before operation (POD-1) and on the first and eighth days after the operation (POD+1, POD+8). Routine blood test and biochemistry analysis were immediately performed at the Department of Clinical Chemistry, Peking University People's Hospital according to standard procedures. Serum vials for analysis of cytokines such as IL-6 and TNF-α were separated and kept at 2℃-8℃ and measured in 24 h. For quantitative detection of IL-6 and TNF-α, enzyme immunoassays were performed according to the manufacturer's instructions with IL-6 or TNF-α enzyme-linked immunosorbent assay (ELISA) kit commercially available from R&D Systems (Minneapolis, MN, USA). Percentage of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes was analyzed by flow cytometry (COULTER EPICS ELITE ESP, USA). Fluorescence-labeled antibodies were purchased from BD (Franklin

Table 3 Counts of white blood cells, platelets, and γ-glutamyltranspeptidase before and after operation in the FO group versus the SO group (mean ± SD)

Group	*n*	WBC (× 10^9)				Plt (× 10^9)				r-GT (U/L)			
		POD-1	POD+1	POD+8	1	POD-1	POD+1	POD+8	1	POD-1	POD+1	POD+8	1
FO	20	6.76 ± 2.01	11.20 ± 2.31	8.17 ± 1.37	-3.03 ± 2.46	241.93 ± 56.62	181.50 ± 73.47	262.72 ± 58.63	81.22 ± 61.58	23.30 ± 11.55	14.30 ± 9.26	37.20 ± 24.49	22.90 ± 21.35
SO	21	7.03 ± 2.59	11.70 ± 3.32	9.03 ± 2.58	-2.67 ± 2.58	221.51 ± 44.20	176.51 ± 41.25	264.60 ± 74.13	88.08 ± 67.07	17.43 ± 5.80	12.76 ± 7.89	48.48 ± 28.41	35.71 ± 25.34
t		0.381	0.567	1.322	0.447	1.290	0.270	0.090	0.341	2.072	0.574	1.358	1.747
P		0.71	0.57	0.19	0.66	0.20	0.79	0.93	0.74	0.05	0.57	0.18	0.09

1: The margin value for POD+8 minus POD+1.

Table 4 Assessment of inflammatory and immunological parameters before and after operation in the FO group versus the SO group (mean ± SD)

Group	*n*	IL-6 (pg/mL)					TNF-α (pg/mL)				
		POD-1	POD+1	POD+8	1	2	POD-1	POD+1	POD+8	1	2
FO	20	9.02 ± 23.25	59.66 ± 31.91	15.23 ± 8.42	50.64 ± 32.21	-44.43 ± 30.53	2.74 ± 2.00	3.31 ± 2.85	2.49 ± 2.06	0.57 ± 3.46	-0.82 ± 2.71
SO	21	10.42 ± 10.75	42.60 ± 50.12	34.21 ± 44.12	32.18 ± 47.69	-8.39 ± 69.08	2.48 ± 3.73	2.66 ± 2.76	2.94 ± 3.12	0.18 ± 4.50	0.27 ± 1.67
t		0.249	1.292	1.935	1.445	2.141	0.270	0.738	0.544	0.312	1.570
P		0.804	0.204	0.066	0.156	0.039	0.789	0.465	0.590	0.757	0.125

Lakes, NJ, USA) and flow-check fluorospheres were obtained from Beckman-Coulter (Fullerton, CA, USA). Cytokines and percentage of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes were analyzed at the Department of Clinical Chemistry, Peking Union Medical College Hospital.

Outcomes of the patients were evaluated considering mortality during the hospital stay, length of postoperative hospital stay, and occurrence of infectious complications.

Statistical analysis

Data were expressed as mean ± SD and tested for statistical significance using the software SPSS (version 10.0). Analysis of variance or Student's *t*-test or chi-square test was used in statistical analyses. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of patients

Only one patient withdrew from the study because of the unresectable disease, whereas 41 patients completed the study, without changes in medication. There were no statistically significant differences between the two groups of patients at entry concerning the clinical characteristics (Table 1). Blood test, biochemistry, serum levels of IL-6 and TNF-α, percentage of $CD4^+$, $CD8^+$ lymphocytes, and ratios of $CD4^+/CD8^+$ are shown in Tables 3 and 4. Both lipid regimens were well tolerated with no adverse events in terms of bleeding complication.

Clinical outcomes

No death occurred in both groups during the hospital stay, and only one case had incision infection in each group. Therefore, no statistical significant difference was found when stratified to death and occurrence of infectious complications. Although patients in the FO group trended to need a shorter postoperative hospital stay, no statistically significant difference was found (17.45 ± 4.80 d *vs* 19.62 ± 5.59 d, $P = 0.19$).

Laboratory parameters

Seven days after parenteral nutrition, no statistically significant difference was observed with respect to routine blood test and biochemical evaluation. White blood cell count and serum level of γ-GT in the FO group were lower than those in the SO group (Table 3). Compared with POD+1, serum IL-6 levels on POD+8 were significantly lower in group FO than in reference group (Table 4, -44.43 ± 30.53 *vs* -8.39 ± 69.08, $P = 0.039$). Simultaneously, the ratios of $CD4^+/CD8^+$ were significantly increased in the FO group (Table 5, 0.92 ± 0.62 *vs* 0.25 ± 1.22, $P = 0.035$) compared with the reference group. In addition, depression of serum TNF-α levels (-0.82 ± 2.71 *vs* 0.27 ± 1.67, $P = 0.125$) and elevation of $CD3^+$ and $CD4^+$ lymphocyte percentage (12.85 ± 11.61 *vs* 3.84 ± 19.62, $P = 0.081$, 17.80 ± 10.86 *vs* 9.66 ± 17.55, $P = 0.084$, respectively) were higher in the FO group than in the reference group (Tables 4 and 6).

DISCUSSION

To obtain a homogenous population, we selected patients with colorectal cancer staging TNM Ⅰ-Ⅲ to undergo radical resection. Patients were enrolled consecutively and randomly assigned to receive TPN supplemented with either SO or SO + FO emulsion. There were no statistically significant differences between the two groups at entry.

It was reported that reduction in platelet aggregation can be modified by increasing omega-3 long-chain fatty acid content of platelet phospholipids in humans[18]. In a randomized, controlled double-blind study, Heller AR

Table 5 Assessment of inflammatory and immunological parameters before and after operation in the FO group versus the SO group (mean ± SD)

Group	*n*	$CD8^+$(%)					Ratio of $CD4^+/CD8^+$				
		POD-1	POD+1	POD+8	1	2	POD-1	POD+1	POD+8	1	2
FO	20	25.89 ± 8.09	28.87 ± 7.63	25.46 ± 7.20	2.99 ± 7.20	-3.41 ± 5.79	1.54 ± 0.79	0.89 ± 0.52	1.80 ± 0.74	-0.65 ± 0.69	0.92 ± 0.62
SO	21	26.12 ± 10.95	26.50 ± 12.08	26.31 ± 9.85	0.38 ± 13.07	-0.19 ± 10.12	1.32 ± 0.50	1.27 ± 1.34	1.52 ± 0.69	-0.05 ± 1.28	0.25 ± 1.22
t		0.079	0.747	0.316	0.786	1.244	1.067	1.195	1.269	1.854	2.186
P		0.937	0.460	0.754	0.437	0.221	0.293	0.239	0.212	0.071	0.035

Table 6 Assessment of inflammatory and immunological parameters before and after operation in the FO group *versus* the SO group (mean ± SD)

Group	*n*	$CD3^+$ (%)					$CD4^+$ (%)				
		POD-1	POD+1	POD+8	1	2	POD-1	POD+1	POD+8	1	2
FO	20	65.81 ± 9.52	56.43 ± 12.57	69.28 ± 9.42	-9.38 ± 9.88	12.85 ± 11.61	35.69 ± 11.48	23.68 ± 10.69	41.48 ± 9.51	-12.02 ± 10.79	17.80 ± 10.86
SO	21	57.41 ± 11.11	59.73 ± 16.06	63.57 ± 10.26	2.32 ± 20.36	3.84 ± 19.62	30.46 ± 9.74	24.41 ± 15.87	34.07 ± 10.17	-6.05 ± 17.95	9.66 ± 17.55
t		2.591	0.731	1.851	2.320	1.799	1.575	0.173	2.405	1.281	1.775
P		0.013	0.469	0.072	0.026	0.081	0.123	0.864	0.021	0.208	0.084

1: The margin value for POD+1 minus POD-1; 2: The margin value for POD+8 minus POD+1.

and colleagues[19,20] demonstrated that no coagulation and platelet abnormalities are evoked by fish oil supplementation as high as 0.2 g/kg per day for five postoperative days. In the present study, the change in platelet counts showed no statistical difference between the two groups. Neither bleeding complication nor other adverse events were observed. This is in line with the notion that a short-term parenteral administration of omega-3 fish oil is safe[9,21]. In addition, our results demonstrate that the serum level of γ-GT on POD+8 in the FO group was lower than that in the SO group. Heller AR *et al*[20] found that after a major abdominal tumor surgery, fish oil supplementation could improve liver and pancreas function. Animal experiments have demonstrated improved perfusion and fewer translocations of viable bacteria from the gut into the mesenteric lymph nodes and liver after omega-3 fatty acid infusion in rats[22,23]. Therefore, our results suggest that parenteral nutrition supplemented with omega-3 fish oil might protect liver function after a major abdominal operation in colorectal cancer patients.

Omega-3 and -6 PUFAs are essential for humans and must be nutritionally provided. Recently, omega-3 PUFA deficiency has been recognized and appreciated[2]. After intravenous administration, EPA and docosahexaenoic acid (DHA) promptly incorporate into the cell membrane, compete with arachidonic acid (AA) in the cyclooxygenase and 5-lipoxygenase pathways, resulting in a reduced generation of diene prostanoids (e.g. PGE_2, PGI_2, TXA_2) and tetraene leukotrienes (e.g. LTB_4), derived from AA in favor of the corresponding triene prostanoids (e.g. PGE_3, PGI_3, TXA_3) and pentaene leukotriene (LTB_5) derived from EPA[13,24]. In a randomized controlled trial, Köller *et al*[17] demonstrated that release of 5-series leukotrienes from isolated leukocytes stimulated with Ca-ionophore is increased in patients receiving fish oil. Leukotrienes have numerous effects on inflammatory and immune functions, such as leucocyte-endothelial interaction, lymphocyte proliferation, and induction of cytokine gene expression (e.g. IL-1, IL-6, or TNF-α)[25,26]. In a randomized controlled study, Wachtler *et al*[25] showed that the systemic levels of IL-10, IL-6 and TNF-α are significantly decreased in surgical patients 5 d after administration of TPN enriched with omega-3 fatty acids. In another clinical trial, Weiss *et al*[27] also found that IL-6 levels are significantly decreased and TNF-α release from monocytes is also decreased in patients receiving fish oil perioperatively. In addition, HLA-DR expression induced by monocytes, an indicator of compensatory potential required to balance immune response, is significantly decreased[28,29]. Mayer *et al*[13] displayed that neutrophil function is significantly improved in patients receiving omega-3 fatty acids, including leukotriene generation and respiratory burst. In our study, serum IL-6 levels were significantly lower in the FO group than t in the reference group. This is in agreement with the previous reports[25,27,30]. Simultaneously, the ratios of $CD4^+/CD8^+$ were significantly increased in the FO group. In addition, depression of serum TNF-α levels and elevation of $CD3^+$ and $CD4^+$ lymphocyte percentage were noted in the FO group. In an experimental animal model, administration of parental fish oil during sepsis could prevent sepsis-induced suppression of lymphocyte proliferation and IL-2 release[31]. These findings suggest that supplementation of omega-3 PUFA may restrain inflammatory response, modulate lymphocyte proliferation, and maintain the function of immunocompetent cells under inflammatory conditions such as surgical trauma.

The lower magnitude of postoperative inflammatory response to administration of omega-3 fatty acids may have a favorable impact on clinical outcomes of patients with CRC. A shorter postoperative hospital

stay was noted in our study. No statistically significant difference was found when stratified to death and occurrence of infectious complications. In a cohort of elective postoperative patients, mortality is such a rare event that changes in mortality is underpowered to be detected. Various factors may influence the outcomes of surgical patients. A short single nutritional intervention is unlikely to produce extensive effects on the outcomes of postoperative patients. Recently, in a randomized controlled trial, Weiss *et al*[27] have demonstrated a shorter postoperative ICU and hospital stay, and a lower rate of severe infections in patients administrating omega-3 fish oil perioperatively beginning on POD-1. These results suggest that supplementation with with omega-3 fatty acids may have a more favorable effect on the outcomes of CRC patients after a major surgery.

In conclusion, postoperative supplementation of omega-3 fatty acids may have a favorable effect on the outcome of colorectal cancer patients by lowering the magnitude of inflammatory responses and modulating the immune response. Perioperative administration of omega-3 fish oil may have a more favorable effect on the outcome of CRC patients after a major surgery. Further prospective, randomized controlled trials are required to delineate this effect in a larger number of patients.

COMMENTS

Background

Omega-3 and -6 polyunsaturated fatty acids (PUFAs) are essential for humans and must be nutritionally provided. After incorporated into cell membrane, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) promptly compete with arachidonic acid (AA) on the cyclooxygenase and 5-lipoxygenase pathways, resulting in a reduced generation of diene prostanoids (e.g. PGE_2, PGI_2, TXA_2) and tetraene leukotrienes (e.g. LTB_4), derived from AA and are in favor of triene prostanoids (e.g. PGE_3, PGI_3, TXA_3) and pentaene leukotriene (LTB_5) derived from EPA. Therefore, the benefit of omega-3 fatty acids is to suppress the system inflammatory response and decrease the risk of postoperative thrombosis, which has been appreciated recently.

Research frontiers

Recently, clinical nutrition has attempted to combine caloric support with modulation of the immune response. Several new generations of lipid emulsion containing n-3 lipids have been introduced, and immunonutrition has become the hot spot or an important area in this research field.

Innovations and breakthroughs

Although several studies have demonstrated the beneficial effects of omega-3 fatty acid supplementation on the outcome or immune competence of patients, randomized controlled clinical trials focusing on the use of parenteral fish oil are scarce, especially in colorectal cancer patients. To obtain a homogenous population, patients with colorectal cancer staging TNM Ⅰ-Ⅲ were selected to undergo radical resection, and concomitant disorders were restricted according to the exclusion criteria. Depression of inflammatory parameters, such as serum level of IL-6 and TNF-α was observed. Elevation of $CD4^+/CD8^+$ ratio, $CD3^+$ and $CD4^+$ lymphocyte percentage, was noted after administration of omega-3 fatty acids supplementation. Meanwhile, a near-significant improvement in clinical outcome was demonstrated. Patients accepted omega-3 fatty acid supplementation trended to need a shorter postoperative hospital stay. In view of the authors, postoperative supplementation of omega-3 fatty acids may have a favorable effect on the outcome of colorectal cancer patients undergoing radical resection by lowering the magnitude of inflammatory responses and modulating the immune response.

Applications

By summing up the available data from surgical patients, we conclude that fish oil should be included in parenteral nutrition yielding positive impact on the outcome of patients.

Terminology

Immunonutrition, which combines caloric support and modulation of the immune response, has become the hot spot in this research field.

Peer review

This article on the effect of omega-3 fatty acid supplementation on colorectal cancer is interesting.

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