

# Omega-3 Fish Oil Reduces Mortality Due to Severe Sepsis with Acute Gastrointestinal Injury Grade III

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Submitted: 22-09-2016

Revised: 08-11-2016

Published: 19-07-2017

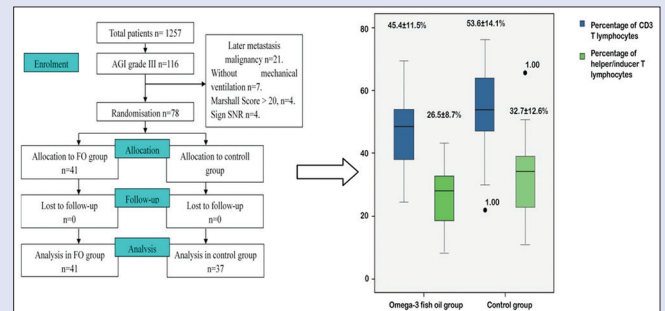
## ABSTRACT

**Background:** Sepsis plays an important role in acute gastrointestinal injury (AGI). Our research was designed to determine the effects of omega-3 fish oil (FO) in patients suffering from severe sepsis combined with AGI III, and the ability of FO to modulate immune function. **Methods:** Seventy-eight patients diagnosed with severe sepsis with AGI III and a need for mechanical ventilation were randomized to two groups. In the FO group, 50 g of long chain fatty acid soybean oil ( $n = 6$ ) and 10 g of FO ( $n = 3$ ) were administered as total parenteral nutrition (TPN). The control group was treated with 50 g of long chain fatty acid soybean oil without addition of FO to TPN. **Results:** At baseline, there were no significant differences between the two groups. The 60-day mortality was lower in the FO group. Multiple factor logistic regression analysis revealed that intra-abdominal pressure (IAP) and abdominal infection were correlated with the FO intervention. The patients with abdominal infection demonstrated a lower mortality rate, fewer CD3 T lymphocytes, and fewer helper/inducer T lymphocytes in the FO group compared with the control group. After 7 days, the Marshall Score was lower in the FO group than in the control group. **Conclusion:** FO has positive effects in terms of improving the long-term prognosis of patients with severe sepsis with AGI III. Patients with a high IAP and abdominal infection might experience greater benefit from FO. This effect might be due, in part, to immunomodulation.

**Key words:** Acute gastrointestinal injury, multiple organ dysfunction syndrome, omega-3 fish oil, severe sepsis

## SUMMARY

- Fish oil (FO) has positive effects in terms of improving the long-term prognosis of patients with severe sepsis with acute gastrointestinal injury Grade III
- Patients with a high intra-abdominal pressure and abdominal infection might experience greater benefit from FO
- This effect might be due, in part, to immunomodulation.



**Abbreviations used:** AGI: Acute gastrointestinal injury; FO: Fish oil; TPN: Total parenteral nutrition; IAP: Intra-abdominal pressure; ICU: Intensive Care Unit; MODS: Multiple organ dysfunction syndrome; TLR4: Toll-like receptor 4; DNR: Do Not Resuscitate; WGAP: Working Group of Abdominal Problem; EN: Enteral nutrition; BP: Low blood pressure; CRI: Catheter-related infection; PBS: Phosphate-buffered saline; ELFA: Enzyme-linked fluorescent assay; SD: Standard deviation; PUFAs: Polyunsaturated fatty acids; EPA: Eicosapentenoic acid; DHA: Docosahexaenoic acid.

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DOI: 10.4103/pm.pm\_418\_16

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## INTRODUCTION

Sepsis is a common clinical syndrome caused by severe injury, infection, or major surgery, and it is a leading cause of morbidity and mortality in the Intensive Care Unit (ICU).<sup>[1,2]</sup> The annual incidence of sepsis in developed countries has increased from 8% to 13% in the past decade, with 750 thousand cases in the United States and 13.5 thousand cases in Europe. In developing countries, the death rate from sepsis is extremely high due to poverty and malnutrition, among others.<sup>[3]</sup> The pathogenesis of sepsis is complicated, and studies have shown that some organs and tissues are damaged in the early stage of sepsis, whereas severe sepsis, septic shock, or multiple organ dysfunction syndrome (MODS) occurs during later stages of sepsis.<sup>[2,4]</sup>

Critically ill patients may suffer an acute gastrointestinal injury (AGI), in which the patient's acute disease causes gastrointestinal dysfunction.<sup>[5,6]</sup> Research has shown that the gastrointestinal tract plays an important role in the progression of sepsis. The gastrointestinal mucosal barrier is damaged by septic inflammation. A large number of toxins and bacteria

are then translocated through the blood through the portal vein and lymphatic system, ultimately resulting in MODS.

Recent studies investigating the pathogenesis of sepsis have demonstrated that excessive levels of cytokines and inflammatory mediators are released, establishing a foundation for sepsis.<sup>[1,4]</sup> Therapies for sepsis typically include the control of infection, improved organ perfusion, and immunomodulation. Among all therapeutic strategies, immunomodulation through the use of omega-3 fish oil (FO) has received increasing attention. FO modulates the

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**Cite this article as:** Chen H, Wang W, Hong C, Zhang M, Hong Y, Wang S, *et al.* Omega-3 fish oil reduces mortality due to severe sepsis with acute gastrointestinal injury grade III. *Phcog Mag* 2017;13:407-12.

immunological response to sepsis through several pathways. It may also decrease the expression of inflammatory factors.<sup>[7]</sup> FO can inhibit Toll-like receptor 4 (TLR4) to block the TLR signaling pathway,<sup>[8]</sup> and it can also block the nuclear factor kappa B pathway. Tsou *et al.* have confirmed that the number of CD4 lymphocytes in peripheral blood and the ratio of CD4 to CD8 cells increased in response to FO pretreatment in a rat model of sepsis.<sup>[9]</sup> FO may also have organ-protective functions. FO has been shown to diminish the requirement for renal replacement and to improve the function of the liver and pancreas.<sup>[10,11]</sup>

In 2012, a working guideline was developed by the Working Group of Abdominal Problem (WGAP) to define and grade AGI.<sup>[6]</sup> In the ICU, the mortality rate of septic patients with intestinal dysfunction (AGI Grade III) is extremely high. Thus, in the present study, we aimed to determine whether omega-3 fatty acid can decrease the mortality of patients suffering from severe sepsis with AGI Grade III. This study is registered on the Chinese Clinical Trial Register Network (<http://www.chictr.org/>, number: ChiCTR-ONRC-12002464) in 2012.

## MATERIALS AND METHODS

### Study population

The inclusion criteria were as follows: (1) age of 18 years or older; (2) severe systemic inflammatory response syndrome (SIRS) induced by severe infection, with the need for mechanical ventilation; (3) Marshall score >3; (4) intestinal dysfunction with AGI Grade III, including abdominal infection, abdominal surgery, or intestinal surgery; and (5) severe infection requiring carbapenems after admission to the ICU. The exclusion criteria were as follows: (1) Marshall score  $\geq 20$ ; (2) life expectancy < 28 days due to chronic or incurable disease such as uncontrolled cancer; (3) life expectancy < 24 h or discharge; (4) ICU stay < 7 days after meeting the inclusion criteria; (5) signing of the Do Not Resuscitate paper; (6) hematological or rheumatic disease; and (7) severe liver dysfunction (Child-Pugh score >10 or Grade C liver function).

### Definition

The diagnostic criteria for sepsis were based on the definition of the International Sepsis Forum.<sup>[12]</sup> In accordance with the criteria of the Europe WGAP, AGI Grade III was defined as the loss and difficulty of recovering gastrointestinal function. Furthermore, the condition of the patient could not be improved despite general interventions. Patients are presented as intolerant to enteral nutrition, which can induce continued or even complete deterioration of MODS. Septic shock is defined as severe sepsis plus persistently low blood pressure (BP) despite the administration of intravenous fluids. Low BP was defined as follows: (1) systolic BP (SBP) <90 mm of mercury (mmHg) or diastolic BP <60 mmHg; (2) mean BP <70 mmHg; (3) a reduction of SBP >40 mmHg, or a decrease of >2 standard deviation (SD) by age; and (4) exclusion of the other causes of low BP.<sup>[13]</sup> Catheter-related infection (CRI) included definitive diagnosis, clinical diagnosis, and suspected diagnosis, according to the prevention and treatment guidelines of the inter-vessel CRI of China.<sup>[14]</sup> The criteria for definitive diagnosis included the following: (1) positive results for semi-quantitative blood cultures from the central venous catheter; (2) both positive blood cultures from the central venous and peripheral catheters, with a positive central venous catheter blood culture obtained at least 2 h before the peripheral blood culture; and (3) the presence of the same microorganisms in both blood cultures. The criteria for the clinical diagnosis included the following: (1) a positive result for the catheter blood culture with a negative result for the peripheral blood culture and (2) the disappearance of infection symptoms 48 h after catheter removal without the use of additional antibiotics. A suspected diagnosis was defined as new symptoms of infection that disappeared after catheter removal.

## Treatment protocols and intervention

All patients received early goal-directed fluid resuscitation, mechanical ventilation, and carbapenem medication. Antibiotics were adjusted according to the drug resistance test results. Carbapenems included imipenem/cilastatin (1.0 g, q8h), meropenem (2 g, q8h), or biapenem (0.3 g q6h). Glycopeptides included vancomycin (1.0 g, q12h), teicoplanin (initial dose of 0.4 g, q12h  $\times$  2 times, followed by 0.4 g, qd; or linezolid 600 mg, q12h). Anti-fungal drugs included fluconazole (0.6 g, qd), voriconazole (initial dose of 0.4 g, q12h 2 times, followed by 0.2 g, q12h), or caspofungin (initial dose of 70 mg, followed by 50 mg qd). The dose was adjusted based on the creatinine clearance rate. Blood glucose was controlled between 8 and 10 mmol/L. Other complications were precluded by the therapies. Patients were treated according to the SSC guidelines<sup>[13]</sup> and randomized into two groups. In the FO group, 100 mL/day of FO ( $n = 3$ , containing 10 g refined FO) was continuously injected in the vein over 24 h as total parenteral nutrition (TPN). The FO was the product of Fresenius Kabi Austria GmbH, and it was repacked by Sino-Swed Pharmaceutical Corp., Ltd. To the TPN, 50 g of long-chain fatty acid soybean oil ( $n = 6$ ) was added. The proportion of  $n = 6/n = 3$  was 5:1. All patients received 20 kcal/kg each day during the first 7 days, following admission to the ICU. After stabilization of the circulation, the caloric count was slowly increased to 30 kcal/kg/day after 7 days, but  $n = 6/n = 3$  remained unchanged. As the control group, 50 g of long-chain fatty acid soybean oil without FO was added to the TPN. The caloric intake was calculated according to the body weight of the patient.

### Randomization

Patients were assigned based on a random number table. Designers, researchers, and patients were blinded. Nurses who did not participate in the data assessment were not blinded to the grouping and medication.

### Study outcomes

Age, gender, and inter-abdominal pressure (IAP) were recorded. Values were documented on the 1<sup>st</sup> and 7<sup>th</sup> day for the 28-day and 60-day mortality, mechanical ventilation time (day), length of stay in the ICU (days), and APACHE II and Marshall scores. Laboratory outcomes included the number of leukocytes (white blood cells [WBCs]) and the levels of hypersensitive C-reactive protein (hsCRP), serum procalcitonin (PCT), immunoglobulin (IgG, IgA, IgM), and complement (C3 and C4) on the 1<sup>st</sup> and 7<sup>th</sup> day of treatment. The percentages of CD3 lymphocytes, ratio of helper to inducer T-lymphocytes, ratio of CD3 to CD19 B lymphocytes, and CD3, CD19, and CD56 natural killer cells (NK cells) on the 1<sup>st</sup> and the 7<sup>th</sup> day of treatment were measured by flow cytometry. The ratio of CD4 to CD8 cells was also calculated automatically by flow cytometry.

#### Measurement of lymphocyte subsets

A BD FACSCanto™ II flow cytometer was used. Two milliliters of the blood sample was anticoagulated with heparin, from which 50  $\mu$ L was used for flow cytometry analysis. Twenty microliters of fluorescent monoclonal antibody was added to the sample, mixed uniformly, and incubated for 20 min at room temperature. Two milliliters of hemolysin was added to the sample and incubated for 10 min. The sample was then centrifuged for 5 min at 1000 rpm, and then the serum was discarded. Next, the sample was resuspended in 2 mL of phosphate-buffered saline (PBS) and then centrifuged for 5 min at 1000 rpm. This process was repeated twice. The sample was then resuspended in 500  $\mu$ L of PBS and assessed by flow cytometry.

#### Measurement of procalcitonin

PCT was measured using a PCT kit from bioMerieux Industry. A bioMerieux-mini-VIDAS immunological analysis meter was used

for detection. The surface plasmon resonance (SPR) fluid was used immediately, and it contained the marine monoclonal Ig antibody PCT.

**Procalcitonin contrast solution**

Two kinds of contrast solution (C1 and C2, freeze-dried) were provided in the kit. They were resuspended in 2 mL of distilled water and combined after 5–10 min.

**Procalcitonin calibration solution**

Two kinds of calibration solution (S1 and S2, freeze drying) were provided in the kit. They were resuspended in 2 mL of distilled water and combined after 5–10 min. The blood samples (3 mL) were anticoagulated with heparin lithium. The blood samples, PCT contrast solution, and calibration solution were added to a PCT slice and a solid phase pipette. In the machine, “PCT” was selected as the detection code. Two hundred milliliters of calibration solution, contrast solution, and sample were added to the sample, and then, the SPRs and slices were immunostained before automatic PCT measurement. The one-stage immunological sandwich assay and enzyme-linked fluorescent assay were used together for the assessment.

**Ethics**

This study was approved by the Medical Ethics Committee of Shenzhen People’s Hospital. The trial is registered at the Chinese Clinical Trial Registry (<http://www.chictr.org/>) under ChiCTR-ONRC-12002464. This study was conducted according to the Declaration of Helsinki, and written informed consent was obtained from all patients.

**Sample size and statistical analysis**

The total sample size required 60 cases (at least 30 cases per group), which was calculated according to our previous study. Quantitative data were reported as the mean ± SD or median and were compared using an independent sample Student’s *t*-test. For data that were nonnormally distributed, means and medians were compared using Mann–Whitney U-test. Qualitative data, such as gender, cases with abdominal infection or abdominal surgery, treatments, and mortality, were compared using Chi-square test. Multiple factor logistic regression analyses were performed if the factor was closely correlated with the clinical prognosis or *P* < 0.05. Abdominal infection was analyzed as the subgroup. *P* < 0.05 was considered statistically significant. SPSS 17.0 (SPSS Inc., Chicago, IL, USA) for Windows was used to analyze the data.

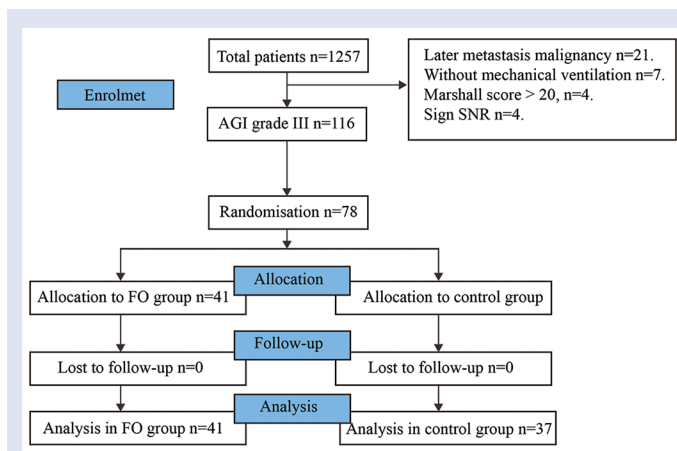
**RESULTS**

**There were no significant differences in the main diagnostic indexes, clinical characteristics, or baseline laboratory results between the fish oil and control group**

Seventy-eight cases were recruited for the study from August 2012 to July 2014. The patients were included in the FO group (41 cases) or the control group (37 cases) [Figure 1]. The main diagnoses are listed in Table 1. Gender, age, abdominal infection, abdominal surgery, IAP, and antibiotics did not differ between the groups [Table 2]. Laboratory results were also comparable between the groups [Table 3]. The positions and locations of the identified microbes are shown in the supplementary file.

**The 60-day mortality rate in the fish oil group was significantly improved compared with the control group**

In the 28-day mortality study, 10 cases (of 41) in the FO and 15 cases



**Figure 1:** Patients included in the analysis

**Table 1:** There were no significant differences in main diagnosis indexes between fish oil and control group

Main diagnosis	Groups	
	FO	Control
Gastrointestinal perforation and intestinal necrosis	16	17
Severe pancreatitis	6	6
Cholecystitis and cholangitis	3	2
Severe urinary infection	1	1
Infection after abdominal surgery	3	1
Blood infection	1	2
Pneumonia	9	7
Severe skin soft-tissue infection	1	1
Chest infection	1	0

$\chi^2=2.62, P=0.96$ . FO: Fish oil

**Table 2:** There were no significant differences in clinical characteristics between fish oil and control group

	FO group (n=41)	Control group (n=37)	P
Male (%)	22 (53.7)	21 (56.8)	0.823
Age (year)	68.0±13.0	69.1±15.5	0.083
Abdominal infection (%)	29 (70.7)	28 (75.7)	0.799
Abdominal surgery (%)	28 (68.3)	25 (67.6)	1.00
IAP (cm H <sub>2</sub> O)	15.1±3.5	15.2±4.4	1.00
APACHE II score	32.0±6.7	30.5±6.2	0.579
Marshall score	9.3±2.9	10.1±3.2	0.434
Glycopeptides (%)	34 (82.9)	27 (73.0)	0.113
Vancomycin	7 (17.1)	8 (21.6)	-
Teicoplanin	23 (56.1)	11 (29.7)	-
Linezolid	4 (9.8)	8 (21.6)	-
Anti-fungal drugs (%)	26 (63.4)	17 (45.9)	0.063
Fluconazole	15 (36.6)	9 (24.3)	-
Voriconazole	6 (14.6)	8 (21.6)	-
Caspofungin	5 (12.2)	0 (0)	-
Hemofiltration (%)	18 (43.9)	19 (51.4)	0.650

IAP: Intra-abdominal pressure; FO: Fish oil

(of 37) in the control group died. In the 60-day mortality study, 11 cases (of 41) in the FO group and 18 cases (of 37) in the control group died. The 60-day mortality rate was significantly improved in the FO group compared with the control group [Table 4]. The relationship between 60-day mortality and FO was analyzed by multiple factor logistic regression. The result revealed a correlation among IAP, abdominal infection, and FO intervention [Table 5].

**Table 3:** There were no significant differences in baseline laboratory results between fish oil and control group

	FO group		Control group		Z	P*
	Case	Mean	Case	Mean		
WBC ( $\times 10^9/L$ )	40	13.6	37	14.9	-0.23	0.82
PCT (ng/mL)	40	6.1	37	12.2	-0.49	0.62
hsCRP (mg/L)	40	101.4	37	108.8	-0.66	0.51
Percentage of total lymphocytes (%)	40	3.4	36	4.5	-0.81	0.42
Percentage of CD3 lymphocytes (%)	40	49.8	36	54.0	-1.84	0.07
Percentage of helper/inducer T-lymphocytes (%)	40	30.7	36	31.5	-0.76	0.45
Percentage of inhibitor T-lymphocytes (%)	40	16.1	36	20.4	-1.72	0.09
Percentage of CD3/CD19 total B lymphocytes (%)	40	22.0	36	20.2	-0.64	0.52
Percentage of natural kill cells (%)	40	16.3	36	13.1	-1.06	0.29
CD4/CD8 (%)	40	2.0	36	1.6	-1.36	0.17
IgG (g/l)	38	8.9	36	8.8	-0.18	0.85
IgA (g/l)	38	1.7	36	1.7	-0.19	0.85
IgM (g/l)	38	0.6	36	0.6	-0.45	0.65
C3 (g/l)	38	0.7	36	0.6	-1.15	0.25
C4 (g/l)	38	0.2	36	0.2	-0.01	1.00

\*Mann-Whitney U-test. WBC: White blood cell; hsCRP: Hypersensitive C-reactive protein; PCT: Procalcitonin; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; FO: Fish oil

**Table 4:** The 60-day mortality rate of fish oil group was significantly lower than the control group

	OF group (%)	Control group (%)	OR (95% CI)	P
28-day mortality rate	24.4	40.5	0.473 (0.180-1.247)	0.127
60-day mortality rate	26.8	48.6	0.387 (0.150-0.996)	0.046

FO: Fish oil; OR: Odds ratio; CI: Confidence interval

**Table 5:** Intra-abdominal pressure, abdominal infection were relevant to the statistical grouping

Interaction factors	Wald	P	OR	95% CI
IAP	9.9	0.002	0.78	0.67-0.91
Abdominal infection	4.0	0.05	0.30	0.10-0.97
By grouping	4.8	0.03	3.29	1.13-9.60

OR: Odds ratio; CI: Confidence interval; IAP: Intra-abdominal pressure

### The clinical outcomes were not significantly different between the fish oil and control group

The length of stay in the ICU and days of mechanical ventilation were similar in the two groups. In addition, the APACHE II Scores and Marshall scores on the 1<sup>st</sup> and 7<sup>th</sup> day were not significantly different. On day 7, there were no differences in total lymphocytes, CD3 T-lymphocytes, helper/inducer T-lymphocytes, inhibit T-lymphocytes, CD3/CD19 total B lymphocytes, NK cell, CD4/CD8, serum IgG, IgA, or IgM, serum complement C3 or C4, WBC, or hsCRP ( $P > 0.05$ , two independent sample *t*-test). The PCT levels in the two groups on day 7 were also similar ( $z = -0.83$ ,  $P = 0.40$ , Mann-Whitney U-test).

### The mortality rate in the fish oil group was significantly improved compared with that in the control group in patients with abdominal infection

Fifty-seven cases (73%) suffered abdominal infection, of whom 29 were in the FO group and the remaining 28 in the control group. In 28 days, 3 patients died in the FO group compared with the 13 patients in the control group. In the 60-day mortality test, 4 patients died in the FO

group compared with 13 in the control group. These differences were statistically significant [Table 6].

### T-lymphocytes and helper/inducer T-lymphocyte counts and the Marshall score were significantly lower in the fish oil group compared with the control group

The length of stay in the ICU and the days of mechanical ventilation were similar between the two groups ( $P = 0.79$  and  $P = 0.67$ , respectively, Mann-Whitney U-test). There were no statistical differences in lymphocytes, immunology, or complement ( $P > 0.05$ ). The numbers of T-lymphocytes and helper/inducer T-lymphocytes were lower in the FO group compared with the control group [Figure 2]. The difference in APACHE II Scores on the 7<sup>th</sup> day was not significant ( $P = 0.19$ , *t*-test). Other baseline outcomes were similar (all  $P > 0.05$ ). However, the Marshall score was significantly lower in the FO group than in the control group ( $3.9 \pm 2.7$  vs.  $6.1 \pm 4.4$ , mean different  $-2.22$  [ $-4.14 \sim -0.29$ ]).

## DISCUSSION

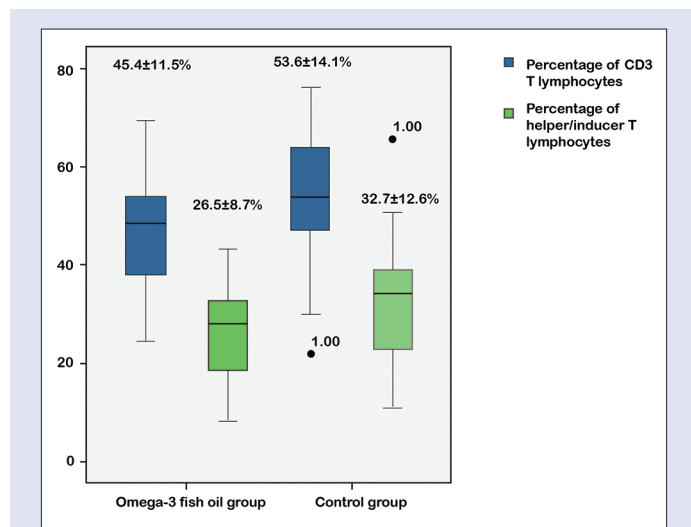
Multiple factors could underlie and exacerbate the progression of AGI,<sup>[15]</sup> of which one of the most important factors is sepsis. Sepsis is a specific kind of SIRS that is induced in response to severe infection. When SIRS is uncontrolled, abnormal tissue perfusion occurs, which ultimately leads to MODS. Data have shown that MODS scores parallel the severity of SIRS.<sup>[16]</sup> Previous research has also demonstrated that thrombus embolism in the gastrointestinal microcirculation can be induced by endotoxemia.<sup>[17]</sup> In return, AGI can result in deterioration of the ectopic intestinal flora and lymphocyte apoptosis, inhibiting the immune functions of lymphocytes.<sup>[18]</sup>

FO contains abundance of polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid and docosahexaenoic acid. It is a nutritional substrate and also an important inhibitor of inflammation. FO can modify membrane lipid rafts by replacing  $n = 6$  with  $n = 3$  PUFA in the cell membrane, which in turn reduces the production of the  $n = 6$  PUFA source to alkanolic acid. Thus, the fluidity of the lymphocyte membrane is protected and stabilized. A certain proportion of  $n = 3$  and  $n = 6$  is considered to be anti-inflammatory. Previous research has suggested that 1:2 ~ 1:4 would be a better proportion for preventing inflammatory reactions.<sup>[19]</sup> In our study, a proportion of 1:5 was used. A positive clinical effect has also been reported in patients with severe sepsis with

**Table 6:** The 28-days and 60-day mortality rate of fish oil group was significantly lower than the control group in patients with abdominal infection

	OF group (%)	Control group (%)	OR (95% CI)	P
28-day mortality rate	10.3	46.4	0.133 (0.033-0.544)	0.02
60-day mortality rate	13.8	53.6	0.139 (0.038-0.504)	0.01

FO: Fish oil; OR: Odds ratio; CI: Confidence interval

**Figure 2:** Subgroup analysis showing fewer baseline CD3 T-lymphocytes (mean different  $-8.21$ , 95% confidence interval  $[-15.11$  to  $-1.31]$ ) and helper/inducer T-lymphocytes (mean different  $-6.22$ , 95% confidence interval  $[-12.02$  to  $-0.42]$ ) in patients with abdominal infection in the fish oil group compared with the control group

AGI Grade III. However, there is no evidence demonstrating that enteral supplements of FO improve the prognosis of severe inflammatory reactions.<sup>[20]</sup> Because of the design of our study, parenteral nutrition was the only choice to supply calories, and therefore, we estimated the effects of the FO supplied by parenteral supplementation. The results obtained for the FO group revealed a better 60-day mortality rate compared with the control group. Patients, who are suffering from high IAP combined with abdominal infection, may obtain a greater benefit from the addition of FO parenteral therapy. Recent animal experiments have demonstrated that FO parenteral supplementation reduces Bax mRNA expression, increases Bcl<sub>2</sub> mRNA expression, promotes the proliferation of intestinal epidermal cells, lengthens the villus, and inhibits apoptosis.<sup>[21]</sup> Thus, among all administration routes, patients are most likely to benefit from parenteral supplementation with FO.

In the present study, we observed a better 28- and 60-day mortality rate in the subgroup with abdominal infection that received FO. On day 7, the Marshall score was also lower in the FO group. These findings suggested that FO could either prevent organ failure or protect organs against failure. This result is consistent with the findings of a previous study.<sup>[22]</sup> Different degrees of abnormal T-lymphocytes were observed before FO supplementation, but the difference between the FO and control groups disappeared on day 7, which suggested that FO could improve the function of T-lymphocytes, potentially by modifying lipid rafts and affecting the fluidity of the lymphocyte plasma membrane.<sup>[23]</sup> FO supplementation has demonstrated negative clinical outcomes in previous cohort studies, but the gastrointestinal functions

were not clearly graded,<sup>[24]</sup> which could have a significant influence on prognosis according to our previous study.

Previous studies have suggested that FO can reduce the levels of some inflammatory factors; however, we did not detect significant differences in leukocytes, hsCRP, or PCT between the two groups. Serum PCT levels have also been shown to be reduced by FO in children who underwent cardiac surgery or esophageal carcinoma surgery. This finding indicates that FO may have a beneficial effect on the control of infection and reduce CRP and the sequential organ failure assessment score<sup>[22]</sup> in patients with severe sepsis. However, a meta-analysis did not demonstrate an effect of FO on the levels of interleukin-6 or tumor necrosis factor- $\alpha$ , both of which are overexpressed during sepsis.<sup>[25]</sup> Thus, additional trials are needed to confirm whether FO can inhibit the production of inflammatory factors.<sup>[26]</sup>

## CONCLUSION

In this study, we discovered that omega-3 FO fatty acid can improve the long-term prognosis of patients suffering from severe sepsis with AGI Grade III. Patients with high IAP and abdominal infection might obtain a greater benefit from FO. The effects of FO may be due, in part, to the modulation of immune functions.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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