Research Square

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Parenteral supplementation of omega-3 fatty acid on the prognosis of sepsis: a retrospective study

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Abstract

Objectives

The role of omega-3 fatty acids in the treatment of sepsis is always on paradox. we tried to retrieve and download the patients' data in a certain period through the hospital information system, used data sorting so as to screen out the patients with sepsis so as to find out the role of omega-3 fatty acids in sepsis.

Methods

Through the hospital information system, retrieve and include the patients who were admitted to the Department of critical medicine of Shenzhen People's Hospital from December 2016 to June 2019, screen out patients diagnosed with sepsis according to a certain criterion. The patients were grouped by whether they were applicated with omega-3 fatty acid or not.

Results

A total of 1733 cases included into analysis, among of whom 303 cases were applicated with omega-3 fatty acid. The amounts and baseline conditions between both groups were imbalance. Severity of omega-3 fatty acid group was higher than that of control group. Chi-square test found that the mortality rate of omega-3 fatty acid was higher than that of control group ($p < 0.0001$). But age, gender, whether there is abdominal infection, whether there is septicemia, shock, the need for mechanical ventilation, and the need for renal replacement therapy may all affect the prognosis of the patients. If these factors were used as covariates, multiple logistic regression analysis showed that there was no significant difference in mortality rate between the treatment group and the control group ($P = 0.574$). Survival analysis showed that the survival rate of treatment group was higher than that of the control group when at the end of total treatment duration ($P = 0.035$).

Conclusion

For patients with more severe sepsis, doctors are more likely to use omega-3 fatty acids in the early stage. Omega-3 fatty acids may improve the long-term prognosis of sepsis, but the conclusion still needs to be accepted carefully.

Background

The role of omega-3 fatty acids in the treatment of sepsis is always on paradox. In terms of mechanism, it seems that omega-3 fatty acids can inhibit the inflammatory response [1], while sepsis is just due to the strong inflammatory response induced by serious infection, leading to further failure of multiple organs, which causes the patient's condition inter critical state, and finally dies. Omega-3 fatty acids have anti-inflammatory effects, including interaction with leukocyte chemotaxis, adhesion molecule expression, and leukocyte endothelial cell adhesion. And it changes cell phospholipid lipid rafts by replacing n-6

molecules on lipid rafts with n-3, inhibiting inflammatory gene expression and activating anti-inflammatory transcription factor peroxidase [2]. However, the outcomes of clinical studies are still quite different. Previous meta-analysis and systematic reviews were used to evaluate the efficacy of omega-3 fatty acids in the treatment of sepsis. Mo et al. Included 721 patients in 12 randomized controlled trials (RCT). It was found that omega-3 fatty acid supplementation can reduce the mortality of sepsis patients and shorten the ICU stay of these patients [3]. However, our team has used the method of randomized controlled trial to evaluate two different series of patients with sepsis and intestinal failure, and found that parenteral supplementation of omega-3 fatty acid has unpredictable outcomes on prognosis of sepsis [4, 5]. In particular, in the second randomized controlled trial, we found that omega-3 fatty acids did not reduce the 28-day mortality rate of sepsis patients. However, in 60 days, we can see that the treatment group has a lower mortality rate. The treatment group has a lower total T-lymphocyte of CD3 at the beginning of the treatment, while in 7 days after the treatment, the two groups tend to have the same counts of lymphocyte [5], which can be referred to It is suggested that omega-3 fatty acids have a certain recovery effect on T lymphocytes in sepsis and improve long-term prognosis? Later, we also conducted another meta-analysis, which included more than twice as many randomized controlled trials as Mo's study, to evaluate the effect of omega-3 fatty acid on survival outcome of sepsis and sepsis induced acute respiratory distress syndrome (ARDS). However, it was found that the mortality of sepsis patients did not improve whether they were supplemented with omega-3 fatty acids enterally or parenterally [6].

The role of omega-3 fatty acids in the treatment of sepsis is always on paradox. In terms of mechanism, it seems that omega-3 fatty acids can inhibit the inflammatory response, while sepsis is just due to the strong inflammatory response induced by serious infection, leading to further failure of multiple organs, which causes the patient's condition inter critical state, and finally dies. Omega-3 fatty acids have anti-inflammatory effects, including interaction with leukocyte chemotaxis, adhesion molecule expression, and leukocyte endothelial cell adhesion. And it changes cell phospholipid lipid rafts by replacing n-6 molecules on lipid rafts with n-3, inhibiting inflammatory gene expression and activating anti-inflammatory transcription factor peroxidase. However, the outcomes of clinical studies are still quite different.With the advent of the era of big data, we tried to retrieve and download the patients’ data in a certain period through the hospital information system, used data sorting so as to screen out the patients with sepsis, and grouped them according to whether they use omega-3 fatty acids as a parenteral supplement or not, so as to analyze and try to find out the role of omega-3 fatty acids in sepsis.With the advent of the era of big data, we tried to retrieve and download the patients’ data in a certain period through the hospital information system, used data sorting so as to screen out the patients with sepsis, and grouped them according to whether they use omega-3 fatty acids as a parenteral supplement or not, so as to analyze and try to find out the role of omega-3 fatty acids in sepsis.

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Methods

Inclusion criteria:

Through the hospital information system, retrieve and include the patients who were admitted to the Department of critical medicine of Shenzhen People's Hospital from December 2016 to June 2019, screen according to the following clinical characteristics of patients (TABLE-1), exclude the non-sepsis patients, and then confirm that the patients included in sepsis meet the ICD-9 sepsis diagnosis standard through the repeated checking of the diagnosis by researchers. This study was carried out with the consent of the ethics committee of the hospital. Each patient signed the informed consent form agreeing to accept the obligations of medical treatment, teaching, scientific research and other aspects of the hospital at the beginning of admission.

Clinical Intervention And Grouping

The selected patients were diagnosed and treated according to their clinical conditions, Clinical decisions included: microbial culture, antibiotics, fluid resuscitation, mechanical ventilation, blood purification, etc., and blood samples were taken for examination according to the needs of patients. The blood routine, liver and kidney function, coagulation function and other indicators of the patients were monitored. The doctor would decide whether omega-3 fatty acids were injected to the patients or not by their own judgement. And patients were grouped according to whether they used omega-3 fatty acids or not. At present, omega-3 fatty acids are fish oil fatty acid preparations (refined fish oil preparations). 10 g / day of fish oil was given intravenously, which was used together with other fat preparations (1:5). The treatment durations of patients were planned by doctors. This study is a retrospective study, and there is no intervention on the start and stop of the treatment plan of patients.

Outcome Measurements

The patients' gender, age, respiratory rate, blood pressure, blood purification, mechanical ventilation, vasoactive medicines, blood routine, high sensitive C reactive protein (hsCRP), Procalcitonin (PCT), hepatorenal function, coagulation function including antithrombin III (AT III) and activated partial thrombin time (APTT) were recorded. The ventilator duration (hours), ICU stay (LOS, days) and clinical final (death) were recorded.

Statistical analysis

The parameters of normal distribution are expressed by means of mean plus minus standard deviation, and the values of non-normal distribution are recorded by means of median. According to whether fish oil is used for grouping, t-test of independent samples or Mann Whitney test is used to assess the differences between the two groups. Multivariate logistic regression analysis was used to evaluate the prognostic effect of other factors on the treatment of sepsis. Draw KM survival curve were drawn and the difference between the two groups of curves were analyzed. The relationship between the total amount of omega-3 fatty acids and the time of ventilator use and the length of stay in ICU was evaluated by fitting

curve and bubble chart. SPSS 20.0 for window and R software package were used to analyze the data, and $P < 0.05$ was taken to indicate that the difference between the groups was statistically significant.

Results

Patient characteristics and baseline condition

From December 2016 to June 2019, a total of 1997 patients were admitted. According to the screening criteria, 264 patients with non-sepsis were excluded and 1733 patients were included in the analysis. Age, gender, infection site and laboratory test index of these patients were recorded and compared in Table 2. Since the Apache and sofa scores of these patients in the retrospective study cannot be obtained, we evaluated the important organ indexes of the patients and presented them in a list (Table 2).

Table 1
Screening criteria for patients with sepsis

evaluation indicator	Explanation
infected focus *	With traceable infection site
Abnormal leukocyte count **	Leukocyte count > 12×10^9/L or < 4×10^9/L
Abnormal respiratory rate**	Respiratory rate > 20 beat per min,or need mechanical ventilation.
Shock***	MAP < 60 mmHg, or norepinephrine is needed.
Abnormal renal function**	SCr > 144umol/L,or continuous renal replacement treatment is needed.
Coagulation disorders **	Platelet count < 100×10^9/L
Abnormal liver function**	TBIL > 34.1umol/l.
Application of antibiotics****	Carbapenems or β - lactams are preferred.
Note: * Necessary condition. ** Two positive items plus * may be considered for sepsis diagnosis. *** One positive item plus * may be considered for sepsis diagnosis. **** Reference condition.	

Table 2

Patients' baseline comparison

	N	Omega-3 fatty acid group	Control group	Statistical value**	P value
Gender(female)	720	100	620	$X^2 = 11.04$	0.0001
Age	1733	67 ± 19	61 ± 20	t = 7.029	0.0001
Infectious foci					
Lung infection	1098	192	906	$X^2 = 0.0001$	1.000
Abdominal infection	83	34	49	$X^2 = 33.312$	0.0001
Biliary tract infection	47	10	37	$X^2 = 0.482$	0.442
Urinary tract infection	8	1	7	$X^2 = 0.138$	1.000
Septicemia	220	70	150	$X^2 = 35.887$	0.001
Other infectious sites	765	135	630	$X^2 = 0.025$	0.899
Mechanical ventilation	1067	221(72.94)	846(59.16)	$X^2 = 20.055$	0.0001
Shock	1458	278(91.75)	1190(83.22)	$X^2 = 14.052$	0.0001
Renal replacement treatment	345	96(31.68)	249(17.41)	$X^2 = 31.934$	0.0001
Laboratory examination*					
WBC ($\times 10^9$/L)	1479	12.94 ± 8.95	13.20 ± 8.47	Z=-1.285	0.199
N(%)	1470	86.16 ± 10.18	83.62 ± 11.99	Z=-3.735	0.0001
L(%)	1470	8.92 ± 8.07	10.96 ± 9.98	Z=-3.964	0.0001
M(%)	1470	8.92 ± 8.07	10.96 ± 9.98	Z=-3.964	0.0001
hsCRP(mg/L)	114	103.94 ± 86.31	70.53 ± 85.64	Z=-2.242	0.025

Note: * WBC□white blood cell. N: percentage of neutrophil. L: percentage of lymphocyte. M: percentage of monocyte. hsCRP: high sensitive C reactive protein. PCT: procalcitonin. BUN: blood urea nitrogen. Cr: creatinine. TBIL: total bilirubin. PLT: platelet. AT III: antithrombin III.

** X^2: Chi-square. t: t-test. Z: Mann Whitney test.

	N	Omega-3 fatty acid group	Control group	Statistical value**	P value
PCT(ng/ml)	494	14.71 ± 32.78	11.51 ± 28.97	Z=-2.655	0.008
BUN(mmol/L)	1405	11.96 ± 10.62	8.87 ± 8.00	t = 5.185	0.0001
Cr(umol/L)	1405	172.13 ± 200.23	150.16 ± 192.55	Z=-1.666	0.096
TBIL(umol/L)	222	25.19 ± 43.30	20.99 ± 32.06	Z=-1.633	0.102
PLT(× 10^9/L)	1480	188.80 ± 115.03	202.51 ± 109.48	t = -1.820	0.069
AT III(%)	950	60.69 ± 17.87	68.39 ± 18.54	t = -4.892	0.0001
Note: * WBC□white blood cell. N: percentage of neutrophil. L: percentage of lymphocyte. M: percentage of monocyte. hsCRP: high sensitive C reactive protein. PCT: procalcitonin. BUN: blood urea nitrogen. Cr: creatinine. TBIL: total bilirubin. PLT: platelet. AT III: antithrombin III.					
** X^2: Chi-square. t: t-test. Z: Mann Whitney test.					

Mortality

96 cases died in the omega-3 fatty acid treatment group, with a mortality rate of 31.68%, while 1430 cases died in the control group, with a mortality rate of only 20.00%. The mortality rate of the treatment group was 11.68% higher than that of the control group. Chi-square test shows that the difference between both groups was significant ($p < 0.0001$, see Fig. 1A). Omega-3 fatty acid was applicated in early state in most patients (see Fig. 1B). However, by observing the table-2, we can see that there is a large difference between the baselines of the two groups. Age, gender, whether there is abdominal infection, whether there is septicemia, shock, the need for mechanical ventilation, and the need for renal replacement therapy may all affect the prognosis of the patients. Therefore, we take death as the end point, and use omega-3 fatty acid as the factor, other factors namely the age, gender, and abdomen Cavity infection, septicemia, shock, mechanical ventilation, renal replacement therapy and other factors were used as covariates. Multiple logistic regression analysis showed that there was no significant difference in mortality between the treatment group and the control group (P = 0.574, see Table 3).

Table 3
Multiple logistic regression

	B	Standard error	Wald	Df	P value	OR	95%CI	
							Lower	upper
Gender	-0.262	0.133	3.904	1	0.048	0.769	0.593	0.998
Age	.023	0.004	41.228	1	0.0001	1.023	1.016	1.030
Abdominal infection	0.315	0.294	1.142	1	0.285	1.370	0.769	2.440
Septicemia	-0.954	0.168	32.410	1	0.000	0.385	0.277	0.535
Septic shock	-0.072	0.192	0.142	1	0.706	0.930	0.638	1.355
Mechanical ventilation	-0.985	0.148	44.256	1	0.0001	0.373	0.279	0.499
Renal replacement treatment	-1.337	0.143	87.695	1	0.000	0.263	0.199	0.347
Factors interaction with Omega 3 fatty acid	0.09	0.160	0.317	1	0.574	1.094	0.800	1.497

Survival Analysis

Take the death of patients as the clinical outcome, the time that patients transferred out or died were calculated as the final date of observation. KM curves were made, and compared. The results showed that the survival rate of omega-3 fatty acid treatment group was lower than that of the control group when up to the 30th day (P = 0.007), while to the 60th day outcome suggested that the survival rate of omega-3 fatty acid treatment group was slightly overturned (P = 0.062). The survival rate of treatment group was higher than that of the control group when at the end of total treatment duration (P = 0.035).

Discussion

Sepsis is a serious syndrome. It is estimated that there are 31.5 million cases of sepsis and 19.4 million cases of sepsis in the world, and 5.3 million people may die every year, which has become a heavy burden in the world [7]. Sepsis is newly defined as fatal multiple organ failure (MODS) caused by severe infection, which weakens the role of systemic inflammatory response syndrome (SIRS) [8]. However, inflammation still plays an important role in the occurrence and development of sepsis. The MODS and death induced by sepsis are mainly attributed to the strong inflammatory response at the initial stage of severe infection and the anti-inflammatory response at the later stage Reaction imbalance, and the complex interaction between inflammation and anti-inflammatory response [9]. It can be seen that the position of inflammation cannot be ignored, and the search for appropriate anti-inflammatory drugs has been the direction of clinical scientists. Among them, omega-3 fatty acid is one of the controversial drugs, but also a nutritional preparation. In this study, 303 patients were treated with omega-3 fatty acids, most

of whom were applicated in the early stage of the disease. Although factor analysis suggested that the mortality rate of omega-3 fatty acid patients was higher than that of the control group, multiple factors suggested that the disease severity of these patients was higher than that of the control group. This suggests that doctors may be more inclined to use omega-3 fatty acids in patients with relative crisis. In fact, there was no difference in mortality between the two groups when these factors imbalanced the baseline interacting with application of omega-3 fatty acid. On the contrary, patients treated with omega-3 fatty acids seem to have a better clinical prognosis as time goes on,and none of these randomized trials reported safety concerns. From the long-term prognosis improvement of sepsis patients after omega-3 fatty acid treatment, it seems to echo the results of our earlier randomized controlled trials [5].

Eicosapentaenoic Acid (EPA) and docosahexaenoic acid (DHA). Low level of AA is an important determinant of prognosis in sepsis patients [10]. The rats were given diets of homocysteine, homoomega-3 fatty acid group and non-omega-3 fatty acid group respectively before the injection of endotoxin, the rats showed different degrees of weight loss and tissue damage among groups. The liver enzyme and pathological outcomes of the rats receiving omega-3 fatty acid diet were better than those of the other diet groups [11]. N-3 fatty acid docosahexaenoic acid (DHA) was used to treat mouse bone marrow-derived dendritic cells, and different toll like receptor (TLR) ligands were used to stimulate them. Flow cytometry was used to detect cell surface maturation markers and intracellular activity. The expression and secretion of cytokines were detected by real-time RT-PCR and ELISA. DHA maintains the immature phenotype of bone marrow-derived DC by preventing the up regulation of MHCII and costimulatory molecules (CD40, CD80 and CD86) and maintaining high level of endocytosis activity. It also inhibited TLR2, 3, 4, and 9 ligand stimulated dendritic cells (DCs) to produce pro-inflammatory cytokines, including IL-12 cytokine family (IL-12p70, IL-23, and IL-27). The inhibit effect of IL-12 expression is through activating PPAR γ and inhibiting NFKAPABP65 translocation. These evidences show that DHA has anti-inflammatory effect in vivo [12].

It was found that the DCs were depleted in both the cecal ligation and puncture mice model and the sepsis patients. This process is related to the increase of apoptosis. The loss of DCs caused by sepsis occurs after the activation of CD3+, CD4 + T cells and the loss of lymph nodes. Before the loss of DCs, there is no continuous increase in its mature state. Mature and immature DCs are easy to be lost. CD8 + DCs has priority loss in local and remote lymph nodes [13]. This suggests that DCs plays a key role in sepsis. Recently, it has been found that in the early stage of inflammation, the activated DCs are characterized by the decrease of antigen cross presenting ability of newly discovered antigens and the production of immunogenic cytokines. The immunosuppression induced by sepsis is mainly due to the depletion of mature immature dendritic cells. However, the late development of immune tolerance can lead to the release of tumor necrosis factor inhibitory cytokines by DCs, which is involved in maintaining the local tolerance environment characterized by Treg cell aggregation [14]. By targeting DCs, it is found that the loss of DC quantity and function caused by sepsis is one of the reasons for the deficiency of CD8 T cell immune function, and the treatment of improving the state of DCs after sepsis may be helpful to the recovery of immune function of CD8 + T cell [15]. Pretreatment of DCs with DHA can prevent the maturation of DCs induced by LPS, maintain the low expression of costimulatory molecules and the lack

of proinflammatory cytokines (IL-12p70, IL-6 and IL-23). T cells co cultured with DC-DHA expressed high levels of TGF β and Foxp3, but showed no functional Treg phenotype. Similar to the results of in vitro experiments, the beneficial effect of DHA is related to the decrease of CD4 + T cells, which was caused by the decrease of IFN γ and IL-17 production in spleen and central nervous system [16].

In addition, omega-3 fatty acids also have effects on other inflammatory cells. It has been found that it can improve the pathogens clearance ability of neutrophils [17], which is mainly related to DHA. EPA can inhibit the migration of neutrophils to the focus. Endothelial cells can participate in the migration of neutrophils by producing prostaglandin (PG) D2. When PG D2 is combined with receptor DP-1 on neutrophils, it will lead to the adhesion and migration of neutrophils. However, the endothelial cells pretreated by EPA may reduce the production of PG D2 and increase the production of PG D3, thus inhibiting the migration of neutrophils [18]. At the same time, omega-3 fatty acids have multiple double bonds in their carbon chain. Because each double bond causes the carbon chain to bend, the accumulation of polyunsaturated fatty acids in the cell membrane cannot be as tight as that of saturated fatty acids. This increases the fluidity of immune inflammatory cells, reduces brittleness, and plays an important role in prolonging cell life [19]. This effect can also appear in other different kinds of immune cells, and it can adjust the immune mechanism of patients. Because leukocyte chemotaxis, migration and pathogen clearance are mainly in the early stage of inflammatory response, omge-3 fatty acids may affect this cell behavior in the early stage.

In the long run, omega-3 fatty acids may inhibit DNA methylation of inflammatory cells. Fatty acids can be modified by DNA methylation in vitro, while in vivo studies showed that total DNA methylation and PDK4 specific DNA methylation were positively correlated with eicosapentaenoic acid and arachidonic acid. There was a negative correlation between HDAC4 methylation and arachidonic acid [20]. One study found that 174 patients with Alzheimer's disease (AD) received 1.7 g DHA and 0.6 g EPA or placebo every day for 6 months. Two of the four CpG sites of peripheral blood leukocytes (PBLs) were significantly reduced in methylation. Hypomethylation at CPG2 and CPG4 sites was negatively correlated with the change of plasma EPA concentration, but not with the change of plasma DHA concentration [21]. However, it is not clear whether omega-3 fatty acids can also play a role in DNA demethylation of blood cells in inflammatory stage of sepsis. However, from bioinformatics research, it was found that the methylation of cg01770232 in IL-6 promoter was related to the increase of IL-6 concentration, while the higher concentration of omega-3 fatty acids inhibited the methylation of cg01770232 in IL-6 promoter, thus also inhibited the expression of IL-6. The relationship between n-3 polyunsaturated fatty acids and cg01770232 methylation depended on rs2961298 genotype [22]. IL-6 is an early indicator of inflammatory reaction, which is caused by severe infection. Patients can soar within 24 hours, then rapidly decline. It is a sensitive and specific indicator for early diagnosis of sepsis [23]. Therefore, the increase of serum concentration of omga-3 fatty acids can possibly inhibit DNA methylation process and early inflammation.

Although omga-3 fatty acids may improve the prognosis of sepsis patients, the dosage and regime are not clear. In our department, the formula of n3: n6 = 1:5 is generally used. The total dose of omega-3 fatty

acids used by each patient is different. This study is the first attempt to use the hospital information system to obtain data, collate and analyze, so there is also a serious imbalance of amounts of patients between the control group. In this retrospective study, the treatment plan could not be intervened, and the existing data could not be used to evaluate the patients and the side effects. Nevertheless, we still try our best to sort out and evaluate the patients' condition from the aspects of organ function and auxiliary treatment. Due to the different severity of the patients' condition, only statistical methods can be used to adjust the data of the patients. Pairing study may be helpful to obtain more accurate results and conclusions.

Conclusion

For patients with more severe sepsis, doctors are more likely to use omega-3 fatty acids in the early stage. Omega-3 fatty acids may improve the long-term prognosis of sepsis, but the conclusion still needs to be accepted carefully. Because the clinical condition of patients is of difference, the results of matching research may be able to draw more accurate conclusions.

Declarations

Ethics approval and consent to participate

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Shenzhen People's Hospital. Written informed consent was obtained from individual or guardian participants.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

Chen,HuaiSheng conceived and designed the study.

XunFa Liu, XueMing Tang contributed significantly to analysis and manuscript preparation.

YiChun Jiang, YongHui Ma helped perform the analysis with constructive discussions.

XueYan Liu reviewed and edited the manuscript.

YouLian Chen was a major contributor in writing the manuscript.

All authors read and approved the final manuscript.

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Figures

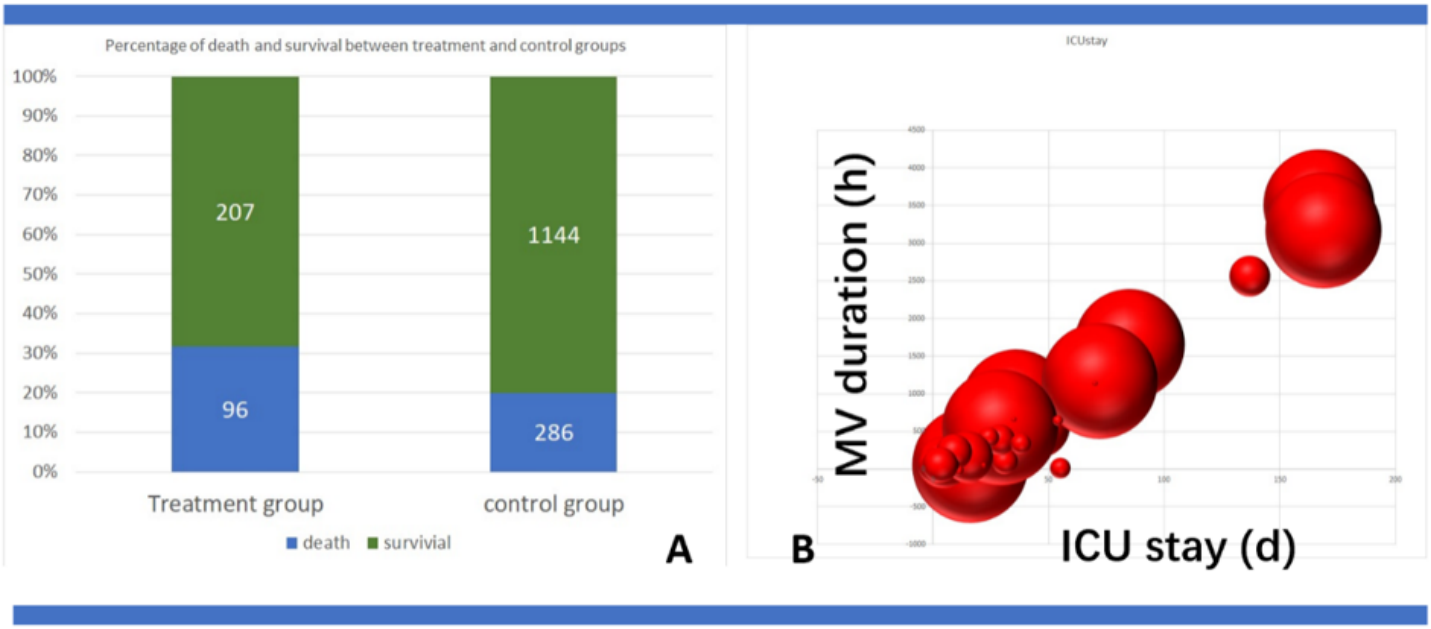


Figure 1

Omega-3 fatty acid on the prognosis of septic patients. (Note: 1A: mortality of omega-3 fatty was higher than that of control group. 2B: Bubble chart: the size of red bubble indicates the total dose of omega-3 fatty acid treatment. In most patients, omega-3 fatty acid was applicated in early state of treatment.)

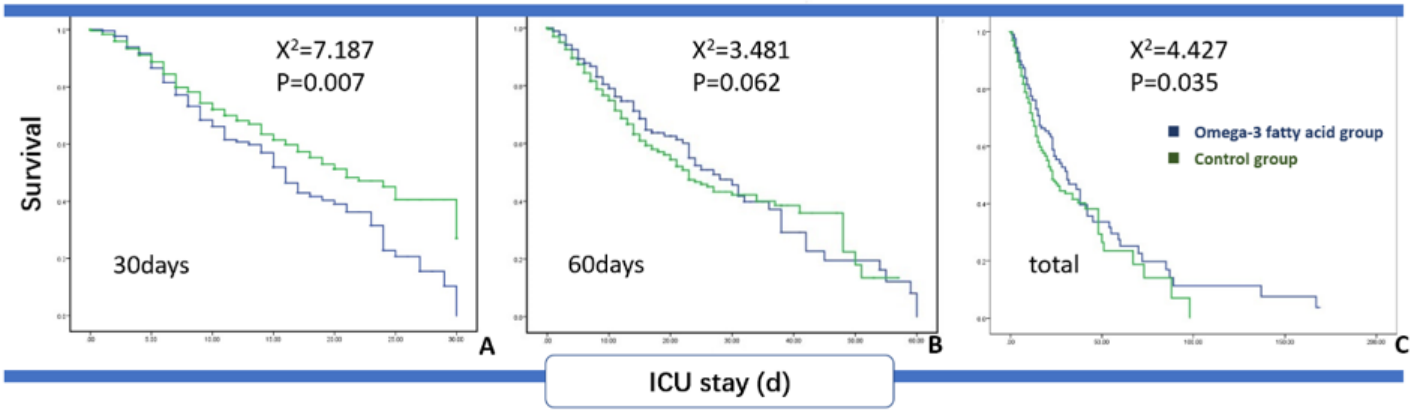


Figure 2

Survival analysis (KM curves). (2A: up to the 30th day. 2B: up to the 60th day. 2C: at the end of total treatment duration.)